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Comparison of medical comorbidity between primary angle closure glaucoma patients and a control cohort:

A population-based study from Taiwan

Hsin-Yi Chen [1,2], Cheng-Li Lin [3]

[1] School of Medicine, Medical College, China Medical University
[2] Department of Ophthalmology, China Medical University Hospital
[3]Management Office for Health Data, China Medical University

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*** Corresponding authors**

Hsin-Yi Chen, MD, Department of Ophthalmology, China Medical University Hospital, Taichung, Taiwan. No. 2, Yuh-Der Road, Taichung 40447, Taiwan.

Tel: 886-4-22081700 / Fax:886-4-22081700; E-mail: hsin7850@url.com.tw; glaucoma0606@gmail.com

Abstract

Objective To determine whether some medical comorbidities were more prevalent in primary angle closure glaucoma (PACG) patients and whether these comorbidities are associated with increased risk of PACG compared to controls.

Methods We included 3322 PACG subjects and randomly selected and matched 13288 subjects as the comparison cohort from the Taiwan National Health Insurance Research database (NHIRD). The univariable and multivariable unconditional logistic regression models were used to estimate the effect of comorbidities on the risk of PACG as indicated by the odds ratio (OR) with 95% confidence interval (CI).

Results The PACG group was composed of 61.1% female and the mean age was 65.2 ±12.7 years. The risk of PACG was greater for patients with the comorbidities of hypertension, hyperlipidemia, headaches, diabetes, liver diseases, peptic ulcers, and depression. For the male group, hypertension, headaches, diabetes, liver diseases, and depression were significantly associated with increased risk of PACG. For the female group, hypertension, hyperlipidemia, headaches, peptic ulcers, and depression were significantly associated with increased risk of PACG. For the age group younger than 64 years, patients with comorbidity of hypertension, hyperlipidemia, headaches, diabetes, renal failure, liver diseases, peptic ulcers, and depression were

significantly associated with increased risk of PACG. For the age group elder than 65 years, patients with hypertension, hyperlipidemia, peripheral vascular disorders, and peptic ulcers were significantly associated with increased risk of PACG.

Conclusions Clinicians should keep in mind that increased PACG risk in the subjects with hypertension, hyperlipidemia, headaches, diabetes, liver diseases, peptic ulcers, and depression.

Keywords: primary angle-closure glaucoma, medical comorbidity, Taiwan.

Article summary

Strengths and limitations of this study

- This is the first original study on the association between medical comorbidity and primary angle closure glaucoma (PACG).
- A strength of this study is the large sample size.
- Clinicians should keep in mind that increased PACG risk in the subjects with hypertension, hyperlipidemia, headaches, diabetes, liver diseases, peptic ulcers, and depression.
- Inherent limitations from claims database, including miscoding problem and selection bias; therefore, these findings cannot be completely generalizable to all populations.

INTRODUCTION

Primary angle-closure glaucoma (PACG) is a leading cause of blindness worldwide, especially very common in Asian country.[1-3] The proposed mechanism of PACG is pupillary block, with anterior lens movement as a strong contributing factor, often due to aging induced cataract formation.[4,5] Risk factors for PACG include aging, female gender, shallow anterior chamber and short axial length in hyperopic eye.[4,5] Contrary to primary open angle glaucoma (POAG), which has been well known to be associated with systemic diseases, including cardiovascular, metabolic, neurodegenerative, psychological diseases and others[6-13] very few studies evaluate the medical illness among the PACG subjects. A recent meta-analysis study shows that PACG affects approximately 0.75% adult Asians, increasing double per decade, and 60% of cases being female.[4] Therefore, it is quite meaningful to understand if some medical illness would be associated with PACG.

Here we use a nationwide dataset from Taiwan to study the prevalence of some common medical comorbidities in the PACG population. We also study if these comorbidities are associated with increased risk of PACG compared to controls. As far as we know that this is the few one using a large claims database to evaluate this important issue.

MATERIALS AND METHODS

Patient and public involvement statement

This work is a retrospective longitudinal case-control study from a claims database. Patients were not involved in the recruitment or conduct of the study.

Data Source

We conducted a nationwide population-based retrospective cohort study using data from the Longitudinal Health Insurance Database 2000 (LHID 2000). The LHID2000 contains the enrollment and claims information of 1 million randomly sampled enrollees of the National Health Insurance (NHI) program in 2000. The NHI program provides mandatory universal health insurance to all Taiwan's 23.75 million citizens, with an enrollment rate of approximately 99%.[14] The LHID 2000 includes all ambulatory care, inpatient services, prescription drugs, traditional Chinese Medicine and dental services claims data. The study was approved by the Institutional Review Board (IRB) of China Medical University and Hospital (CMUH-104-REC2-115). Diseases are coded according to the International Classification of Diseases ICD-9-CM, 2001 edition.

Sampled Participants

From LHID 2000, we identified patients aged more than 20 years with a diagnosis of primary angle closure glaucoma (PACG) (ICD-9-CM code 365.2) between 1 January 2005 and 31 December 2011 as case group. The date of diagnosis of PACG was defined as the index date. We excluded patients with a history of primary open angle glaucoma (POAG) (ICD-9-CM code 365.1) diagnosed before the index date. For each PACG case, 4 insured beneficiaries with no history of glaucoma (ICD-9-CM code 365), were assigned to a non-PACG control group, frequency matched with the patients in the PACG case group according to age (every 5-years), sex, and index year of PACG diagnosis and used same exclusion criteria as PACG case group.

Potential co-morbidities associated with PACG

The baseline comorbidities included hypertension (ICD-9-CM codes 401-405), ischemic heart disease (ICD-9-CM codes 410-414), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM code 428), cardiac arrhythmias (ICD-9-CM codes 426, 427), peripheral vascular disorders (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, 447.9), stroke (ICD-9-CM codes 430-438), headaches (ICD-9-CM code 784.0), migraine (ICD-9-CM code 346), epilepsy (ICD-9-CM code 345), dementia (ICD-9-CM code 290, 294.1, 331.0), rheumatoid arthritis (ICD-9-CM code 714), systemic lupus erythematosus (ICD-9-CM code 710.0), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 496), asthma-(ICD-9-CM code 493), pulmonary circulation disorders (ICD-9-CM codes 415-417), diabetes (ICD-9-CM code 250), hypothyroidism (ICD-9-CM codes 243, 244), renal failure (ICD-9-CM codes 584-586), liver diseases (ICD-9-CM codes 570-573), peptic ulcers (ICD-9-CM codes 531-533), hepatitis B (ICD-9-CM codes V02.61, 070.20, 070.22, 070.30, and 070.32), tuberculosis (ICD-9-CM codes 011-018), deficiency anemias (ICD-9-CM codes 280, 281) , depression (ICD-9-CM codes 296.2, 296.3, 300.4, 311), psychosis (ICD-9-CM codes 295-299), metastatic cancer (ICD-9-CM codes 196-198), and solid tumor (ICD-9-CM codes 140-195).

Statistical analysis

The baseline characteristics, and comorbidities of the PACG case group and non-PACG control group were compared. Chi-square test and t-test were used to test the difference of categorical and continuous variables, respectively, between the two groups. The univariable and multivariable unconditional logistic regression models

were used to estimate the effect of comorbidities on the risk of PACG as indicated by the odds ratio (OR) with 95% confidence interval (CI). All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Carey, NC) and the significance level was set at 0.05 for the two-tailed tests.

RESULTS

A total of 3322 PACG cases were eligible for the study, and 13288 subjects frequency matched according to sex, and age were selected as the control group (**Table 1**). The PACG group was composed of 61.1% female and 57.6% were elder than 65 years of age. The mean age of the study patients was 65.2 ±12.7 years for the PACG group and 64.8 ± 13.0 years for the controls. Compared to the controls, PACG patients were significantly higher prevalence of hypertension, ischemic heart disease, hyperlipidemia, cardiac arrhythmias, peripheral vascular disorders, headaches, chronic obstructive pulmonary disease, asthma, diabetes, renal failure, liver diseases, peptic ulcers, hepatitis B, depression, and solid tumor ($p<0.05$).

Table 2 shows the crude and adjusted ORs for the model fitted to examine the association between potential risk factors and the risk of PACG. In the multivariate model, the risk of PACG was greater for patients with the comorbidities of hypertension, hyperlipidemia, headaches, diabetes, liver diseases, peptic ulcers, and depression. For the male group, hypertension, headaches, diabetes, liver diseases, and

depression were significant associated with increasing PACG risk (**Table 3**). For the female group, hypertension, hyperlipidemia, headaches, peptic ulcers, and depression were significant associated with increasing PACG risk were significant associated with increasing PACG risk. For the age group younger than 64 years, patients with comorbidity of hypertension, hyperlipidemia, headaches, diabetes, renal failure, liver diseases, peptic ulcers, and depression were significant associated with increasing PACG risk (**Table 4**). For the age group elder than 65 years, patients with hypertension, hyperlipidemia, peripheral vascular disorders, and peptic ulcers were significantly associated with increasing PACG risk.

DISCUSSION

This study, in which data from 3322 PACG cases were analyzed, found that 60.6 % of them had hypertension and 41.8 % of them had hyperlipidemia and 42.4 % of them had headache and peptic ulcer. When compared to the controls , PACG patients had a significantly higher prevalence of hypertension, ischemic heart disease, hyperlipidemia, cardiac arrhythmias, peripheral vascular disorders, headaches, chronic obstructive pulmonary disease, asthma, diabetes, renal failure, liver diseases, peptic ulcers, hepatitis B, depression, and solid tumor ($p<0.05$). Further analysis shows that the risk of PACG was only greater for patients with the comorbidities of hypertension, hyperlipidemia, headaches, diabetes, liver diseases, peptic ulcers, and

depression in the multivariate model. Furthermore, for the female group, patients with hypertension, hyperlipidemia, headaches, peptic ulcers, and depression were significantly associated with increased PACG risk. The same risk factors for both genders are hypertension, headache and depression.

Our study is the few one which discussed the medical comorbidity in a large PACG cohort. Potential explanations about the strong relationship between the above 7 medical illness and the risk of PACG should be mentioned as below.

Pathogenetic mechanisms of PACG

PACG has its characteristic anatomy features and unique pathological process, including a crowded anterior segment and narrow anterior chamber angle.[15] The progression that the anterior chamber angle develops from narrow to become closed is quite complicated and involves many different factors. The role of cataract formation in the development of PACG has been well described.[5,6,15]

Association between hypertension, hyperlipidemia and diabetes and PACG

In one Korean epidemiological study, hypercholesterolemia, hypertension, and diabetes mellitus (DM) were independent risk factors for development of any cataract.[16] Also in one study that the authors show that metabolic syndrome and its components appear to be associated with age-related cataract only among Korean women.[17] We believe that the potential reasons for hypertension, diabetes and

hyperlipidemia in the risk of PACG from our result could be attributed to the increased risk of cataract. Further longitudinal observational study should be needed to address this issue.

Association between depression and PACG

It has been well known that antidepressant agents with anticholinergic effect associate with increased risk of PACG.[18-20] Furthermore, studies have provided evidence of a significant positive association between antidepressants use and risk of cataract.[5] Therefore, our results support again that that depression is a significant risk factor for PACG.

Association between liver disease and PACG

One recent study also from Taiwan reported that HCV infection, even without the complication of cirrhosis, is associated with an increased risk of cataract.[21] Another study from Korean reports that HBV and HCV infection was significantly associated with cataract.[22] We think the strong association between liver disease and the risk of PACG might be the increased risk of cataract in liver disease patients. However, further study is needed to further elucidate this interesting result.

Association between headache and PACG

PACG patients used to complain of headache which is caused by increased intraocular pressure. [23,24] It is not uncommon that PACG patients would seek for medical help

due to headache before PACG was diagnosed. From our result, we found that headache is the risk factor for PACG, which reminds the clinicians of the potential risk of glaucoma in headache patients.

Association between peptic ulcers and PACG

To our knowledge, no previous study has reported the presence or absence of an association between peptic ulcers and PACG. We speculate that Histamine 2 receptor antagonist which was widely used in peptic ulcer treatment might induce or precipitate angle-closure glaucoma.[25] Further longitudinal study is mandatory in this interesting topics.

Despite these promising results, our study had certain limitations. First, glaucoma and medical comorbidity were defined entirely on the basis of claims data (ICD-9-CM codes assigned by clinicians).[20] This approach should be less accurate than diagnosing personally through a standardized procedure.[20] The second limitation was a selection bias.[20] Because the NHI database only comprises data of patients who have received treatment, patients who have received no treatment for glaucoma or any of these medial disease might have been recruited in the comparison cohort. Third, despite the large sample, the study cohort comprised Taiwanese patients. Therefore, these findings cannot be completely generalizable to other populations. Nevertheless, our study has the following strengths. First, the strength of the database is excellent

because of the large sample randomization.[20] We could follow patient cases over time to assess the relationship between medical illness and the subsequent onset of PACG. Second, the database includes data of people with diverse sociodemographic profiles, unlike some smaller studies that recruited patients from specific regions and thus lack in representativeness.

In conclusion, our population-based study by using the NHIRD revealed that the risk of PACG was greater for patients with the comorbidities of hypertension, hyperlipidemia, headaches, diabetes, liver diseases, peptic ulcers, and depression. Clinicians should keep in mind when meeting patients with these diseases.

Contributors H Y Chen: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtaining funding; C L Lin: statistical expertise, conception and design, critical revision of the manuscript for important intellectual content.

Competing interests None declared.

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Data sharing statement No additional data available.

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Table 1. Demographic comparison between PACG cases and controls

	PACG Cases N= 3322		Controls N= 13288		
	n	(%)	n	(%)	p-value
Sex					0.99
female	2031	61.1	8124	61.1	
male	5164	38.9	1291	38.9	
Age group (years)					0.99
20-49	398	12.0	1592	12.0	
50-64	1011	30.4	4044	30.4	
≥65	1913	57.6	7652	57.6	
Age (year), mean (SD) †	65.2	12.7	64.8	13.0	0.10
Comorbidity					
Hypertension	2025	60.6	6896	51.9	<0.001
Ischemic heart disease	1097	33.0	3561	26.8	<0.001
Hyperlipidemia	1389	41.8	4399	33.1	<0.001
Congestive heart failure	213	6.41	849	6.39	0.96
Cardiac arrhythmias	540	16.3	1826	13.7	<0.001
Peripheral vascular disorders	201	6.05	571	4.30	<0.001
Stroke	246	7.41	994	7.48	0.88
Headaches	1407	42.4	4772	35.9	<0.001
Migraine	125	3.76	456	3.43	0.35
Epilepsy	30	0.90	144	1.08	0.36
Dementia	110	3.31	448	3.37	0.86
Rheumatoid arthritis	11	0.33	45	0.34	0.95
Systemic lupus erythematosus	3	0.09	8	0.06	0.55
Chronic obstructive pulmonary disease	675	20.3	2343	17.6	<0.001
Asthma	418	12.6	1455	11.0	0.008
Pulmonary circulation disorders	26	0.78	85	0.64	0.37
Diabetes	710	21.4	2148	16.2	<0.001
Hypothyroidism	36	1.08	110	0.83	0.16
Renal failure	448	13.5	1435	10.8	<0.001
Liver diseases	898	27.0	2775	20.9	<0.001
Peptic ulcers	1409	42.4	4503	33.9	<0.001

Hepatitis B	182	5.48	610	4.59	0.03
Tuberculosis	86	2.59	294	2.21	0.19
Deficiency anemia	114	3.43	381	2.87	0.09
Depression	328	9.87	922	6.94	<0.001
Psychosis	153	4.61	518	3.90	0.06
Metastatic cancer	1	0.03	2	0.02	0.56
Solid tumor	190	5.72	630	4.74	0.02

Data are presented as the number of subjects in each group, with percentages given in parentheses.

Chi-square test; † t-test

Table 2. Odds ratio and 95% confidence interval of PACG associated with comorbidities

	Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)
Comorbidity				
Hypertension	1.45	(1.34, 1.56)***	1.18	(1.08, 1.29)***
Ischemic heart disease	1.35	(1.24, 1.46)***	1.05	(0.95, 1.15)
Hyperlipidemia	1.45	(1.34, 1.57)***	1.19	(1.09, 1.29)***
Congestive heart failure	1.00	(0.86, 1.17)	-	-
Cardiac arrhythmias	1.22	(1.10, 1.35)***	0.98	(0.88, 1.10)
Peripheral vascular disorders	1.44	(1.22, 1.69)***	1.14	(0.97, 1.36)
Stroke	0.98	(0.86, 1.14)	-	-
Headaches	1.31	(1.21, 1.42)***	1.17	(1.08, 1.26)***
Migraine	1.10	(0.90, 1.35)	-	-
Epilepsy	0.83	(0.56, 1.24)	-	-
Dementia	0.98	(0.79, 1.21)	-	-
Rheumatoid arthritis	0.98	(0.51, 1.89)	-	-
Systemic lupus erythematosus	1.50	(0.40, 5.66)	-	-
Chronic obstructive pulmonary disease	1.19	(1.08, 1.31)***	0.99	(0.89, 1.11)
Asthma	1.17	(1.04, 1.32)***	0.99	(0.88, 1.13)
Pulmonary circulation disorders	1.23	(0.79, 1.90)	-	-
Diabetes	1.41	(1.28, 1.55)***	1.16	(1.05, 1.29)**
Hypothyroidism	1.31	(0.90, 1.92)	-	-
Renal failure	1.29	(1.15, 1.44)***	1.03	(0.91, 1.16)
Liver diseases	1.40	(1.29, 1.53)***	1.15	(1.05, 1.27)**
Peptic ulcers	1.44	(1.33, 1.55)***	1.22	(1.13, 1.33)***
Hepatitis B	1.21	(1.02, 1.43)*	1.04	(0.87, 1.24)
Tuberculosis	1.18	(0.92, 1.50)	-	-
Deficiency anemia	1.20	(0.97, 1.49)	-	-
Depression	1.47	(1.29, 1.68)***	1.22	(1.07, 1.40)**
Psychosis	1.19	(0.99, 1.43)	-	-
Metastatic cancer	2.01	(0.18, 22.1)	-	-
Solid tumor	1.22	(1.03, 1.44)*	1.13	(0.96, 1.34)

Abbreviations: odds ratio (OR); confidence interval (CI)

†Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

Table 3. Odds ratio and 95% confidence interval of PACG associated with comorbidities By sex

	Male				Female			
	Crude		Adjusted †		Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Comorbidity								
Hypertension	1.60	(1.41, 1.81)***	1.25	(1.08, 1.44)**	1.36	(1.23, 1.50)***	1.14	(1.02, 1.28)*
Ischemic heart disease	1.43	(1.25, 1.63)***	1.06	(0.90, 1.23)	1.30	(1.17, 1.44)***	1.03	(0.91, 1.17)
Hyperlipidemia	1.54	(1.35, 1.75)***	1.13	(0.98, 1.31)	1.41	(1.28, 1.56)***	1.22	(1.09, 1.37)***
Congestive heart failure	1.15	(0.91, 1.46)	-	-	0.91	(0.74, 1.12)	-	-
Cardiac arrhythmias	1.24	(1.05, 1.48)***	0.94	(0.78, 1.14)	1.20	(1.06, 1.37)***	1.00	(0.87, 1.16)
Peripheral vascular disorders	1.52	(1.17, 1.98)***	1.14	(0.87, 1.50)	1.38	(1.12, 1.71)***	1.15	(0.93, 1.43)
Stroke	1.10	(0.89, 1.36)	-	-	0.90	(0.74, 1.10)	-	-
Headaches	1.35	(1.19, 1.55)***	1.17	(1.02, 1.34)*	1.30	(1.18, 1.44)***	1.18	(1.06, 1.30)**
Migraine	1.09	(0.70, 1.70)	-	-	1.10	(0.88, 1.39)	-	-
Epilepsy	0.91	(0.50, 1.67)	-	-	0.78	(0.46, 1.31)	-	-
Dementia	1.04	(0.74, 1.45)	-	-	0.95	(0.72, 1.25)	-	-
Rheumatoid arthritis	2.01	(0.37, 11.0)	-	-	0.88	(0.43, 1.81)	-	-
Systemic lupus erythematosus	4.00	(0.25, 64.0)	-	-	1.15	(0.24, 5.52)	-	-
Chronic obstructive pulmonary disease	1.34	(1.17, 1.54)***	1.07	(0.91, 1.26)	1.07	(0.94, 1.23)	-	-
Asthma	1.30	(1.08, 1.56)***	1.04	(0.85, 1.28)	1.10	(0.95, 1.28)	-	-
Pulmonary circulation disorders	1.07	(0.49, 2.34)	-	-	1.31	(0.77, 2.24)	-	-

Diabetes	1.67	(1.44, 1.94)***	1.34	(1.14, 1.58)***	1.26	(1.11, 1.42)***	1.06	(0.92, 1.21)
Hypothyroidism	1.18	(0.43, 3.20)	-	-	1.34	(0.89,2 .01)	-	-
Renal failure	1.46	(1.23, 1.73)***	1.11	(0.93, 1.33)	1.17	(1.00, 1.36)*	0.95	(0.81, 1.12)
Liver diseases	1.57	(1.37, 1.80)***	1.30	(1.12, 1.50)***	1.30	(1.16, 1.46)***	1.07	(0.95, 1.21)
Peptic ulcers	1.40	(1.24, 1.59)***	1.12	(0.98, 1.29)	1.46	(1.32, 1.61)***	1.28	(1.15, 1.43)***
Hepatitis B	1.25	(0.97, 1.61)	-	-	1.17	(0.93, 1.47)	-	-
Tuberculosis	1.29	(0.95, 1.75)	-	-	1.02	(0.68, 1.52)	-	-
Deficiency anemia	1.48	(0.99, 2.20)	-	-	1.12	(0.87, 1.44)	-	-
Depression	1.67	(1.31, 2.13)***	1.36	(1.06, 1.75)*	1.40	(1.20, 1.64)***	1.18	(1.01, 1.39)*
Psychosis	1.13	(0.81, 1.59)	-	-	1.22	(0.98, 1.52)	-	-
Metastatic cancer	-	-	-	-	-	-	-	-
Solid tumor	1.23	(0.93, 1.61)	-	-	1.22	(0.98, 1.50)	-	-

Abbreviations: odds ratio (OR); confidence interval (CI)

[†]Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

Table 4. Odds ratio and 95% confidence interval of PACG associated with comorbidities By age

	Age ≦64				Age ≧65			
	Crude		Adjusted †		Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Comorbidity								
Hypertension	1.77	(1.57, 2.00)***	1.26	(1.09, 1.45)**	1.35	(1.20, 1.51)***	1.18	(1.04, 1.33)**
Ischemic heart disease	1.79	(1.54, 2.08)***	1.14	(0.95, 1.36)	1.23	(0.11, 1.36)***	1.05	(0.93, 1.18)
Hyperlipidemia	1.81	(1.60, 2.06)***	1.26	(1.08, 1.45)**	1.28	(1.15, 1.41)***	1.13	(1.01, 1.26)*
Congestive heart failure	1.75	(1.24, 2.48)***	1.00	(0.69, 1.45)	0.89	(0.74, 1.06)	-	-
Cardiac arrhythmias	1.49	(1.22, 1.83)***	1.03	(0.82, 1.28)	1.14	(1.01, 1.29)*	1.00	(0.87, 1.14)
Peripheral vascular disorders	1.65	(1.14, 2.40)***	1.02	(0.69, 1.51)	1.40	(1.16, 1.68)***	1.23	(1.01, 1.48)*
Stroke	1.40	(0.99, 1.96)	-	-	0.92	(0.78, 1.08)	-	-
Headaches	1.48	(1.31, 1.67)***	1.21	(1.07, 1.38)**	1.20	(1.09, 1.33)***	1.11	(1.00, 1.23)
Migraine	1.13	(0.83, 1.52)	-	-	1.08	(0.83, 1.42)	-	-
Epilepsy	1.17	(0.61, 2.24)	-	-	0.70	(0.42, 1.15)	-	-
Dementia	2.46	(1.16, 5.21)***	1.72	(0.79, 3.74)	0.92	(0.73, 1.15)	-	-
Rheumatoid arthritis	1.26	(0.50, 3.17)	-	-	0.77	(0.30, 2.00)	-	-
Systemic lupus erythematosus	2.01	(0.18, 22.1)	-	-	1.33	(0.27, 6.61)	-	-
Chronic obstructive pulmonary disease	1.60	(1.33, 1.93)***	1.18	(0.96, 1.45)	1.09	(0.97, 1.22)	-	-
Asthma	1.42	(1.15, 1.76)***	1.00	(0.79, 1.25)	1.08	(0.94, 1.25)	-	-

Pulmonary circulation disorders	1.72	(0.66, 4.48)	-	-	1.13	(0.69, 1.86)	-	-
Diabetes	1.92	(1.63, 2.25)***	1.34	(1.12,1 .61)**	1.21	(1.08, 1.37)**	1.08	(0.96, 1.22)
Hypothyroidism	1.28	(0.71, 2.30)	-	-	1.34	(0.81, 2.19)	-	-
Renal failure	1.82	(1.48, 2.24)***	1.26	(1.01, 1.57)*	1.13	(0.99, 1.30)	-	-
Liver diseases	1.64	(1.43, 1.87)***	1.18	(1.02, 1.37)*	1.26	(1.13, 1.42)***	1.08	(0.96, 1.22)
Peptic ulcers	1.70	(1.50, 1.92)***	1.31	(1.15, 1.50)***	1.32	(1.19, 1.45)***	1.18	(1.06, 1.32)**
Hepatitis B	1.06	(0.83, 1.35)	-	-	1.37	(1.08, 1.73)***	1.20	(0.94, 1.53)
Tuberculosis	1.08	(0.64, 1.82)	-	-	1.21	(0.92, 1.59)	-	-
Deficiency anemia	1.36	(0.95, 1.92)	-	-	1.13	(0.86, 1.47)	-	-
Depression	1.78	(1.45, 2.20)***	1.33	(1.06, 1.66)*	1.31	(1.10, 1.55)**	1.14	(0.96, 1.36)
Psychosis	1.27	(0.95, 1.69)	-	-	1.14	(0.90, 1.45)	-	-
Metastatic cancer	-	-	-	-	-	-	-	-
Solid tumor	1.16	(0.83, 1.60)	-	-	1.25	(1.02, 1.51)*	1.21	(1.00, 1.48)

Abbreviations: odds ratio (OR); confidence interval (CI)

[†]Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods	6-8

taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			**Reported on Page No.**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	x
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8,9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8,9*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8,9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9
		(*b*) Report category boundaries when continuous variables were categorized	8,9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8,9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Comparison of medical comorbidity between primary angle closure glaucoma patients and a control cohort: A population-based study from Taiwan

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Comparison of medical comorbidity between primary angle-closure glaucoma patients and a control cohort: A population-based study from Taiwan

Hsin-Yi Chen [1,2], Cheng-Li Lin [3]

[1] School of Medicine, Medical College, China Medical University
[2] Department of Ophthalmology, China Medical University Hospital
[3]Management Office for Health Data, China Medical University

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*** Corresponding authors**

Hsin-Yi Chen, MD, Department of Ophthalmology, China Medical University Hospital, Taichung, Taiwan. No. 2, Yuh-Der Road, Taichung 40447, Taiwan.

Tel: 886-4-22081700 / Fax:886-4-22081700; E-mail: hsin7850@url.com.tw; glaucoma0606@gmail.com

Abstract

Objective To determine the prevalence and risk of systemic comorbidities in primary angle-closure glaucoma in Taiwan population.

Methods We included 3322 PACG subjects and randomly selected patients without PACG from the Taiwan National Health Insurance Research Database and frequency matched four of them (n = 13288) to each PACG patient, based on age and sex. The univariable and multivariable unconditional logistic regression models were used to estimate the effect of comorbidities on the risk of PACG as indicated by the odds ratio with 95% confidence interval.

Results The mean age of the PACG group was 65.2 ± 12.7 years, and 61.1% of the patients were female. Compared with the controls, the PACG patients exhibited significantly higher prevalence of hypertension (60.6%), ischemic heart disease (33.0%), hyperlipidemia (41.8%), cardiac arrhythmias (16.3%), peripheral vascular disorders (6.05%), headaches (42.4%), chronic obstructive pulmonary disease (20.3%), asthma (12.6%), diabetes (21.4%), renal failure (13.5%), liver diseases (27.0%), peptic ulcers (42.4%), hepatitis B (5.48%), depression (9.87%), solid tumor (5.72%), and cataract (62.9%). The risk of PACG was greater for patients with the comorbidities of hyperlipidemia, headaches, liver diseases, peptic ulcers, and cataract. For the male

group, diabetes, liver diseases, and cataract were associated with increasing PACG risk. For the female group, hyperlipidemia, headaches, peptic ulcers, and cataract were associated with increasing PACG risk. For the age group of 64 years and younger, patients with comorbidities of hyperlipidemia, peptic ulcers, and cataract were associated with increasing PACG risk. For the age group of 65 years and older, patients with cataract were associated with increasing PACG risk.

Conclusions Clinicians should be aware of slightly increased PACG risk in the subjects with the medical comorbidities of hyperlipidemia, headaches, liver diseases, and peptic ulcers. However, cataract is the strongest risk factor of PACG.

Keywords: primary angle-closure glaucoma, medical comorbidity, cataract, Taiwan.

Article summary

Strengths and limitations of this study

- This is the first original study on the association between medical comorbidity and primary angle-closure glaucoma.
- A strength of this study is the large sample size.
- Clinicians should be aware of slightly increased PACG risk in the subjects with hyperlipidemia, headaches, liver diseases, and peptic ulcers.
- Cataract is the strongest risk factor of PACG in any age group and gender.
- This study has inherent limitations from the claims database, including miscoding and selection bias; the findings are thus not generalizable to all populations.

INTRODUCTION

Primary angle-closure glaucoma (PACG) is a leading cause of blindness worldwide; it is especially common in Asian countries.[1-3] A recent meta-analysis study shows that PACG affects approximately 0.75% of adult Asians, and this percentage doubles every decade; 60% of cases are in females.[4] The proposed mechanism of PACG is pupillary block, with anterior lens movement as a strong contributing factor, often due to aging-induced cataract formation.[4,5] Risk factors for PACG are aging, female gender, shallow anterior chamber, and short axial length in hyperopic eye.[4,5] Contrary to primary open angle glaucoma (POAG)—which has been associated with systemic diseases, including cardiovascular, metabolic, neurodegenerative, psychological diseases, and others[6-13]—few studies have evaluated medical illness among PACG subjects. Age is the main factor contributing to the coexisting of systemic comorbidities and cataract formation. Therefore, whether some medical illness and cataract are associated with PACG warrants study.

Here, we use a nationwide dataset from Taiwan to determine the prevalence of some common medical comorbidities in the PACG population. We also study whether these comorbidities are associated with the increased risk of PACG compared with controls. This is the first original study using a large claims database to evaluate this important topic.

MATERIALS AND METHODS

Patient and public involvement statement

This work is a retrospective longitudinal case–control study from a claims database. Patients were not involved in the recruitment or conduct of the study.

Data Source

We conducted a nationwide population-based retrospective cohort study using data from the Longitudinal Health Insurance Database 2000 (LHID 2000). The LHID 2000 contains the enrollment and claims information of 1 million randomly sampled enrollees of the National Health Insurance (NHI) program in 2000. The NHI program provides mandatory universal health insurance to Taiwan's 23.75 million citizens and residents, with an enrollment rate of approximately 99%.[14] The LHID 2000 includes all ambulatory care, inpatient services, prescription drugs, traditional Chinese Medicine, and dental services claims data. The study was approved by the Institutional Review Board of China Medical University and Hospital (CMUH-104-REC2-115). Diseases are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), 2001 edition.

Sampled Participants

From the LHID 2000, we identified patients aged more than 20 years with a diagnosis of PACG (ICD-9-CM code 365.2) between January 1, 2005, and December 31, 2011 as the case group. The diagnosis of PACG was based on definitions agreed on by the World Glaucoma Association.[15] The date of diagnosis of PACG was defined as the index date. We excluded patients with a history of POAG (ICD-9-CM code 365.1) diagnosed before the index date. Secondary, juvenile, and congenital glaucoma were also excluded. For each PACG case, four insured beneficiaries with no history of glaucoma (ICD-9-CM code 365) were assigned to a non-PACG control group,

frequency matched to the patients in the PACG case group according to age (every 5 years), sex, and index year of PACG diagnosis; the same exclusion criteria used for the PACG case group was applied.

Common medical comorbidity

The comorbidities were hypertension (ICD-9-CM codes 401–405), ischemic heart disease (ICD-9-CM codes 410–414), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM code 428), cardiac arrhythmias (ICD-9-CM codes 426 and 427), peripheral vascular disorders (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9), stroke (ICD-9-CM codes 430–438), headaches (ICD-9-CM code 784.0), migraine (ICD-9-CM code 346), epilepsy (ICD-9-CM code 345), dementia (ICD-9-CM code 290, 294.1, and 331.0), rheumatoid arthritis (ICD-9-CM code 714), systemic lupus erythematosus (ICD-9-CM code 710.0), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496), asthma (ICD-9-CM code 493), pulmonary circulation disorders (ICD-9-CM codes 415–417), diabetes (ICD-9-CM code 250), hypothyroidism (ICD-9-CM codes 243 and 244), renal failure (ICD-9-CM codes 584–586), liver diseases (ICD-9-CM codes 570–573), peptic ulcers (ICD-9-CM codes 531–533), hepatitis B (ICD-9-CM codes V02.61, 070.20, 070.22, 070.30, and 070.32), tuberculosis (ICD-9-CM codes 011–018), deficiency anemias (ICD-9-CM codes 280, and 281), depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), psychosis (ICD-9-CM codes 295–299), metastatic cancer (ICD-9-CM codes 196–198), solid tumor (ICD-9-CM codes 140–195), and cataract (ICD-9-CM code 366).

Statistical analysis

The baseline characteristics and comorbidities of the PACG case group and non-PACG control group were compared. Chi squared test and *t* test were used to evaluate the

difference of categorical and continuous variables, respectively, between the two groups. Univariable and multivariable unconditional logistic regression models were used to estimate the effect of comorbidities on the risk of PACG as indicated by the odds ratio (OR) with 95% confidence interval (CI). All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Carey, NC), and the significance level was set at 0.05 for the two-tailed tests.

RESULTS

A total of 3322 PACG cases met the study criteria, and 13288 subjects were matched according to sex and age to form the control group (**Table 1**). The PACG group comprised 61.1% women, and 57.6% were older than 65 years. The mean age was 65.2 ± 12.7 years in the PACG group and 64.8 ± 13.0 years in the control group. Compared with the controls, PACG patients have significantly higher prevalence of hypertension, ischemic heart disease, hyperlipidemia, cardiac arrhythmias, peripheral vascular disorders, headaches, chronic obstructive pulmonary disease, asthma, diabetes, renal failure, liver diseases, peptic ulcers, hepatitis B, depression, solid tumor, and cataract ($p < 0.05$).

The crude and adjusted ORs for the model were fitted to examine the association between medical comorbidities and the risk of PACG (**Table 2**). In the multivariate model, the risk of PACG was greater for patients with the comorbidities of

hyperlipidemia (ORs: 1.11), headaches (ORs: 1.13), liver diseases (ORs: 1.14), peptic ulcers (ORs: 1.10), and cataract (ORs: 3.80). For the male group, diabetes (ORs: 1.19), liver diseases (ORs: 1.29), and cataract (ORs: 4.30) were significantly associated with increasing PACG risk (**Table 3**). For the female group, hyperlipidemia (ORs: 1.13), headaches (ORs: 1.15), peptic ulcers (ORs: 1.14), and cataract (ORs: 3.54) were significantly associated with increasing PACG risk. For the age group of 64 years and younger, patients with comorbidity of hyperlipidemia (ORs: 1.20), peptic ulcers (ORs: 1.21), and cataract (ORs: 5.91) were significantly associated with increasing PACG risk (**Table 4**). For the age group of 65 years and older, patients with cataract were significantly associated with increasing PACG risk (ORs: 5.07).

DISCUSSION

Among the 3322 PACG patients, 41.8 % had hyperlipidemia, 42.4 % had headache and peptic ulcer, and 62.9% had cataract. The risk of PACG was greater for patients with the comorbidities of hyperlipidemia, headaches, liver diseases, peptic ulcers, and cataract. For the male group, diabetes, liver diseases, and cataract were significantly associated with increasing PACG risk. For the female group, hyperlipidemia, headaches, peptic ulcers, and cataract were significantly associated with increasing PACG risk. For both the genders, cataract was the same and strongest risk factor for PACG development (ORs: 4.30 for the male group; ORs: 3.54 for the female group).

Regarding the effect of age on the risk of PACG, we subclassified the study groups into two. Interesting results were obtained; patients with comorbidity of hyperlipidemia, peptic ulcers, and cataract were associated with increasing PACG risk in the age group of 64 years and younger. However, for the age group of 65 years and older, cataract was the only factor for the increased risk of PACG. Cataract was the same and strongest risk factor for PACG onset for both the age groups (ORs: 5.91 for the age group younger than 65 years; ORs :5.07 for the age group older than 65 years).

Our study is the first one that discussed the medical comorbidity in a large PACG cohort using a large claims database. Potential explanations about the strong relationship between some medical illness and the risk of PACG should be mentioned as below.

Pathogenetic mechanisms of PACG and association between cataract and PACG

Our study reveals that cataract is the strongest risk factor for PACG in any age group and gender compared with other medical comorbidity. PACG has its characteristic anatomy features and unique pathological process, including a crowded anterior segment and narrow anterior chamber angle.[15] The lens is considered to play a crucial role in the pathogenesis of PACG either because of an increase in its thickness or a more anterior position resulting in angle crowding and a greater predisposition to pupillary block.[5,6,15,16] Furthermore, the lens thickness increases with age and makes

the narrow anterior chamber angle even more crowded, which might be why most PACG occurs in patients older than 40 years.[15,16] Our study result supports that ocular anatomical factor plays a more important role in the pathogenesis of PACG than any other medical comorbidities in Taiwan Chinese population.

Association between hyperlipidemia and diabetes and PACG

In one Korean epidemiological study, hypercholesterolemia, hypertension, and diabetes mellitus were independent risk factors for the development of any cataract.[17] Moreover, in one study, the authors demonstrated that metabolic syndrome and its components are associated with age-related cataract only among Korean women.[18] We believe that the potential reasons for diabetes and hyperlipidemia in the risk of PACG from our result could be attributed to the increased risk of cataract. Further, longitudinal observational study is needed to address this issue.

Association between liver disease and PACG

One recent study from Taiwan reported that hepatitis C infection, even without the complication of cirrhosis, is associated with an increased risk of cataract.[19] Another study from Korean reported that hepatitis B and hepatitis C infection were significantly associated with cataract.[20] The strong association between liver disease and the risk of PACG might increase the risk of cataract in liver disease patients. However, further study is needed to elucidate this interesting result.

Association between headache and PACG

PACG patients complain of headache caused by increased intraocular pressure. [21,22] PACG patients seek medical help due to headache before the diagnosis of PACG. Our results indicate that headache is associated with higher risk for PACG. Headache may be a symptom of PACG missed by the physician. Therefore, clinicians should consider the possibility of PACG in patients with headache.

Association between peptic ulcers and PACG

No previous study has reported the presence or absence of an association between peptic ulcers and PACG. We speculate that Histamine 2 receptor antagonist that was widely used in peptic ulcer treatment might induce or precipitate PACG.[23] Further longitudinal study is mandatory in this interesting topic.

Despite these promising results, our study had certain limitations. First, glaucoma and medical comorbidity were defined entirely on the basis of claims data (ICD-9-CM codes assigned by clinicians).[21] This approach is less accurate than diagnosing personally through a standardized procedure.[21] The second limitation is selection bias.[21] Because the NHI database only comprises data of patients who have received treatment, patients who have received no treatment for glaucoma or any of these medial disease might have been recruited in the comparison cohort. Third, despite the large sample, the study cohort comprised Taiwanese patients. Therefore, these findings cannot be

generalized to other populations. Nevertheless, our study has the following strengths. First, the strength of the database is excellent because of the large sample randomization.[21] We could follow patient cases over time to assess the relationship between medical illness and the subsequent onset of PACG. Second, the database includes data of people with diverse sociodemographic profiles, unlike some smaller studies that recruited patients from specific regions and thus lack in representativeness.

In conclusion, our population-based study using the NHIRD revealed that the PACG risk is strongest in cataract patients and is slightly higher in patients with medical comorbidities of hyperlipidemia, headaches, liver diseases, and peptic ulcers. Clinicians should be aware of these findings when encountering patients with these diseases.

Contributors H Y Chen: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtaining funding; C L Lin: statistical expertise, conception and design, critical revision of the manuscript for important intellectual content.

Competing interests None declared.

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Data sharing statement No additional data available.

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Table 1. Demographic comparison between PACG cases and controls

	PACG Cases N= 3322		Controls N= 13288		
	n	(%)	n	(%)	p-value
Sex					0.999
female	2031	61.1	8124	61.1	
male	5164	38.9	1291	38.9	
Age group (years)					0.999
20-49	398	12.0	1592	12.0	
50-64	1011	30.4	4044	30.4	
≥65	1913	57.6	7652	57.6	
Age (year), mean (SD) †	65.2(12.7)		64.8(13.0)		0.100
Comorbidity					
Hypertension	2025	60.6	6896	51.9	<0.001
Ischemic heart disease	1097	33.0	3561	26.8	<0.001
Hyperlipidemia	1389	41.8	4399	33.1	<0.001
Congestive heart failure	213	6.41	849	6.39	0.962
Cardiac arrhythmias	540	16.3	1826	13.7	<0.001
Peripheral vascular disorders	201	6.05	571	4.30	<0.001
Stroke	246	7.41	994	7.48	0.883
Headaches	1407	42.4	4772	35.9	<0.001
Migraine	125	3.76	456	3.43	0.353
Epilepsy	30	0.90	144	1.08	0.360
Dementia	110	3.31	448	3.37	0.863
Rheumatoid arthritis	11	0.33	45	0.34	0.957
Systemic lupus erythematosus	3	0.09	8	0.06	0.546
Chronic obstructive pulmonary disease	675	20.3	2343	17.6	<0.001
Asthma	418	12.6	1455	11.0	0.008
Pulmonary circulation disorders	26	0.78	85	0.64	0.366
Diabetes	710	21.4	2148	16.2	<0.001
Hypothyroidism	36	1.08	110	0.83	0.158
Renal failure	448	13.5	1435	10.8	<0.001
Liver diseases	898	27.0	2775	20.9	<0.001
Peptic ulcers	1409	42.4	4503	33.9	<0.001
Hepatitis B	182	5.48	610	4.59	0.032
Tuberculosis	86	2.59	294	2.21	0.194
Deficiency anemia	114	3.43	381	2.87	0.087

Depression	328	9.87	922	6.94	<0.001
Psychosis	153	4.61	518	3.90	0.064
Metastatic cancer	1	0.03	2	0.02	0.564
Solid tumor	190	5.72	630	4.74	0.020
Cataract	2088	62.9	4077	30.7	<0.001

Data are presented as the number of subjects in each group, with percentages given in parentheses.

Chi-square test; † t-test

Table 2. Odds ratio and 95% confidence interval of PACG associated with comorbidities

	Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)
Comorbidity				
Hypertension	1.45	(1.34, 1.56)***	0.97	(0.88, 1.07)
Ischemic heart disease	1.35	(1.24, 1.46)***	0.92	(0.83, 1.01)
Hyperlipidemia	1.45	(1.34, 1.57)***	1.11	(1.01, 1.21)*
Congestive heart failure	1.00	(0.86, 1.17)	-	-
Cardiac arrhythmias	1.22	(1.10, 1.35)***	0.91	(0.81, 1.02)
Peripheral vascular disorders	1.44	(1.22, 1.69)***	1.02	(0.86, 1.21)
Stroke	0.98	(0.86, 1.14)	-	-
Headaches	1.31	(1.21, 1.42)***	1.13	(1.04, 1.23)***
Migraine	1.10	(0.90, 1.35)	-	-
Epilepsy	0.83	(0.56, 1.24)	-	-
Dementia	0.98	(0.79, 1.21)	-	-
Rheumatoid arthritis	0.98	(0.51, 1.89)	-	-
Systemic lupus erythematosus	1.50	(0.40, 5.66)	-	-
Chronic obstructive pulmonary disease	1.19	(1.08, 1.31)***	0.88	(0.79, 1.00)
Asthma	1.17	(1.04, 1.32)***	0.98	(0.86, 1.11)
Pulmonary circulation disorders	1.23	(0.79, 1.90)	-	-
Diabetes	1.41	(1.28, 1.55)***	1.03	(0.93, 1.15)
Hypothyroidism	1.31	(0.90, 1.92)	-	-
Renal failure	1.29	(1.15, 1.44)***	0.93	(0.82, 1.05)
Liver diseases	1.40	(1.29, 1.53)***	1.14	(1.03, 1.25)*
Peptic ulcers	1.44	(1.33, 1.55)***	1.10	(1.01, 1.20)*
Hepatitis B	1.21	(1.02, 1.43)*	1.09	(0.91, 1.31)
Tuberculosis	1.18	(0.92, 1.50)	-	-
Deficiency anemia	1.20	(0.97, 1.49)	-	-
Depression	1.47	(1.29, 1.68)***	1.12	(0.98, 1.29)
Psychosis	1.19	(0.99, 1.43)	-	-
Metastatic cancer	2.01	(0.18, 22.1)	-	-
Solid tumor	1.22	(1.03, 1.44)*	1.01	(0.85, 1.20)
Cataract	3.82	(3.53, 4.14)***	3.80	(3.49, 4.14)***

Abbreviations: odds ratio (OR); confidence interval (CI)

†Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

*p<0.05; **p<0.01; ****p<0.001

Table 3. Odds ratio and 95% confidence interval of PACG associated with comorbidities By sex

	Male				Female			
	Crude		Adjusted †		Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Comorbidity								
Hypertension	1.60	(1.41, 1.81)***	1.01	(0.87, 1.18)	1.36	(1.23, 1.50)***	0.94	(0.83, 1.06)
Ischemic heart disease	1.43	(1.25, 1.63)***	0.92	(0.78, 1.08)	1.30	(1.17, 1.44)***	0.90	(0.79, 1.02)
Hyperlipidemia	1.54	(1.35, 1.75)***	1.12	(0.96, 1.30)	1.41	(1.28, 1.56)***	1.13	(1.00, 1.26)*
Congestive heart failure	1.15	(0.91, 1.46)	-	-	0.91	(0.74, 1.12)	-	-
Cardiac arrhythmias	1.24	(1.05, 1.48)***	0.86	(0.71, 1.05)	1.20	(1.06, 1.37)***	0.93	(0.80, 1.07)
Peripheral vascular disorders	1.52	(1.17, 1.98)***	0.97	(0.73, 1.29)	1.38	(1.12, 1.71)***	1.04	(0.84, 1.31)
Stroke	1.10	(0.89, 1.36)	-	-	0.90	(0.74, 1.10)	-	-
Headaches	1.35	(1.19, 1.55)***	1.15	(1.00, 1.33)	1.30	(1.18, 1.44)***	1.15	(1.04, 1.28)**
Migraine	1.09	(0.70, 1.70)	-	-	1.10	(0.88, 1.39)	-	-
Epilepsy	0.91	(0.50, 1.67)	-	-	0.78	(0.46, 1.31)	-	-
Dementia	1.04	(0.74, 1.45)	-	-	0.95	(0.72, 1.25)	-	-
Rheumatoid arthritis	2.01	(0.37, 11.0)	-	-	0.88	(0.43, 1.81)	-	-
Systemic lupus erythematosus	4.00	(0.25, 64.0)	-	-	1.15	(0.24, 5.52)	-	-
Chronic obstructive pulmonary disease	1.34	(1.17, 1.54)***	0.89	(0.75, 1.05)	1.07	(0.94, 1.23)	-	-
Asthma	1.30	(1.08, 1.56)***	0.99	(0.80, 1.23)	1.10	(0.95, 1.28)	-	-

Pulmonary circulation disorders	1.07	(0.49, 2.34)	-	-	1.31	(0.77, 2.24)	-	-
Diabetes	1.67	(1.44, 1.94)***	1.19	(1.00, 1.40)*	1.26	(1.11, 1.42)***	0.93	(0.81, 1.07)
Hypothyroidism	1.18	(0.43, 3.20)	-	-	1.34	(0.89,2 .01)	-	-
Renal failure	1.46	(1.23, 1.73)***	0.96	(0.80, 1.16)	1.17	(1.00, 1.36)*	0.87	(0.74, 1.03)
Liver diseases	1.57	(1.37, 1.80)***	1.29	(1.11, 1.50)**	1.30	(1.16, 1.46)***	1.05	(0.92, 1.19)
Peptic ulcers	1.40	(1.24, 1.59)***	1.01	(0.87, 1.16)	1.46	(1.32, 1.61)***	1.14	(1.02, 1.28)*
Hepatitis B	1.25	(0.97, 1.61)	-	-	1.17	(0.93, 1.47)	-	-
Tuberculosis	1.29	(0.95, 1.75)	-	-	1.02	(0.68, 1.52)	-	-
Deficiency anemia	1.48	(0.99, 2.20)	-	-	1.12	(0.87, 1.44)	-	-
Depression	1.67	(1.31, 2.13)***	1.20	(0.93, 1.57)	1.40	(1.20, 1.64)***	1.11	(0.94, 1.31)
Psychosis	1.13	(0.81, 1.59)	-	-	1.22	(0.98, 1.52)	-	-
Metastatic cancer	-	-	-	-	-	-	-	-
Solid tumor	1.23	(0.93, 1.61)	-	-	1.22	(0.98, 1.50)	-	-
Cataract	4.37	(3.84,4.96)***	4.30	(3.74, 4.94)***	3.54	(3.20, 3.92)***	3.54	(3.18, 3.95)***

Abbreviations: odds ratio (OR); confidence interval (CI)

†Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

Table 4. Odds ratio and 95% confidence interval of PACG associated with comorbidities By age

	Age ≦64				Age ≧65			
	Crude		Adjusted †		Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Comorbidity								
Hypertension	1.77	(1.57, 2.00)***	1.15	(0.99, 1.34)	1.35	(1.20, 1.51)***	1.10	(0.97, 1.25)
Ischemic heart disease	1.79	(1.54, 2.08)***	1.00	(0.83, 1.21)	1.23	(0.11, 1.36)***	0.95	(0.84, 1.07)
Hyperlipidemia	1.81	(1.60, 2.06)***	1.20	(1.03, 1.40)*	1.28	(1.15, 1.41)***	1.04	(0.92, 1.16)
Congestive heart failure	1.75	(1.24, 2.48)***	0.96	(0.64, 1.44)	0.89	(0.74, 1.06)	-	-
Cardiac arrhythmias	1.49	(1.22, 1.83)***	1.01	(0.80, 1.28)	1.14	(1.01, 1.29)*	0.92	(0.80, 1.06)
Peripheral vascular disorders	1.65	(1.14, 2.40)***	0.84	(0.55, 1.28)	1.40	(1.16, 1.68)***	1.13	(0.93, 1.38)
Stroke	1.40	(0.99, 1.96)	-	-	0.92	(0.78, 1.08)	-	-
Headaches	1.48	(1.31, 1.67)***	1.14	(1.00, 1.30)	1.20	(1.09, 1.33)***	1.04	(0.93, 1.16)
Migraine	1.13	(0.83, 1.52)	-	-	1.08	(0.83, 1.42)	-	-
Epilepsy	1.17	(0.61, 2.24)	-	-	0.70	(0.42, 1.15)	-	-
Dementia	2.46	(1.16, 5.21)***	1.31	(0.57, 3.05)	0.92	(0.73, 1.15)	-	-
Rheumatoid arthritis	1.26	(0.50, 3.17)	-	-	0.77	(0.30, 2.00)	-	-
Systemic lupus erythematosus	2.01	(0.18, 22.1)	-	-	1.33	(0.27, 6.61)	-	-
Chronic obstructive pulmonary disease	1.60	(1.33, 1.93)***	1.08	(0.87, 1.34)	1.09	(0.97, 1.22)	-	-
Asthma	1.42	(1.15, 1.76)***	1.00	(0.78, 1.28)	1.08	(0.94, 1.25)	-	-

Pulmonary circulation disorders	1.72	(0.66, 4.48)	-	-	1.13	(0.69, 1.86)	-	-
Diabetes	1.92	(1.63, 2.25)***	1.08	(0.89, 1.31)	1.21	(1.08, 1.37)**	0.96	(0.84, 1.09)
Hypothyroidism	1.28	(0.71, 2.30)	-	-	1.34	(0.81, 2.19)	-	-
Renal failure	1.82	(1.48, 2.24)***	1.08	(0.85, 1.37)	1.13	(0.99, 1.30)	-	-
Liver diseases	1.64	(1.43, 1.87)***	1.12	(0.96, 1.31)	1.26	(1.13, 1.42)***	1.02	(0.90, 1.16)
Peptic ulcers	1.70	(1.50, 1.92)***	1.21	(1.05, 1.40)**	1.32	(1.19, 1.45)***	1.06	(0.95, 1.19)
Hepatitis B	1.06	(0.83, 1.35)	-	-	1.37	(1.08, 1.73)***	1.20	(0.93, 1.54)
Tuberculosis	1.08	(0.64, 1.82)	-	-	1.21	(0.92, 1.59)	-	-
Deficiency anemia	1.36	(0.95, 1.92)	-	-	1.13	(0.86, 1.47)	-	-
Depression	1.78	(1.45, 2.20)***	1.18	(0.93, 1.50)	1.31	(1.10, 1.55)**	1.01	(0.85, 1.21)
Psychosis	1.27	(0.95, 1.69)	-	-	1.14	(0.90, 1.45)	-	-
Metastatic cancer	-	-	-	-	-	-	-	-
Solid tumor	1.16	(0.83, 1.60)	-	-	1.25	(1.02, 1.51)*	1.15	(0.94, 1.41)
Cataract	6.95	(6.00, 8.05)***	5.91	(5.07, 6.90)***	5.18	(4.56, 5.87)***	5.07	(4.46, 5.77)***

Abbreviations: odds ratio (OR); confidence interval (CI)

†Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods	6-8

taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			**Reported on Page No.**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	x
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8,9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8,9*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8,9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9
		(*b*) Report category boundaries when continuous variables were categorized	8,9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8,9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Comparison of medical comorbidity between primary angle closure glaucoma patients and a control cohort: A population-based study from Taiwan

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Comparison of medical comorbidity between primary angle-closure glaucoma patients and a control cohort: A population-based study from Taiwan

Hsin-Yi Chen [1,2], Cheng-Li Lin [3]

[1] School of Medicine, Medical College, China Medical University
[2] Department of Ophthalmology, China Medical University Hospital
[3]Management Office for Health Data, China Medical University

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*** Corresponding authors**

Hsin-Yi Chen, MD, Department of Ophthalmology, China Medical University Hospital, Taichung, Taiwan. No. 2, Yuh-Der Road, Taichung 40447, Taiwan.

Tel: 886-4-22081700 / Fax:886-4-22081700; E-mail: hsin7850@url.com.tw; glaucoma0606@gmail.com

Abstract

Objective To determine the prevalence and risk of systemic comorbidities in primary angle-closure glaucoma in Taiwan population.

Methods We included 3322 PACG subjects and randomly selected patients without PACG from the Taiwan National Health Insurance Research Database and frequency matched four of them (n = 13288) to each PACG patient, based on age and sex. The univariable and multivariable unconditional logistic regression models were used to estimate the effect of comorbidities on the risk of PACG as indicated by the odds ratio with 95% confidence interval.

Results The mean age of the PACG group was 65.2 ± 12.7 years, and 61.1% of the patients were female. The risk of PACG was greater for patients with the comorbidities of hyperlipidemia (ORs: 1.11), headaches (ORs: 1.13), liver diseases (ORs: 1.14), peptic ulcers (ORs: 1.10), and cataract (ORs: 3.80). For the male group, diabetes (ORs: 1.19), liver diseases (ORs: 1.29), and cataract (ORs: 4.30) were significantly associated with increasing PACG risk. For the female group, hyperlipidemia (ORs: 1.13), headaches (ORs: 1.15), peptic ulcers (ORs: 1.14), and cataract (ORs: 3.54) were significantly associated with increasing PACG risk. For the age group of 64 years and younger, patients with comorbidity of hyperlipidemia (ORs:

1.20), peptic ulcers (ORs: 1.21), and cataract (ORs: 5.91) were significantly associated with increasing PACG risk. For the age group of 65 years and older, patients with cataract were significantly associated with increasing PACG risk (ORs: 5.07).

Conclusions Clinicians should be aware of slightly increased PACG risk in the subjects with the medical comorbidities of hyperlipidemia, headaches, liver diseases, and peptic ulcers. However, cataract is the strongest risk factor of PACG.

Keywords: primary angle-closure glaucoma, medical comorbidity, cataract, Taiwan.

Article summary

Strengths and limitations of this study

- This is the first original study on the association between medical comorbidity and primary angle-closure glaucoma.
- A strength of this study is the large sample size.
- Clinicians should be aware of slightly increased PACG risk in the subjects with hyperlipidemia, headaches, liver diseases, and peptic ulcers.
- Cataract is the strongest risk factor of PACG in any age group and gender.
- This study has inherent limitations from the claims database, including miscoding and selection bias; the findings are thus not generalizable to all populations.

INTRODUCTION

Primary angle-closure glaucoma (PACG) is a leading cause of blindness worldwide; it is especially common in Asian countries.[1-3] A recent meta-analysis study shows that PACG affects approximately 0.75% of adult Asians, and this percentage doubles every decade; 60% of cases are in females.[4] The proposed mechanism of PACG is pupillary block, with anterior lens movement as a strong contributing factor, often due to aging-induced cataract formation.[4,5] Risk factors for PACG are aging, female gender, shallow anterior chamber, and short axial length in hyperopic eye.[4,5] Contrary to primary open angle glaucoma (POAG)—which has been associated with systemic diseases, including cardiovascular, metabolic, neurodegenerative, psychological diseases, and others[6-13]—few studies have evaluated medical illness among PACG subjects. Age is the main factor contributing to the coexisting of systemic comorbidities and cataract formation. Therefore, it is quite meaningful to understand if age related medical illness would be associated with PACG which is also a very important issue in our population because of very high prevalence of this type of glaucoma in Taiwan.

Here, we use a nationwide dataset from Taiwan to determine the prevalence of some common medical comorbidities in the PACG population. We also study whether these comorbidities are associated with the increased risk of PACG compared with controls. This is the first original study using a large claims database to evaluate this important topic.

MATERIALS AND METHODS

Patient and public involvement statement

This work is a retrospective longitudinal case–control study from a claims database. Patients were not involved in the recruitment or conduct of the study.

Data Source

We conducted a nationwide population-based retrospective cohort study using data from the Longitudinal Health Insurance Database 2000 (LHID 2000). The LHID 2000 contains the enrollment and claims information of 1 million randomly sampled enrollees of the National Health Insurance (NHI) program in 2000. The NHI program provides mandatory universal health insurance to Taiwan's 23.75 million citizens and residents, with an enrollment rate of approximately 99%.[14] The LHID 2000 includes all ambulatory care, inpatient services, prescription drugs, traditional Chinese Medicine, and dental services claims data. The study was approved by the Institutional Review Board of China Medical University and Hospital (CMUH-104-REC2-115). Diseases are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), 2001 edition.

Sampled Participants

From the LHID 2000, we identified patients aged more than 20 years with a diagnosis of PACG (ICD-9-CM code 365.2) between January 1, 2005, and December 31, 2011 as the case group. The diagnosis of PACG was based on definitions agreed on by the World Glaucoma Association.[15] The date of diagnosis of PACG was defined as the index date. We excluded patients with a history of POAG (ICD-9-CM code 365.1) diagnosed before the index date. Secondary, juvenile, and congenital glaucoma were

also excluded. For each PACG case, four insured beneficiaries with no history of glaucoma (ICD-9-CM code 365) were assigned to a non-PACG control group, frequency matched to the patients in the PACG case group according to age (every 5 years), sex, and index year of PACG diagnosis; the same exclusion criteria used for the PACG case group was applied.

Common medical comorbidity

The comorbidities were hypertension (ICD-9-CM codes 401–405), ischemic heart disease (ICD-9-CM codes 410–414), hyperlipidemia (ICD-9-CM code 272), congestive heart failure (ICD-9-CM code 428), cardiac arrhythmias (ICD-9-CM codes 426 and 427), peripheral vascular disorders (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, 443, 444.22, 444.8, 447.8, and 447.9), stroke (ICD-9-CM codes 430–438), headaches (ICD-9-CM code 784.0), migraine (ICD-9-CM code 346), epilepsy (ICD-9-CM code 345), dementia (ICD-9-CM code 290, 294.1, and 331.0), rheumatoid arthritis (ICD-9-CM code 714), systemic lupus erythematosus (ICD-9-CM code 710.0), chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, and 496), asthma (ICD-9-CM code 493), pulmonary circulation disorders (ICD-9-CM codes 415–417), diabetes (ICD-9-CM code 250), hypothyroidism (ICD-9-CM codes 243 and 244), renal failure (ICD-9-CM codes 584–586), liver diseases (ICD-9-CM codes 570–573), peptic ulcers (ICD-9-CM codes 531–533), hepatitis B (ICD-9-CM codes V02.61, 070.20, 070.22, 070.30, and 070.32), tuberculosis (ICD-9-CM codes 011–018), deficiency anemias (ICD-9-CM codes 280, and 281), depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), psychosis (ICD-9-CM codes 295–299), metastatic cancer (ICD-9-CM codes 196–198), and solid tumor (ICD-9-CM codes 140–195).

Cataract (ICD-9-CM code 366) was also evaluated because of higher prevalence in the elderly population.

Statistical analysis

The baseline characteristics and comorbidities of the PACG case group and non-PACG control group were compared. Chi squared test and *t* test were used to evaluate the difference of categorical and continuous variables, respectively, between the two groups. Univariable and multivariable unconditional logistic regression models were used to estimate the effect of comorbidities on the risk of PACG as indicated by the odds ratio (OR) with 95% confidence interval (CI). All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Carey, NC), and the significance level was set at 0.05 for the two-tailed tests.

RESULTS

A total of 3322 PACG cases met the study criteria, and 13288 subjects were matched according to sex and age to form the control group (**Table 1**). The PACG group comprised 61.1% women, and 57.6% were older than 65 years. The mean age was 65.2 ± 12.7 years in the PACG group and 64.8 ± 13.0 years in the control group. Compared with the controls, PACG patients have significantly higher prevalence of hypertension, ischemic heart disease, hyperlipidemia, cardiac arrhythmias, peripheral vascular disorders, headaches, chronic obstructive pulmonary disease, asthma, diabetes, renal failure, liver diseases, peptic ulcers, hepatitis B, depression, solid tumor, and cataract ($p < 0.05$).

The crude and adjusted ORs for the model were fitted to examine the association between medical comorbidities and the risk of PACG (**Table 2**). Hyperlipidemia increased the risk of PACG by 1.11 fold (95% CI: 1.01-1.21). Headaches increased the risk of PACG by 1.13 fold (95% CI: 1.04-1.23). Liver diseases inreased the risk of PACG by 1.14 fold (95% CI: 1.03-1.25). Peptic ulcers increased the risk of PACG by 1.10 fold (95% CI: 1.01-1.20). Cataract increased the risk of PACG by 3.80 fold (95% CI: 3.49-4.14).

For the male group, diabetes (ORs: 1.19, 95% CI: 1.00-1.40), liver diseases (ORs: 1.29, 95% CI: 1.11-1.50), and cataract (ORs: 4.30, 95%CI: 3.74-4.94) were significantly associated with increasing PACG risk (**Table 3**). For the female group, hyperlipidemia (ORs: 1.13, 95% CI: 1.00-1.26), headaches (ORs: 1.15, 95% CI: 1.04-1.28), peptic ulcers (ORs: 1.14, 95% CI: 1.02-1.28), and cataract (ORs: 3.54, 95% CI: 3.18-3.95) were significantly associated with increasing PACG risk.

For the age group of 64 years and younger, patients with comorbidity of hyperlipidemia (ORs: 1.20, 95% CI: 1.03-1.40), peptic ulcers (ORs: 1.21, 95% CI: 1.05-1.40), and cataract (ORs: 5.91, 95% CI: 5.07-6.90) were significantly associated with increasing PACG risk (**Table 4**). For the age group of 65 years and older, patients with cataract were significantly associated with increasing PACG risk (ORs: 5.07, 95% CI: 4.46-5.77).

DISCUSSION

Among the 3322 PACG patients, 41.8 % had hyperlipidemia, 42.4 % had headache and peptic ulcer, and 62.9% had cataract. The risk of PACG was greater for patients with the comorbidities of hyperlipidemia, headaches, liver diseases, peptic ulcers, and cataract. For the male group, diabetes, liver diseases, and cataract were significantly associated with increasing PACG risk. For the female group, hyperlipidemia, headaches, peptic ulcers, and cataract were significantly associated with increasing PACG risk. For both the genders, cataract was the same and strongest risk factor for PACG development (ORs: 4.30 for the male group; ORs: 3.54 for the female group).

Regarding the effect of age on the risk of PACG, we subclassified the study groups into two. Interesting results were obtained; patients with comorbidity of hyperlipidemia, peptic ulcers, and cataract were associated with increasing PACG risk in the age group of 64 years and younger. However, for the age group of 65 years and older, cataract was the only factor for the increased risk of PACG. Cataract was the same and strongest risk factor for PACG onset for both the age groups (ORs: 5.91 for the age group younger than 65 years; ORs :5.07 for the age group older than 65 years).

Our study is the first one that discussed the medical comorbidity in a large PACG cohort using a large claims database. Potential explanations about the strong relationship between some medical illness and the risk of PACG should be mentioned

as below.

Pathogenetic mechanisms of PACG and association between cataract and PACG

Our study reveals that cataract is the strongest risk factor for PACG in any age group and gender compared with other medical comorbidity. PACG has its characteristic anatomy features and unique pathological process, including a crowded anterior segment and narrow anterior chamber angle.[15] The lens is considered to play a crucial role in the pathogenesis of PACG either because of an increase in its thickness or a more anterior position resulting in angle crowding and a greater predisposition to pupillary block.[5,6,15,16] Furthermore, the lens thickness increases with age and makes the narrow anterior chamber angle even more crowded, which might be why most PACG occurs in patients older than 40 years.[15,16] Our study result supports that ocular anatomical factor plays a more important role in the pathogenesis of PACG than any other medical comorbidities in Taiwan Chinese population.

Association between hyperlipidemia and diabetes and PACG

In one Korean epidemiological study, hypercholesterolemia, hypertension, and diabetes mellitus were independent risk factors for the development of any cataract.[17] Moreover, in one study, the authors demonstrated that metabolic syndrome and its components are associated with age-related cataract only among Korean women.[18] We believe that the potential reasons for diabetes and hyperlipidemia in the risk of PACG from our result

could be attributed to the increased risk of cataract. Further, longitudinal observational study is needed to address this issue.

Association between liver disease and PACG

One recent study from Taiwan reported that hepatitis C infection, even without the complication of cirrhosis, is associated with an increased risk of cataract.[19] Another study from Korean reported that hepatitis B and hepatitis C infection were significantly associated with cataract.[20] The strong association between liver disease and the risk of PACG might increase the risk of cataract in liver disease patients. However, further study is needed to elucidate this interesting result.

Association between headache and PACG

PACG patients complain of headache caused by increased intraocular pressure. [21,22] PACG patients seek medical help due to headache before the diagnosis of PACG. Our results indicate that headache is associated with higher risk for PACG. Headache may be a symptom of PACG missed by the physician. Therefore, clinicians should consider the possibility of PACG in patients with headache.

Association between peptic ulcers and PACG

No previous study has reported the presence or absence of an association between peptic ulcers and PACG. We speculate that Histamine 2 receptor antagonist that was widely used in peptic ulcer treatment might induce or precipitate PACG.[23] Further

longitudinal study is mandatory in this interesting topic.

Despite these promising results, our study had certain limitations. First, glaucoma and medical comorbidity were defined entirely on the basis of claims data (ICD-9-CM codes assigned by clinicians).[21] This approach is less accurate than diagnosing personally through a standardized procedure.[21] The second limitation is selection bias.[21] Because the NHI database only comprises data of patients who have received treatment, patients who have received no treatment for glaucoma or any of these medial disease might have been recruited in the comparison cohort. Third, despite the large sample, the study cohort comprised Taiwanese patients. Therefore, these findings cannot be generalized to other populations. Nevertheless, our study has the following strengths. First, the strength of the database is excellent because of the large sample randomization.[21] We could follow patient cases over time to assess the relationship between medical illness and the subsequent onset of PACG. Second, the database includes data of people with diverse sociodemographic profiles, unlike some smaller studies that recruited patients from specific regions and thus lack in representativeness.

In conclusion, our population-based study using the NHIRD revealed that the PACG risk is strongest in cataract patients and is slightly higher in patients with medical comorbidities of hyperlipidemia, headaches, liver diseases, and peptic ulcers. Clinicians should be aware of these findings when encountering patients with these

diseases.

Contributors H Y Chen: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, obtaining funding; C L Lin: statistical expertise, conception and design, critical revision of the manuscript for important intellectual content.

Competing interests None declared.

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Table 1. Demographic comparison between PACG cases and controls

	PACG Cases N= 3322		Controls N= 13288		
	n	(%)	n	(%)	p-value
Sex					0.999
female	2031	61.1	8124	61.1	
male	5164	38.9	1291	38.9	
Age group (years)					0.999
20-49	398	12.0	1592	12.0	
50-64	1011	30.4	4044	30.4	
≥65	1913	57.6	7652	57.6	
Age (year), mean (SD) †	65.2(12.7)		64.8(13.0)		0.100
Comorbidity					
Hypertension	2025	60.6	6896	51.9	<0.001
Ischemic heart disease	1097	33.0	3561	26.8	<0.001
Hyperlipidemia	1389	41.8	4399	33.1	<0.001
Congestive heart failure	213	6.41	849	6.39	0.962
Cardiac arrhythmias	540	16.3	1826	13.7	<0.001
Peripheral vascular disorders	201	6.05	571	4.30	<0.001
Stroke	246	7.41	994	7.48	0.883
Headaches	1407	42.4	4772	35.9	<0.001
Migraine	125	3.76	456	3.43	0.353
Epilepsy	30	0.90	144	1.08	0.360
Dementia	110	3.31	448	3.37	0.863
Rheumatoid arthritis	11	0.33	45	0.34	0.957
Systemic lupus erythematosus	3	0.09	8	0.06	0.546
Chronic obstructive pulmonary disease	675	20.3	2343	17.6	<0.001
Asthma	418	12.6	1455	11.0	0.008
Pulmonary circulation disorders	26	0.78	85	0.64	0.366
Diabetes	710	21.4	2148	16.2	<0.001
Hypothyroidism	36	1.08	110	0.83	0.158
Renal failure	448	13.5	1435	10.8	<0.001
Liver diseases	898	27.0	2775	20.9	<0.001
Peptic ulcers	1409	42.4	4503	33.9	<0.001
Hepatitis B	182	5.48	610	4.59	0.032
Tuberculosis	86	2.59	294	2.21	0.194
Deficiency anemia	114	3.43	381	2.87	0.087

Depression	328	9.87	922	6.94	<0.001
Psychosis	153	4.61	518	3.90	0.064
Metastatic cancer	1	0.03	2	0.02	0.564
Solid tumor	190	5.72	630	4.74	0.020
Cataract	2088	62.9	4077	30.7	<0.001

Data are presented as the number of subjects in each group, with percentages given in parentheses.

Chi-square test; † t-test

Table 2. Factors associated with risk of PACG

	Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)
Comorbidity				
Hypertension	1.45	(1.34, 1.56)***	0.97	(0.88, 1.07)
Ischemic heart disease	1.35	(1.24, 1.46)***	0.92	(0.83, 1.01)
Hyperlipidemia	1.45	(1.34, 1.57)***	1.11	(1.01, 1.21)*
Congestive heart failure	1.00	(0.86, 1.17)	-	-
Cardiac arrhythmias	1.22	(1.10, 1.35)***	0.91	(0.81, 1.02)
Peripheral vascular disorders	1.44	(1.22, 1.69)***	1.02	(0.86, 1.21)
Stroke	0.98	(0.86, 1.14)	-	-
Headaches	1.31	(1.21, 1.42)***	1.13	(1.04, 1.23)***
Migraine	1.10	(0.90, 1.35)	-	-
Epilepsy	0.83	(0.56, 1.24)	-	-
Dementia	0.98	(0.79, 1.21)	-	-
Rheumatoid arthritis	0.98	(0.51, 1.89)	-	-
Systemic lupus erythematosus	1.50	(0.40, 5.66)	-	-
Chronic obstructive pulmonary disease	1.19	(1.08, 1.31)***	0.88	(0.79, 1.00)
Asthma	1.17	(1.04, 1.32)***	0.98	(0.86, 1.11)
Pulmonary circulation disorders	1.23	(0.79, 1.90)	-	-
Diabetes	1.41	(1.28, 1.55)***	1.03	(0.93, 1.15)
Hypothyroidism	1.31	(0.90, 1.92)	-	-
Renal failure	1.29	(1.15, 1.44)***	0.93	(0.82, 1.05)
Liver diseases	1.40	(1.29, 1.53)***	1.14	(1.03, 1.25)*
Peptic ulcers	1.44	(1.33, 1.55)***	1.10	(1.01, 1.20)*
Hepatitis B	1.21	(1.02, 1.43)*	1.09	(0.91, 1.31)
Tuberculosis	1.18	(0.92, 1.50)	-	-
Deficiency anemia	1.20	(0.97, 1.49)	-	-
Depression	1.47	(1.29, 1.68)***	1.12	(0.98, 1.29)
Psychosis	1.19	(0.99, 1.43)	-	-
Metastatic cancer	2.01	(0.18, 22.1)	-	-
Solid tumor	1.22	(1.03, 1.44)*	1.01	(0.85, 1.20)
Cataract	3.82	(3.53, 4.14)***	3.80	(3.49, 4.14)***

Abbreviations: odds ratio (OR); confidence interval (CI)

†Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

*p<0.05; **p<0.01; ****p<0.001

Table 3. Factors affecting the risk of PACG according to sex

	Male				Female			
	Crude		Adjusted †		Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Comorbidity								
Hypertension	1.60	(1.41, 1.81)***	1.01	(0.87, 1.18)	1.36	(1.23, 1.50)***	0.94	(0.83, 1.06)
Ischemic heart disease	1.43	(1.25, 1.63)***	0.92	(0.78, 1.08)	1.30	(1.17, 1.44)***	0.90	(0.79, 1.02)
Hyperlipidemia	1.54	(1.35, 1.75)***	1.12	(0.96, 1.30)	1.41	(1.28, 1.56)***	1.13	(1.00, 1.26)*
Congestive heart failure	1.15	(0.91, 1.46)	-	-	0.91	(0.74, 1.12)	-	-
Cardiac arrhythmias	1.24	(1.05, 1.48)***	0.86	(0.71, 1.05)	1.20	(1.06, 1.37)***	0.93	(0.80, 1.07)
Peripheral vascular disorders	1.52	(1.17, 1.98)***	0.97	(0.73, 1.29)	1.38	(1.12, 1.71)***	1.04	(0.84, 1.31)
Stroke	1.10	(0.89, 1.36)	-	-	0.90	(0.74, 1.10)	-	-
Headaches	1.35	(1.19, 1.55)***	1.15	(1.00, 1.33)	1.30	(1.18, 1.44)***	1.15	(1.04, 1.28)**
Migraine	1.09	(0.70, 1.70)	-	-	1.10	(0.88, 1.39)	-	-
Epilepsy	0.91	(0.50, 1.67)	-	-	0.78	(0.46, 1.31)	-	-
Dementia	1.04	(0.74, 1.45)	-	-	0.95	(0.72, 1.25)	-	-
Rheumatoid arthritis	2.01	(0.37, 11.0)	-	-	0.88	(0.43, 1.81)	-	-
Systemic lupus erythematosus	4.00	(0.25, 64.0)	-	-	1.15	(0.24, 5.52)	-	-
Chronic obstructive pulmonary disease	1.34	(1.17, 1.54)***	0.89	(0.75, 1.05)	1.07	(0.94, 1.23)	-	-
Asthma	1.30	(1.08, 1.56)***	0.99	(0.80, 1.23)	1.10	(0.95, 1.28)	-	-

Pulmonary circulation disorders	1.07	(0.49, 2.34)	-	-	1.31	(0.77, 2.24)	-	-
Diabetes	1.67	(1.44, 1.94)***	1.19	(1.00, 1.40)*	1.26	(1.11, 1.42)***	0.93	(0.81, 1.07)
Hypothyroidism	1.18	(0.43, 3.20)	-	-	1.34	(0.89,2 .01)	-	-
Renal failure	1.46	(1.23, 1.73)***	0.96	(0.80, 1.16)	1.17	(1.00, 1.36)*	0.87	(0.74, 1.03)
Liver diseases	1.57	(1.37, 1.80)***	1.29	(1.11, 1.50)**	1.30	(1.16, 1.46)***	1.05	(0.92, 1.19)
Peptic ulcers	1.40	(1.24, 1.59)***	1.01	(0.87, 1.16)	1.46	(1.32, 1.61)***	1.14	(1.02, 1.28)*
Hepatitis B	1.25	(0.97, 1.61)	-	-	1.17	(0.93, 1.47)	-	-
Tuberculosis	1.29	(0.95, 1.75)	-	-	1.02	(0.68, 1.52)	-	-
Deficiency anemia	1.48	(0.99, 2.20)	-	-	1.12	(0.87, 1.44)	-	-
Depression	1.67	(1.31, 2.13)***	1.20	(0.93, 1.57)	1.40	(1.20, 1.64)***	1.11	(0.94, 1.31)
Psychosis	1.13	(0.81, 1.59)	-	-	1.22	(0.98, 1.52)	-	-
Metastatic cancer	-	-	-	-	-	-	-	-
Solid tumor	1.23	(0.93, 1.61)	-	-	1.22	(0.98, 1.50)	-	-
Cataract	4.37	(3.84,4.96)***	4.30	(3.74, 4.94)***	3.54	(3.20, 3.92)***	3.54	(3.18, 3.95)***

Abbreviations: odds ratio (OR); confidence interval (CI)

†Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

Table 4. factors affecting the risk of PACG according to the age

	Age ≦64				Age ≧65			
	Crude		Adjusted †		Crude		Adjusted †	
Variable	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)	OR	(95%CI)
Comorbidity								
Hypertension	1.77	(1.57, 2.00)***	1.15	(0.99, 1.34)	1.35	(1.20, 1.51)***	1.10	(0.97, 1.25)
Ischemic heart disease	1.79	(1.54, 2.08)***	1.00	(0.83, 1.21)	1.23	(0.11, 1.36)***	0.95	(0.84, 1.07)
Hyperlipidemia	1.81	(1.60, 2.06)***	1.20	(1.03, 1.40)*	1.28	(1.15, 1.41)***	1.04	(0.92, 1.16)
Congestive heart failure	1.75	(1.24, 2.48)***	0.96	(0.64, 1.44)	0.89	(0.74, 1.06)	-	-
Cardiac arrhythmias	1.49	(1.22, 1.83)***	1.01	(0.80, 1.28)	1.14	(1.01, 1.29)*	0.92	(0.80, 1.06)
Peripheral vascular disorders	1.65	(1.14, 2.40)***	0.84	(0.55, 1.28)	1.40	(1.16, 1.68)***	1.13	(0.93, 1.38)
Stroke	1.40	(0.99, 1.96)	-	-	0.92	(0.78, 1.08)	-	-
Headaches	1.48	(1.31, 1.67)***	1.14	(1.00, 1.30)	1.20	(1.09, 1.33)***	1.04	(0.93, 1.16)
Migraine	1.13	(0.83, 1.52)	-	-	1.08	(0.83, 1.42)	-	-
Epilepsy	1.17	(0.61, 2.24)	-	-	0.70	(0.42, 1.15)	-	-
Dementia	2.46	(1.16, 5.21)***	1.31	(0.57, 3.05)	0.92	(0.73, 1.15)	-	-
Rheumatoid arthritis	1.26	(0.50, 3.17)	-	-	0.77	(0.30, 2.00)	-	-
Systemic lupus erythematosus	2.01	(0.18, 22.1)	-	-	1.33	(0.27, 6.61)	-	-
Chronic obstructive pulmonary disease	1.60	(1.33, 1.93)***	1.08	(0.87, 1.34)	1.09	(0.97, 1.22)	-	-
Asthma	1.42	(1.15, 1.76)***	1.00	(0.78, 1.28)	1.08	(0.94, 1.25)	-	-

Pulmonary circulation disorders	1.72	(0.66, 4.48)	-	-	1.13	(0.69, 1.86)	-	-
Diabetes	1.92	(1.63, 2.25)***	1.08	(0.89, 1.31)	1.21	(1.08, 1.37)**	0.96	(0.84, 1.09)
Hypothyroidism	1.28	(0.71, 2.30)	-	-	1.34	(0.81, 2.19)	-	-
Renal failure	1.82	(1.48, 2.24)***	1.08	(0.85, 1.37)	1.13	(0.99, 1.30)	-	-
Liver diseases	1.64	(1.43, 1.87)***	1.12	(0.96, 1.31)	1.26	(1.13, 1.42)***	1.02	(0.90, 1.16)
Peptic ulcers	1.70	(1.50, 1.92)***	1.21	(1.05, 1.40)**	1.32	(1.19, 1.45)***	1.06	(0.95, 1.19)
Hepatitis B	1.06	(0.83, 1.35)	-	-	1.37	(1.08, 1.73)***	1.20	(0.93, 1.54)
Tuberculosis	1.08	(0.64, 1.82)	-	-	1.21	(0.92, 1.59)	-	-
Deficiency anemia	1.36	(0.95, 1.92)	-	-	1.13	(0.86, 1.47)	-	-
Depression	1.78	(1.45, 2.20)***	1.18	(0.93, 1.50)	1.31	(1.10, 1.55)**	1.01	(0.85, 1.21)
Psychosis	1.27	(0.95, 1.69)	-	-	1.14	(0.90, 1.45)	-	-
Metastatic cancer	-	-	-	-	-	-	-	-
Solid tumor	1.16	(0.83, 1.60)	-	-	1.25	(1.02, 1.51)*	1.15	(0.94, 1.41)
Cataract	6.95	(6.00, 8.05)***	5.91	(5.07, 6.90)***	5.18	(4.56, 5.87)***	5.07	(4.46, 5.77)***

Abbreviations: odds ratio (OR); confidence interval (CI)

†Covariables which were significantly associated with risk of PACG in univariable unconditional logistic regression model were further analyzed by multivariable unconditional logistic regression model.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Reported on Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6,7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	6-8
		(*c*) Explain how missing data were addressed	6-8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods	6-8

taking account of sampling strategy	
(*e*) Describe any sensitivity analyses	8

Continued on next page

Results			**Reported on Page No.**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	x
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*8,9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*8,9*
		Cross-sectional study—Report numbers of outcome events or summary measures	*8,9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8,9
		(*b*) Report category boundaries when continuous variables were categorized	8,9
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8,9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8,9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9,10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.