



REVIEW

Metformin, A Potential Role in Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Currently, no generally approved medical treatment can delay the onset of age-related macular degeneration (AMD) or slow the progression of degenerative changes. Repurposing drugs with beneficial effects on AMD pathophysiology offers a route to new treatments which is faster, cost-effective, and safer for patients. Recent studies indicate a potential role for metformin in delaying AMD development and progression. In this context, we conducted a systematic review and meta-analysis to look for beneficial associations between metformin and AMD.

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Methods: We systematically searched Medline and Embase (via Ovid), Web of Science, and ClinicalTrials.gov databases for clinical studies in humans that examined the associations between metformin treatment and AMD published from inception to February 2021. We calculated pooled odds ratio (OR) with 95% confidence interval (CI) considering a random effect model in the meta-analysis.

Results: Five retrospective studies met the inclusion criteria. There are no prospective studies that have reported the effect of metformin in AMD. The meta-analysis showed that people taking metformin were less likely to have AMD although statistical significance was not met (pooled adjusted OR = 0.80, 95% CI 0.54–1.05, $I^2 = 98.8\%$). Subgroup analysis of the association between metformin and early and late AMD could not be performed since the data was not available from the included studies.

Conclusions: Analysis of retrospective data suggests a signal that metformin may be associated with decreased risk of any AMD. It should be interpreted with caution because of the failure to meet statistical significance, the small number of studies, and the limitation of routine record data. However prospective studies are warranted in generalizable populations without diabetes, of varied ethnicities, and AMD stages. Clinical trials are needed to determine if metformin has efficacy in treating early and late-stage AMD.

Keywords: Metformin; Age-related macular degeneration; Age-related maculopathy; Systematic review; Meta-analysis

Key Summary Points

Metformin is postulated to delay ageing and ageing-related diseases, including age-related macular degeneration.

We performed a systematic review and meta-analysis on five retrospective populations studies investigating metformin use and presence of AMD, showing an odds ratio of 0.80 (95% CI 0.54–1.05)

Laboratory and clinical studies support a potential role for metformin in delaying AMD development and progression through multiple modes of action.

There are no published data from prospective studies of the effect of metformin on AMD. Prospective studies are needed to further investigate this positive signal.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14308706>

INTRODUCTION

Age-related macular degeneration (AMD) is the most common cause of blindness in high-income countries with prevalence rising exponentially with age [1]. Globally, AMD is a top five cause of vision loss [2]. In the next decades with aging population, the number of people with AMD in the world is estimated to increase by 50% to 288 million in 2040 with the highest

burden in Asia [1]. AMD can be divided into early and advanced stages [3] with the latter having serious impacts on vision. Advanced AMD has two forms: (1) atrophic/dry/non-neovascular and (2) neovascular/wet/exudative [4].

Treatments for AMD are limited to arresting neovascular AMD (nAMD). Anti-vascular endothelial growth factor (anti-VEGF) therapies, delivered by intravitreal injections, are successful at treating the active neovascular component of nAMD [5]. However, treatment is not curative, the benefit does not extend to atrophic or fibrotic changes, and requires a series of expensive injections over a long period of time [6]. Unfortunately, there is currently no therapy for geographic atrophy (GA) or other forms of degenerative AMD which in all account for approximately 90% of the disease burden [7]. Despite widespread opinion on antioxidant supplementation, the evidence of their benefit is weak [8–10]. The Age-Related Eye Disease Study (AREDS) [11] did not meet primary endpoints, and evidence of effect was based on post hoc subgroup analysis [12, 13]. Age-Related Eye Disease Study 2 (AREDS2) did not provide data on whether antioxidants are effective in preventing AMD progression as it did not include a placebo arm [14, 15].

Currently, dry or non-neovascular AMD remains an unmet medical need, and the commonest cause of registered blindness in high-income countries [16]. GA is the target of clinical trials for new treatments, but patients with non-GA, enlarging drusen, drusenoid pigment epithelial detachment (PED), and vitelliform-type degeneration are currently underserved in drug development pipelines. New therapies that are effective in the prevention of AMD and limiting its progression are urgently needed, since its incidence is increasing and because of limitations on existing therapies. Developing new drugs is expensive in cost and time [17]. Repurposing existing drugs to find new functional benefits or indications can be an alternative. There is growing interest in metformin as a candidate drug for treating AMD and reducing its progression. This is because of its antioxidant, anti-inflammatory, antiangiogenic, and antifibrotic effects [18–21]. Metformin is postulated to delay ageing and ageing-

related diseases [22, 23]. Metformin is well tolerated and has a good safety profile with a long history as a treatment for type 2 diabetes mellitus (T2DM) [24]. Therefore, we performed a systematic review and conducted a meta-analysis underpinning the potential use of metformin in AMD.

METHOD

Eligibility Criteria and Literature Search Strategy

We performed a systematic review and meta-analysis following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [25] and the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement [26]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Studies were included if they met the following criteria: (1) studies in human; (2) one study objective is to explore the association between metformin treatment and the risk of AMD; (3) there is control group; (4) the studies provided the effect estimate or calculable information from the available data presented in the article; (5) peer reviewed article; (6) the studies stated the definition and classification of AMD clearly in the paper; (7) published in English. The latest information published was to be used if there were serial publications using the same subjects.

A systematic electronic search of Medline and Embase (via Ovid) and Web of Science Databases including conference papers and abstracts from the earliest record in databases until February 2021 was performed. An additional search was performed on ClinicalTrials.gov to capture unpublished studies. The search strategy included the generic keyword combinations of “metformin” and “macular degeneration” with further details listed in Supplementary Material A. The references of eligible studies were also searched, and expert reference suggestion was included to make sure all relevant materials were captured.

Study Selection

We used Covidence software (Veritas Health Innovation, <https://www.covidence.org>) for data extraction, data organisation, and literature screening. After the duplicate check, two reviewers independently identified relevant titles and abstracts. Full-text articles were reviewed if on the basis of the title and abstract they appeared to meet the inclusion criteria, or if there was any uncertainty.

Data Collection and Study Quality Assessment

Data obtained included data source, sample size, study design, study period, AMD diagnostic criteria, the unadjusted and adjusted effect estimate and/or calculable information from the available data, adjustments for potential confounders, and study outcome. Quality of study assessment was conducted using the Downs and Black checklist [27, 28], which includes 27 items to assess the quality of reporting (10 items), external validity (3 items), internal validity including bias and confounding (13 items), and statistical power (1 item).

The original Downs and Black checklist allows a cumulative score of 32 points, one item having a maximum two points in the quality of reporting section and five points in the statistical power section. An adjustment was made to the scoring of item 27 that refers to the statistical power of the study. We rated a single point if the study had sufficient power to detect a clinically important effect, instead of scoring based on the available range of study powers. Therefore, the maximum score for the checklist was 28. The Downs and Black score ranges were assigned according to quality levels into four groups: less than 14 (low), 14–18 (moderate), 19–23 (good), and more than 23 (excellent) [29]. The quality of each study was independently assessed by two reviewers, with discrepancies resolved through discussion.

Data Synthesis and Statistical Analysis

We converted any kind of risk estimates and any calculable information reported from the included studies to an odds ratio (OR) for pooled result calculation. Heterogeneity between studies was tested by Cochrane chi-square χ^2 (Cochran *Q*) and I^2 statistic. The *P* value less than 0.1 was set as a threshold for statistical significance in using Cochran's *Q* statistical test to assess heterogeneity [30]. Threshold interpretation of heterogeneity in I^2 statistic was considered as low, moderate, and high for I^2 upper limits of 25%, 50%, and 75%, respectively [31]. A sensitivity analysis was conducted by removing single studies to determine if any individual study has a significant impact on the pooled OR. All analyses were conducted using STATA software version 16.1 (StataCorp LLC, Texas, USA).

RESULTS

Literature Systematic Search

A total of 204 records were screened from the literature search. Figure 1 shows the study selection process for articles included in meta-analysis. There was no disagreement between the two independent reviewers who conducted the study selection. We found five published retrospective studies using AMD diagnosis criteria based on the International Classification of Diseases Ninth and/or Tenth Edition (ICD-9, ICD-10) listed in Supplementary Material B with metformin medication documented from the medical records examining the relationship between AMD and the use of metformin medications (Table 1). Table 2 provides the methodological quality assessment of each included study according to the Downs and Black tool. All included studies were of moderate quality with scores ranging from 15 to 17 points, out of a possible 28 points.

Three studies were conducted in the USA. The first study [32] analysed 7788 patient records (1947 AMD and 5841 non-AMD) of people aged 55 years and older from the University of Florida electronic health record

who attended at least four times from June 2011 to June 2017, and found that metformin was associated with substantially decreased risk of developing any AMD (ICD-9 diagnostic codes) using univariate analysis (OR 0.39; 95% CI 0.31–0.49, $P < 0.001$) and conditional multivariable logistic regression (OR 0.58; 95% CI 0.43–0.79, $P < 0.001$). In a subgroup analysis just of patients with diabetes, metformin use had decreased odds of developing any AMD (OR 0.70; 95% CI 0.49–0.98, $P = 0.043$). This study suggests a large reduction in risk of any AMD associated with metformin use, but is limited by its retrospective use of routine health records. Causality of course is not demonstrated since other inevitable exposure cannot be controlled in a non-randomised study and possibility of data misclassification.

The second study in the USA [33] gathered data from University of California San Francisco electronic medical record of people aged 60 years and older with diabetes, and having an ophthalmology encounter from April 2012 to August 2019. It reported that in 3120 patients, metformin was associated with decreased odds of any AMD (OR 0.70; 95% CI 0.55–0.88, $P = 0.003$) and non-neovascular AMD (OR 0.59; 95% CI 0.46–0.77, $P < 0.001$) using propensity score-weighted logistic regression models. It should be noted that this study only included patients who had seen an ophthalmologist, and this is more likely if they have AMD. This is a potential source of bias.

The third study in the USA [34] used data of 624,780 patient records (312,404 AMD and 312,376 non-AMD) of people aged 55 years and older who had eye examinations at least two times during the previous 12 months from IBM MarketScan Commercial and Medicare Supplemental Databases from January 2008 to December 2017. In multivariable logistic regression analysis, the use of metformin was reported to slightly lower the odds of having any AMD in a whole study population (OR 0.94; 95% CI 0.92–0.96, $P < 0.001$) and in a subgroup of people with diabetes (OR 0.95; 95% CI 0.93–0.97, $P < 0.001$). The metformin doses of 1–270 g over 2 years had the highest reduction in odds of having AMD (OR 0.91; 95% CI 0.89–0.94, $P < 0.001$) compared to higher doses

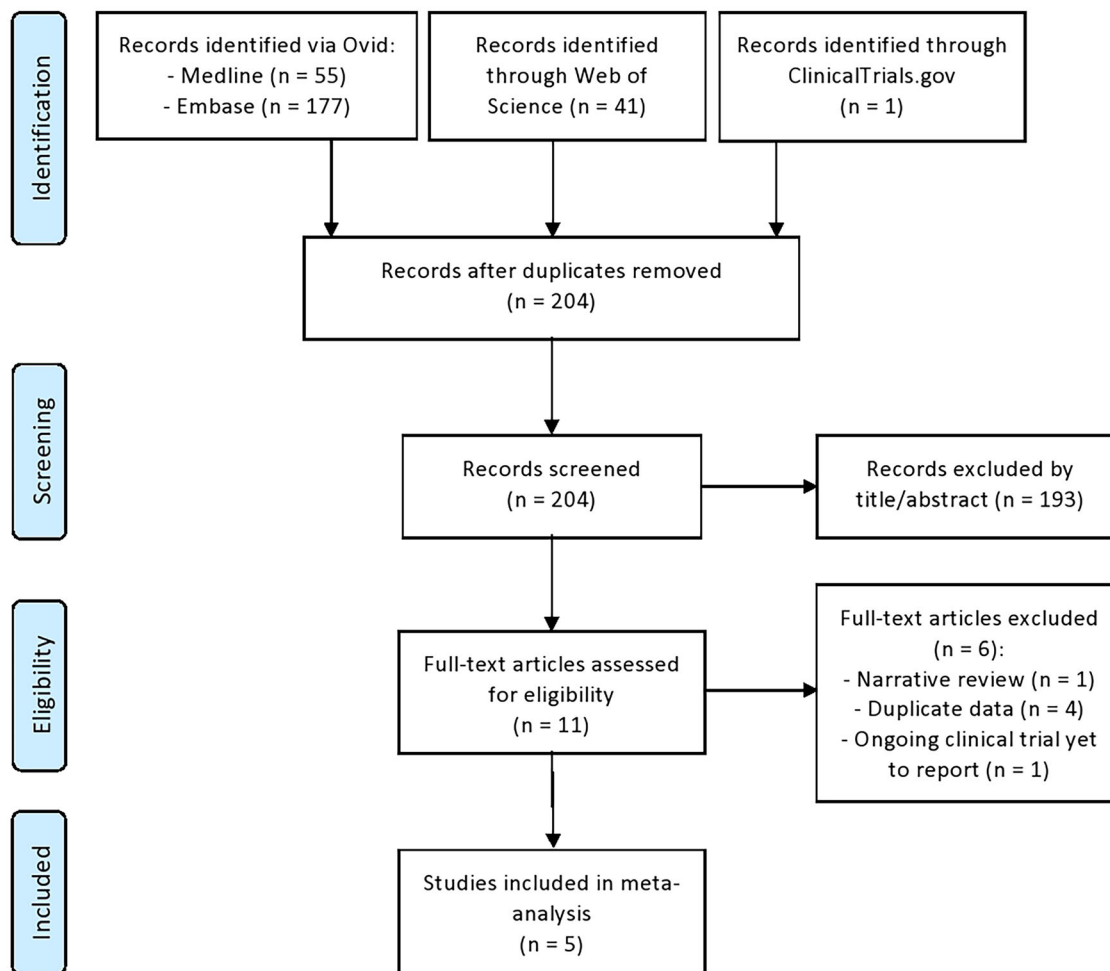


Fig. 1 PRISMA flowchart of study selection process

in a whole study population. This study matched the risk factors and comorbidities within 1 year before the index date, while metformin exposure was within 2 years before the index date. This introduced a risk of bias in sample selection since the comorbidities may have developed after metformin exposure.

A study in Taiwan [35] was a population-based retrospective cohort study in patients with T2DM (45,524 patients taking metformin and 22,681 control subjects) using the Taiwan National Health Insurance Research Database from 2001 to 2013. Cox regression analysis demonstrated substantially less AMD developing within the metformin group after adjusting for age, sex, and systemic comorbidities compared to controls (HR 0.54; 95% CI 0.50–0.58,

$P < 0.001$). People in the metformin group were still at a lower risk of AMD after adjustment of propensity score in the Cox regression analysis (HR 0.57; 95% CI 0.52–0.63, $P < 0.001$). Decreasing risk of AMD was observed with a longer duration and higher dose of metformin (Cox regression analysis, $P < 0.05$).

A study in Korea using National Health Insurance Service data [36] included 2330 cases of AMD and 23,278 controls from patient records of people who were diagnosed with diabetes or cardiovascular diseases in 2002. Metformin users had no reduction in any AMD (ICD-10 diagnostic code) risk (adjusted OR 1.15, 95% CI 0.91–1.45). The study concluded that metformin was not associated with a decreased risk of any AMD after adjusting for

Table 1 Summary of five studies included in the meta-analysis

First author, year (country)	Data source	Sample size (met/total)	Study design	Inclusion period	Age (year)	Diagnostic criteria	Adjusted effect sizes (95% CI)	Adjustment variables
Blitzer et al. 2021 (USA) [34]	In people with diabetes IBM MarketScan commercial and medicare supplemental databases	76,968/ 160,759	Retrospective	January 2006–December 2017	≥ 55	ICD-9 and ICD-10	0.95 (0.93–0.97)	Age, sex, region, hypertension, hyperlipidaemia, obesity, CCI score, diabetes, smoking, diabetic medications, statins, and DR
	In people with and without diabetes							
	IBM MarketScan commercial and medicare supplemental databases	80,811/ 624,780	Retrospective	January 2006–December 2017	≥ 55	ICD-9 and ICD-10	0.94 (0.92–0.96)	Age, sex, region, hypertension, hyperlipidaemia, obesity, CCI score, smoking, diabetic medications, statins, and DR
Stewart et al. 2020 (USA) [33]	University of California San Francisco electronic medical record of diabetes patients	1807/3120	Retrospective	April 2012–August 2019	≥ 60	ICD-9 and/or ICD-10	0.70 (0.55–0.88)	Age, smoking status, metabolic syndrome, and socioeconomic status (insurance status, gender, and race)

Table 1 continued

First author, year (country)	Data source	Sample size (met/total)	Study design	Inclusion period	Age (year) criteria	Diagnostic criteria	Adjusted effect sizes (95% CI)	Adjustment variables
Brown et al. 2019 (USA) [32]	In people with diabetes Integrated data repository from University of Florida health clinic	660/4947	Retrospective	June 2011–June 2017	≥ 55	ICD-9	0.70 (0.49–0.98)	Age, sex, race, insurance status, BMI, CCI score, hypertension, ocular comorbidities, and medications used
	In people with and without diabetes							
	Integrated data repository from University of Florida health clinic	695/7788	Retrospective	June 2011–June 2017	≥ 55	ICD-9	0.58 (0.43–0.79)	Age, sex, race, insurance status, BMI, CCI score, diabetes, hypertension, ocular comorbidities, and medications used
Chen et al. 2019 (Taiwan) [35]	Taiwan National Health Insurance Research Database of newly diagnosed T2DM patient	45,524/ 68,205	Retrospective	January 2001–31 December 2013	≥ 43	ICD-9	0.54 (0.50–0.58)	Age, sex, hypertension, hyperlipidaemia, coronary artery disease, obesity, DR, chronic kidney disease, and insulin treatment

Table 1 continued

First author, year (country)	Data source	Sample size (met/total)	Study design	Inclusion period	Age (year) criteria	Diagnostic criteria	Adjusted effect sizes (95% CI)	Adjustment variables
Lee et al. 2019 (South Korea) [36]	Korean National Health Insurance Service Database Record of patients with diabetes or cardiovascular diseases	1173/ 25,608	Retrospective	January 2012–December 2015	≥ 65	ICD-10	1.15 (0.91–1.45)	Income level, CCI, number of prescriptions, cerebrovascular disease history, complicated or uncomplicated diabetes, hyperlipidaemia, hypertension and peripheral vascular disease, and medications used. Cases and controls are matched by age, sex, cohort entry date, and follow-up duration

BMI body mass index, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *DR* diabetic retinopathy, *ICD* International Classification of Diseases, *T2DM* type 2 diabetes mellitus, *USA* United States of America

Table 2 Results of study quality assessment using the Downs and Black assessment tool

Study ID	Reporting	External validity	Internal validity		Power	Total
			Bias	Confounding		
Blitzer et al. [34]	9	1	3	3	1	17
Stewart et al. [33]	8	1	2	3	1	15
Brown et al. [32]	9	1	3	3	1	17
Chen et al. [35]	9	1	3	3	1	17
Lee et al. [36]	9	1	3	3	1	17

socioeconomic status, healthcare resource utilization, combined medication use, and comorbidities. Compared to other studies, only this study included people with cardiovascular diseases as the study population. This is a potential source of bias as cardiovascular disease is reported to have an association with AMD [37–40].

We identified that there are no published prospective studies that have investigated metformin in AMD. Only two studies in the meta-analysis presented the association of metformin and AMD in people with and without diabetes [32, 34] and one study in people with diabetes or cardiovascular disease [36]. A phase 2 randomized clinical trial study began in 2016 to investigate the effects of metformin on the progression of geographic atrophy and drusen in AMD in patients without diabetes initiated by University of California; no data or results have been reported (ClinicalTrials.gov Identifier NCT02684578). The clinical trials completion date is expected in October 2021.

META-ANALYSIS

We performed a meta-analysis for the association of metformin and any AMD in people with diabetes. We could not generalize the results in people without diabetes, as only two studies reported data in this group [32, 34]. We analysed ‘any AMD’ since all studies included all AMD, not only atrophic and neovascular AMD, but also unspecified form of macular degeneration (Supplementary Material B). Only one study presented data of an AMD subtype, non-

neovascular AMD, in the analysis [33]. Thus, it is not possible to perform meta-analysis by classifying the AMD subtypes.

The forest plot of our meta-analysis from the adjusted effect estimates of five retrospective studies is shown in Fig. 2. The overall OR of any AMD from metformin use was 0.80 with 95% CI 0.54–1.05. In a sensitivity analysis, the OR remained stable and the upper limit of the confidence interval remained close to 1.0, affecting the statistical significance (removing study by Blitzer et al. [34]: OR 0.75, 95% CI 0.52–0.97, $P < 0.001$, $I^2 = 87.1\%$; Stewart et al. [33]: OR 0.82, 95% CI 0.53–1.12, $P < 0.001$, $I^2 = 99.1\%$; Brown et al. [32]: OR 0.82, 95% CI 0.54–1.11, $P < 0.001$, $I^2 = 99.1\%$; Chen et al. [35]: OR 0.87, 95% CI 0.70–1.05, $P = 0.002$, $I^2 = 79.7\%$; Lee et al. [36]: 0.72, 95% CI 0.44–1.01, $P < 0.001$, $I^2 = 99.1\%$).

The heterogeneity of included studies was high ($I^2 = 98.8\%$). After excluding study by Chen et al. [35] and Blitzer et al. [34], we observed that the heterogeneity I^2 decreased from 98.8% to 79.7% and 87.1%. We did not perform stratified analysis across a number of participants characteristic because of the small number of studies included.

DISCUSSION

In this novel systematic review and meta-analysis, we found a beneficial odds ratio between metformin use and decreased risk of AMD from retrospective data, although it is not statistically significant. Retrospective, routinely collected data will not determine whether metformin will

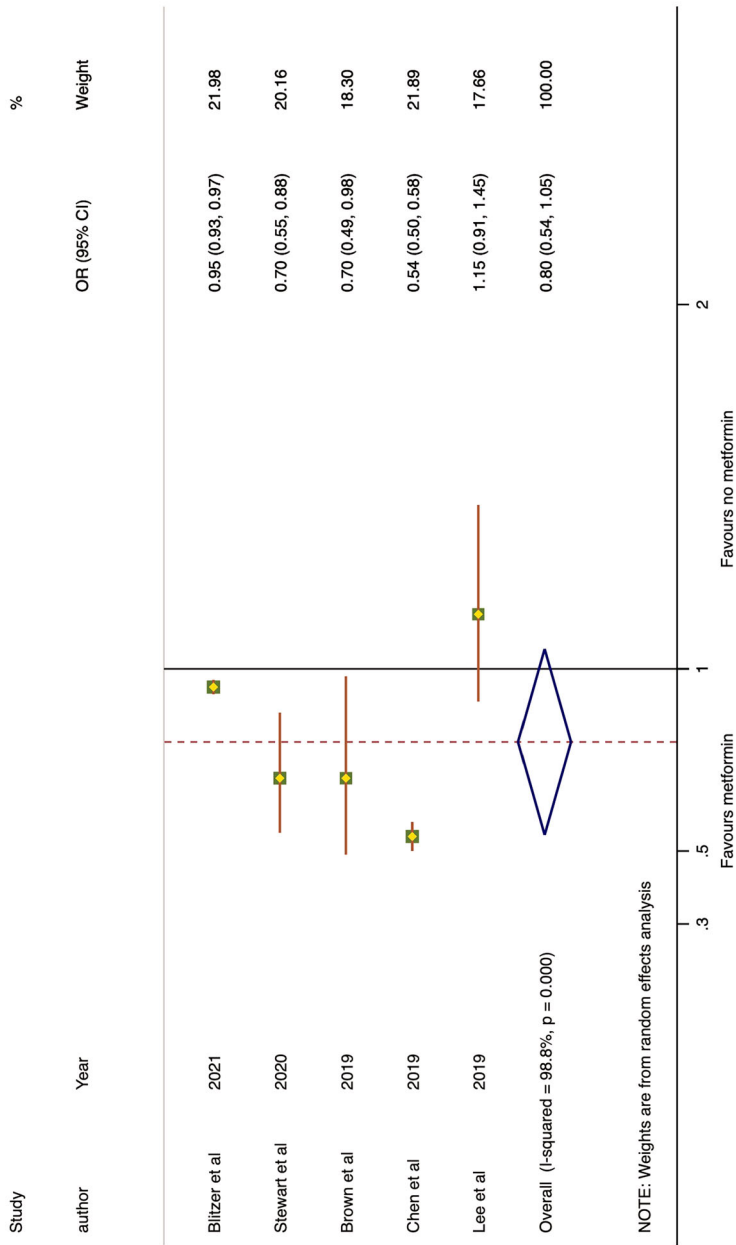


Fig. 2 Forest plot on the association between metformin use and age-related macular degeneration from five retrospective studies (data from adjusted effect estimates). The dot box and the horizontal line indicate the odds ratio (OR) and 95% confidence intervals (CI) for each study. The size of the dot box is proportional to the percentage weight of each study. The blue diamond indicates the pooled OR

be of benefit for AMD, but the signal found justifies further research and clinical investigation. AMD is by far the commonest cause of blindness in wealthy countries with currently no treatment for the majority.

In the epidemiological studies, people with diabetes have shown a greater burden of AMD [41–43]. The pathophysiology of AMD is thought to share some pathways with diabetes, especially oxidative stress and chronic inflammation [41, 42, 44–48]. Laboratory and clinical studies have investigated the potential role of metformin in suppression of oxidative stress [49] and inflammation [50], supporting the hypothesis of its potential role in delaying AMD progression.

Metformin is considered to have a beneficial role in ageing-related diseases owing to its antioxidant [51–55] and anti-inflammatory effects [50]. Metformin suppresses oxidative stress on retinal pigment epithelium (RPE) by stimulating the AMPK (adenosine monophosphate-activated protein kinase) signalling pathway in an AMD mouse model [20]. The model uses sodium iodate to cause oxidative damage to RPE that imitates the oxidative stress in early AMD. AMPK is a cellular mechanism that is activated in response to metabolic stress conditions to restore energy homeostasis through balancing the adenosine triphosphate (ATP) levels [56]. ATP is vital to meet the high metabolic demands of the retina and RPE [57, 58]. Increased ATP levels are observed in the retinal degenerative mouse model treated with metformin [20].

Ageing and oxidative stress are not only known for causing increased intracellular damage but are also thought to be related to impaired autophagy [59]. Metformin is able to induce autophagy and reduce apoptosis of retinal cells caused by vital dyes, indocyanine green (ICG) and brilliant blue G (BBG), in studies on human RPE cell lines (ARPE-19) and rat models [60]. This suggests the possible role of metformin in improving autophagy processes in AMD. Autophagy is important in cellular homeostasis for clearance of dysfunctional cell components [61]. A significant decrease in cellular autophagy is presumed to play an important role in development of AMD [62–64].

A systematic review and meta-analysis of metformin in neurodegenerative disease included 14 studies (seven cohorts, four cross-sectional, two RCTs, and one case–control) showed a protective effect against neurodegenerative diseases in patients with T2DM including dementia, Alzheimer's disease, and cognitive impairment in the elderly [22]. These findings in other diseases that associated with age and AMD [39–41, 65] promote a potential role for metformin delaying AMD and preventing its progression.

Abnormal angiogenesis driven by VEGF defines the neovascular form of AMD [66]. Metformin decreases levels of serum VEGF [67], so might have an effect on the macula angiogenic pathway. In mouse model and cultured human umbilical vein endothelial cell (HUVEC) studies of ischaemia-related retinopathy, metformin suppressed the vascular endothelial growth factor receptor (VEGFR) Flk-1, the key mediator of the angiogenic effects of VEGF [68]. Metformin is reported to reduce tumour progression with its antiangiogenic effect through suppression of hypoxic factors [69]. However in other studies, metformin has a cardioprotective effect by inducing angiogenesis, reducing angiogenic inhibitors, and increasing VEGFA [70]. The contradictory results of different studies on the angiogenic effects of metformin are thought to be due to tissue-specific angiogenic pathways [19, 71]. Further research is needed to know the effect of metformin on angiogenesis in nAMD.

The transdifferentiation of cells to myofibroblasts or epithelial–mesenchymal transition (EMT) is related to subretinal fibrosis in AMD [72]. Suppression of EMT in RPE is reported to attenuate fibrosis [73], and metformin inhibits hypoxia-induced EMT in keloid fibroblasts [74]. Thus, EMT is a potential target of metformin in reducing fibrosis associated with late-stage AMD, warranting further research.

We have followed PRISMA and STROBE guidelines and using the adjusted effect estimates in the meta-analysis to ensure reliable results. However, some limitations need to be considered when interpreting our results. First, the literature search was limited to studies written in English, so there might be a language

bias. Second, significant heterogeneity between studies exists, thereby limiting the strength of conclusions from this meta-analysis. Third, the population of included studies was based on US and East Asian populations, thus further studies in other locations and ethnicities are required. Our meta-analysis only included patients with diabetes as almost all patients routinely on metformin have diabetes; however prospective studies in non-diabetic populations are required to determine if an association exists in patients without diabetes. There is a first clinical trial investigating the effects of metformin on the progression of geographic atrophy and drusen in AMD in patients without diabetes (ClinicalTrials.gov Identifier NCT02684578). If this trial is positive, larger multicentre phase 2 and 3 studies will be needed to determine the clinical role of metformin in treating AMD.

Lastly, the studies included in our meta-analysis are retrospective, relatively few in number, and rely on data collected for other purposes. Therefore, the results must be interpreted cautiously. They use broad diagnostic categories of AMD so give no indication as to whether metformin may be beneficial in preventing progression of early AMD or improving outcomes in more advanced AMD. However, overall, they provide a signal of a possible beneficial effect of metformin in AMD. Although it is not statistically significant, further investigation into metformin's effect on AMD in prospective studies is warranted.

CONCLUSION

At present, data from five retrospective clinical studies include four with large reductions in risk of AMD associated with metformin. This is reflected in our meta-analysis albeit with an OR which does not meet significance at the 5% level. Given metformin's potential favourable effects on AMD's pathophysiology, a reduction in risk seems plausible.

Prospective studies of metformin in AMD are needed to elucidate fully the role of metformin in AMD, as none reporting results were identified. The use of data and images from populations that are routinely screened for diabetic

retinopathy also provides an opportunity to investigate metformin's effect on AMD cost-effectively before conducting randomized clinical trials, since the data is collected prospectively and systematically. There is certainly an unmet treatment need at all stages of AMD which metformin has an exciting potential to fulfil. The mechanism of metformin as a treatment in AMD might due to its antioxidant, anti-inflammatory, antiangiogenic, and antifibrotic effects. Further study is needed to investigate whether these beneficial effects on RPE cells and in animal models are replicated in patients with AMD.

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has been submitted; and agree to be accountable for all aspects of the work.

Disclosures. Dewi Fathin Romdhoniyyah, Simon P Harding, Christopher P Cheyne, Nicholas AV Beare have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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