Risk of Non-infectious Uveitis with Metformin Therapy in a Large Healthcare Claims Database

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Abstract

Purpose: To determine if metformin is associated with non-infectious uveitis (NIU).

Methods: Patients in an insurance claims database who initiated metformin (n=359,139) or other oral anti-diabetic medications (n=162,847) were followed for NIU development. Both cohort and case-control analyses were performed to assess differing exposure lengths using Cox and conditional logistic regression, respectively.

Results: The hazard ratio (HR) for incident NIU was not significantly different between the metformin and non-metformin cohorts [HR=1.19, 95% Confidence Interval (CI): 0.92-1.54, P=0.19]. The case-control analysis similarly showed no association between any metformin use 2 years before the outcome date and NIU [Odds ratio (OR)=0.64, 95% CI: 0.39-1.04, P=0.07]. However, there was a protective association between cumulative metformin duration [445-729 days adjusted OR (aOR)=0.49, 95% CI: 0.27-0.90, P=0.02) and dosage (>390,000 mg aOR=0.44, 95% CI: 0.25-0.78, P=0.001] compared with no metformin use.

Conclusions: Our results suggest metformin use for longer durations may be protective of NIU onset.

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Uveitis is a significant cause of permanent vision loss[1-3] accounting for up to 10% of blindness.[3-5] Etiologically, uveitis is categorized as infectious or non-infectious (immune-mediated), with most cases in developed countries being non-infectious.[6] As uveitis often affects younger people of working age, the disease is responsible for longer durations of blindness and a higher per case cost to society compared to other age-associated ocular diseases.[7] Though the human and economic costs correlated with the disease are severe, because of the challenges of conducting studies for less common diseases, few population-based studies currently exist that identify factors that affect uveitis incidence.[8-11]

Non-infectious uveitis (NIU) is typically treated with corticosteroids and/or systemic immunomodulatory agents.[12] These are effective therapies but can also be associated with serious adverse effects, although such side effects are uncommon when treatment occurs according to expert panel recommendations.[13,14] A notable proportion of NIU cases are recurrent or chronic, requiring effective secondary prevention strategies to prevent vision loss.[9,15]

Metformin, an oral drug commonly prescribed for treating type 2 diabetes mellitus (T2DM), is known to have anti-inflammatory effects regardless of one's diabetes status.[16] In addition, previous studies have demonstrated that a metformin analog can prevent uveitis onset in two animal models.[17,18] These preliminary findings suggest metformin could modify uveitis risk. To date, no human studies of metformin and uveitis have been performed. As a relatively safe and inexpensive medication, metformin could be a good candidate as adjunctive therapy to reduce incidence of uveitis, to induce remission, or to prevent relapse.[19] The purpose of this study is to utilize a large dataset assembled from a United States (US) medical claims database to determine whether use of metformin is associated with a lower risk of NIU incidence.

Methods

Study Population

Optum's Clinformatics™ Data Mart Database contains the de-identified medical claims of all beneficiaries in a large US insurer's commercial and Medicare Advantage administrative database and was used for this study. Included within the database are all outpatient medical claims (office visits, associated diagnoses, and in-office procedures), all pharmaceutical prescriptions filled, all laboratory testing claims (including selected results) and demographic data for each beneficiary during their enrollment in the insurance plan. The subset of data available for this study included all claims from January 1, 2000 to June 30, 2019. The Massachusetts Eye and Ear Infirmary's and University of Pennsylvania's Institutional Review Boards deemed this study exempt from review due to the de-identified nature of the data.

Study Design

We planned *a priori* two parallel analyses which were performed to examine the risk of NIU with regards to metformin use. First, we conducted a cohort study using similar methodology to a previous study evaluating the risk of uveitis associated with female

hormonal therapy.[20] The first analysis assessed a new user cohort study design with exposure status determined at baseline to most closely emulate a clinical trial with per protocol analysis using observational data. However, this study design can be problematic due to low statistical power if patients are only adherent to their baseline exposure for a short period of time, particularly for less common outcomes like uveitis and in situations where prolonged exposure is required to elicit a benefit. Therefore, as an additional analysis, we also performed a case-control study (described in detail below) using the same population identified for the cohort study.

Cohort Study

A new user active comparator cohort design was used to create cohorts from patients newly exposed to metformin (metformin cohort) or other oral anti-diabetic medications (non-metformin cohort). Patients who started a combination drug that included metformin were considered metformin users. All patients 18 years old or over who filled a prescription for an oral anti-diabetic medication were eligible for inclusion. The index date was defined as the date the first prescription for an oral anti-diabetic medication was filled. Patients with a prior diagnosis of infectious uveitis or NIU were also excluded. Please see eTable 1 in the Supplement for a full list of the International Classifications of Diseases (ICD), Ninth and Tenth Revisions (ICD-9 and ICD-10) codes used. Patients with less than one-year enrollment in the insurance plan (to ensure new user status) or who did not have a visit to an eye care provider prior to the index date (to reduce the possibility of undiagnosed subclinical uveitis) were excluded. In addition, to reduce variability in T2DM disease severity, patients were excluded if they had a prescription for insulin prior to the index date.

To account for differences between individuals taking metformin vs. other oral anti-diabetic medications, a propensity score for having been prescribed metformin was created using multivariable logistic regression. Covariates included in the propensity score were age at the index date, gender, race, education level, household income, geographic region of the country, index year, history of hypertension, hypercholesterolemia, chronic kidney disease, or systemic disease associated with uveitis, smoking status, the diabetes complications severity index (DCSI), number of health care visits within 1 year of index date, and hemoglobin A1c (HbA1c) level within 1 year of index date (with the closest to the index being used if more than one was available). The DCSI is a diabetes disease severity scale derived from outpatient ICD codes that are divided into six diabetes-related complication categories, each scored $0 - 2$.[21] While smoking often is not directly coded in administrative datasets, we applied an approach using smoking diagnosis codes, use of antismoking drugs and Current Procedural Terminology (CPT) codes for smoking cessation counseling. This method has previously found smoking rates in administrative databases of 10-11%, similar to the general population.[22] To account for differences in these baseline covariates between the metformine and non-metformin cohorts, inverse probability of treatment weighting (IPTW) using the estimated propensity scores was performed in all subsequent analyses.

The primary outcome for the cohort analysis was incident NIU defined as two ICD-9 or ICD-10 codes for NIU within a 120-day period. The date of incidence was set to the date of the second confirming NIU code. In addition, to increase the likelihood of our cases being

truly "incident", we required patients who developed uveitis to have at least 2 years in the dataset prior to the index date without a diagnosis of uveitis for inclusion in the study.[23] Sub-analyses focusing on anatomic subtype of uveitis were also performed. The different anatomic subtypes of uveitis are indicated in eTable 1.

A secondary outcome definition in which a prescription for a corticosteroid or a CPT code for an intraocular/periocular corticosteroid injection within 120 days of the uveitis code was used instead of requiring a second uveitis code as in our primary outcome definition. This approach has been used previously,[20,24,25] and the rationale for this outcome is to capture a slightly different and partially overlapping set of uveitis patients who were seen once for NIU and may have improved significantly with corticosteroid treatment and were not seen again due to resolution of uveitis. For this group, the date of incidence was set to the date of the corticosteroid treatment.

Case-Control Study

As a sensitivity analysis, we conducted a case-control study within the cohort of patients used for the primary analysis. Cases of uveitis were defined using the primary uveitis outcome definition. The date of the second diagnosis code was defined as the outcome date. Controls were randomly selected using incidence density sampling at a 20:1 ratio of controls to cases, and controls were assigned the outcome date of their matched case.

Statistical Analysis Methods

For the cohort study, data were analyzed using Cox proportional hazards regression modeling with IPTW.[26] Cumulative incidence of NIU was summarized using Kaplan-Meier curves with IPTW. In this model, patients were censored at disenrollment from the insurance plan, one year after the index date, any occurrence of a cohort exclusion criterion (including diagnosis of infectious uveitis), use of metformin in the non-metformin cohort or vice versa, or at the end of a 30-day gap in oral diabetic prescription coverage. To reduce potential misclassification of postoperative inflammation as uveitis, all patients who had an intraocular surgery were censored at the time of surgery. All patients were censored at 365 days.

For the case-control study, conditional logistic regression adjusting for demographic and clinical covariates was performed to examine the association between NIU and metformin use within 2 years before outcome date. This time point was chosen to examine putative long term effects of metformin on uveitis. An ordinal categorical model was used to calculate Wald p-values for metformin dose and duration effects. Patients using other classes of diabetic medications within 45 days of outcome date were considered active users of those medications and included in the multivariate analysis.

SAS version 9.4 (SAS Institute Inc., Cary, NC) software was used for all statistical analyses. We defined statistical significance using a two-sided alpha = 0.025, as recommended for exploratory, hypothesis-generating studies like this one.[27]

Results

Cohort Study

There were 359,139 new users of metformin (metformin cohort) and 162,847 new users of other oral anti-diabetic medications (non-metformin cohort) who met eligibility criteria. eFigure 1 delineates the inclusion and exclusion criteria for the cohorts. Table 1 compares the baseline characteristics of the metformin cohort and the non-metformin cohort both before and after IPTW. As noted in the table, IPTW achieved excellent balance between the cohorts for most variables (less than 0.1 standardized mean difference after weighting). The metformin cohort was followed for a median of 166 days [Interquartile range (IQR): 64, 365)] after the index date compared to a median of 130 days (IQR: 60, 351) in the non-metformin cohort.

Primary Outcome

Figure 1a shows the Kaplan-Meier curves for incident uveitis diagnosis. For the primary outcome, the metformin cohort had 230 events over 195,300 years (unweighted incidence rate=0.12 per 100 person-years) and the non-metformin cohort had 104 events over 80,660 years (unweighted incidence rate=0.13 per 100 person-years). Table 2 provides the results for the Cox regression analyses for the primary outcome. NIU incidence was not significantly different between the metformin and non-metformin cohorts [Hazard Ratio (HR) = 1.19, 95% Confidence Interval (CI): 0.92-1.54, P=0.19]. In the sub-analyses based on uveitis anatomic subtype, no statistically significant difference in the rate of incident anterior uveitis (HR=1.33, 95% CI: 0.97-1.83, P=0.08), intermediate uveitis (HR=1.71, 95% CI: 0.52-5.60, P=0.38) or posterior/panuveitis (HR=0.63, 95% CI: 0.10-4.07, P=0.63) was found.

Secondary Outcome

Figure 1b provides the Kaplan-Meier curves for the pre-specified secondary outcome analysis where the outcome definition included a NIU diagnosis code and corticosteroid prescription. In this analysis, the metformin cohort had 237 events over 195,309 years (unweighted incidence rate=0.12 per 100 person-years) and the non-metformin cohort had 131 events over 80,651 years (unweighted incidence rate=0.16 per 100 person-years). Table 3 shows the results using this outcome. The hazard for NIU was not significantly different between the metformin and non-metformin cohorts (HR=0.97, 95% CI: 0.75-1.24, P=0.80). No significant differences were found based on uveitis subtype either (anterior uveitis - HR=1.12, 95% CI: 0.83-1.52, P=0.46; intermediate uveitis - HR=0.48, 95% CI: 0.19-1.23, P=0.12; posterior/panuveitis - HR=0.96, 95% CI: 0.20-4.64, P=0.95).

Case-Control Analysis

For the primary outcome definition of NIU, we identified 502 NIU cases and selected 10,040 controls. eTable 2 presents the characteristics of these cases and controls. Table 4 presents the results of the conditional logistic regression analysis comparing the use of metformin within 2 years prior to the index date between cases and controls. NIU cases had a non-statistically significant lower odds of having any metformin use within the 2

years before the index date [adjusted odds ratio (aOR) = 0.64, 95% CI: 0.39–1.04, P=0.07]. However, when assessing duration of metformin use, a linear trend analysis found lower odds of uveitis with longer use when compared to the reference group of no metformin use (445-729 days of use - aOR=0.49; 95% CI: 0.27-0.90, trend P=0.02). Assessment of cumulative dose found a similar trend with higher metformin doses being associated with a lower odds of uveitis when compared to the reference group of no metformin use (165,001 – 390,000 mg - aOR=0.57; 95% CI: 0.34-0.98; >390,000 mg - aOR=0.44; 95% CI: 0.25-0.78, P=0.001).

Discussion

We performed two main types of analyses to assess the association between metformin and NIU. The first was a cohort analysis which compared new users of metformin to new users of other oral anti-diabetic medications. Our primary outcome definition of uveitis that used multiple diagnosis codes within 120 days found no difference in the hazard (HR=1.19) based on exposure. Analyses using our secondary outcome definition of diagnosis plus use of a corticosteroid was also not statistically significant. Of note, the median follow up time in the metformin cohort was only 166 days and all patients were censored after 365 days.

Recognizing the possible limitation of our method to detect differences for longer metformin exposure, we also performed a case-control analysis that allowed for two years of assessment. When examining the association with any metformin use within two years prior to the outcome date, there was no statistically significant difference between uveitis cases and controls. However, a statistically significantly decreased odds of uveitis was found in assessing (1) longer duration of metformin use and (2) higher metformin cumulative doses. The odds of uveitis decreased incrementally with each quartile of higher cumulative metformin duration and dose (duration P=0.02 and dose P=0.001). Onset of NIU is an uncommon event and the triggers of uveitis onset, which are not well understood, may result from haphazardly occurring trigger events over time. These circumstances may explain why the effects of a putatively protective medication like metformin may only be detectable over longer periods of exposure, which would allow a large number of these trigger events to occur and be suppressed by metformin to detect differences between groups.

Animal studies have suggested that a related agent, aminoimidazole carboxamide ribofuranoside (AICAR), can attenuate uveitis in animal models through reducing expression of pro-inflammatory cytokines and inhibiting T-cell proliferation.[17,18] Both metformin and AICAR activate AMP-activated protein kinase (AMPK) and have been shown to exert anti-inflammatory activity in many experimental models by reducing oxidative stress and interleukin (IL)-1 beta-induced pro-inflammatory cytokines (IL-6 and IL-8) production in macrophages and endothelial cells.[28] It is possible the protective association between longer-term use of metformin and lower uveitis incidence are due to a similar physiologic pathway.

An additional question is whether the hypoglycemic effects of metformin may contribute to its impact on NIU risk. Randomized controlled trials have shown that metformin achieves lower HbA1c levels than glyburide, a common sulfonylurea, but higher HbA1c levels than

rosiglitazone, a common thiazolidinedione.[29] Sulfonylureas and thiazolidinediones made up nearly 70% of the medications in non-metformin cohort. Given its intermediate effects on blood glucose, it is less likely that the hypoglycemic effects of metformin account for the difference in NIU risk.

Some limitations to our study should be noted. First, although we made efforts to reduce differences in disease severity through controlling for the DCSI, HbA1c level, and insulin use after the index date, it is still possible that the common practice of using metformin as a first line therapy for T2DM treatment allowed for unmeasured confounding. We did not have a complete dataset for HbA1c; we had HbA1c on approximately 30% and 19% of patients in the metformin and non-metformin cohorts, respectively, and therefore could not completely account for differences in hyperglycemia severity in propensity scores. Also, we cannot be certain that patients who were prescribed metformin, actually took the metformin. This, however, would cause a misclassification bias which biases to a null (no difference) finding if non-adherence is non-differential with respect to other patient characteristics. This could in fact explain why only prolonged metformin use was associated with a protective effect with respect to uveitis.

The database does not allow independent verification of the accuracy of the ICD codes with medical chart level data. However, ICD codes have been shown to correlate highly with the corresponding clinical diagnosis and are widely used in health research, including in the ophthalmic literature.[22,30-33] While the dataset has the strength of being a national, multiethnic data set, the insurance-based nature may limit the generalizability to patients not covered by this specific insurance company. The majority of patients in this analysis had T2DM (apart from a small subset that might have received metformin for a non-T2DM indication such as polycystic ovarian syndrome), whereas the majority of patients with uveitis do not have T2DM. This may limit the generalizability of the findings. Despite this dataset being the largest of its kind to be used for risk factor studies in uveitis, the rare nature of uveitis is still evident in the small number of patients in the analyses of the rarer anatomic subtypes of uveitis, intermediate and posterior/panuveitis.

In summary, our analysis suggested that metformin may be protective after prolonged periods of exposure for incident uveitis. While not all analyses were significant, the duration of exposure and cumulative dose results suggest that metformin as a protective agent warrants further investigation, particularly because it is a generally safe agent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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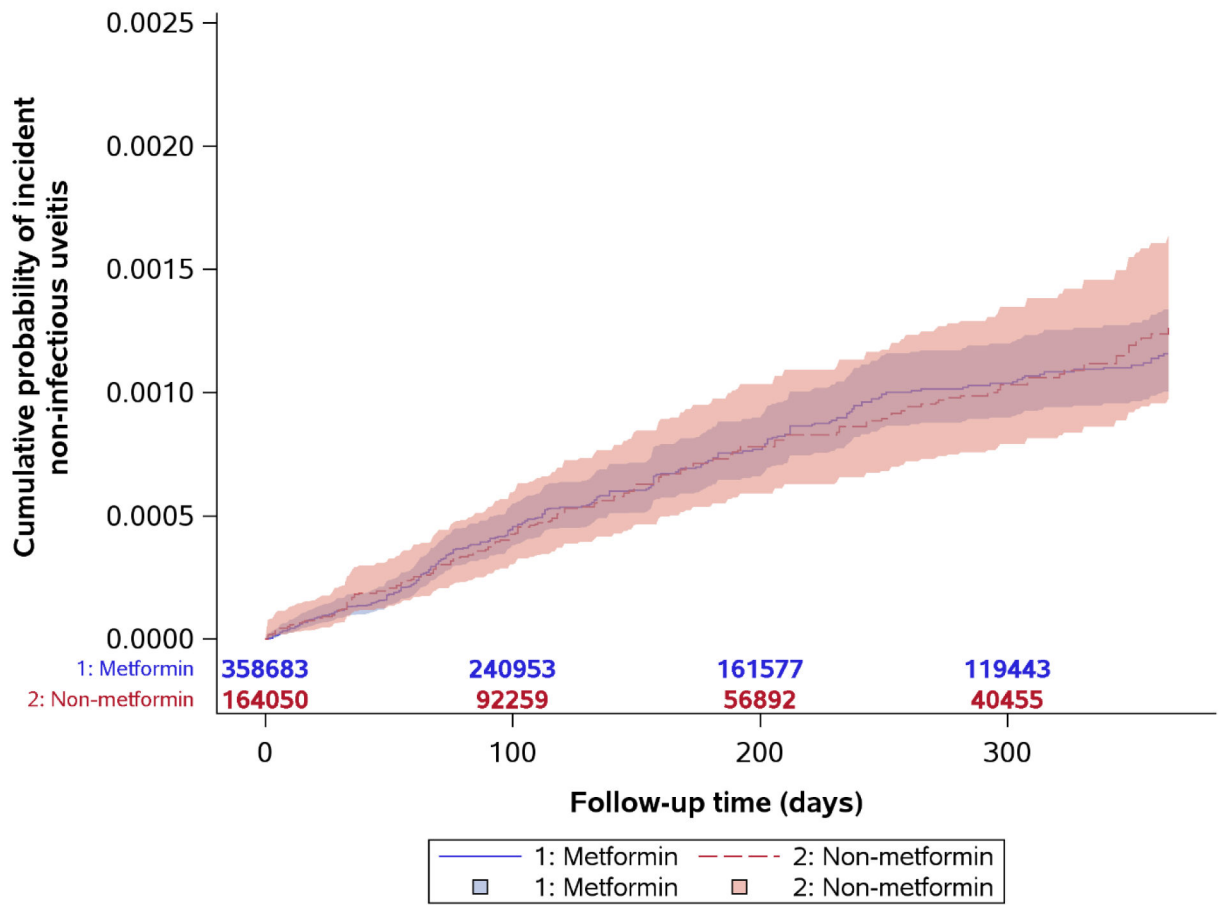
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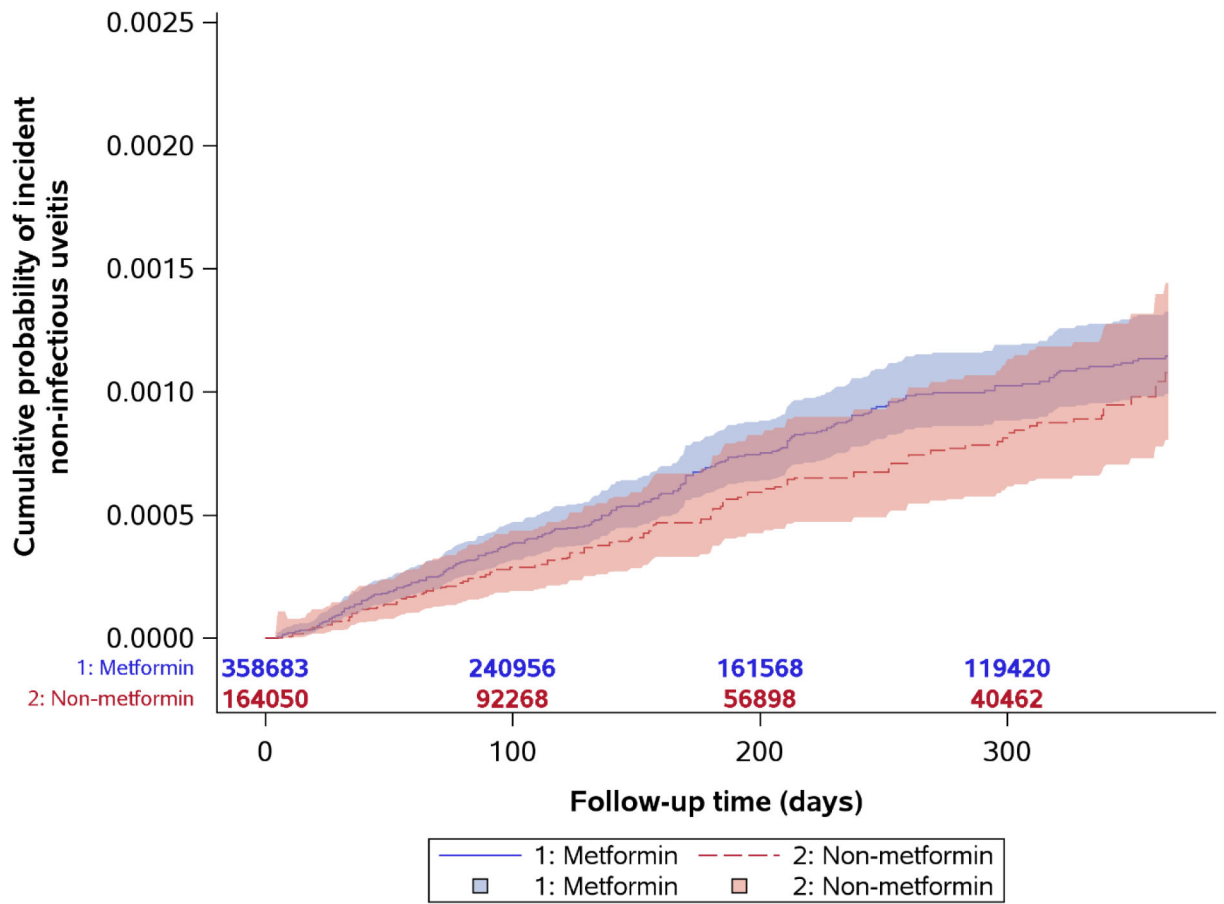
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Figure 1.
Kaplan-Meier curves for incident non-infectious uveitis by metformin exposure status

Table 1.

Comparison of baseline characteristics between metformin and non-metformin cohorts before and after inverse probability of treatment weighting (IPTW)

	Non-metformin cohort	Metformin cohort	Standardized Mean difference	Weighted non-metformin users	Weighted metformin users	Standardized Mean difference
Age [Mean years (SD)]	64.3 (13.3)	61.2 (13.9)	−0.226	61.5 (14.7)	62.1 (13.7)	0.042
Gender (Female)	86928 (53%)	201210 (56%)	0.054	92850 (57%)	198987 (55%)	0.023
Race			0.103			0.005
White	105010 (64%)	226967 (63%)		103902 (63%)	227596 (63%)	
Black	21436 (13%)	42131 (12%)		19835 (12%)	43630 (12%)	
Hispanic	12940 (8%)	37608 (10%)		16083 (10%)	35011 (10%)	
Asian	5294 (3%)	14349 (4%)		6257 (4%)	13556 (4%)	
Unknown	18167 (11%)	38084 (11%)		17972 (11%)	38891 (11%)	
Education level			0.084			0.002
High School Diploma	52513 (32%)	104044 (29%)		49095 (30%)	107502 (30%)	
<Bachelor Degree	77196 (47%)	177759 (49%)		80029 (49%)	175072 (49%)	
Bachelor Degree	18593 (11%)	47068 (13%)		20595 (13%)	45003 (13%)	
Unknown	14545 (9%)	30268 (8%)		14331 (9%)	31106 (9%)	
Household income			0.244			0.004
<$40K	32530 (20%)	69134 (19%)		31960 (20%)	69928 (20%)	
$40K - $49K	9317 (6%)	21388 (6%)		9652 (6%)	21126 (6%)	
$50K - $59K	9668 (6%)	23658 (7%)		10412 (6%)	22945 (6%)	
$60K - $74K	12862 (8%)	32714 (9%)		14321 (9%)	31436 (9%)	
$75K - $99K	16988 (10%)	46178 (13%)		19727 (12%)	43375 (12%)	
$100K+	26342 (16%)	79362 (22%)		33401 (20%)	72767 (20%)	
Unknown	55140 (34%)	86705 (24%)		44576 (27%)	97106 (27%)	
Geographic location			0.165			0.009
Upper Midwest	40283 (25%)	87351 (24%)		39811 (24%)	86989 (24%)	
Southern Midwest	29571 (18%)	68354 (19%)		31409 (19%)	67819 (19%)	
Northeast	16332 (10%)	36690 (10%)		16475 (10%)	36473 (10%)	
Mountain	8525 (5%)	28627 (8%)		11600 (7%)	25511 (7%)	
Pacific	11992 (7%)	34150 (10%)		14692 (9%)	31649 (10%)	
South Atlantic	55648 (34%)	102824 (29%)		49561 (30%)	109124 (30%)	
Unknown	496 (0%)	1143 (0%)		502 (0%)	1119 (0%)	
Index year			0.816			0.010
2001	4249 (3%)	3803 (1%)		2522 (2%)	5591 (2%)	
2002	5703 (4%)	3872 (1%)		2996 (2%)	6647 (2%)	
2003	6348 (4%)	3415 (1%)		3035 (2%)	6585 (2%)	
2004	8793 (5%)	1670 (0%)		3259 (2%)	6979 (2%)	
2005	14049 (9%)	7259 (2%)		6616 (4%)	14591 (4%)	
2006	13323 (8%)	13365 (4%)		8274 (5%)	18219 (5%)	
2007	14650 (9%)	16468 (5%)		9771 (6%)	21455 (6%)	

	Non-metformin cohort	Metformin cohort	Standardized Mean difference	Weighted non-metformin users	Weighted metformin users	Standardized Mean difference
2008	15553 (10%)	15746 (4%)		9794 (6%)	21574 (6%)	
2009	10210 (6%)	27743 (8%)		12034 (7%)	26157 (7%)	
2010	11335 (7%)	23504 (7%)		10881 (7%)	23974 (7%)	
2011	9236 (6%)	27331 (8%)		11525 (7%)	25170 (7%)	
2012	8170 (5%)	21537 (6%)		9235 (6%)	20378 (6%)	
2013	8273 (5%)	26150 (7%)		10835 (7%)	23655 (7%)	
2014	6008 (4%)	23801 (7%)		9518 (6%)	20509 (6%)	
2015	6733 (4%)	31343 (9%)		11879 (7%)	26156 (7%)	
2016	5441 (3%)	30317 (8%)		11440 (7%)	24584 (7%)	
2017	6247 (4%)	32645 (9%)		12433 (8%)	26774 (7%)	
2018	5380 (3%)	31100 (9%)		11453 (7%)	25100 (7%)	
2019	3146 (2%)	18070 (5%)		6551 (4%)	14586 (4%)	
Hypertension	132323 (81%)	276663 (77%)	−0.104	126867 (77%)	280673 (78%)	0.022
High cholesterol	133671 (82%)	284980 (79%)	−0.069	130186 (79%)	287690 (80%)	0.021
Uveitis-associated diseases [*]	20445 (13%)	40028 (11%)	−0.044	19268 (12%)	41903 (12%)	−0.002
Smokers	29484 (18%)	78669 (22%)	0.095	33911 (21%)	74307 (21%)	0.001
Chronic kidney disease			0.183			0.002
No disease	123113 (76%)	295642 (82%)		131614 (80%)	287553 (80%)	
Chronic kidney disease	35060 (22%)	59273 (17%)		29678 (18%)	65135 (18%)	
End-stage renal disease	4674 (3%)	4224 (1%)		2758 (2%)	5996 (2%)	
Diabetes Complication Severity Index [Mean (SD)]	1.8 (2.1)	1.3 (1.7)	−0.285	1.4 (1.8)	1.5 (1.8)	0.009
N of health care visits within 1 year before index date [Mean (SD)]	9.1 (6.9)	7.7 (6.2)	−0.202	8.2 (6.4)	8.2 (6.7)	−0.009
HbA1c within 1 year before index date [Mean (SD)] [†]	7.3 (1.6)	7.0 (1.4)	−0.203	7.1 (1.8)	7.1 (1.4)	0.018

[*] A list of uveitis-associated diseases can be found in eTable 1.

[†] HbA1c was available on 30% of patients in the metformin cohort and 19% of patients in the non-metformin cohort.

K = thousand

Table 2.

Cox regression results of primary outcome weighted by IPTW

Cohort	N	Person-years	N of events	KM-estimated cumulative incidence at 1 year	Hazard Ratio (95% CI)	P value
		Unweighted summary statistics		**Propensity score-weighted results**		
Any Uveitis						0.19
Non-metformin	162847	80660	104	0.0011	REF	
Metformin	359139	195300	230	0.0011	1.19 (0.92, 1.54)	
Anterior Uveitis						0.08
Non-metformin	162847	80670	66	0.0007	REF	
Metformin	359139	195320	164	0.0008	1.33 (0.97, 1.83)	
Intermediate Uveitis						0.38
Non-metformin	162847	80670	4	0.00004	REF	
Metformin	359139	195320	11	0.00005	1.71 (0.52, 5.60)	
Posterior/Panuveitis						0.63
Non-metformin	162847	80670	2	0.00002	REF	
Metformin	359139	195320	3	0.00001	0.63 (0.10, 4.07)	

KM = Kaplan Meier, IPTW = inverse probability of treatment weighting

Table 3.

Cox regression results of secondary outcome weighted by IPTW

Cohort	N	Person-years	N of events	KM-estimated cumulative incidence at 1 year	Hazard Ratio (95% CI)	P value
		Unweighted summary statistics		Propensity-score weighted results		
Any Uveitis						0.80
Non-metformin	162847	80651	131	0.0013	REF	
Metformin	359139	195309	237	0.0012	0.97 (0.75, 1.24)	
Anterior Uveitis						0.46
Non-metformin	162847	80662	77	0.0007	REF	
Metformin	359139	195326	158	0.0008	1.12 (0.83, 1.52)	
Intermediate Uveitis						0.12
Non-metformin	162847	80662	12	0.00012	REF	
Metformin	359139	195326	9	0.00004	0.48 (0.19, 1.23)	
Posterior/Panuveitis						0.95
Non-metformin	162847	80662	3	0.00004	REF	
Metformin	359139	195326	7	0.00004	0.96 (0.20, 4.64)	

KM = Kaplan Meier, IPTW = inverse probability of treatment weighting

Table 4.

Conditional logistic regression analysis for association between metformin use 2 years before outcome date and incident non-infectious uveitis

Use of metformin within 2 years before index date	Case N=502 n (%)	Control N=10,040 n (%)	Adjusted Odds Ratio (95% CI)*	Adjusted P value*¶
No	167 (33%)	2871 (29%)	REF	0.07
Yes	335 (67%)	7169 (71%)	0.64 (0.39, 1.04)	
Cumulative duration (days)£				
0	167 (33%)	2871 (29%)	REF	0.02
4-68	90 (18%)	1795 (18%)	0.76 (0.43, 1.34)	
69-176	86 (17%)	1796 (18%)	0.69 (0.40, 1.20)	
177-444	81 (16%)	1780 (18%)	0.60 (0.34, 1.06)	
445-729	78 (16%)	1797 (18%)	0.49 (0.27, 0.90)	
Cumulative dosage (mg)£				
0	167 (33%)	2871 (29%)	REF	0.001
2,000 – 60,000	95 (19%)	1843 (18%)	0.81 (0.46, 1.41)	
60,001 – 165,000	89 (18%)	1725 (17%)	0.76 (0.45, 1.31)	
165,001 – 390,000	82 (16%)	1799 (18%)	0.57 (0.34, 0.98)	
390,001 – 1,777,350	69 (14%)	1801 (18%)	0.44 (0.25, 0.78)	

*Adjusted for age, gender, race, education, income, geographic location, history of hypertension, hypercholesterolemia, chronic kidney disease, uveitis-associated diseases, smoking, diabetes complications severity index, use of insulin, use of other diabetic medication within 45 days before the index date (sulfonylurea, thiazolidinedione, alpha glucosidase inhibitor, meglitinide, dipeptidyl peptidase 4 inhibitor, bile sequestrant), HbA1c level and number of health care visits within 1 year before index date.

£Categories based on quartiles.

¶Linear trend p value

REF= reference group