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Metformin and risk of age-related macular degeneration in individuals with type 2 diabetes: a retrospective cohort study

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Synopsis

In a large retrospective cohort study with time-dependent exposure, we found no evidence for a differential risk of developing AMD between patients prescribed metformin and those prescribed other diabetes medications among patients with type 2 diabetes.

Abstract

Background

Age-related macular degeneration (AMD) in its late stages is a leading cause of sight loss in developed countries. Some previous studies have suggested that metformin may be associated with a reduced risk of developing AMD, but the evidence is inconclusive.

Aims

To explore the relationship between metformin use and development of AMD among patients with type 2 diabetes in the UK.

Methods

A large, population-based retrospective open cohort study with a time-dependent exposure design was carried out using IQVIA Medical Research Data, 1995-2019. Patients aged ≥40 with diagnosed type 2 diabetes were included.

The exposed group were those prescribed metformin (with or without any other antidiabetic medications); the comparator (unexposed) group were those prescribed other antidiabetic medications only. The exposure status was treated as time-varying, collected at 3-monthly time intervals.

Extended Cox proportional hazards regression was used to calculate the adjusted hazard ratios for development of the outcome, newly diagnosed AMD.

Results

A total of 173,689 patients, 57% male, mean (SD) age 62.8 (11.6) years, with incident type 2 diabetes and a record of one or more antidiabetic medications were included in the study. Median follow-up was 4.8 (IQR 2.3-8.3, range 0.5-23.8) years. 3,111 (1.8%) patients developed AMD. The adjusted hazard ratio for diagnosis of AMD was 1.02 (95% CI 0.92 - 1.12) in patients prescribed metformin (with or without other antidiabetic medications) compared to those prescribed any other antidiabetic medication only.

Conclusion

We found no evidence that metformin was associated with risk of age-related macular degeneration in primary care patients requiring treatment for type 2 diabetes.

Keywords: Age-related macular degeneration, type 2 diabetes, metformin, primary care, electronic health records

Introduction

Loss of vision is one of the most common adverse events of older age, being associated with loss of independence, loss of earnings (for the individual and carers), and profound impact on quality of life[1]. Age-related macular degeneration (AMD) in its late stages is a leading cause of blindness and moderate and severe vision impairment adults aged 50 years and over globally, and especially in high income regions[2]. It has been estimated that globally around 196 million people are living with AMD, rising to 288 million by 2040[3]. In the UK it is estimated that about 8 million people have any form of AMD[4]; around 600 000 people have sight loss caused by AMD with around 70 000 new cases every year[5]. Each year, AMD costs the UK economy £2.6 billion – over half of which (53 percent) falls outside health and social care[6], and in excess of £500million in medication costs[7]. At the current rate, by 2050 there will be 1.3million people with sight loss due to AMD[8].

Although the advent of anti- vascular endothelial growth factor (anti-VEGF) drugs has dramatically improved the outcomes of wet AMD patients[9], there are no treatments for the remaining majority of dry AMD patients. With a quickly ageing population, it is imperative that new treatments are identified – ideally stopping AMD in its earlier, non-sight threatening stages or offering protection against the onset of AMD. There is some evidence to suggest that certain commonly prescribed medications may impact on ageing or on age-related diseases including AMD. Metformin, commonly used to treat patients with diabetes, has long been reported to have 'anti-ageing' properties in laboratory studies[10]. There is biological plausibility to explore the effect of metformin on risk of incident AMD for a number of reasons: first, the 'metabolic ecosystem' of the eye is extreme and may therefore may have limited resilience[11]; second, links to metabolic dysregulation in AMD are observed across a range of study contexts including animal models of AMD (including light-induced photoreceptor cell death)[12], genetic studies of AMD (dry and wet forms)[13,14], and in systemic profiles of patients with AMD indicating oxidative stress[15]; third, in animal models, metformin was reported to stimulate glucose metabolism in the retina and protect the photoreceptors and retinal pigment epithelium (RPE) from oxidative stress[16]; fourth, the mechanism of metformin's action appears to be via AMPK, mutations of which are associated with photoreceptor degeneration and 'accelerated ageing' phenotypes[17].

Despite this, exploration of a potential effect of metformin on AMD development in patients is very limited. Retrospective case-control studies report conflicting results: a single health centre US study (n=1947 cases, n=5841 controls) found a significant decrease in odds of developing AMD among participants using metformin compared to non-users[18], while a study using the Korean National Health Insurance Service database (n=2330 cases, n=23278 controls) found no significant association[19]. A retrospective cohort study using the Taiwan National Health Insurance Research Database reported a decrease in the hazard of AMD amongst diabetic users of metformin (n=45,524) compared to non-users (n=22,681)[20]. It is recognised, however, that AMD presentation differs in East Asian populations compared to Western populations.

The association between metformin and risk of AMD has not previously been explored in a large UK cohort study. The aim of this study, therefore, was to investigate whether treatment with metformin is associated with reduced risk of AMD in primary care patients with type 2 diabetes.

Materials and Methods

Study design

This pharmacoepidemiological study was a population-based retrospective open cohort study with a time-dependant exposure design.[21,22] Participants newly diagnosed with type 2 diabetes and initiated on medications were included. This study design mitigates survival bias, bias associated with effects on variables in the causal pathway, and under-ascertainment of outcomes occurring soon after initiation of therapy. We used the Data Extractor for Epidemiological Research (DExtER) to automate extraction of study data based on the chosen study design[23].

Data source

Data was derived from IQVIA Medical Research Data (IMRD-UK), formerly known as The Health Improvement Network (THIN). IMRD-UK is a national database comprising anonymised electronic primary care records for more than 15 million patients from 787 general practices across the UK. IMRD-UK is generalizable to the UK population in terms of demographic structure and prevalence of common chronic conditions[24]. The database has been used in numerous epidemiological studies in patients with type 2 diabetes[25–27]. Information relating to symptoms, diagnoses and investigations are recorded within IMRD-UK as Read codes, a hierarchical clinical coding system[28]. The database also includes records of prescriptions issued in primary care (linked to British National Formulary codes) and laboratory test results.

General practice eligibility

To improve data quality, general practices were eligible for inclusion at the later of 12 months after they began using electronic medical records software or 12 months after the practice acceptable mortality recording (AMR) dates[29,30].

Study population

The study period was 1st January 1995 to 31st Sept 2019. Adult patients aged 40 years and over, registered with an eligible general practice for at least one year before the index date (start of follow-up) and with an incident diagnosis of type 2 diabetes (newly diagnosed after registration with the practice and during the study period) were included. Only newly diagnosed patients were included to ensure that all drugs prescribed for the management of type 2 diabetes were captured.

Patients were eligible for inclusion in the study from the date when they had both a record of an incident diagnosis of type 2 diabetes, defined by a record of a relevant clinical (Read) code, and a prescription for an antidiabetic medication. Patients with a record of type 1 diabetes were excluded. We also excluded any patient who was diagnosed with AMD before

they were diagnosed with type 2 diabetes and prescribed antidiabetic medication. Patients with a diagnosis of type 2 diabetes but no prescription for an antidiabetic medication were excluded. Diabetes is part of the Quality and Outcomes Framework (QOF), a payment-incentivised recording system for GPs within the UK,[31] and is therefore well recorded in primary care.

Exposure

The exposure group was defined as patients prescribed metformin with or without any other antidiabetic medications. Comparator (unexposed) patients were those prescribed other antidiabetic medications only (sulphonylureas, dipeptidyl peptidase-4 (DPP4) inhibitors, acarbose, glinides, glitazones, sodium-glucose co-transporter-2 (SGLT2) inhibitors, insulin, glucagon-like peptide-1 (GLP-1) agonists – and not prescribed metformin). We treated the exposure as time-dependent and collected exposure (antidiabetic treatment) data for each patient at 3-month time intervals for the duration of follow-up.

Outcome

The outcome of interest was a diagnosis of AMD, defined by a record of a relevant clinical code (Supplementary Table 1). AMD diagnoses in primary care have been previously validated.[32] Progression of AMD to an advanced AMD diagnosis such as 'wet', or advanced neovascular, AMD is poorly coded in primary care data and so it was not possible to distinguish between types of AMD.

Follow-up period

The index date for all patients was the date they met the inclusion criteria of both an incident diagnosis of type 2 diabetes and a record of a prescription for an antidiabetic medication. Patients were followed up from the index date until the earliest of the following (exit date): outcome (AMD) date, study end date, last date of data collection from the general practice, date patient transferred from the practice, and death date.

Covariates

In our analysis we included the following potential confounders: age; sex; ethnicity; Townsend deprivation quintile (a measure of socioeconomic deprivation)[33,34]; smoking status (categorised as smoker, ex-smoker, non-smoker); Charlson comorbidity index (CCI);[35,36] physical measurements and blood test results (included as categorical variables): body mass index (BMI) (underweight (BMI <18 kg/m^2), normal weight (BMI 18-25 kg/m^2), overweight (BMI 25-30 kg/m^2) and obese (BMI >30 kg/m^2)), systolic blood pressure (<100, 100-120, 121-140, 140-160, 160-180, >180 mm Hg), HbA1c (a measure of glycaemic control, <6.5, 6.5-7, 7-7.5, 7.5-8, 8-8.5, >8.5%); diabetes complications: peripheral neuropathy, sight-threatening retinopathy, foot ulcer or amputation due to diabetes; statin prescription (treated as time-varying); cardiovascular disease; chronic kidney disease (CKD) stage; and hypothyroidism. CCI was modified to exclude type 2 diabetes. HbA1c and complications of diabetes were included to account for severity of diabetes that may have resulted in change of antidiabetic medication. All covariates were measured at baseline; we treated only the exposure and statin prescription as a time-dependent variables measured at 3-month

intervals from index date to exit date, recognising that other covariates may be in the causal pathway.

Missing data

There was some missing information for the following variables: ethnicity, Townsend quintile, smoking status, BMI, systolic blood pressure, HbA1c and CKD stage. We categorised the missing values in our analysis. In calculating CCI the absence of a record of any diagnosis was taken to indicate the absence of the condition.

Statistical analysis: Time-dependent analysis

We employed an extended Cox proportional hazards model for the time-dependent analysis[37]. Time-varying covariance occurs when a given covariate changes as a function of time during the follow-up period[38]. The data was organised in a counting process style with fixed follow-up intervals of 3 months. In our analysis we added a latency period of one time interval (3 months) for the drug exposures in order to allow sufficient time for the medications to have an effect.

All analyses were performed in R 3.5. A p-value <0.05 was considered statistically significant.

Sensitivity and subgroup analyses

We performed four sensitivity analyses: 1) HbA1c was treated as a time-varying covariate and diabetes duration was added as a covariate in the model; 2) the exposure group was re-categorised as metformin only, or metformin in combination with other antidiabetic medications to compare any potential differences in hazard of developing AMD; 3) metformin exposure was categorised by duration of exposure (up to 1.5 years, 1.5-3 years, 3-4.5 years and >4.5 years); 4) participants who developed AMD within 2 years or who had fewer than 2 years of follow-up were excluded to allow for a longer latency period.

A subgroup analysis was performed stratifying patients by sex. To explore the impact of missing data, a complete case analysis was also performed.

Results

Baseline characteristics

A total of 173,689 patients with incident type 2 diabetes and a record of one or more antidiabetic medications were included in the study. Of these, 154,016 (89%) patients were initiated on metformin. Table 1 describes the baseline characteristics of the study participants. All values displayed are the latest available at baseline. At index date (after the 3-month latency period), the mean age of participants was 62.8 years and 57% were male (Table 1). The mean (SD) follow-up period was 5.7 (4.1) years, median follow-up was 4.8 (IQR 2.3-8.3, range 0.5-23.8) years. On average females (64 years) were older than males (62 years) at study entry, and a higher proportion of females were in the more deprived Townsend quintile.

At baseline, 60% of females and 52% of males were obese. Males were more likely to be current or ex-smokers. Systolic blood pressure was similar in both groups, and HbA1c was

slightly higher in males than in females. In comparison, females had a higher proportion of kidney disease. Co-existing diabetes complications were similar in both sexes (peripheral neuropathy 5.6 and 4.9%, sight threatening retinopathy 1.9 and 2.1%, and foot ulcer/amputation 2.2 and 2.5% in males and females, respectively), while cardiovascular diseases were higher in males (26.5%, compared to 19.6% in females) and females had more hypothyroidism (14.3%, compared to 3.4% in males).

Table 1: Baseline characteristics of study participants (at start of follow-up, after 3-month latency period)

	Male	Female	All participants
Patient demographics and lifestyle variables			
Sex	99,093 (57.1%)	74596 (42.9%)	173,689
Age, years			
(Mean (SD), [Median])	61.9 (11.2), [61.6]	64.0 (11.9), [63.8]	62.8 (11.6), [62.5]
Follow-up period, years			
Mean (SD), [Median]	5.66 (4.05), [4.75]	5.65 (4.05), [4.75]	5.65 (4.05), [4.75]
Townsend			
1 (Least Deprived)	19,167 (19.3%)	12,448 (16.7%)	31,615 (18.2%)
2	17,494 (17.7%)	12,691 (17.0%)	30,185 (17.4%)
3	18,200 (18.4%)	13,717 (18.4%)	31,917 (18.4%)
4	16,322 (16.5%)	13,578 (18.2%)	29,900 (17.2%)
5 (Most Deprived)	12,186 (12.3%)	10,810 (14.5%)	22,996 (13.2%)
Missing	15,724 (15.9%)	11,352 (15.2%)	27,076 (15.6%)
Ethnicity			
White	43,369 (43.8%)	32,226 (43.2%)	75,595 (43.5%)
Black	1,337 (1.3%)	1,216 (1.6%)	2,553 (1.5%)
South Asian	2,893 (2.9%)	2,519 (3.4%)	5,412 (3.1%)
Mixed Race	656 (0.7%)	538 (0.7%)	1,194 (0.7%)
Other ethnicity	215 (0.2%)	185 (0.2%)	400 (0.2%)
Missing	50,623 (51.1%)	37,912 (50.8%)	88,535 (51.0%)
Smoking Status			
Non-smoker	38,685 (39.0%)	41,392 (55.5%)	80,077 (46.1%)
Ex-smoker	40,691 (41.1%)	20,055 (26.9%)	60,746 (35.0%)
Smoker	18,277 (18.4%)	12,020 (16.1%)	30,297 (17.4%)
Missing	1,440 (1.5%)	1,129 (1.5%)	2,569 (1.5%)
Physical measurements and blood test results			
Systolic Blood Pressure, mm Hg			
<100	1,075 (1.1%)	756 (1.0%)	1,831 (1.1%)
100-120	14,702 (14.8%)	10,872 (14.6%)	25,574 (14.7%)
121-140	49,639 (50.1%)	36,786 (49.3%)	86,425 (49.8%)
140-160	25,683 (25.9%)	19,282 (25.8%)	44,965 (25.9%)
160-180	5,908 (6.0%)	5,002 (6.7%)	10,910 (6.3%)
180+	1,347 (1.4%)	1,458 (2.0%)	2,805 (1.6%)
Missing	739 (0.7%)	440 (0.6%)	1,179 (0.7%)
Body Mass Index (BMI)			
Underweight	216 (0.2%)	371 (0.5%)	587 (0.3%)
Normal weight	10,124 (10.2%)	7,775 (10.4%)	17,899 (10.3%)
Overweight	33,037 (33.3%)	19,039 (25.5%)	52,076 (30.0%)
Obese	51,749 (52.2%)	44,537 (59.7%)	96,286 (55.4%)
Missing	3,967 (4.0%)	2,874 (3.9%)	6,841 (3.9%)
HbA1c, % (mmol/mol)			

<6.5 (<48)	6,314 (6.4%)	5,208 (7.0%)	11,522 (6.6%)
6.5-7 (48-53)	7,995 (8.1%)	7,372 (9.9%)	15,367 (8.8%)
7-7.5 (53-58.5)	11,348 (11.5%)	9,630 (12.9%)	20,978 (12.1%)
7.5-8 (58.5-64)	12,934 (13.1%)	10,372 (13.9%)	23,306 (13.4%)
8-8.5 (64-69.5)	7,410 (7.5%)	5,680 (7.6%)	13,090 (7.5%)
8.5+ (69.5+)	35,166 (35.5%)	22,770 (30.5%)	57,936 (33.4%)
Missing	17,926 (18.1%)	13,564 (18.2%)	31,490 (18.1%)
Chronic Kidney Disease (CKD) Stage			
1	30,223 (30.5%)	18,039 (24.2%)	48,262 (27.8%)
2	49,367 (49.8%)	35,884 (48.1%)	85,251 (49.1%)
3	13,229 (13.4%)	15,806 (21.2%)	29,035 (16.7%)
4	567 (0.6%)	796 (1.1%)	1,363 (0.8%)
5	84 (0.1%)	58 (0.1%)	142 (0.1%)
Missing	5,623 (5.7%)	4,013 (5.4%)	9,636 (5.5%)
Pre-existing Medical Conditions			
Peripheral Neuropathy	5,512 (5.6%)	3,674 (4.9%)	9,186 (5.3%)
Sight Threatening Retinopathy	1,930 (1.9%)	1,579 (2.1%)	3,509 (2.0%)
Foot ulcer or amputation	2,207 (2.2%)	1,852 (2.5%)	4,059 (2.3%)
Hypothyroidism	3,349 (3.4%)	10,656 (14.3%)	14,005 (8.1%)
Cardiovascular disease	26,243 (26.5%)	14,616 (19.6%)	40,859 (23.5%)
Charlson Comorbidity Index (CCI)			
0	56,995 (57.5%)	40,876 (54.8%)	97,871 (56.3%)
1	23,663 (23.9%)	19,123 (25.6%)	42,786 (24.6%)
2+	18,435 (18.6%)	14,597 (19.6%)	33,032 (19.0%)
Prescriptions			
Metformin exposure			
Other Antidiabetic Drugs only	10,809 (10.9%)	8,016 (10.7%)	18,825 (10.8%)
Metformin only or in combination with other antidiabetic medications	87,830 (88.6%)	66,186 (88.7%)	154,016 (88.7%)
No drug	454 (0.5%)	394 (0.5%)	848 (0.5%)
Statin prescription	60,978 (61.5%)	43,025 (57.7%)	104,003 (59.9%)

Risk of incident AMD: Metformin exposure

A total of 3,934,184 3-month time intervals (983,546 person-years) were included in the analysis, of which 3,047,298 (77.5%) were for exposure to metformin. During follow-up, 3,111 (1.8%) patients developed AMD (Table 2). A slightly lower proportion of males experienced outcomes (1,416 (1.4%)) compared to females (1,695 (2.3%)).

Among patients with type 2 diabetes, there was no evidence of association between treatment with metformin and the subsequent development of AMD: adjusted hazard ratio (aHR) 1.02 (95% CI 0.92 - 1.12) for metformin with or without other antidiabetic medications

compared to any other antidiabetic medication only (Table 2). Addition of diabetes duration as a covariate and inclusion of HbA1c as a time-varying covariate did not affect the result (Supplementary Table 2).

Females had significantly higher risk of developing AMD (aHR 1.39 (95% CI 1.29 - 1.50)) compared to males (Table 3). Older age was a significant risk factor for developing AMD (aHR 1.07 (1.07 - 1.07) for every year of age). Current smokers (aHR 1.14 (95% CI 1.01 - 1.27)) and ex-smokers (aHR 1.16 (95% CI 1.07 - 1.26)) were also at a higher risk, as were participants with high HbA1c (>8.5%, aHR 1.26 (95% CI 1.07 - 1.48)).

A sensitivity analysis in which the exposure group was stratified into participants prescribed metformin only and those prescribed metformin in combination with other antidiabetic medications showed no difference in results between the two exposure groups (Supplementary Table 2). There were no statistically significant associations between metformin exposure and development of AMD when exposure was stratified by duration of exposure or when a longer latency period was introduced (Supplementary Table 2).

In a subgroup analysis by sex, no evidence of association was observed between metformin exposure and development of AMD in either females or males (Supplementary Table 2).

Restricting the analysis to complete cases (with no missing data) had no impact on the result (Supplementary Table 2).

Table 2: Crude and adjusted hazard ratios for age-related macular degeneration in patients with type 2 diabetes prescribed metformin (alone or in combination with other antidiabetes medications) compared to those prescribed other antidiabetes medications only

Exposure status	**Other antidiabetes medications only**	**Metformin or metformin in combination with other antidiabetes medications**	**No drug**
Person-years	125,363.25	761,824.50	96,358.25
Number of outcomes	534	2300	277
Unadjusted hazard ratio (95% CI)	Reference	0.70 (0.64 - 0.77)	0.80 (0.69 - 0.92)
Adjusted hazard ratio (95% CI)	Reference	1.02 (0.92 - 1.12)	0.92 (0.79 - 1.07)

Table 3: Adjusted hazard ratios for age-related macular degeneration in patients with type 2 diabetes prescribed metformin (alone or in combination with other antidiabetes medications) compared to those prescribed other antidiabetes medications only and for all covariates

Covariate	Adjusted hazard ratio (95% confidence interval)
Metformin Exposure (reference: Other antidiabetic drugs without metformin)	
Metformin only or in combination with other antidiabetic medication	1.02 (0.92 - 1.12)
No drug	0.92 (0.79 - 1.07)
Sex: Female	1.39 (1.29 - 1.50)
Age	1.07 (1.07 - 1.07)
Townsend (reference = 1 (Least deprived))	
2	1.05 (0.93 - 1.18)
3	0.96 (0.85 - 1.08)
4	1.06 (0.94 - 1.20)
5	1.12 (0.98 - 1.27)
Missing	1.30 (1.15 - 1.46)
Ethnicity (reference: White)	
Black	0.68 (0.46 - 1.02)
South Asian	0.84 (0.64 - 1.09)
Mixed Race	1.03 (0.60 - 1.74)
Other Ethnicity	0.84 (0.31 - 2.24)
Missing	0.80 (0.75 - 0.86)
Smoking status (reference: non-smokers)	(-)
Current Smoker	1.14 (1.01 - 1.27)
Ex-smoker	1.16 (1.07 - 1.26)
Missing	1.15 (0.89 - 1.50)
Systolic Blood Pressure (reference: 100-120 mm Hg)	
<100	1.28 (0.90 - 1.83)
121-140	1.10 (0.98 - 1.23)
140-160	1.12 (0.99 - 1.27)
160-180	1.22 (1.04 - 1.43)
>180	1.17 (0.91 - 1.50)
Missing	0.98 (0.60 - 1.61)
Body Mass Index (BMI) (reference: normal weight)	
Underweight	0.80 (0.41 - 1.55)
Overweight	0.98 (0.87 - 1.10)
Obese	0.96 (0.86 - 1.08)
Missing	0.85 (0.69 - 1.06)
HbA1c (reference: <6.5%)	
6.5-7	1.03 (0.84 - 1.27)
7-7.5	1.15 (0.96 - 1.38)
7.5-8	1.19 (1.00 - 1.42)
8-8.5	1.08 (0.89 - 1.32)
>8.5	1.26 (1.07 - 1.48)
Missing	1.19 (1.00 - 1.41)
Chronic Kidney Disease Stage (reference: stage 1)	
2	1.00 (0.88 - 1.13)
3	1.04 (0.90 - 1.19)
4	0.88 (0.62 - 1.26)

5	0.04 (0.00 - 28.6)
Missing	1.05 (0.88 - 1.25)
Peripheral Neuropathy	1.03 (0.89 - 1.18)
Sight Threatening Retinopathy	1.45 (1.19 - 1.76)
Foot ulcer or Amputation	0.94 (0.75 - 1.17)
Hypothyroidism	1.01 (0.90 - 1.14)
Cardiovascular disease	1.05 (0.96 - 1.15)
Charlson Comorbidity Index (CCI) (reference: 0)	
1	1.01 (0.92 - 1.11)
2+	1.17 (1.06 - 1.29)
Statins	0.99 (0.91 - 1.07)

Discussion

Summary of findings

In this large retrospective cohort, we found no evidence of association between metformin use and development of AMD in patients with type 2 diabetes.

Female sex, older age, being a current or ex-smoker, and high HbA1c level were associated with increased odds of developing AMD. There was also evidence of a positive correlation between the degree of oxidative stress and glycated haemoglobin, suggesting that a high HbA1c may accelerate the development of AMD. An association between AMD and sight-threatening retinopathy was also observed; this could be the result of misclassification, or result from the fact the metabolic stress in the retina increases the risk of both AMD and retinopathy, also supported by the association between increased HbA1c and AMD. The role of oxidative stress has long been recognised as a hallmark of the disease pathogenesis of AMD.[15]

Context

Previous studies, in the USA and East Asia, have reported conflicting findings. Some of the differences may be explained by the impact of selection bias, prescription by indication bias or immortal time bias on findings. The retrospective, propensity score-matched cohort study of patients with type 2 diabetes using the Taiwan National Database reported a significant reduction in the odds of developing AMD in metformin-using participants with diabetes compared to non-users [aHR 0.57 (95% CI 0.52–0.63)].[20] However, among metformin users, index date was defined as type 2 diabetes diagnosis date and therefore the time between type 2 diabetes diagnosis and metformin initiation appears to have been misclassified as exposed time; this may introduce immortal time bias. The study suggests a dose and duration dependent protective effect of metformin, which may also be observed as a result of immortal time bias: patients classified as high total dose or long duration users of metformin must have been free of AMD for a longer duration in order to have the opportunity to be prescribed high doses of metformin or be exposed for long periods of time.

A smaller US case-control study also reported a protective effect of metformin on developing AMD [aOR 0.58 (95% CI 0.43 - 0.79)].[18] This study's analysis does not appear to have accounted for exposure time windows of different lengths between AMD cases and matched controls. Furthermore, the study included only hospital patients, and there were more individuals with diabetes (itself a risk factor for AMD) who would be prescribed metformin among the cases than controls, thereby introducing prescription by indication bias. A further US cross-sectional study also found an inverse correlation between metformin use and AMD [aOR 0.70 (95% CI 0.55 - 0.88)], but the possibility of time window bias was also present in this study.[39]

Conversely, a nested case-control study conducted in Korea showed no protective effect of metformin for developing AMD [aOR 1.15 (95% CI 0.91 - 1.45)].[19] In this study, the authors performed risk set sampling of the outcome, and matched AMD cases to controls for cohort entry date (±60 days) and follow-up duration, thereby overcoming some of the limitations of the US study. However, the Korean study evaluated multiple drug exposures and the population therefore included not only patients with type 2 diabetes but also those with cardiovascular conditions.

A recent US case-control study using nationwide health insurance claims found a very small but statistically significant association between metformin and development of AMD: OR 0.94 (95%CI, 0.92-0.96).[40] The authors also suggested the association was dose-dependent, but this was not borne out by the reported ORs for different metformin doses. Again, however, biases inherent to the case-control study design may have impacted findings. Indeed this was highlighted by McGuinness et al in a commentary accompanying the paper, which recommended that such retrospective case-control studies be interpreted 'in light of their limitations'.[41]

Strengths and limitations

Our study included a large cohort of approximately 180,000 participants representative of patients with type 2 diabetes in the UK, and is the largest study of its kind in a diabetic patient cohort. We performed a more sophisticated approach to metformin exposure than previous studies, using a time-varying analysis to account for changes in medication over time, and included a lag period to allow time for medications to impact participant outcomes.

However, there are several limitations. Our cohort included only patients with type 2 diabetes, and therefore conclusions regarding the association between metformin use and risk of AMD cannot be generalised to patients without type 2 diabetes. The IMRD database includes data on medications prescribed in primary care; it does not include information on whether these prescriptions were collected by the patient or whether the patient took the medications as prescribed. It is therefore not possible to confirm use of the prescribed medications by the patient. There is a possibility of misdiagnosis of AMD, however AMD records in primary care have been validated in previous studies;[32] in some patients with type 2 diabetes, AMD may be under-recognised, or attributed to changes arising from diabetic retinopathy. No inferences regarding the underlying mechanisms can be made as multiple factors such as genetic phenotype data, which may influence the association

between exposures and outcome, are unavailable in this routinely collected dataset. Information on consultations with optometrists or ophthalmologists is not available in the IMRD database, and it was therefore not possible to adjust for such consultation rates in the analysis; higher consultation rates might be association with higher rates of detection, however, in the UK all patients with diabetes are required to have yearly retinopathy screening and it is therefore unlikely that consultation rates differed substantially between the different exposure groups. Ethnicity data is poorly recorded in the IMRD database, so it was not possible to stratify by ethnicity.

Furthermore, it was not possible to distinguish between 'wet' and 'dry' forms of AMD. If metformin were protective for the late 'dry' form of AMD, geographic atrophy, this might not be detected in our analysis since geographic atrophy typically develops over the age of 80,[42] while the mean age of our cohort was 62.9 years, with a mean follow-up of 5.5 years; it is therefore possible that longer follow-up might be needed to observe differences in AMD outcomes, particularly 'dry' AMD.

Conclusion

Using a larger dataset and a more sophisticated study design than has been available previously, this study provides new evidence regarding the hypothesised association between metformin use and risk of AMD. Among individuals with type 2 diabetes in the UK, this study found no evidence for a differential risk of developing AMD between patients prescribed metformin and those prescribed other diabetes medications only. Further studies are needed to evaluate whether metformin has an impact on disease progression following a diagnosis of AMD.

Ethics

Use of IMRD is approved by the UK Research Ethics Committee (reference number: 18/LO/0441); in accordance with this approval, the study protocol was reviewed and approved by an independent Scientific Review Committee (SRC) (reference number: 20SRC033). IMRD incorporates data from The Health Improvement Network (THIN), A Cegedim Database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care.

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Contribution statement

PAK, KN and AD conceived the research question. KN, KMG and NJA designed the analysis. KMG performed the analysis, with supervision and contributions by KN and NJA. NJA and KMG drafted the manuscript. All authors (KG, NJA, AS, WHL, DH, JC, TB, AD, PK, KN) reviewed and revised the manuscript, provided critical feedback, and agreed to its publication.

Conflict of interest disclosures

Drs Adderley, Nirantharakumar and Denniston reported a grant from Action Against Age-related Macular Degeneration during the conduct of the study. Dr Adderley reported receiving grants from MRC UKRI and NIHR RfPB outside the submitted work. Dr Nirantharakumar reported receiving grants from Medical Research Council, National Institute for Health Research, AstraZeneca, MSD, Boehringer Ingelheim, Vifor, and Health Data Research UK and personal fees from Sanofi outside the submitted work. Dr Denniston reported receiving grant support from Health Data Research UK outside the submitted work. Dr Braithwaite reported receiving salary support from the patient charity Olivia's Vision. No other disclosures were reported.

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