

Original Article

Bidirectional associations between glaucoma and skin neoplasms: a global retrospective cohort study

Chen-Yu Lin^{1*}, Shao-Wei Lo², Christine Hsu³, Mi-Lun Huang⁴, Yung-Fang Tu⁵, Yi-Sheng Jhang⁶, Hui-Chin Chang^{1,7,8}, Shih-Chi Yang⁴, Meng-Che Wu^{1,9,10*}, Shuo-Yan Gau^{11,12}

¹School of Medicine, Chung Shan Medical University, Taichung, Taiwan; ²Department of Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA; ³Department of Medicine, Monmouth Medical Center, Robert Wood Johnson/Barnabas Health Care System, Long Branch, NJ, USA; ⁴Education Center, College of Medicine, National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan; ⁵Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA; ⁶Department of Pharmacy, Chung Shan Medical University Hospital, Taichung, Taiwan; ⁷Evidence-Based Medicine Center, Chung Shan Medical University Hospital, Taichung, Taiwan; ⁸Library, Chung Shan Medical University Hospital, Taichung, Taiwan; ⁹Division of Pediatric Gastroenterology, Children's Medical Center, Taichung Veterans General Hospital, Taichung, Taiwan; ¹⁰Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan; ¹¹Department and Graduate Institute of Business Administration, National Taiwan University, Taipei, Taiwan; ¹²Institute of Allergology, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Charité - Universitätsmedizin Berlin, Berlin, Germany. *Equal contributors and co-first authors.

Received April 4, 2026; Accepted September 16, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Glaucoma and skin neoplasms are common disorders in older adults, but whether they are longitudinally associated remains unclear. Biological links have been proposed based on shared susceptibility to oxidative injury and ultraviolet radiation. We used the TriNetX Global Collaborative Network to examine the relationship between glaucoma and skin neoplasms in both temporal directions. After propensity score matching, the glaucoma analysis included 873,294 patients in each cohort. Glaucoma was associated with a higher subsequent risk of skin neoplasms (HR 1.220; 95% CI 1.185-1.256), with similar findings for melanoma (HR 1.197; 95% CI 1.101-1.301) and non-melanoma skin cancer (HR 1.228; 95% CI 1.191-1.266). In analyses stratified by race, the association was observed among White patients (HR 1.274; 95% CI 1.233-1.317), but did not reach statistical significance among Black or Asian patients. The reciprocal analysis included 1,456,093 patients in each matched cohort. A history of skin neoplasms was associated with subsequent glaucoma (HR 1.881; 95% CI 1.841-1.922), and the association remained significant across the racial groups examined. Several glaucoma-related conditions also showed elevated risks, including glaucoma suspect states. Our findings demonstrate longitudinal associations between glaucoma and skin neoplasms in both directions. The results may increase clinical awareness of these coexisting conditions, although the observational design does not establish causality or justify routine cross-specialty screening. Further studies are needed to determine the mechanisms underlying these associations and whether risk-based surveillance has clinical value.

Keywords: Glaucoma, skin cancer, retrospective cohort study, real-world study

Introduction

Glaucoma is a major cause of irreversible visual impairment and remains an important health burden in aging populations worldwide [1]. Beyond its ocular manifestations, glaucoma has been associated with a range of systemic comorbidities [2-4], suggesting that its clinical relevance may extend beyond the eye. Skin neoplasms likewise represent an increasing

clinical concern, with the burden of both melanoma and non-melanoma skin cancer (NMSC) rising substantially among older adults [5]. Although these conditions involve different organ systems, several observations have raised the possibility that they may share underlying susceptibility.

Oxidative stress has been implicated in glaucomatous optic nerve damage and also plays an

important role in cutaneous carcinogenesis [6, 7]. Ultraviolet (UV) radiation provides another potential link. It is a well-established environmental risk factor for skin cancer, while UV-related oxidative damage has also been implicated in ocular pathology [8, 9]. Biological similarities between ocular and cutaneous tissues offer further rationale for investigating this relationship. In particular, ocular and cutaneous melanocytes share a neural crest origin, suggesting that susceptibility affecting melanocyte homeostasis may have implications beyond a single organ system [10, 11].

Despite this biological rationale, epidemiological evidence remains limited. Previous research has generally examined the relationship in only one direction or has focused on selected disease subtypes. A cohort study, for example, reported an increased risk of exfoliation glaucoma among individuals with a history of NMSC, supporting cumulative UV exposure as one possible explanation [12]. Another population-based study evaluated subsequent cancer risk among patients with glaucoma [13]. Whether a broader relationship exists between glaucoma and skin neoplasms remains uncertain. It is also unclear whether such an association can be observed in both temporal directions. Evidence across different racial groups is particularly limited, which is relevant given the marked racial variation in the epidemiology of both diseases.

We therefore conducted two complementary retrospective cohort analyses using the TriNetX Global Collaborative Network to examine the relationship between glaucoma and skin neoplasms in both temporal directions. The principal innovation of this study lies in evaluating both directions of this association within the same large-scale analytical framework rather than restricting the investigation to a single disease subtype or temporal sequence. The global population further enabled assessment across clinically relevant subgroups and specific disease phenotypes. These findings may also have practical relevance for both dermatologic and ophthalmologic care.

Materials and methods

Data source and study design

We conducted a retrospective cohort study using the TriNetX Global Collaborative Network

(<https://live.trinetx.com/>). TriNetX provides access to anonymized electronic health records (EHRs) from more than 100 million patients treated at healthcare organizations worldwide and has been used in previous epidemiological studies [14-16]. The study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (CS1-25002) and conducted in accordance with the Declaration of Helsinki.

Population selection and eligibility

Eligible participants were older than 50 years at cohort entry and were required to have at least two documented clinical encounters. Two complementary cohorts were constructed to evaluate the association in each temporal direction.

For the glaucoma-to-skin neoplasm analysis, the exposure cohort included patients with a documented diagnosis of glaucoma. The comparison cohort consisted of individuals undergoing general health examinations who had no history of glaucoma. Patients with a diagnosis of skin neoplasm before the index date were excluded to restrict the analysis to incident outcomes during follow-up.

For the skin neoplasm-to-glaucoma analysis, the exposure cohort included patients with a documented diagnosis of skin neoplasm. The comparison cohort consisted of individuals undergoing general health examinations without a history of skin neoplasms. Patients with glaucoma before the index date were excluded from this analysis. Patients recorded as deceased before cohort entry were excluded from both study directions. The diagnostic codes used to define the study populations are provided in **Table 1**, while the complete patient selection process is shown in **Figure 1**.

Propensity score matching

Patients were matched 1:1 using greedy nearest-neighbor matching with a caliper of 0.1 pooled standard deviations of the logit of the propensity score. Covariates included age, sex, race, comorbidities (hypertension, hyperlipidemia, diabetes), socioeconomic factors, and healthcare utilization (inpatient/ambulatory visits). Missing covariate values were retained as a separate category rather than excluded

Glaucoma and skin cancer

Table 1. Utilized proxy codes

Description	ICD-10-CM codes
Glaucoma-skin neoplasm cohort	
Glaucoma	H40-H42
Malignant melanoma of skin	C43
Other and unspecified malignant neoplasm of skin	C44
Neoplasms	C00-D49
Encounter for general examination without complaint, suspected or reported diagnosis	Z00
Trabeculoplasty by laser surgery	CPT code: 65855
Trabeculotomy ab externo	CPT code: 65850
Trabeculotomy ab externo	SNOMED: 30880003
Trabeculotomy of right eye	SNOMED: 1287866001
Trabeculotomy of left eye	SNOMED: 1287865002
Goniotomy	CPT code: 65820
Removal of blood clot, anterior segment of eye	CPT code: 65930
Drainage of Left Anterior Chamber, Percutaneous Approach	ICD-10-PCS: 08933ZZ
Drainage of Right Anterior Chamber, Percutaneous Approach	ICD-10-PCS: 08923ZZ
Fistulization of sclera for glaucoma; trabeculectomy ab externo in absence of previous surgery	CPT code: 66170
Fistulization of sclera for glaucoma; trabeculectomy ab externo with scarring from previous ocular surgery or trauma (includes injection of antifibrotic agents)	CPT code: 66172
Transluminal dilation of aqueous outflow canal (eg, canaloplasty); without retention of device or stent	CPT code: 66174
Transluminal dilation of aqueous outflow canal (eg, canaloplasty); with retention of device or stent	CPT code: 66175
Aqueous shunt to extraocular equatorial plate reservoir, external approach; without graft	CPT code: 66179
Aqueous shunt to extraocular equatorial plate reservoir, external approach; with graft	CPT code: 66180
Insertion of anterior segment aqueous drainage device, without extraocular reservoir, external approach	CPT code: 66183
Revision of aqueous shunt to extraocular equatorial plate reservoir; with graft	CPT code: 66185
Repair of iris, ciliary body (as for iridodialysis)	CPT code: 66680
Ciliary body destruction; cyclophotocoagulation, transscleral	CPT code: 66710
Ciliary body destruction; cyclophotocoagulation, endoscopic, without concomitant removal of crystalline lens	CPT code: 66711
Ciliary body destruction; cryotherapy	CPT code: 66720
Iridoplasty by photocoagulation (1 or more sessions) (eg, for improvement of vision, for widening of anterior chamber angle)	CPT code: 66762
Aspiration of release of vitreous, subretinal or choroidal fluid, pars plana approach (posterior sclerotomy)	CPT code: 67015
Capsulotomy	CPT code: 1005411
Reformation of anterior chamber of eye	SNOMED: 172517004
Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the suprachoroidal space	CPT code: 0253T

Glaucoma and skin cancer

Insertion of anterior segment aqueous drainage device, with creation of intraocular reservoir, internal approach, into the supraciliary space	CPT code: 0474T
Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; initial insertion	CPT code: 0191T
Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork	CPT code: 1022278
Insertion of anterior segment aqueous drainage device, without extraocular reservoir, internal approach, into the trabecular meshwork; each additional device insertion (List separately in addition to code for primary procedure)	CPT code: 0376T
Insertion of anterior segment aqueous drainage device into the trabecular meshwork, without external reservoir, and without concomitant cataract removal, one or more	CPT code: 0671T
Beta blocking agents	ATC code: C07
Skin neoplasm-glaucoma cohort	
Glaucoma	H40-H42
Malignant melanoma of skin	C43
Other and unspecified malignant neoplasm of skin	C44
Neoplasms	C00-D49
Encounter for general examination without complaint, suspected or reported diagnosis	Z00
Mohs micrographic surgery procedures	CPT code: 1003602
Mohs surgery	SNOMED: 418024000
Electrodesiccation	SNOMED: 8401003
Curettage	SNOMED: 68688001
Imiquimod	RxNorm code: 59943
Nivolumab	RxNorm code: 1597879
Pembrolizumab	RxNorm code: 1547545
Fluorouracil	RxNorm code: 4492
Ipilimumab	RxNorm code: 1094833
Dabrafenib	RxNorm code: 1424911
Trametinib	RxNorm code: 1425099
Dacarazine	RxNorm code: 3098

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification; ICD-10-PCS: International Classification of Diseases, Tenth Revision Procedure Coding System; CPT: Current Procedural Terminology; SNOMED: Systematized Nomenclature of Medicine; ATC: Anatomical Therapeutic Chemical.

Glaucoma and skin cancer

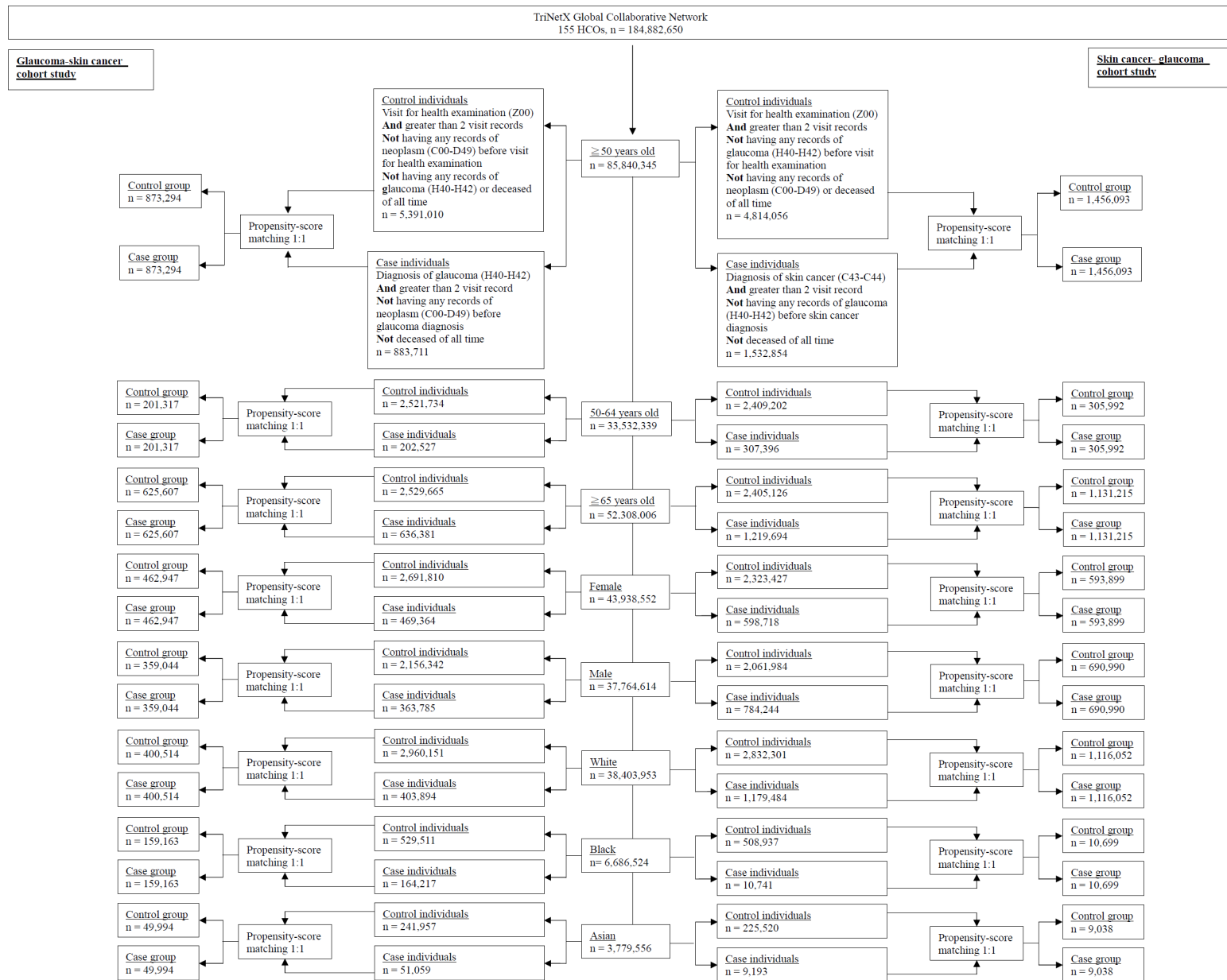


Figure 1. Patient selection process.

from the analysis. Covariate balance after matching was evaluated using standardized mean differences (SMDs); values below 0.1 were considered adequately balanced.

Study outcomes and follow-up

The study period extended from January 1, 2005, through December 31, 2023. Outcomes were assessed after the index date during follow-up. In the glaucoma-to-skin neoplasm analysis, the primary outcome was incident skin neoplasm. Melanoma and non-melanoma skin cancer were evaluated as secondary outcomes. In the reciprocal analysis, the primary outcome was incident glaucoma. Specific glaucoma subtypes and glaucoma-related conditions were evaluated as secondary outcomes. The primary analyses assessed outcomes over up to 15 years of follow-up. Participants were followed from the index date until the occurrence of the outcome of interest or the end of the 15-year follow-up period, whichever came first.

Statistical analysis

All analyses were performed using the TriNetX Analytics platform, via the function “Advanced Analysis”. Covariate balance before and after matching was assessed using standardized mean differences, with an absolute value below 0.1 indicating adequate balance. Time-to-event analyses were performed after matching. Kaplan-Meier methods were used to estimate cumulative event-free probabilities, with between-group differences evaluated using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. Statistical significance was defined as a two-sided *P* value <0.05. Sensitivity analyses included varying washout periods (12, 24, 36 months) and using stricter algorithm definitions (combining diagnosis codes with procedure or medication codes). Age, sex, and race were selected for stratified analyses because of their established relevance to the epidemiology of both glaucoma and skin neoplasms. These demographic characteristics are routinely captured within the TriNetX network and permit clinically interpretable subgroup comparisons. Other measured baseline characteristics were addressed primarily as potential confounders through propensity score matching. Multivariable regression analysis after propensity score matching could not be performed because this

function is not supported by the TriNetX Analytics platform. ROC curve and area under the curve analyses were likewise unavailable. Details of the sensitivity analyses are provided in **Table 2**. This study followed the STROBE guidelines for reporting [17].

Results

Baseline characteristics

The analysis included two matched cohorts. For the glaucoma-to-skin neoplasm analysis, 873,294 patients with glaucoma were matched 1:1 to controls without the outcome of interest. The mean age of patients with glaucoma was 66.5 ± 12.0 years, and 56.6% were female. White patients accounted for 49.9% of the cohort, compared with 17.5% who were Black or African American and 5.7% who were Asian.

The skin neoplasm-to-glaucoma analysis included 1,456,093 patients with skin neoplasms and an equal number of matched controls. The mean age was 66.8 ± 11.3 years, and 50.3% were male. White patients comprised 76.8% of this cohort, a higher proportion than in the glaucoma cohort. After matching, the case and control groups showed adequate balance across the measured baseline characteristics (**Table 3**).

Risk of skin neoplasms in glaucoma patients

Patients with glaucoma had a higher subsequent risk of skin neoplasms than matched controls (HR, 1.220; 95% CI, 1.185-1.256) (**Table 4**). Similar associations were found for melanoma (HR, 1.197; 95% CI, 1.101-1.301) and NMSC (HR, 1.228; 95% CI, 1.191-1.266). When the analysis was stratified by race, an increased risk was found among White patients (HR, 1.274; 95% CI, 1.233-1.317), whereas the estimates for Black and Asian patients did not reach statistical significance. Results were similar between men (HR, 1.217; 95% CI, 1.168-1.269) and women (HR, 1.187; 95% CI, 1.138-1.238) (**Table 5**).

Risk of glaucoma in skin neoplasm patients

In the reciprocal analysis, patients with a history of skin neoplasms had a higher risk of new-onset glaucoma (HR, 1.881; 95% CI, 1.841-1.922) (**Table 4**). Increased risks were

Glaucoma and skin cancer

Table 2. Description of all applied sensitivity analysis models

Models	Description
Glaucoma-skin neoplasm cohort	
Applying various proxy-based glaucoma definition	
Algorithm 1	Only patients with documented inpatient encounters associated with the ICD-10-CM diagnosis code H40-H42 (glaucoma) were classified into the glaucoma cohort for this model.
Algorithm 2	Patients were included in the glaucoma cohort for this model only if they had a documented diagnosis of glaucoma (ICD-10-CM code H40-H42) along with any of following glaucoma-associated surgery record (CPT code 65820, 65850, 65855, 65930, 66170, 66172, 66174, 66175, 66179, 66180, 66183, 66185, 66680, 66710, 66711, 66720, 66762, 67015, 0253T, 0474T, 0191T, 1022278, 0376T, 0671T; ICD-10-PCS code 08933ZZ, 08923ZZ; SNOMED code 30880003, 1287866001, 1287865002, 172517004).
Algorithm 3	Patients were included in the glaucoma cohort for this model only if they had a documented diagnosis of glaucoma (ICD-10-CM code H40-H42) along with a prescription record for beta blocking agents (ATC code: C07).
Applying different wash-out period after index date	
12 months/24 months/36 months after index date	Outcome events occurring during the designated washout period were excluded from subsequent analyses. For all sub-analyses, a fixed follow-up duration of 15 years was applied.
5 years/10 years/15 years after index date	Only outcome events occurring within the predefined follow-up period were considered for analysis. In all sub-analyses, a washout period of three months was applied.
Applying different matching covariates	
Crude model	Hazard ratio was calculated based on the population without propensity score matching.
Matching model 1	Matching covariates include age at index and sex.
Matching model 2	Matching covariates include age at index, sex, race, and medical utilization status.
Skin neoplasm-glaucoma cohort	
Applying various proxy-based skin neoplasm definition	
Algorithm 1	Only patients with documented inpatient encounters associated with the ICD-10-CM diagnosis code C43-C44 (malignant melanoma of skin and other unspecified neoplasms of the skin) were classified into the skin neoplasm cohort for this model.
Algorithm 2	Patients were included in the skin neoplasm cohort for this model only if they had a documented diagnosis of malignant melanoma of skin and other unspecified neoplasms of the skin (ICD-10-CM code C43-C44) along with any of following skin neoplasms surgery (CPT code: 1003602, SNOMED: 418024000, 8401003, 68688001).
Algorithm 3	Patients were included in the skin neoplasm cohort for this model only if they had a documented diagnosis of malignant melanoma of skin and other unspecified neoplasms of the skin (ICD-10-CM code C43-C44) along with a prescription record for any of following skin neoplasms medications (RxNorm code: 59943, 1597879, 1547545, 4492, 1094833, 1424911, 1425099, 3098).
Applying different wash-out period after index date	
12 months/24 months/36 months after index date	Outcome events occurring during the designated washout period were excluded from subsequent analyses. For all sub-analyses, a fixed follow-up duration of 15 years was applied.
5 years/10 years/15 years after index date	Only outcome events occurring within the predefined follow-up period were considered for analysis. In all sub-analyses, a washout period of three months was applied.
Applying different matching covariates	
Crude model	Hazard ratio was calculated based on the population without propensity score matching.
Matching model 1	Matching covariates include age at index and sex.
Matching model 2	Matching covariates include age at index, sex, race, and medical utilization status.

Glaucoma and skin cancer

Table 3. Baseline characteristics: propensity score-matched cohorts and controls

Characteristics	Glaucoma - Skin Neoplasm Study ^a			Skin Neoplasm - Glaucoma Study ^a		
	Glaucoma Cohort (n = 873,294)	Control Cohort (n = 873,294)	SMD	Skin Neoplasm Cohort (n = 1,456,093)	Control Cohort (n = 1,456,093)	SMD
Age at index (years)						
Mean ± SD	66.5 ± 12.0	66.5 ± 12.0	0.01	66.8 ± 11.3	67.0 ± 11.6	0.02
Sex, No. (%)						
Male	254,105 (40.6)	253,732 (40.6)	0.00	732,987 (50.3)	688,832 (47.3)	0.06
Female	354,177 (56.6)	354,354 (56.6)	0.00	686,296 (47.1)	728,731 (50.0)	0.06
Unknown	17,325 (2.8)	17,521 (2.8)	0.00	36,810 (2.5)	38,530 (2.6)	0.01
Race, No. (%)						
White	311,852 (49.9)	313,681 (50.1)	0.01	1,118,078 (76.8)	1,121,729 (77.0)	0.01
Black or African American	109,658 (17.5)	108,904 (17.4)	0.00	10,965 (0.8)	10,960 (0.8)	0.00
Asian	35,530 (5.7)	36,311 (5.8)	0.01	9,105 (0.6)	8,887 (0.6)	0.00
American Indian or Alaska Native	2,122 (0.3)	2,011 (0.3)	0.00	1,850 (0.1)	2,869 (0.2)	0.02
Native Hawaiian or Other Pacific Islander	5,433 (0.9)	5,711 (0.9)	0.00	7,748 (0.5)	7,207 (0.5)	0.01
Other Race	24,853 (4.0)	25,034 (4.0)	0.00	36,324 (2.5)	52,900 (3.6)	0.07
Unknown Race	136,159 (21.8)	133,955 (21.4)	0.01	272,023 (18.7)	251,541 (17.3)	0.04
Labs						
BMI, mean ± SD	29.2 ± 6.89	28.8 ± 6.95	0.10	28.3 ± 5.90	28.7 ± 6.37	0.06
BMI at least 25 kg/m ² , No. (%)	148,280 (23.7)	150,072 (24.0)	0.01	443,604 (30.5)	453,368 (31.1)	0.01
Comorbidities, No. (%)						
Essential hypertension	198,772 (31.8)	201,502 (32.2)	0.01	419,679 (28.8)	439,196 (30.2)	0.03
Hyperlipidemia	116,793 (18.7)	119,267 (19.1)	0.01	309,239 (21.2)	322,934 (22.2)	0.02
Diabetes mellitus	107,995 (17.3)	110,547 (17.7)	0.01	139,393 (9.6)	143,646 (9.9)	0.01
Lifestyle & Socioeconomic, No. (%)						
Mental and behavioral disorders due to psychoactive substance use	29,303 (4.7)	29,909 (4.8)	0.00	94,507 (6.5)	93,702 (6.4)	0.00
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	5,521 (0.9)	5,418 (0.9)	0.00	15,627 (1.1)	15,049 (1.0)	0.00
Medical utilization, No. (%)						
Visit: Ambulatory	393,242 (62.9)	395,329 (63.2)	0.01	1,062,892 (73.0)	1,064,961 (73.1)	0.00
Visit: Inpatient Acute	1,578 (0.3)	1,555 (0.2)	0.00	836 (0.1)	658 (0.0)	0.01

BMI, body mass index; SD, standard deviation; SMD, standardized mean difference. ^aCovariates matched included age, sex, race, health risks tied to socioeconomic and psychosocial factors, mental and behavioral disorders associated with psychoactive substance use, comorbidities (including essential hypertension, hyperlipidemia, diabetes mellitus), medical utilization (ambulatory, inpatient acute).

Glaucoma and skin cancer

Table 4. Risk of developing the secondary condition in propensity score-matched cohorts

Outcome of Interest	Study Cohort	Control Cohort	Hazard Ratio (95% CI)
	No. of events (%)	No. of events (%)	
Direction 1 ^a : Risk of Skin Neoplasms in Patients with Glaucoma	n = 873,294	n = 873,294	
Any skin neoplasm	10,648 (1.3)	7,854 (0.9)	1.220 (1.185, 1.256)
Melanoma	1,295 (0.2)	973 (0.1)	1.197 (1.101, 1.301)
Non-Melanoma Skin Cancer	9,655 (1.1)	7,063 (0.8)	1.228 (1.191, 1.266)
Direction 2 ^b : Risk of Glaucoma in Patients with Skin Neoplasms	n = 1,456,093	n = 1,456,093	
Any glaucoma	26,433 (1.8)	12,083 (0.8)	1.881 (1.841, 1.922)
Primary/Secondary			
Primary	5,361 (0.4)	2,464 (0.2)	1.824 (1.739, 1.914)
Secondary	673 (0.0)	337 (0.0)	1.689 (1.481, 1.925)
Open-angle/Angle-closure			
Open-angle glaucoma	6,027 (0.4)	2,725 (0.2)	1.852 (1.770, 1.938)
Primary angle-closure glaucoma	685 (0.0)	321 (0.0)	1.791 (1.568, 2.046)
Glaucoma suspect status			
Glaucoma suspect	17,294 (1.2)	6,324 (0.4)	2.339 (2.273, 2.408)
Preglaucoma	7,304 (0.5)	2,953 (0.2)	2.083 (1.995, 2.174)
Open angle with borderline findings	6,505 (0.4)	1,807 (0.1)	3.070 (2.914, 3.235)
Anatomical narrow angle	2,099 (0.1)	733 (0.1)	2.447 (2.249, 2.662)
Ocular hypertension	3,815 (0.3)	1,448 (0.1)	2.225 (2.094, 2.364)

CI, Confidence interval. ^a Direction 1 represents the risk of developing skin cancer in patients with a history of glaucoma compared to non-glaucoma controls over a 15-year follow-up period. ^b Direction 2 represents the risk of developing glaucoma in patients with a history of skin neoplasms compared to non-skin neoplasm controls over a 15-year follow-up period.

Table 5. Stratification analyses of the bidirectional association by age, sex, and race in 15-year follow-up period

Subgroups	Risk of Skin Neoplasm in Glaucoma Patients			Risk of Glaucoma in Skin Neoplasm Patients
	All Skin Cancers HR (95% CI) ^a	Melanoma HR (95% CI) ^a	NMSC HR (95% CI) ^a	Any Glaucoma HR (95% CI) ^a
Age				
50-64 years	1.168 (1.060, 1.287)	1.207 (0.939, 1.551)	1.162 (1.047, 1.290)	1.835 (1.715, 1.963)
≥65 years	1.209 (1.172, 1.247)	1.251 (1.144, 1.369)	1.213 (1.174, 1.253)	1.948 (1.904, 1.994)
Sex				
Male	1.217 (1.168, 1.269)	1.180 (1.050, 1.327)	1.233 (1.180, 1.288)	1.707 (1.652, 1.763)
Female	1.187 (1.138, 1.238)	1.265 (1.118, 1.431)	1.185 (1.134, 1.239)	2.079 (2.010, 2.150)
Race				
White	1.274 (1.233, 1.317)	1.274 (1.158, 1.403)	1.285 (1.241, 1.330)	1.988 (1.941, 2.036)
Black/African American	0.810 (0.642, 1.022)	0.672 (0.416, 1.084)	0.860 (0.660, 1.121)	1.705 (1.449, 2.006)
Asian	0.790 (0.599, 1.040)	0.911 (0.387, 2.146)	0.764 (0.573, 1.020)	2.160 (1.733, 2.694)

HR, Hazard ratio; NMSC, Non-melanoma skin cancer; CI, Confidence interval. ^aCovariates matched included age, sex, race, health risks tied to socioeconomic and psychosocial factors, mental and behavioral disorders associated with psychoactive substance use, comorbidities (including essential hypertension, hyperlipidemia, diabetes mellitus), medical utilization (ambulatory, inpatient acute).

found for primary glaucoma (HR, 1.824; 95% CI, 1.739-1.914) and secondary glaucoma (HR, 1.689; 95% CI, 1.481-1.925) (Table 4). Among glaucoma-related conditions, open-angle with borderline findings had the highest estimate (HR, 3.070; 95% CI, 2.914-3.235), followed by anatomical narrow angle (HR, 2.447; 95% CI,

2.249-2.662). The association with subsequent glaucoma was also present within each racial subgroup. The HR was 1.988 (95% CI, 1.941-2.036) among White patients and 1.705 (95% CI, 1.449-2.006) among Black patients. Among Asian patients, the HR was 2.160 (95% CI, 1.733-2.694) (Table 5).

Table 6. Sensitivity analyses for the risk of all skin cancers in patients with glaucoma

Outcome: all skin cancers	Study cohort with incident outcome event, n (%)		Hazard ratio (95% CI)
	Case patients	Control patients	
Sensitivity Analyses			
Applying various proxy-based skin neoplasm definition			
Algorithm 1	7836 (2.2)	3597 (1.0)	2.123 (2.041, 2.208)
Algorithm 2	1060 (1.6)	690 (1.1)	1.442 (1.310, 1.587)
Algorithm 3	5362 (1.6)	3535 (1.1)	1.623 (1.555, 1.693)
Applying various wash-out periods			
12 months	9249 (1.1)	6583 (0.8)	1.254 (1.215, 1.294)
24 months	8285 (1.0)	5639 (0.7)	1.275 (1.233, 1.319)
36 months	7014 (0.8)	4601 (0.5)	1.293 (1.246, 1.342)
Applying various follow-up periods			
5 years	8612 (0.8)	6763 (0.6)	1.196 (1.154, 1.240)
10 years	9783 (1.2)	7320 (0.9)	1.218 (1.181, 1.255)
15 years	10648 (1.3)	7854 (0.9)	1.220 (1.185, 1.256)
Applying various matching algorithms			
Crude model	10792 (1.2)	42248 (0.8)	1.574 (1.541, 1.607)
Matching Model 1	10519 (1.3)	8847 (1.1)	1.064 (1.034, 1.095)
Matching Model 2	10525 (1.3)	12364 (0.9)	1.218 (1.183, 1.255)

Sensitivity analyses

The findings remained consistent across the sensitivity analyses. Similar estimates were obtained when stricter case definitions requiring medication or procedure codes were applied and when the washout period was extended to 36 months. Changing the duration of follow-up or the matching approach did not materially alter the results (Tables 6-9).

Discussion

In this large cohort study, glaucoma and skin neoplasms were associated in both temporal directions. Patients with glaucoma had a 22% higher risk of subsequent skin neoplasms, while a history of skin neoplasms was associated with an 88% higher risk of glaucoma. The associations were similar across the sensitivity analyses.

Previous epidemiological studies have reported associations between glaucoma and cutaneous malignancy. One cohort study found a higher risk of exfoliation glaucoma among individuals with NMSC and suggested cumulative UV exposure as a possible explanation [12]. Our results show that the association with skin neoplasms is not limited to exfolia-

tion glaucoma, as increased risks were also found for other glaucoma phenotypes. Population-based research has examined the reverse temporal relationship by evaluating cancer risk after glaucoma [13]. In our study, skin neoplasms were more common after glaucoma, and glaucoma was also more common after skin neoplasms. Observing these associations in both directions within the same study provides additional epidemiological evidence for a relationship between the two conditions, although it does not establish causality.

Biological and genetic mechanisms

UV exposure and oxidative stress may provide one explanation for the observed association. Chronic UV exposure is a well-established contributor to cutaneous carcinogenesis and has also been implicated in exfoliation glaucoma (XFG), possibly through oxidative damage to the anterior ocular segment [9, 18]. Kang et al. reported a 40% higher risk of XFG among patients with a history of non-melanoma skin cancer and proposed skin cancer as a marker of cumulative lifetime UV exposure [12]. In our study, however, the association with skin neoplasms was also observed for primary open-angle glaucoma. This finding suggests that the

Table 7. Sensitivity analyses for the risk of melanoma in patients with glaucoma

Outcome: melanoma	Study cohort with incident outcome event, n (%)		Hazard ratio (95% CI)
	Case patients	Control patients	
Sensitivity Analyses			
Applying various proxy-based skin neoplasm definition			
Algorithm 1	923 (0.3)	397 (0.1)	2.242 (1.993, 2.522)
Algorithm 2	147 (0.2)	102 (0.2)	1.350 (1.049, 1.739)
Algorithm 3	683 (0.2)	414 (0.1)	1.753 (1.551, 1.980)
Applying various wash-out periods			
12 months	1141 (0.1)	814 (0.1)	1.252 (1.144, 1.370)
24 months	996 (0.1)	712 (0.1)	1.214 (1.103, 1.337)
36 months	837 (0.1)	587 (0.1)	1.211 (1.090, 1.346)
Applying various follow-up periods			
5 years	843 (0.1)	681 (0.1)	1.177 (1.064, 1.302)
10 years	1191 (0.1)	913 (0.1)	1.188 (1.090, 1.295)
15 years	1295 (0.2)	973 (0.1)	1.197 (1.101, 1.301)
Applying various matching algorithms			
Crude model	1316 (0.1)	5890 (0.1)	1.370 (1.291, 1.454)
Matching Model 1	1275 (0.2)	1108 (0.1)	1.030 (0.950, 1.116)
Matching Model 2	1280 (0.2)	973 (0.1)	1.153 (1.061, 1.254)

Table 8. Sensitivity analyses for the risk of non-melanoma skin cancer in patients with glaucoma

Outcome: non-melanoma skin cancer	Study cohort with incident outcome event, n (%)		Hazard ratio (95% CI)
	Case patients	Control patients	
Sensitivity Analyses			
Applying various proxy-based skin neoplasm definition			
Algorithm 1	7169 (2.0)	3273 (0.9)	2.132 (2.045, 2.222)
Algorithm 2	952 (1.5)	608 (1.0)	1.468 (1.326, 1.626)
Algorithm 3	4844 (1.4)	3197 (1.0)	1.621 (1.550, 1.695)
Applying various wash-out periods			
12 months	8373 (1.0)	5916 (0.7)	1.261 (1.220, 1.304)
24 months	7527 (0.9)	5058 (0.6)	1.290 (1.245, 1.337)
36 months	6371 (0.8)	4132 (0.5)	1.306 (1.256, 1.359)
Applying various follow-up periods			
5 years	6079 (0.7)	4811 (0.6)	1.202 (1.158, 1.248)
10 years	8856 (1.1)	6573 (0.8)	1.226 (1.188, 1.266)
Applying various matching algorithms			
Crude model	9784 (1.1)	37319 (0.7)	1.615 (1.580, 1.652)
Matching Model 1	9544 (1.1)	7941 (1.0)	1.074 (1.043, 1.107)
Matching Model 2	9539 (1.1)	6755 (0.8)	1.233 (1.195, 1.272)

relationship may not be restricted to XFG, although our data cannot determine whether UV-related injury accounts for the broader association.

Genetic susceptibility may also contribute to the association. Melanocytes in the eye and

skin share a neural crest origin, raising the possibility that some biological processes affecting these cells may be relevant to both organs. CYP1B1 is involved in the metabolism of endogenous estrogens and environmental carcinogens, and variants in this gene have been implicated in primary open-angle glauco-

Table 9. Sensitivity analyses for the risk of new-onset glaucoma in patients with skin neoplasms

Outcome: New-onset glaucoma	Study cohort with incident outcome event, n (%)		Hazard ratio (95% CI)
	Case patients	Control patients	
Sensitivity Analyses			
Applying various proxy-based skin neoplasm definition			
Algorithm 1	18388 (3.0)	5666 (0.9)	2.992 (2.904, 3.082)
Algorithm 2	7203 (2.2)	2927 (0.9)	2.177 (2.085, 2.273)
Algorithm 3	5328 (2.9)	1656 (0.9)	3.054 (2.890, 3.227)
Applying various wash-out periods			
12 months	24302 (1.7)	10217 (0.7)	2.000 (1.955, 2.047)
24 months	21570 (1.5)	8300 (0.6)	2.115 (2.062, 2.169)
36 months	18786 (1.3)	6721 (0.5)	2.194 (2.133, 2.256)
Applying various follow-up periods			
5 years	17063 (1.2)	8612 (0.6)	1.871 (1.823, 1.920)
10 years	24076 (1.7)	11327 (0.8)	1.893 (1.851, 1.935)
Applying various matching algorithms			
Crude model	27797 (1.8)	38688 (0.8)	2.249 (2.214, 2.284)
Matching Model 1	27243 (1.8)	14599 (1.0)	1.560 (1.529, 1.592)
Matching Model 2	26686 (1.8)	12364 (0.8)	1.840 (1.801, 1.880)

ma as well as several cancers [19]. Another potential link involves GSTM1. The null genotype reduces the capacity to detoxify reactive oxygen species and has been associated with susceptibility to glaucomatous neurodegeneration and cutaneous malignancy [8]. Although these observations offer possible biological explanations for our findings, the present study did not examine genetic variants or related molecular pathways directly.

Clinical relevance and subgroup findings

Previous studies have focused mainly on exfoliation glaucoma (XFG) and non-melanoma skin cancer, with UV exposure and LOXL1-related susceptibility proposed as possible links between the two conditions [12, 20]. Evidence for other forms of glaucoma remains limited. We found that a history of skin neoplasms was associated with diagnosed glaucoma as well as glaucoma-related conditions, including open-angle with borderline findings and anatomical narrow angle. The reverse relationship was also present, as patients with glaucoma had higher subsequent risks of melanoma and NMSC. Thus, the association observed here was not confined to XFG, although our data cannot determine the mechanisms involved.

The associations were present in both age groups. A previous study reported a stronger association between NMSC and XFG among individuals younger than 65 years (MVRR, 2.56; 95% CI, 1.62-4.05) [12], whereas we observed somewhat higher HRs among patients aged 65 years or older. This discrepancy may be related to differences in the study populations or outcome definitions. The earlier study also examined XFG specifically, making direct comparison with our broader definition of glaucoma difficult.

Variation by sex was modest. Previous studies have reported sex differences in cancer risk among patients with glaucoma, and racial variation in glaucoma burden has been described in other populations [13, 21-23]. Skin neoplasms were more strongly associated with subsequent glaucoma among women than men in our analysis, whereas the reverse association was similar between sexes. A different pattern emerged across racial groups. Glaucoma was associated with subsequent skin neoplasms among White patients, but not significantly among Black or Asian patients. Variation in baseline skin cancer susceptibility, including differences related to cutaneous melanin pigmentation, may contribute to this finding [24, 25]. Fewer events in some racial

subgroups may also have reduced statistical precision. By comparison, skin neoplasms were associated with subsequent glaucoma across all racial groups examined. These subgroup results are exploratory, and the observed differences should not be interpreted as evidence of race-specific effects.

Strengths and limitations

The large sample size and broad geographic coverage of the TriNetX network allowed us to examine the association in both temporal directions and to perform several subgroup analyses. Propensity score matching achieved adequate balance in the measured baseline characteristics between the study cohorts [26-28]. The main findings changed little when alternative case definitions were used or when longer washout periods were applied [28].

Several limitations should be considered when interpreting these findings. TriNetX relies on routinely collected EHR data, and diagnoses recorded in clinical practice may be misclassified or lack information on disease severity. Detailed cancer characteristics, such as whether a lesion was in situ or invasive, were also unavailable [26, 29]. Information on UV exposure behavior and family history was not available, and genetic background could not be adequately captured [30, 31]. Although measured baseline characteristics were balanced through propensity score matching, residual confounding cannot be excluded. Additional multivariable regression after matching was not available through the TriNetX Analytics platform. The platform also does not support ROC curve or area under the curve analyses, precluding further assessment using these measures. Surveillance bias is another concern because patients receiving care for one condition may have more opportunities for the other condition to be detected [13, 32, 33]. However, elevated risks were still observed after extending the washout period to 3 years and during longer follow-up, making surveillance alone an unlikely explanation for the observed associations.

Conclusion

We report that glaucoma and skin neoplasms were associated in both temporal directions. Patients with skin neoplasms had a higher sub-

sequent risk of glaucoma, while patients with glaucoma had a higher risk of skin neoplasms, particularly among White patients. These findings may increase awareness of the coexistence of these conditions in dermatologic and ophthalmologic practice. Further studies are needed to determine whether targeted surveillance of higher-risk patients would provide clinical benefit.

Acknowledgements

This study was partially supported by Chung Shan Medical University Hospital (CSH-2025-C-007).

Informed consent of participants was waived by the Institutional Review Board.

Disclosure of conflict of interest

None.

Address correspondence to: Hui-Chin Chang, Evidence-Based Medicine Center, Chung Shan Medical University Hospital, No. 110, Sec. 1, Jianguo N. Rd., South Dist., Taichung 402306, Taiwan. E-mail: changhc01@gmail.com

References

- [1] Wu C, Cao F, Chu B, Liu X, Zeng S, Wang Y, Feng H, Chen X, Wang N and Hou S. Global, regional, and national trends in glaucoma burden among adults aged 45 years and older, 1990-2021. *Adv Ophthalmol Pract Res* 2026.
- [2] Chang HC, Lai VP, Su YJ, Chen SJ, Wu MC and Gau SY. Alopecia areata patients are associated with increased risk of glaucoma: a multicenter, retrospective cohort study. *Front Immunol* 2026; 17: 1870857.
- [3] Li YF, Su YJ, Chang HC, Lee TY, Wu MC and Gau SY. Association between eosinophilic esophagitis and coded ocular diagnoses: a retrospective cohort study. *Life (Basel)* 2026; 16: 1156.
- [4] Su YJ, Gau SY and Shiue YL. Risk of new-onset glaucoma in people with carpal tunnel syndrome: a global-federated, multicenter retrospective cohort study. *Int J Med Sci* 2026; 23: 661-669.
- [5] Zhou L, Zhong Y, Han L, Xie Y and Wan M. Global, regional, and national trends in the burden of melanoma and non-melanoma skin cancer: insights from the global burden of disease study 1990-2021. *Sci Rep* 2025; 15: 5996.
- [6] Xu W, Zhang F and Huang J. Identification and validation of oxidative stress signature genes

- in the trabecular meshwork of glaucoma. *Sci Rep* 2025; 15: 31260.
- [7] Xian D, Lai R, Song J, Xiong X and Zhong J. Emerging perspective: role of increased ROS and redox imbalance in skin carcinogenesis. *Oxid Med Cell Longev* 2019; 2019: 8127362.
 - [8] Izzotti A, Saccà SC, Cartiglia C and De Flora S. Oxidative deoxyribonucleic acid damage in the eyes of glaucoma patients. *Am J Med* 2003; 114: 638-646.
 - [9] Di Girolamo N. Signalling pathways activated by ultraviolet radiation: role in ocular and cutaneous health. *Curr Pharm Des* 2010; 16: 1358-1375.
 - [10] Brombin A and Patton EE. Melanocyte lineage dynamics in development, growth and disease. *Development* 2024; 151: dev201266.
 - [11] Johansson PA, Palmer JM, McGrath L, Warrier S, Hamilton HR, Beckman T, D'Mellow MG, Brooks KM, Glasson W, Hayward NK and Pritchard AL. Germline variants in patients affected by both uveal and cutaneous melanoma. *Pigment Cell Melanoma Res* 2025; 38: e13199.
 - [12] Kang JH, VoPham T, Laden F, Rosner BA, Wirostko B, Ritch R, Wiggs JL, Qureshi A, Nan H and Pasquale LR. Cohort study of nonmelanoma skin cancer and the risk of exfoliation glaucoma. *J Glaucoma* 2020; 29: 448-455.
 - [13] Jung Y, Han K, Na KS, Kim GH, Ha M, Paik JS and Moon JI. Risk of cancer in patients with glaucoma: a nationwide population-based cohort study. *Sci Rep* 2020; 10: 8170.
 - [14] Liao WC, Su YJ, Li YF, Lo SW, Lee CY, Chang HC and Gau SY. Human papillomavirus infection is associated with increased risk of glaucoma: evidence in an electronic health record study. *Ophthalmology* 2025; 132: 1161-1168.
 - [15] Gau SY, Lo SW, Hsu C, Chen SJ, Zuberbier T and Chang HC. Human papillomavirus infection is associated with increased risk of new-onset hidradenitis suppurativa: a population-based cohort study. *J Am Acad Dermatol* 2025; 92: 444-451.
 - [16] Wu CL, Su YJ, Chang HC, Wu YH, Jhang YS, Wu MC, Chen SJ and Gau SY. Risk of hidradenitis suppurativa in patients with carpal tunnel syndrome: a population-based cohort study. *In Vivo* 2025; 39: 2931-2939.
 - [17] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP and STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg* 2014; 12: 1495-1499.
 - [18] Dai J, Suo L, Xian H, Pan Z and Zhang C. Investigating the impact of Sun/UV protection and ease of skin tanning on the risk of pseudoexfoliation glaucoma: a mendelian randomization study. *Invest Ophthalmol Vis Sci* 2023; 64: 4.
 - [19] Alsoubait A, Aldossary W, Rashid M, Algamdi A and Alirfaei BM. CYP1B1 gene: implications in glaucoma and cancer. *J Cancer* 2020; 11: 4652-4661.
 - [20] Ozaki M. Mechanisms of glaucoma in exfoliation syndrome. *J Glaucoma* 2018; 27 Suppl 1: S83-S86.
 - [21] Ehrlich JR, Burke-Conte Z, Wittenborn JS, Saadine J, Omura JD, Friedman DS and Flaxman AD. Prevalence of glaucoma among US adults in 2022. *JAMA Ophthalmol* 2024; 142: 1046-1053.
 - [22] Jayaram H, Kolko M, Friedman DS and Gazzard G. Glaucoma: now and beyond. *Lancet* 2023; 402: 1788-1801.
 - [23] Ko F, Boland MV, Gupta P, Gadkaree SK, Vitale S, Guallar E, Zhao D and Friedman DS. Diabetes, triglyceride levels, and other risk factors for glaucoma in the national health and nutrition examination survey 2005-2008. *Invest Ophthalmol Vis Sci* 2016; 57: 2152-2157.
 - [24] Ahmed S, van Bodegraven B, Proby C, Harwood CA, Ascott A, Gran S, Ho B, Arder-Jones MR, Millington GWM, Mistry K, Sommerlad M, Vernon S and Venables ZC; BAD-NDRS Working Party Group. Ethnicity and the epidemiology of skin cancer incidence: a national retrospective population-based study in England, 2013-20. *Br J Dermatol* 2026; 194: 273-282.
 - [25] Gurung NK, Alsoudi AF, Gautam P, Kandel RP, O'Brien KS, Wittberg DM, Moe CA, Stamper RL and Keenan JD. Cutaneous melanin and glaucoma: a case control study. *Curr Eye Res* 2021; 46: 1428-1431.
 - [26] Ayoubi M, Sayed MS, Khodeiry MM, Elhusseiny AM and Lee RK. Big data in ophthalmology: comparative databases and research applications. *Curr Opin Ophthalmol* 2026; 37: 81-88.
 - [27] Loke YK and Mattishent K. Propensity score methods in real-world epidemiology: a practical guide for first-time users. *Diabetes Obes Metab* 2020; 22 Suppl 3: 13-20.
 - [28] Rassen JA, Blin P, Kloss S, Neugebauer RS, Platt RW, Pottegård A, Schneeweiss S and Toh S. High-dimensional propensity scores for empirical covariate selection in secondary database studies: planning, implementation, and reporting. *Pharmacoepidemiol Drug Saf* 2023; 32: 93-106.
 - [29] Gavrilov-Yusim N and Friger M. Use of administrative medical databases in population-based research. *J Epidemiol Community Health* 2014; 68: 283-287.
 - [30] Nørgaard M, Ehrenstein V and Vandenbroucke JP. Confounding in observational studies based on large health care databases: problems

- and potential solutions - a primer for the clinician. *Clin Epidemiol* 2017; 9: 185-193.
- [31] Reiffel JA. Propensity score matching: the 'Devil is in the details' where more may be hidden than you know. *Am J Med* 2020; 133: 178-181.
- [32] Small J, Wallace K, Hill EG, Thiers BH, Leach BC and Alberg AJ. A cohort study of personal and family history of skin cancer in relation to future risk of non-cutaneous malignancies. *Cancer Causes Control* 2019; 30: 1213-1221.
- [33] Gau SY. Antibiotic exposures could lead to overestimation of incident outcomes-a commentary on "Prevalence of type 2 inflammatory diseases in pediatric patients with atopic dermatitis: real-world evidence". *J Am Acad Dermatol* 2022; 86: e219.