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The Association Between Metformin Use and New-Onset *ICD* Coding of Geographic Atrophy

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Purpose. Metformin has been suggested to protect against the development of age-related macular degeneration (AMD) in multiple observational studies. However, the association between metformin and geographic atrophy (GA), a debilitating subtype of AMD, has not been analyzed.

Methods. We conducted a case-control study of patients ages 60 years and older with new-onset *International Classification of Diseases* (*ICD*) coding of GA in the Merative MarketScan Commercial and Medicare Databases between 2017 and 2021. Cases were matched with propensity scores estimated by age, region, hypertension, and Charlson Comorbidity Index to a control without GA of the same year. Exposure to metformin was assessed for cases and controls in the year prior to their index visit. Conditional multivariable logistic regression, adjusting for AMD risk factors, was used to calculate odd ratios and 95% confidence intervals (CIs). This study design and analysis were repeated in a sample of patients without diabetes.

Results. In the full sample, we identified 10,505 cases with GA and 10,502 matched controls without GA. In total, 1149 (10.9%) cases and 1277 (12.2%) controls were exposed to metformin, and in multivariable regression, metformin decreased the odds of new-onset *ICD* coding of GA by 12% (95% CI, 0.79–0.99). In the sample of patients without diabetes, we identified 7611 cases with GA and 7608 matched controls without GA. Twenty-nine (0.4%) cases and 63 (0.8%) controls were exposed to metformin, and in multivariable regression, metformin decreased the odds of new-onset *ICD* coding of GA by 47% (95% CI, 0.33–0.83).

Conclusions. Metformin may hold promise as a noninvasive, alternative agent to prevent the development of GA. This finding is notable due to shortcomings in recently approved therapeutics for GA and metformin's overall ease of use and few adverse effects. Additional studies are required to explore our findings further and motivate a clinical trial.

Keywords: AMD, metformin, geographic atrophy, drug repurposing, retina

Age-related macular degeneration (AMD) affects an estimated 20 million Americans, including approximately 1.5 million individuals who have late-stage AMD.[1] Late-stage AMD is classically divided into two forms: (1) wet AMD, which is defined by the presence of choroidal neovascularization, and (2) geography atrophy (GA), which is characterized by progressive and irreversible photoreceptor and retinal pigment epithelium (RPE) loss.[2] Wet AMD and GA are both major contributors to severe vision loss in the United States; wet AMD accounts for almost 90% of blindness in patients with any form of AMD,[3] and approximately 40% of patients with GA ultimately develop blindness.[4] While anti-VEGF injections have revolutionized the treatment of wet AMD,[5,6] up to 40% of patients treated with anti-VEGF injections develop GA within 5 years.[7,8] Developments for treating and preventing GA have been slower to emerge. In 2023, the US Food and Drug Administration approved the first two agents, pegcetacoplan and avacincaptad pegol. These medications were designed to slow the progression of GA, but they do not prevent GA altogether, nor do they improve visual acuity.[9,10]

Multiple studies suggest metformin may reduce the odds of developing AMD.[11–14] However, investigation into the AMD subtypes for which metformin may offer protection against has been limited.[15,16] Metformin has been shown to protect against the development of dry AMD in multiple studies, but these studies did not include GA as a primary outcome.[16–18] Instead, a diagnosis of GA was included among a broader categorization of any dry AMD. A bioinformatics model of drug–gene interactions also suggested that metformin acts on genes related to GA development.[19] Despite the encouraging findings from these studies, the shortcomings in therapeutics for GA, and the debilitating visual impacts associated with GA, no observational study of metformin and AMD has specifically designated GA as its primary outcome. The limited research about metformin

and GA may be a consequence of medical classification: GA was added to the *International Classification of Disease, Tenth Revision* (*ICD-10*) in 2017.[20] Therefore, we conducted a case-control study investigating the association between metformin and new-onset *ICD* coding of GA.

Methods

We conducted a case-control study in the Merative MarketScan Commercial and Medicare Databases between January 2016 and December 2021. These annual databases include the health services of employees, dependents, and retirees in the United States with primary or Medicare Supplementary coverage through privately insured health plans. Approximately 24 million patients were in the database in 2021, 30 million patients in 2016, and between 24 million and 30 million patients in all other years. The University of Chicago Institutional Review Board exempted this study because personal identifiable information was not available in these data. Data analysis was performed in SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

We identified cases as patients ages 60 years and older with new-onset *ICD* coding of GA between January 2017 and December 2021 (Supplementary Table S1). The date of the GA diagnosis was a case's index visit, and every case was required to be continuously enrolled in a health insurance plan with outpatient prescription drug coverage in the year prior to that visit. The GA diagnosis was able to have occurred in outpatient or inpatient settings.

Cases were required to have had an outpatient or inpatient eye examination on the index visit date, as defined by *Current Procedural Terminology* (Supplementary Table S2). These eye examinations confirmed that GA was diagnosed in an ophthalmic setting. Cases were excluded if they were diagnosed with wet AMD, as defined by *ICD* codes, between 2017 and the date of the GA diagnosis (Supplementary Table S1). By excluding patients with concurrent wet AMD, we could analyze the association between metformin use and GA without concern that the documented atrophy occurred from an anti-VEGF injection for wet AMD.[21]

Age at the index visit was grouped as 60 to 69, 70 to 79, 80 to 89, and ≥90 years, and US Census Bureau region was provided as Northeast, South, North Central, West, and Unknown. We excluded cases in Unknown regions because region was a matching variable. Comorbidities were selected to compute a modified Charlson Comorbidity Index (CCI).[22] We excluded from the CCI calculation (1) diabetes with and without complications because we wanted to investigate the independent effect of diabetes on GA and (2) peripheral vascular disease to stay consistent with similar AMD-related case-control studies.[12,13] Thus, the CCI range was from 0 to 26, which we grouped as 0, 1, 2, and ≥3. We also identified risk factors for AMD, including female sex and diagnoses of hypertension, hyperlipidemia, obesity, diabetes, smoking, nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy, as well as diagnoses of prediabetes. Comorbidities, risk factors, and diagnoses of prediabetes required an outpatient or inpatient claim with a relevant *ICD* code in the year prior to and including the index visit date (Supplementary Table S1).

Every case was matched with propensity scores estimated by age, region, CCI (0, 1, 2, ≥3), and hypertension to a control of the same year (Supplementary Note 1 for technical details of match).[23] Controls met the same inclusion criteria as the cases, except without a GA diagnosis. Randomly selected eye examinations served as a control's index visits. Controls could be in control pools in multiple years if they had not yet been matched to a case or diagnosed with GA.

The exposures in this study were antidiabetic medications, including metformin, insulin, sulfonylureas, glitazones, meglitinides, other diabetes medications (i.e., exenatide, sitagliptin, or pramlintide), and statins. An exposure required an outpatient prescription drug claim with a relevant National Drug Code in the year prior to and including the index visit date. National Drug Codes were identified from the generic names of the antidiabetic medications (Supplementary Table S3).

We calculated descriptive statistics of cases, controls, and control pools. For categorical variables, this included frequencies and percentages, and for continuous variables, this included means and standard deviations. We also calculated the exposure rates of cases and controls to each antidiabetic medication.

We tested the association between metformin use and new-onset *ICD* coding of GA in conditional multivariable logistic regression. We implemented conditional logistic regression to account for the matched pairs (i.e., case-control) study design. This technique ensured that cases and controls of the same year, age group (not age), CCI group, hypertension status, and region were compared[24] and that nonmatched cases were still able to have explanatory power. The regressions adjusted for the AMD risk factors and other antidiabetic medications. Statistical significance was set at $\alpha = 0.05$.

Finally, we were interested in the association between metformin use and GA in patients without diabetes. As described earlier, the protective effect of metformin was recently suggested to extend to patients without diabetes,[16] and patients without diabetes comprise a majority of patients with AMD.[12,25] Therefore, we selected the cases without diabetes, matched them to controls without diabetes, and repeated the statistical analysis. Rematching cases and controls was necessary because diabetes was not a matching variable in the original analysis, which meant a case with/without diabetes was able to have been matched to a control without/with diabetes.

Results

Full Sample

In the full sample, we identified 10,505 cases with new-onset *ICD* coding of GA. Compared to the 10,674,645 patients in control pools without GA, and from whom the controls were selected, cases were older, more frequently resided in the Northeast and North Central regions, had higher average CCIs, and were more often diagnosed with hypertension (Table 1).

We matched the 10,505 cases with GA (mean [SD] age, 82.1 [9.6] years; 6603 females [62.9%]) to 10,502 controls without GA (mean [SD] age, 82.1 [9.6] years; 6014 females [57.3%]) (Table 2). Cases and controls were balanced on the matching variables of age, region, year, CCI group, and hypertension, as defined by the absolute values of their standardized differences and distributions of their estimated propensity scores (Supplemental Tables S4 and S5, respectively).[26] In total, 2894 (27.6%) cases and 2935 (28%)

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Table 1. Sample Characteristics Before Matching

Characteristic	Full Sample		Patients Without Diabetes	
	Cases	Control Pools	Cases	Control Pools
Total, *N*	10,505	10,674,645	7611	9,336,904
Age, *n* (%)				
60–69	1295 (12.3)	7,478,707 (70.1)	947 (12.4)	6,684,818 (71.6)
70–79	2442 (23.3)	2,082,598 (19.5)	1669 (21.9)	1,726,689 (18.5)
80–89	4246 (40.4)	918,694 (8.6)	3028 (39.8)	753,796 (8.1)
≥90	2522 (24.0)	194,646 (1.8)	1967 (25.8)	171,601 (1.8)
Age, mean (SD), y	82.1 (9.6)	67.4 (8.0)	82.4 (9.8)	67.1 (7.9)
Region, *n* (%)				
Northeast	2936 (28.0)	2,387,893 (22.4)	2157 (28.3)	2,081,965 (22.3)
North Central	3401 (32.4)	2,940,141 (27.5)	2412 (31.7)	2,573,970 (27.6)
South	2999 (28.6)	4,075,959 (38.2)	2142 (28.1)	3,496,538 (37.5)
West	1166 (11.1)	1,270,652 (11.9)	900 (11.8)	1,184,431 (12.7)
Study year, *n* (%)				
2017	2607 (24.8)	2,371,042 (22.2)	1895 (24.9)	1,975,504 (21.2)
2018	2731 (26.0)	1,913,591 (17.9)	2028 (26.7)	1,740,793 (18.6)
2019	1662 (15.8)	1,990,906 (18.7)	1247 (16.4)	1,892,955 (20.3)
2020	1730 (16.5)	2,297,101 (21.5)	1184 (15.6)	1,970,466 (21.1)
2021	1772 (16.9)	2,102,005 (19.7)	1257 (16.5)	1,757,186 (18.8)
CCI, *n* (%)				
0	3873 (36.9)	6,365,412 (59.6)	3079 (40.5)	6,496,386 (69.6)
1	2173 (20.7)	1,866,208 (17.5)	1605 (21.1)	1,366,775 (14.6)
2	1884 (17.9)	1,301,600 (12.2)	1327 (17.4)	903,240 (9.7)
≥3	2572 (24.5)	1,141,425 (10.7)	1600 (21.0)	570,503 (6.1)
CCI, mean (SD)	1.6 (1.8)	0.9 (1.5)	1.4 (1.7)	0.6 (1.2)
Hypertension, *n* (%)	8137 (77.5)	6,475,623 (60.7)	5584 (73.4)	4,304,723 (46.1)

Region refers to the US Census Bureau region.

controls were diagnosed with diabetes (Table 2), and 1149 (10.9%) GA cases and 1277 (12.2%) controls were exposed to metformin (Table 3). Exposures to other antidiabetic medications are shown in Table 3. In a multivariable regression that adjusted for AMD risk factors and other antidiabetic medications, metformin decreased the odds of new-onset *ICD* coding of GA by 12% (95% confidence interval [CI], 0.79–0.99; Table 4).

Patients Without Diabetes

In the sample of patients without diabetes, we identified 7611 cases with new-onset *ICD* coding of GA. Compared to the 9,336,904 patients in control pools without GA and diabetes, and from whom the controls were selected, cases were older, more frequently resided in the Northeast and North Central regions, had higher average CCIs, and were more often diagnosed with hypertension (Table 1).

We matched the 7611 cases with GA (mean [SD] age, 82.4 [9.8] years; 4973 females [65.3%]) to 7608 controls without GA (mean [SD] age, 82.4 [9.8] years; 4547 females [59.8%]) (Table 2). Cases and controls were balanced on the matching variables of age, region, year, CCI group, and hypertension, as defined by the absolute values of their standardized differences and distributions of their estimated propensity scores (Supplemental Tables S6 and S7, respectively).[26] In total, 286 cases (3.8%) and 263 (3.5%) controls had prediabetes, and 29 (0.4%) GA cases and 63 (0.8%) controls were exposed to metformin (Table 3). Exposures to other antidiabetic medications are shown in Table 3. In a multivariable regression that adjusted for AMD risk factors and other antidiabetic medications, metformin decreased the odds of developing GA by 47% (95% CI, 0.33–0.83; Table 4).

Discussion

This case-control study identified an association between metformin and decreased new-onset *ICD* coding of GA. This association controlled for AMD risk factors and other antidiabetic medications, and the association persisted in patients without diabetes. Therefore, metformin may offer a noninvasive, alternative medication to prevent GA.

It is notable that the protective effect of metformin against GA persisted and was more pronounced in patients without diabetes (odds ratio [OR] = 0.53 vs. OR = 0.88). Metformin was recently shown to broadly protect against dry AMD in patients without diabetes, but until now, a protective association against GA in patients without diabetes had not been described.[16] This is a notable finding as a small minority of patients with AMD also have comorbid diabetes.[12,27] Hence, a medication that can be used safely and effectively for AMD among the broader patient population without diabetes is warranted. Metformin is widely accessible, has an excellent side effect profile, and has seen increasing off-label use for various metabolic, endocrine, cardiovascular, and reproductive disorders.[28] In light of this, our findings suggest that metformin may represent an ideal candidate to be repurposed for treating and preventing GA.

Furthermore, we calculated the number needed to treat (NNT) based on the ORs from the multivariable regression analyses of the full sample and among patients without diabetes.[29,30] We used a patient's expected event rate of 2.4%, which was identified in a retrospective cohort study from the United Kingdom as the percentage of study eyes with bilateral early or intermediate AMD that progressed to GA within 2 years.[31] The NNT was 355 patients (95% CI, 203–4268) for the full sample and 90 patients (95% CI, 63–250) for patients without diabetes. Notably, studies of claims databases that

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Table 2. Sample Characteristics After Matching

Characteristic	Full Sample		Patients Without Diabetes	
	Cases	Controls	Cases	Controls
Total, *N*	10,505	10,502	7611	7608
Age, *n* (%), y				
60–69	1295 (12.3)	1295 (12.3)	947 (12.4)	947 (12.5)
70–79	2442 (23.3)	2442 (23.3)	1669 (21.9)	1669 (21.9)
80–89	4246 (40.4)	4246 (40.4)	3028 (39.8)	3028 (39.8)
≥90	2522 (24.0)	2519 (24.0)	1967 (25.8)	1964 (25.8)
Age, mean (SD), y	82.1 (9.6)	82.1 (9.6)	82.4 (9.8)	82.4 (9.8)
Female, *n* (%)	6603 (62.9)	6014 (57.3)	4973 (65.3)	4547 (59.8)
Region, *n* (%)				
Northeast	2937 (28.0)	2936 (28.0)	2157 (28.3)	2156 (28.3)
North Central	3402 (32.4)	3401 (32.4)	2412 (31.7)	2411 (31.7)
South	2999 (28.6)	2999 (28.6)	2142 (28.1)	2142 (28.2)
West	1167 (11.1)	1166 (11.1)	900 (11.8)	899 (11.8)
Study year, *n* (%)				
2017	2607 (24.8)	2607 (24.8)	1895 (24.9)	1894 (24.9)
2018	2733 (26.0)	2731 (26.0)	2028 (26.7)	2027 (26.6)
2019	1663 (15.8)	1662 (15.8)	1247 (16.4)	1246 (16.4)
2020	1730 (16.5)	1730 (16.5)	1184 (15.6)	1184 (15.6)
2021	1772 (16.9)	1772 (16.9)	1257 (16.5)	1257 (16.5)
CCI, *n* (%)				
0	3874 (36.9)	3873 (36.9)	3079 (40.5)	3079 (40.5)
1	2174 (20.7)	2173 (20.7)	1605 (21.1)	1604 (21.1)
2	1884 (17.9)	1884 (17.9)	1327 (17.4)	1326 (17.4)
≥3	2573 (24.5)	2572 (24.5)	1600 (21.0)	1599 (21.0)
CCI, mean (SD)	1.6 (1.8)	1.6 (1.8)	1.4 (1.7)	1.4 (1.7)
Hypertension, *n* (%)	8139 (77.5)	8137 (77.5)	5584 (73.4)	5581 (73.4)
Hyperlipidemia, *n* (%)	6602 (62.9)	6750 (64.3)	4392 (57.7)	3934 (51.7)
Obesity, *n* (%)	1605 (15.3)	1547 (14.7)	894 (11.8)	687 (9.0)
Smoking, *n* (%)	925 (8.8)	832 (7.9)	657 (8.6)	425 (5.6)
Prediabetes, *n* (%)	286 (2.7)	356 (3.4)	286 (3.8)	263 (3.5)
Diabetes, *n* (%)	2894 (27.6)	2935 (28.0)	NA	NA
Nonproliferative DR, *n* (%)	488 (4.7)	265 (2.5)	NA	NA
Proliferative DR, *n* (%)	101 (1.0)	47 (0.5)	NA	NA

Region refers to the US Census Bureau region. DR, diabetic retinopathy; NA, not applicable.

Table 3. Medication Exposure Rates

Medication	*n* (%)			
	Full Sample		Patients Without Diabetes	
	Cases (*n* = 10,505)	Controls (*n* = 10,502)	Cases (*n* = 7611)	Controls (*n* = 7608)
Metformin	1149 (10.9)	1278 (12.2)	29 (0.4)	63 (0.8)
Insulin	633 (6.0)	541 (5.2)	0 (0.0)	9 (0.1)
Sulfonylureas	619 (5.9)	663 (6.3)	4 (0.1)	13 (0.2)
Glitazones	90 (0.9)	133 (1.3)	0 (0.0)	9 (0.1)
Meglitinides	42 (0.4)	46 (0.4)	1 (0.0)	0 (0.0)
Other diabetes medications	351 (3.3)	372 (3.5)	4 (0.1)	13 (0.2)
Statins	5556 (52.9)	5701 (54.3)	3557 (46.7)	3564 (46.9)

Other diabetes medications include medications with the generic names exenatide, sitagliptin, or pramlintide.

use propensity score matching often yield concordant findings with subsequent randomized clinical trials (RCTs).[32] As such, RCTs likely provide better estimations of NNT, but our study provides strong evidence that metformin may have a protective effect against GA. While these NNTs are large, the accessibility of metformin combined with the increasing prevalence of AMD motivates further investigation into metformin and its potential to prevent or treat GA.

Newly approved intravitreal therapeutics for GA, pegcetacoplan and avacincaptad pegol, slow the growth of GA lesions. However, they have not been shown to have a functional benefit for patients at 24 months, as measured by best-corrected visual acuity (BCVA), low-luminance visual acuity (LLVA), maximum reading speed, Functional Reading Independence Index, and mean threshold microperimetry.[9,10,33–35] Hence, there remains an unmet need for a medication that slows GA progression and also provides an improvement in either visual acuity or a functional benefit to patients. Additionally, patients treated with pegcetacoplan and avacincaptad pegol appear to be at a higher risk

Table 4. Multivariable Conditional Logistic Regression Model Estimates

Characteristic	OR (95% CI)	
	Full Sample (N = 21,007)	Patients Without Diabetes (N = 15219)
Female sex	1.28 (1.21–1.35)	1.28 (1.20–1.37)
Hyperlipidemia	0.95 (0.89–1.01)	1.34 (1.25–1.45)
Obesity	1.05 (0.97– 1.14)	1.32 (1.18–1.47)
Smoking	1.16 (1.05–1.28)	1.58 (1.38–1.80)
Diabetes	0.96 (0.88–1.05)	NA
Nonproliferative DR	1.99 (1.68–2.35)	NA
Proliferative DR	1.63 (1.12–2.37)	NA
Metformin	0.88 (0.79–0.99)	0.53 (0.33–0.83)
Insulin	1.05 (0.92–1.21)	NA
Sulfonylureas	0.95 (0.84–1.09)	0.50 (0.16–1.61)
Glitazones	0.73 (0.55–0.97)	NA
Meglitinides	0.93 (0.59–1.44)	NA
Other diabetes medications	1.01 (0.86–1.19)	0.46 (0.14–1.50)
Statins	0.98 (0.92–1.05)	0.89 (0.83–0.96)

Other diabetes medications include medications with the generic names exenatide, sitagliptin, or pramlintide. Insulin, meglitinides, and glitazones were not included in the patients without diabetes regression model because they demonstrated perfect collinearity (Table 3).

of developing wet AMD and require an intense treatment regimen of monthly injections, which may be a burden to patients and carries a risk of endophthalmitis and retinal inflammation.[33,36] In fact, the American Society of Retina Specialists Research and Safety in Therapeutics Committee has recently reported cases of retinal vasculitis in 14 eyes of 13 patients, all developing following their first injection of pegcetacoplan.[37] The poor functional data and drastic side effect profile for these recently approved therapeutics underscore the ongoing shortcomings in the treatment of GA.

A mechanism to explain metformin's protection against GA development is unclear, but there are several possibilities. Given that metformin was the only diabetes medication in this study that demonstrated a protective association with GA, there is reason to believe it acts outside of an antihyperglycemic effect. This is further supported by evidence shown in this study that metformin protects against GA in patients without diabetes. Metformin's proposed geroprotective effects have been attributed to antioxidative and anti-inflammatory properties.[38] In mouse models of retinal degeneration, metformin has been shown to protect photoreceptors and the RPE from oxidative stress through stimulation of adenosine monophosphate-activated protein kinase (AMPK).[39] Similarly, in vitro studies have demonstrated that metformin protects RPE cells from oxidative damage by inducing autophagy through AMPK pathway activation.[40] While the exact pathogenesis of GA is unknown, oxidative damage is likely to be a key contributor.[41] Hence, metformin may protect against GA development by preventing the effects of oxidative damage on photoreceptors and the RPE.

Dysregulation of the complement system has also been heavily implicated in GA development. Genetic variants in the C3 gene are strongly linked as risk factors for GA,[42] while complement products have been found deposited within drusen.[43] Pegcetacoplan and avacincaptad pegol were designed to inhibit the complement system, targeting C3 and C5, respectively.[9,10] In a randomized trial of patients with diabetes, metformin was not shown to significantly alter levels of C3.[44] However, metformin's interactions with the complement pathway remain understudied in the current literature. As such, it remains to be seen if it offers a protective effect against GA through this pathway.

Our finding conflicts with a small randomized clinical trial (METforMIN) that did not demonstrate an association between metformin and GA progression, as measured by the annualized enlargement rate of the square root of total GA area on fundus autofluorescence (FAF) imaging.[45] Additionally, the trial did not report a difference in the decline of BCVA between the metformin-treated and observation groups. However, the trial did report an interesting finding that approached statistical significance ($P = 0.06$): patients in the metformin group had a lower decline in LLVA compared to the observation group (–0.8 vs. –7.3 letters/y), suggesting that metformin may protect against photoreceptor degeneration, which has been proposed in animal models.[39] Differences in the reported outcomes between our study and the clinical trial may be due to the following: (1) the trial's small sample size (n = 66) may have limited statistical power; (2) the clinical trial enrolled patients with a large GA area at baseline (>1.25 mm^2), where slowing the rate of progression may be more difficult to achieve; and (3) the trial investigated end points related to progression of established GA and not prevention at earlier stages, which our study evaluated. It may be worthwhile to investigate differences in GA progression in patients with AMD randomized to metformin with high-risk features for GA development, including but not necessarily limited to large drusen and pigmentary changes, drusen located proximal to the fovea, hyperreflective foci on optical coherence tomography (OCT), or drusenoid pigment epithelial detachments.[46] In fact, the authors of METforMIN conclude that additional trials are warranted for the use of metformin in earlier stages of AMD.[45]

Limitations of this study include its claims-based data source, which lack clinical granularity. For example, we did not have access to valuable imaging data from fundus photography, FAF, or OCT, which would have allowed for us to verify GA lesions and track their growth throughout the course of metformin therapy.[41] Additionally, these databases do not provide access to the results of ophthalmic testing, such as BCVA, which would be a useful marker to longitudinally assess if metformin also offers a functional benefit. A further limitation of the study is that the cases

with GA were not necessarily new onset. The *ICD-10* was expanded to include diagnostic codes for GA in 2017.[20] Thus, the presence of such diagnostic codes for GA may reflect the first time those codes were billed for, even though patients may have been diagnosed with GA prior to 2017. Notably, we did exclude patients with a history of wet AMD prior to the date of their GA diagnosis. Patients with wet AMD who are treated with anti-VEGF injections can develop atrophic areas resembling those seen in GA,[21] so this exclusion criterion helped to ensure that patients had GA as opposed to atrophy related to anti-VEGF injections. A further strength of this study is the extremely low exposure rate to antidiabetic medications besides metformin among both the cases and the controls without diabetes. This supports that our inclusion criteria successfully identified patients without diabetes and that misclassification may not have biased the results. However, the number of patients exposed to metformin among the nondiabetic cohort was relatively small (29 cases and 63 controls exposed to metformin; Table 3). As a result, our estimated odds ratio and confidence interval for metformin may not have been precise (OR, 0.53; 95% CI, 0.33–0.83). To assess the precision of these estimates, we performed a robustness check in which we investigated 1:2 and 1:3 matching of cases/controls without diabetes. Additional controls yield a greater number of patients exposed to metformin, leading to more stable estimation. In total, 119 of 15,204 controls in the 1:2 match and 168 of 22,801 controls in the 1:3 match were exposed to metformin, and the effect size and statistical significance of metformin's association with GA persisted in regression analyses of both samples (1:2 matching: OR, 0.54; 95% CI, 0.36–0.83; 1:3 matching: OR, 0.61; 95% CI, 0.41–0.92). These robustness checks help verify the precision of our estimates; however, future studies with greater numbers of patients exposed to metformin should still be considered to further validate our findings, and those studies should become increasingly accessible as administrative data with GA diagnosis coding become more available.[20] Our findings may also lack generalizability. We studied privately insured patients or patients with Medicare Supplemental coverage, so it is unclear if or how our findings would extend to patients who are publicly insured or uninsured. Furthermore, studies indicate that GA is more prevalent among white patients compared to black patients (1.8% vs. 0.3%).[47] We did not have access to patients' race and ethnicity, which could be a source of confounding if cases and controls were not balanced on these characteristics. Our study design should thus be replicated in databases that include patients' race and ethnicity as well as in samples of publicly insured or uninsured patients.

Given the findings from this study, metformin's ease of use, and the shortcomings of current therapeutics for GA, metformin may hold promise as an alternative agent that can be repurposed for preventing GA. As more recent administrative data become available, additional studies are needed to confirm the associations identified herein and to motivate a clinical trial.

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References

1. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140(12):1202–1208.
2. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet*. 2018;392(10153):1147–1159.
3. Ferris FL, III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102(11):1640–1642.
4. Klein R, Wang Q, Klein BE, Moss SE, Meuer SM. The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. *Invest Ophthalmol Vis Sci*. 1995;36(1):182–191.
5. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six–week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193–201.
6. CATT Research Group; Martin DF, Maguire MG, Ying G, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897–1908.
7. Grunwald JE, Pistilli M, Daniel E, et al. Incidence and growth of geographic atrophy during 5 years of comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2017;124(1):97–104.
8. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group,Maguire MG, Martin DF, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(8):1751–1761.
9. Liao DS, Grossi FV, Mehdi DE, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127(2):186–195.
10. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: a randomized pivotal phase 2/3 trial. *Ophthalmology*. 2021;128(4):576–586.
11. Liang KH, Chen CH, Tsai HR, Chang CY, Chen TL, Hsu WC. Association between oral metformin use and the development of age-related macular degeneration in diabetic patients: a systematic review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2022;63(13):10.
12. Blitzer AL, Ham SA, Colby KA, Skondra D. Association of metformin use with age-related macular degeneration. *JAMA Ophthalmol*. 2021;139(3):302–309.
13. Brown EE, Ball JD, Chen Z, Khurshid GS, Prosperi M, Ash JD. The common antidiabetic drug metformin reduces odds of developing age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2019;60(5):1470–1477.
14. Romdhoniyyah DF, Harding SP, Cheyne CP, Beare NAV. Metformin, a potential role in age-related macular degeneration: a systematic review and meta-analysis. *Ophthalmol Ther*. 2021;10(2):245–260.
15. Khanna S, Shaw L, Hyman MJ, et al. Association of metformin use with risk of newly onset neovascular age-related macular degeneration development. *Retina*. 2024;44(2):205–213.
16. Aggarwal S, Moir J, Hyman MJ, et al. Metformin use and age-related macular degeneration in patients without diabetes. *JAMA Ophthalmol*. 2024;142(1):53–57.
17. Starr MR, Dalvin LA, AbouChehade JE, et al. Incidence of metformin use in patients with age-related macular degen-

eration versus normal controls: a population-based study in Olmsted County, Minnesota. *Eye*. 2023;37(9):1861–1865.
18. Kaufmann GT, Hyman MJ, Gonnah R, Hariprasad S, Skondra D. Association of metformin and other diabetes medication use and the development of new-onset dry age-related macular degeneration: a case–control study. *Invest Ophthalmol Vis Sci*. 2023;64(11):22.
19. Nadeem U, Xie B, Xie EF, et al. Using advanced bioinformatics tools to identify novel therapeutic candidates for age-related macular degeneration. *Transl Vis Sci Technol*. 2022;11(8):10.
20. American Academy of Ophthalmology. How to use the ICD-10 codes for age-related macular degeneration, https://www.aao.org/eyenet/article/how-to-use-the-icd-10-codes-for-amd. Accessed October 3, 2023.
21. Sadda SR, Guymer R, Monés JM, Tufail A, Jaffe GJ. Anti–vascular endothelial growth factor use and atrophy in neovascular age-related macular degeneration: systematic literature review and expert opinion. *Ophthalmology*. 2020;127(5):648–659.
22. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676–682.
23. Yao XI, Wang X, Speicher PJ, et al. Reporting and guidelines in propensity score analysis: a systematic review of cancer and cancer surgical studies. *J Natl Cancer Inst*. 2017;109(8):djw323.
24. Breslow NE, Day NE, Halvorsen KT, Prentice RL, Sabai C. Estimation of multiple relative risk functions in matched case-control studies. *Am J Epidemiol*. 1978;108(4):299–307.
25. Vassilev ZP, Ruigómez A, Soriano-Gabarró M, García Rodríguez LA. Diabetes, cardiovascular morbidity, and risk of age-related macular degeneration in a primary care population. *Invest Ophthalmol Vis Sci*. 2015;56(3):1585–1592.
26. Yang D, Dalton JE. A unified approach to measuring the effect size between two groups using SAS. 2012, https://support.sas.com/resources/papers/proceedings12/335-2012.pdf. Accessed October 3, 2023.
27. Vassilev ZP, Ruigómez A, Soriano-Gabarró M, García Rodríguez LA. Diabetes, cardiovascular morbidity, and risk of age-related macular degeneration in a primary care population. *Invest Ophthalmol Vis Sci*. 2015;56(3):1585–1592.
28. Le S, Lee GC. Emerging trends in metformin prescribing in the United States from 2000 to 2015. *Clin Drug Investig*. 2019;39(8):757–763.
29. Centre for Evidence-Based Medicine (CEBM), University of Oxford. Number needed to treat (NNT), https://www.cebm.ox.ac.uk/resources/ebm-tools/number-needed-to-treat-nnt. Accessed February 20, 2024.
30. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ*. 1995;310(6977):452–454.
31. Chakravarthy U, Bailey CC, Scanlon PH, et al. Progression from early/intermediate to advanced forms of age-related macular degeneration in a large UK cohort: rates and risk factors. *Ophthalmol Retina*. 2020;4(7):662–672.
32. Wang SV, Schneeweiss S, Franklin JM, et al. Emulation of randomized clinical trials with nonrandomized database analyses. *JAMA*. 2023;329(16):1376–1385.
33. Spaide RF, Vavvas DG. Complement inhibition for geographic atrophy: review of salient functional outcomes and perspective. *Retina*. 2023;43(7):1064.
34. Iveric Bio. Iveric Bio announces positive topline data from Zimura GATHER2 phase 3 clinical trial in geographic atrophy, https://investors.ivericbio.com/news-releases/news-release-details/iveric-bio-announces-positive-topline-data-zimurar-gather2-phase. Accessed December 5, 2023.
35. Apellis Pharmaceuticals, Inc. Apellis announces topline results from phase 3 DERBY and OAKS studies in geographic atrophy (GA) and plans to submit NDA to FDA in the first half of 2022, https://investors.apellis.com/news-releases/news-release-details/apellis-announces-top-line-results-phase-3-derby-and-oaks. Accessed December 5, 2023.
36. Cruz-Pimentel M, Wu L. Complement inhibitors for advanced dry age-related macular degeneration (geographic atrophy): some light at the end of the tunnel? *J Clin Med*. 2023;12(15):5131.
37. Witkin AJ, Jaffe GJ, Srivastava SK, Davis JL, Kim JE. Retinal vasculitis after intravitreal pegcetacoplan: report from the ASRS Research and Safety in Therapeutics (ReST) Committee. *J Vitreoretin Dis*. 2024;8(1):9–20.
38. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. *Cell Metab*. 2020;32(1):15–30.
39. Xu L, Kong L, Wang J, Ash JD. Stimulation of AMPK prevents degeneration of photoreceptors and the retinal pigment epithelium. *Proc Natl Acad Sci*. 2018;115(41):10475–10480.
40. Zhao X, Liu L, Jiang Y, Silva M, Zhen X, Zheng W. Protective effect of metformin against hydrogen peroxide-induced oxidative damage in human retinal pigment epithelial (RPE) cells by enhancing autophagy through activation of AMPK pathway. *Oxid Med Cell Longev*. 2020;2020:2524174.
41. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Campagne ML. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079–1091.
42. Yates JRW, Sepp T, Matharu BK, et al. Complement C3 variant and the risk of age-related macular degeneration. *N Engl J Med*. 2007;357(6):553–561.
43. Johnson LV, Ozaki S, Staples MK, Erickson PA, Anderson DH. A potential role for immune complex pathogenesis in drusen formation. *Exp Eye Res*. 2000;70(4):441–449.
44. Carter AM, Bennett CE, Bostock JA, Grant PJ. Metformin reduces C-reactive protein but not complement factor C3 in overweight patients with type 2 diabetes mellitus. *Diabetic Med*. 2005;22(9):1282–1284.
45. Shen LL, Keenan JD, Chahal N, et al. METformin FOR the MINimization of Geographic Atrophy Progression (METforMIN)—a randomized trial. *Ophthalmol Sci*. 2023;4(3):100440.
46. Heesterbeek TJ, Lorés-Motta L, Hoyng CB, Lechanteur YTE, den Hollander AI. Risk factors for progression of age-related macular degeneration. *Ophthalmic Physiol Opt*. 2020;40(2):140–170.
47. Bressler SB, Muñoz B, Solomon SD, West SK; Salisbury Eye Evaluation (SEE) Study Team. Racial differences in the prevalence of age-related macular degeneration: the Salisbury Eye Evaluation (SEE) project. *Arch Ophthalmol*. 2008;126(2):241–245.

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