J Nephropharmacol. 2024; 13(2): e12690.

https://jnephropharmacology.com DOI: 10.34172/npj.2024.12690

Journal of Nephropharmacology

The relationship between metformin administration and age-related macular degeneration; a systematic review and meta-analysis of observational studies

Abdulateef Abdulkadhium Mashaf[1*], Mohammed Abdul-Mounther Othman[2], Omer Mansib Kassid[3], Hakim S. Sultan Aljibori[4], Abdul Amir H Kadhum[5], Ahmed Ali Mohammed[6], Raed Muslim Mhaibes[7]

[1]General Directorate of Missan Education, Iraqi Ministry of Education, Missan, Iraq
[2]Department of Biochemistry, College of Medicine, Missan University, Missan, Iraq
[3]College of Medicine, University of Missan, 62001 Missan, Iraq
[4]College of Engineering, University of Warith Al-Anbiyaa, Karbala, Iraq
[5]University of Al-Ameed, Karbala, Iraq
[6]Dental Technology Department, College of Medical Technology, Al-Farahidi University, Baghdad, Iraq
[7]Department of Biochemistry College of Medicine Missan University, Missan Iraq

ARTICLE INFO

Article Type:
Meta-analysis

Article History:
Received: 15 Mar. 2024
Accepted: 30 May 2024
ePublished: 29 Jun. 2024

Keywords:
Glucophage, Metformin, Metformin hydrochloride, Macular degeneration, Age-related macular degeneration

ABSTRACT

Introduction: Vision loss due to age-related macular degeneration (AMD) is a major and growing health issue. Given that no definitive treatment is available for AMD, this study aims to evaluate the association between metformin use and AMD risk using a systematic review and meta-analysis approach.

Materials and Methods: In this study, databases including ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar search engines were searched without time restriction until April 20, 2024, based on PRISMA statement guidelines. Data were analyzed using STATA 14 software at a significance level of $P < 0.05$.

Results: Overall, metformin administration reduced the risk of AMD (OR: 0.86, 95% CI: 0.80, 0.94). Concerning the dosage, a metformin dose of 1-270 g per 2 years (OR: 0.93, 95% CI: 0.90, 0.96) and 271-600 g per 2 years (OR: 0.91, 95% CI: 0.89, 0.94) mitigated the risk of AMD. Metformin use in women increased the risk of AMD (OR: 1.14, 95% CI: 1.09, 1.18). However, no significant relationship was noticed between metformin use and AMD risk in men (OR: 0.86, 95% CI: 0.73, 1.01). In addition, metformin was associated with a lower risk of AMD in case-control (OR: 0.93, 95% CI: 0.89, 0.97) and cohort (OR: 0.69, 95% CI: 0.51, 0.95) studies. Likewise, metformin use was associated with a lower risk of AMD in the age groups of 50-59 years (OR: 0.54, 95% CI: 0.50, 0.58) and 70-79 years (OR: 0.90, 95% CI: 0.84, 0.97).

Conclusion: Metformin administration lowered the risk of AMD by 14%. Moreover, female gender was identified as a risk factor for AMD development. However, further studies are required on this subject to reach a definite conclusion.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024539904) and Research Registry (UIN: reviewregistry1824) website.

Meta-analysis

Implication for health policy/practice/research/medical education:
Our systematic review and meta-analysis of observational studies showed, metformin can lower the risk of age-related macular degeneration by 14%.

Please cite this paper as: Abdulkadhium Mashaf A, Abdul-Mounther Othman M, Mansib Kassid O, S. Sultan Aljibori H, Amir H Kadhum A, Ali Mohammed A, Muslim Mhaibes R. The relationship between metformin administration and age-related macular degeneration; a systematic review and meta-analysis of observational studies. J Nephropharmacol. 2024;13(2):e12690. DOI: 10.34172/npj.2024.12690.

***Corresponding author**: Abdulateef Abdulkadhium Mashaf, Email: abdalatif451992@gmail.com

Introduction

Age-related macular degeneration (AMD) is a progressive retinal disorder that affects the central part of the retina, known as macula (1). AMD is the leading cause of irreversible vision loss in individuals above 65 years in industrialized countries (2). From a clinical perspective, AMD is classified into different stages: early, intermediate, and two late stages (3). The estimated number of patients affected by AMD was 196 million in 2020 and is projected to reach 288 million people globally by 2040. The population aging is considered a significant reason for the rising incidence of AMD (4). In addition, AMD is a multi-factorial condition that is caused by a combination of a strong genetic component and environmental risk factors, including advanced age, smoking, obesity, hypertension, and hypercholesterolemia (5).

Metformin is an oral antidiabetic medication. However, evidence suggests that metformin can exert several beneficial effects beyond its antidiabetic action (6-8). It can reduce retinal cell necrosis induced by various pathological factors, mitigate diabetic retinopathy, and inhibit corneal and intraocular neovascularization (9-13). Additionally, metformin plays a role in increasing lifespan and lowering the risk of age-related conditions, such as cancer, diabetes mellitus, and cardiovascular diseases (14,15).

At present, there is no therapeutic method available to delay or prevent the progression of AMD during early stages (16). Inconsistencies exist among the studies examining the relationship between metformin use and AMD risk. While some previous studies could not report a statistically significant relationship between metformin and AMD risk (17,18), others have found metformin administration beneficial in reducing the risk of AMD (19,20). Based on these considerations, the present study aims to assess the relationship between metformin use and AMD risk using a systematic review and meta-analysis approach.

Materials and Methods

Study design

This research adopted a systematic review and meta-analysis approach based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (21). The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) website.

Search strategy

International databases, including ProQuest, PubMed, Web of Science, Cochrane, and the Google Scholar search engine, were searched without time and location restrictions from the inception until April 20, 2024. The search query was developed using Medical Subject Headings (MeSH) keywords, including "Metformin," "Metformin Hydrochloride," "Glucophage," "Macular Degeneration," and "Age-related Macular Degeneration." Different combinations of keywords with the Boolean operators "AND" and "OR" were used to ensure an extensive search. Moreover, for completeness of the research and maximum coverage, the reference lists of the initially identified studies were searched to identify additional studies. The search strategy for PubMed included the following: (Glucophage OR Metformin OR Metformin Hydrochloride) AND (Macular Degeneration OR Age-Related Macular Degeneration).

PICO components

- Population: Observational studies assessing the effect of metformin use on AMD.
- Intervention: Metformin use.
- Comparison: Individuals who did not use metformin.
- Outcome: The risk of AMD.

Inclusion criteria

Studies that met the following criteria entered the systematic review: observational studies whose objective was to study the effect of metformin on AMD.

Exclusion criteria

The exclusion criteria for the studies were as follows: clinical trials, meta-analyses, abstract meetings, mini-review studies, the unavailability of the full text, duplicate studies, studies with poor quality, studies with incomplete data for analysis, and studies that evaluated the effect of metformin combined with another drug.

Quality assessment of the studies

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was utilized to assess the quality of the retrieved articles (22). This checklist contains 22 questions, with its final score ranging from 0 to 44. The cutoff point of this checklist was a score of 18. Discrepancies in responses to the checklist items were assessed, and a single choice was selected by consensus.

Data extraction

Two researchers extracted the data using a checklist containing the author's name, publication year, country, study type, sample size and age, the odds ratio between metformin use and AMD, and its 95% confidence interval. A third researcher checked the extracted data to resolve any inconsistencies.

Statistical analysis

Logarithmic odds ratio (OR) was obtained for each study and used to pool the results. The I^2 index was employed to assess heterogeneity. Additional analyses, including meta-regression and publication bias, were conducted as well. A random-effect model was applied in this study. Data were analyzed using STATA software version 14 at a significance level of $P<0.05$.

Results

Study selection

Of the 279 articles retrieved from the initial search, 112 duplicates were removed. Abstracts of the remaining 167 articles were reviewed, and 16 studies were removed as their full text was unavailable. The full text of 151 articles was screened, and 31 articles were discarded due to incomplete data for analysis. Of the remaining 120 articles, 105 were excluded based on the other exclusion criteria. Eventually, 15 articles entered meta-analysis (Figure 1). This systematic review and meta-analysis involved six case-control studies, six cohort studies, and three cross-sectional studies. Table 1 provides details of the included studies.

Primary outcome

Figure 2 displays a statistically significant relationship between metformin use and AMD risk, indicating a significant reduction in AMD risk with metformin use (OR: 0.86, 95% CI: 0.80, 0.94).

Sub-group analysis

Figure 3 demonstrates that metformin use reduced the risk of AMD in case-control (OR: 0.93, 95% CI: 0.89, 0.97) and cohort (OR: 0.69, 95% CI: 0.51, 0.95) studies. However, cross-sectional studies found no statistically significant association between metformin use and AMD risk (OR: 0.99, 95% CI: 0.71, 1.38).

As Figure 4 illustrates, metformin use lowered the risk of AMD in the US (OR: 0.94, 95% CI: 0.89, 0.99), the Netherlands (OR: 0.69, 95% CI: 0.49, 0.98), China and Japan (OR: 0.24, 95% CI: 0.13, 0.43). Nevertheless, there was no statistically significant association between metformin and AMD risk in England (OR: 1.02, 95% CI: 0.92, 1.13), Taiwan (OR: 0.81, 95% CI: 0.54, 1.21), and South Korea (OR: 1.15, 95% CI: 0.91, 1.45).

According to Figure 5, metformin use mitigated the risk of AMD in the age groups of 50-59 years (OR: 0.54, 95% CI: 0.50, 0.58) and 70-79 years (OR: 0.90, 95% CI: 0.84, 0.97). Still, metformin use and AMD risk were not significantly related in the age groups of 40-49 years (OR: 1, 95% CI: 0.87, 1.15) and 60-69 years (OR: 0.96, 95% CI: 0.81, 1.15).

Notably, metformin use elevated the risk of AMD in women (OR: 1.14, 95% CI: 1.09, 1.18) (Figure 6). However, no statistically significant association was observed between metformin use and AMD risk in men (OR: 0.86, 95% CI: 0.73, 1.01) (Figure 7).

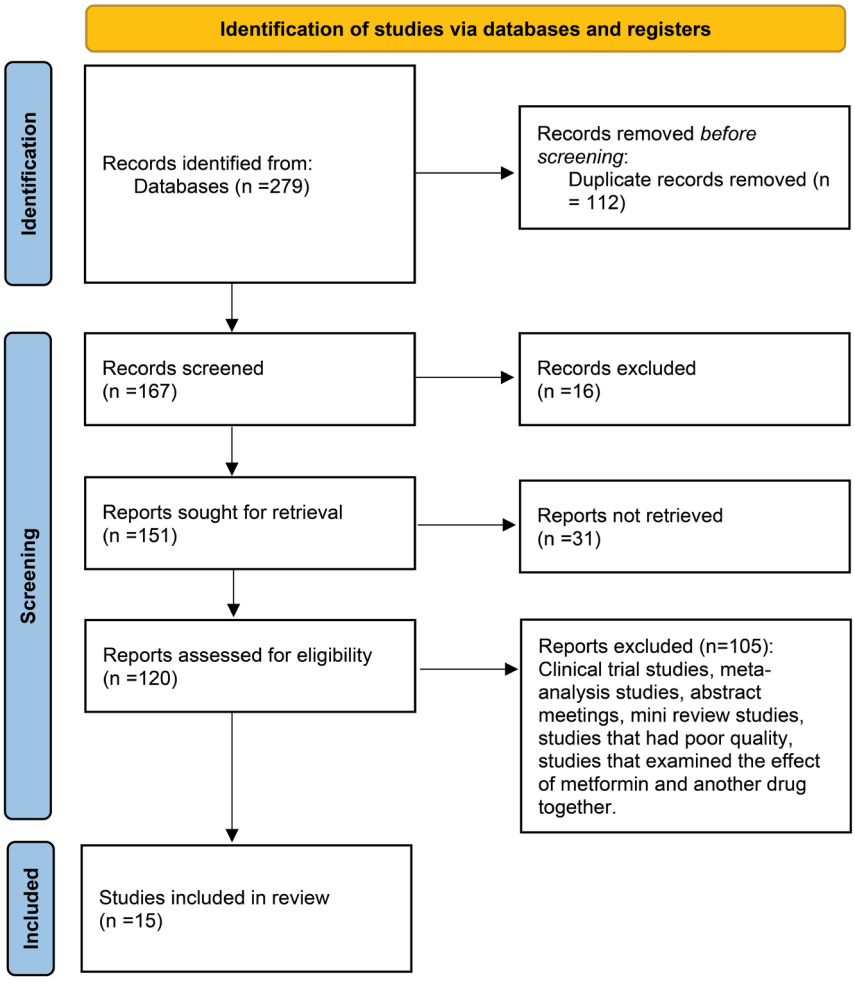

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Background data of articles

Index	First author, year	Country	Type of Study	Total number	Total age (year)	Number of metformin user	Age of metformin user (year)	Number of non-user(year)	Age of non-user	Duration of study
OR	Aggarwal S, 2024 (19)	USA	Case–control	NR	NR	231 142	75.1	232 879	74.9	2006 to 2017
OR	Khanna S, 2024 (20)	USA	Case–control	NR	NR	86 930	75.4	86 918	65.8	between January 2003 and December 2019
HR	Gokhale KM, 2023 (17)	UK	Cohort	173 689	62.8	NR	NR	NR	NR	1995-2019
OR	Huang KH, 2023 (23)	Taiwan	Cross-sectional	728 703	62.06	377 878	61.21	350 825	62.98	2001 to 2018
OR	Kaufmann GT, 2023 (24)	USA	Case–control	NR	NR	194 135	74.16	193 990	74.15	2008 and 2017
OR	Tseng CH, 2023 (25)	Taiwan	Cohort	NR	NR	13 303	>50	13 303	>50	1999 to 2005
OR	Domalpally A, 2023 (26)	USA	Cross-sectional	NR	NR	1592	NR	546	49.3	2017-2019
OR	Vergroesen JE, 2022 (27)	Netherlands	Cohort	11 260	65.1	NR	NR	NR	NR	between April 23, 1990, and June 25, 2014
OR	Jiang J, 2022 (28)	China-Japan	Cohort	NR	NR	209	66	115	68	September 2015 to August 2020
HR	Eton EA, 2022 (29)	USA	Cohort	1 007 226	67.5	NR	NR	NR	NR	2002 to 2016
OR	Blitzer AL, 2021 (30)	USA	Case–control	NR	NR	312 404	≥55	312 376	≥55	January 2008 to December 2017
OR	Stewart JM, 2020 (31)	USA	Cross-sectional	3120	≥ 60	NR	NR	NR	NR	from April 18, 2012 until August 31, 2019
OR	Brown EE, 2019 (32)	USA	Case–control	NR	NR	1947	75	5841	77	between June 1, 2011, and June 1, 2017
OR	Lee H, 2019 (18)	South Korea	Case–control	NR	NR	2330	66.5	23 278	66.4	between January 2012 and December 2015
HR	Chen YY, 2019 (33)	Taiwan	Cohort	NR	NR	45 524	55.2	22 681	57.8	2001 to 2013

NR, Not reported; OR, Odds ratio; HR, Hazard ratio.

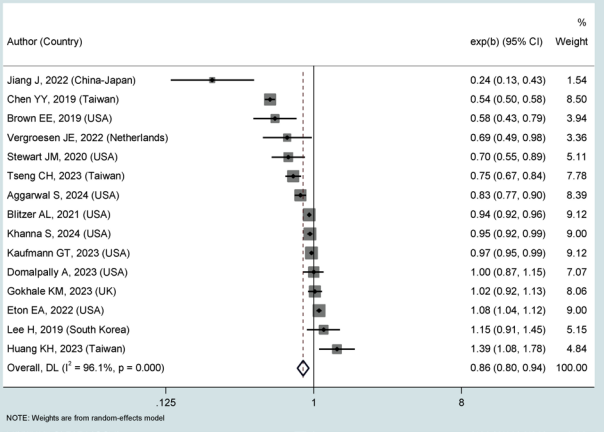

Figure 2. Forest plot of association between metformin administration and age-related macular degeneration with its 95% confidence interval.

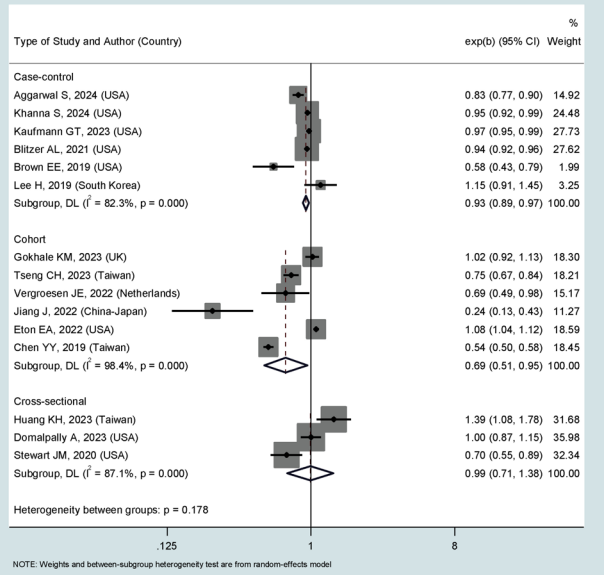

Figure 3. Forest plot of association between metformin use and age-related macular degeneration by type of study.

Furthermore, the results indicated no statistically significant relationship between metformin use and the risk of dry AMD (OR: 0.97, 95% CI: 0.88, 1.07) (Figure 8).

Metformin administration at a dose of 1-270 g per 2 yearsdecreased the risk of AMD (OR: 0.93, 95% CI: 0.90, 0.96) (Figure 9).

Similarly, metformin doses of 271-600 g per 2 years lowered the risk of AMD (OR: 0.91, 95% CI: 0.89, 0.94) (Figure 10).

However, a metformin dose of 600-1080 g per 2 years had no statistically significant effect on reducing the risk of AMD (OR: 0.96, 95% CI: 0.93, 1) (Figure 11).

Increasing metformin dosage to above 1080 g per 2 years did not significantly affect the AMD risk (OR: 1.03, 95% CI: 0.99, 1.08) (Figure 12).

Additional analysis

Meta-regression analysis found no statistically significant

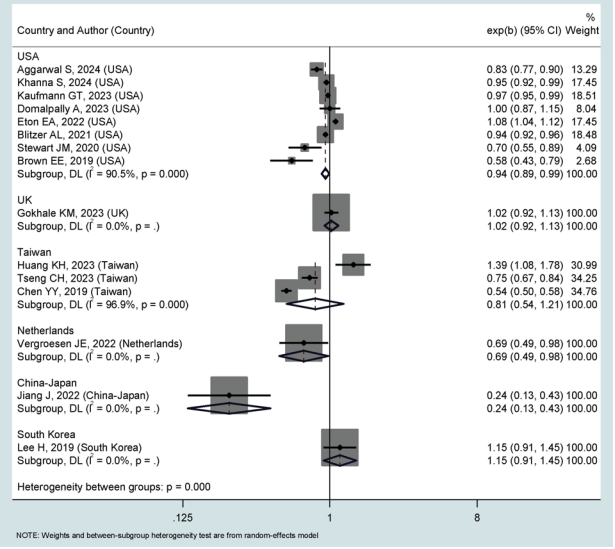

Figure 4. Forest plot of association between metformin use and age-related macular degeneration by countries.

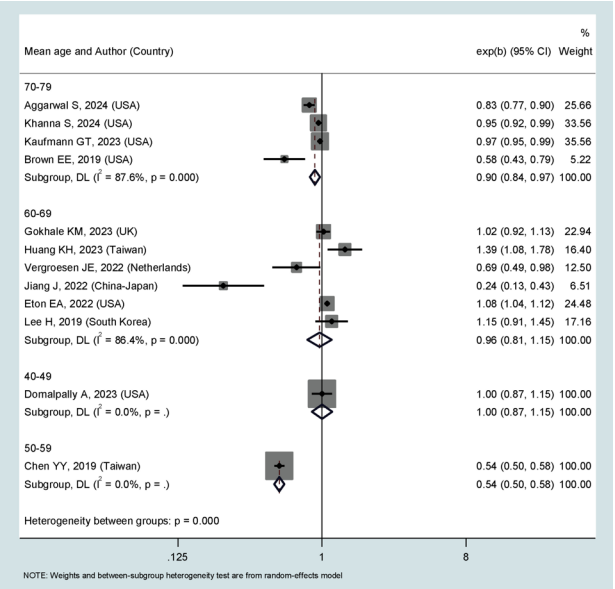

Figure 5. Forest plot of association between metformin use and age-related macular degeneration by mean age.

relationship between "the association between metformin use and the risk of AMD" and the sample size ($P = 0.136$) or publication year ($P = 0.243$) of the studies (Figures 13 and 14).

Figure 15 illustrates the publication bias plot. As shown, no publication bias was present, suggesting a comprehensive and unbiased literature search ($P = 0.191$).

Discussion

The results suggest that metformin use lowered the risk of AMD by 14%. Concerning the dosage, metformin doses of 1-270 g per 2 years and 271-600 g per 2 years were associated with a 7% and 9% reduction in the risk of

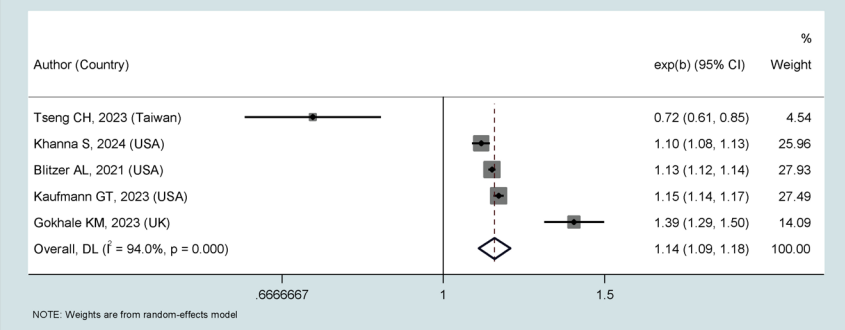

Figure 6. Forest plot of association between metformin use and age-related macular degeneration in women.

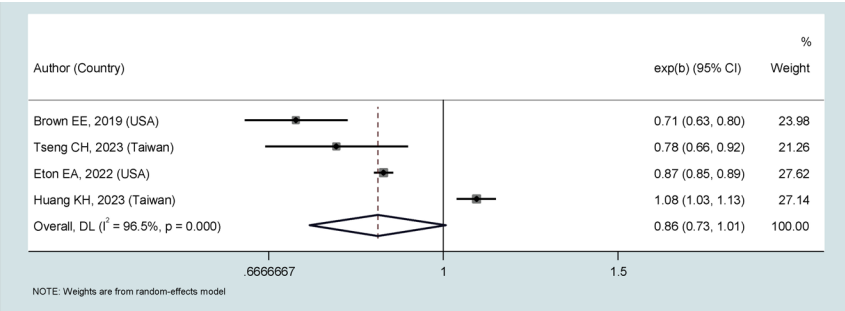

Figure 7. Forest plot of association between metformin use and age-related macular degeneration in men.

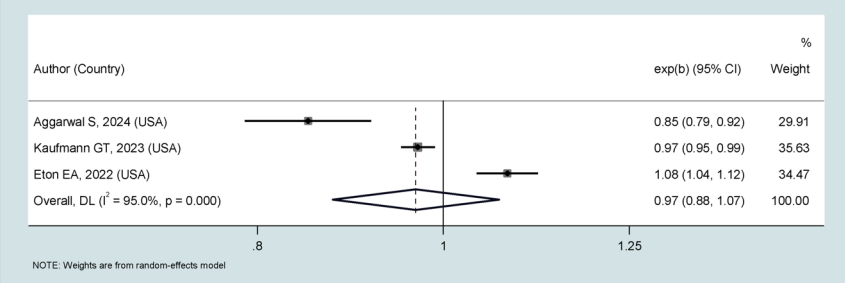

Figure 8. Forest plot of association between metformin use and dry age-related macular degeneration.

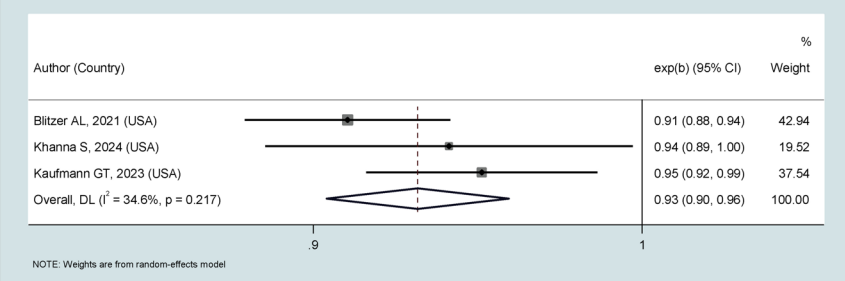

Figure 9. Forest plot of association between metformin administration and age-related macular degeneration for metformin dose 1–270 g per 2 years.

AMD, respectively. In addition, metformin administration caused a 7% reduction in AMD risk in case-control studies and a 31% reduction in cohort studies. Regarding the age of metformin users, the risk of AMD decreased by 46% in the age group of 50-59 years and 10% in the age group of 70-79 years. In women, metformin use increased the AMD risk by 14% and was considered a risk factor for AMD development. However, metformin was not significantly associated with AMD risk in men.

In a meta-analysis by Holtz et al, aiming to assess the

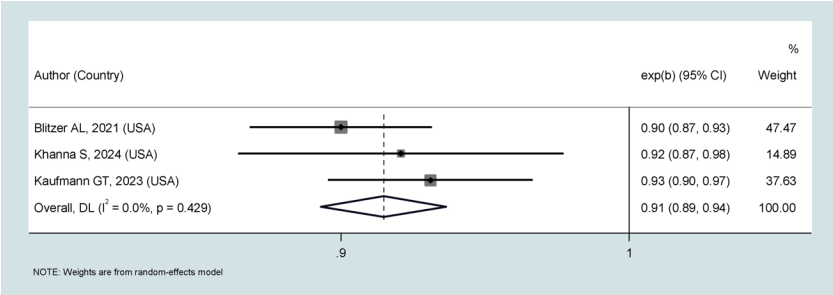

Figure 10. Forest plot of association between metformin administration and age-related macular degeneration for Metformin dose 271-600 g per 2 years.

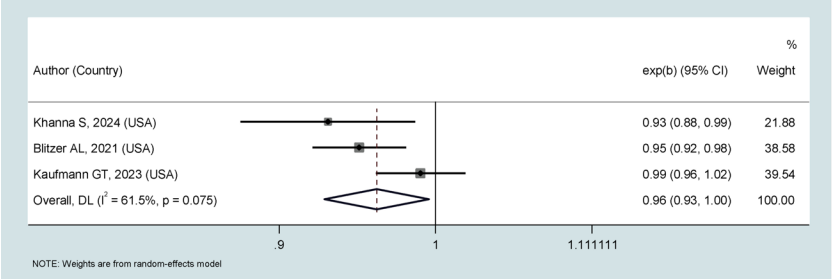

Figure 11. Forest plot of association between metformin use and age-related macular degeneration for Metformin dose 601-1080 g per 2 years.

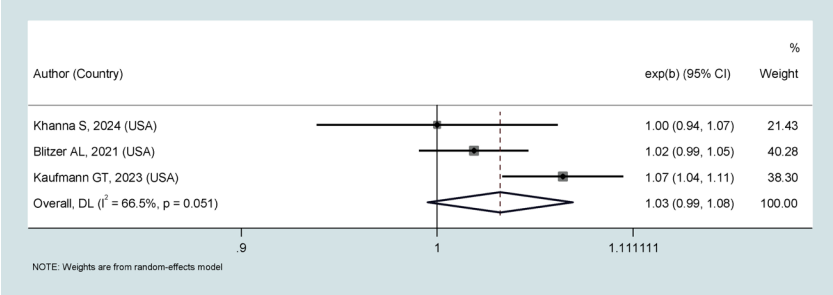

Figure 12. Forest plot of association between metformin use and age-related macular degeneration for Metformin dose >1080 g per 2 years.

relationship between oral metformin and AMD risk, the likelihood of AMD development was considerably lower in patients using metformin (OR: 0.63, 95% CI: 0.46, 0.86) (34). Another meta-analysis by Mauschitz et al studied the association between lipid-lowering and antidiabetic drugs with AMD in the European population. The results suggested that lipid-lowering drugs (OR: 0.85, 95% CI: 0.79, 0.91) and antidiabetic drugs (OR: 0.78, 95% CI: 0.66, 0.91) decreased the risk of AMD development (35). In a meta-analysis by Liang et al involving nine observational studies, metformin was associated with a lower risk of AMD (OR: 0.81, 95% CI: 0.70, 0.93) (36). Romdhoniyyah et al conducted a meta-analysis on five retrospective studies and concluded that patients taking metformin were less likely to develop AMD (OR: 0.80, 95% CI: 0.54, 1.05) (6). The results of the above studies indicate that metformin use can notably lower the risk of AMD.

In a systematic review, Dang et al reported the functions of metformin in regulating lipid metabolism, inhibiting inflammation, preventing retinal cell death, and inhibiting corneal neovascularization formation, which makes metformin a good candidate to prevent and treat AMD (37). The present meta-analysis is similar to the mentioned studies in terms of the type and outcome of the study. However, our study provided a more up-to-date and thorough search compared to past meta-analyses by including more studies and larger sample size. Moreover, our study involved a subgroup analysis to assess the effect of different variables, including age, location, gender, dose of metformin, and type of basic studies.

Kim et al performed a meta-analysis and reported no statistically significant relationship between metformin use and the incidence of open-angle glaucoma (HR: 1.05, 95% CI: 0.79, 1.40) (38). Tan et al performed an umbrella review of meta-analyses and found that patients taking metformin did not have a lower risk of diabetic retinopathy

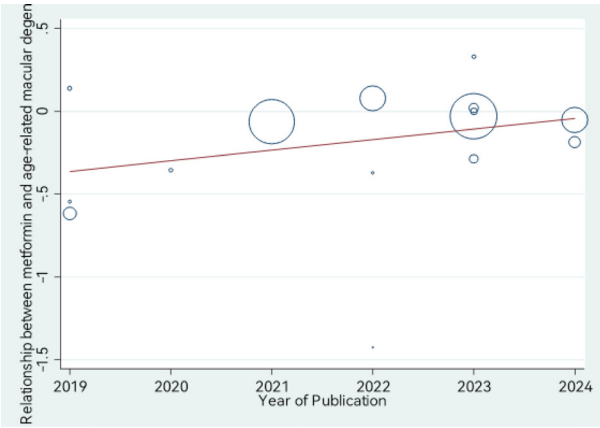

Figure 13. Meta-regression plot of association between metformin use and age-related macular degeneration by year of publication.

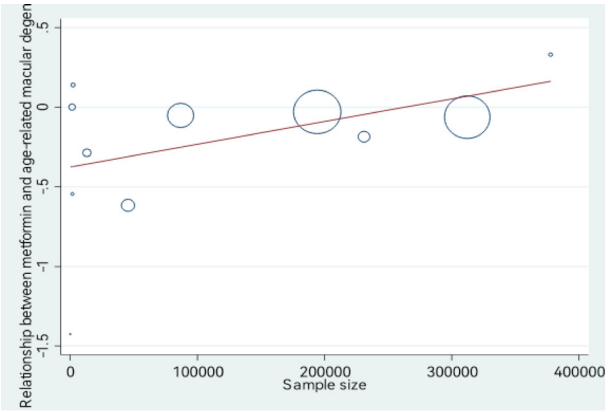

Figure 14. Meta-regression plot of association between metformin administration and age-related macular degeneration by sample size.

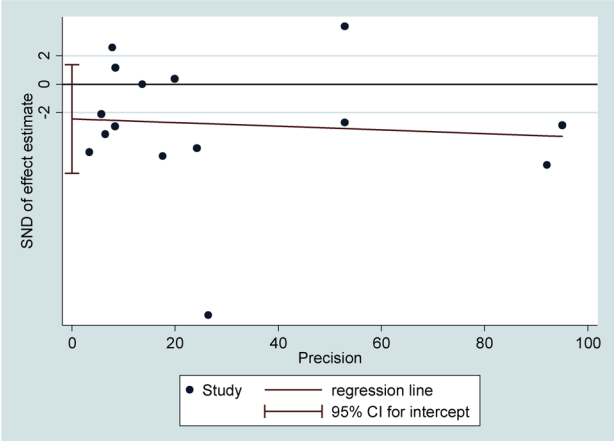

Figure 15. Publication bias.

than those using other antidiabetic drugs (RR: 1.15, 95% CI: 0.81, 1.63) (39). The results of these studies contradict our meta-analysis and highlight the ineffectiveness of metformin in reducing the risk of ocular diseases, such as open-angle glaucoma and diabetic retinopathy. However, it should be noted that the type of ocular disease examined in these studies differs from that of our study.

Other studies have addressed the favorable and significant effect of metformin on lowering the risk of certain conditions, which can support our result. According to the meta-analysis conducted by O'Connor et al, metformin was associated with reduced risk of cancer development in case-control (RR: 0.55, 95% CI: 0.30, 0.80) and prospective cohort (RR: 0.65, 95% CI: 0.37, 0.93) studies (40). A meta-analysis by Zhang et al revealed that taking metformin contributed to a lower incidence of cognitive disorders in diabetic patients (aHR: 0.92, 95% CI: 0.85, 0.99) (41). Another meta-analysis conducted by Campbell et al suggested a lower incidence of dementia in metformin users (HR: 0.76, 95% CI: 0.39, 0.88) (42).

Conclusion

In conclusion, metformin use decreased the risk of AMD by 14%, and a metformin dose of 271-600 g per 2 years was the most effective dose for lowering AMD risk. In addition, metformin administration reduced the risk of AMD by 46% in patients aged 50 to 59 years, and this age group achieved the most benefit from metformin taking. Moreover, metformin use is not recommended for women who are at risk of AMD development.

Study limitations

A limited number of cross-sectional studies have focused on this subject. Most studies did not report the type of AMD or the duration of drug consumption. Therefore, we were unable to perform an analysis based on the effect of metformin on different types of AMD or the duration of drug consumption. Thus, future studies are suggested to address these limitations.

Acknowledgments

The authors would like to thanks Hamid Nasri and Diana Sarokhani for guidance and editing of manuscript registration on the PROSPERO website.

Authors' contribution

Conceptualization: Abdulateef Abdulkadhium Mashaf.
Data curation: Abdulateef Abdulkadhium Mashaf, Mohammed Abdul-Mounther Othman.
Formal analysis: All authors.
Investigation: Abdulateef Abdulkadhium Mashaf, Raed Muslim Mhaibes.
Methodology: Omer Mansib Kassid, Hakim S. Sultan Aljibori, Abdul Amir H Kadhum.
Project administration: Abdulateef Abdulkadhium Mashaf.
Resources: All authors.
Supervision: Abdulateef Abdulkadhium Mashaf. **Validation:** Omer Mansib Kassid, Hakim S. Sultan Aljibori, Abdul Amir H Kadhum.
Visualization: Ahmed Ali Mohammed, Omer Mansib Kassid, Hakim S. Sultan Aljibori, Abdul Amir H Kadhum.
Writing–original draft: All authors.
Writing–review & editing: All authors.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website with (ID: CRD42024539904) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1824). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Conflicts of interest

The authors declare that they have no competing interests.

Funding/Support

None.

References

1. Fleckenstein M, Keenan T, Guymer R, Chakravarthy U, Schmitz-Valckenberg S, Klaver C, et al. Age-related macular degeneration. Nat Rev Dis Primers. 2021;7:31. doi: 10.1038/s41572-021-00265-2
2. Congdon N, Friedman D, Lietman T. Important causes of visual impairment in the world today. JAMA. 2003;290:2057-60. doi: 10.1001/jama.290.15.2057
3. Ferris III F, Wilkinson C, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013:844-51. doi: 10.1016/j.ophtha.2012.10.036
4. Wong W, Su X, Li X, Cheung C, Klein R, Cheng C, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014;2:e106-16. doi: 10.1016/S2214-109X(13)70145-1
5. Kaarniranta K, Uusitalo H, Blasiak J, Felszeghy S, Kannan R, Kauppinen A, et al. Mechanisms of mitochondrial dysfunction and their impact on age-related macular degeneration. Prog Retin Eye Res. 2020;79:100858. doi: 10.1016/j.preteyeres.2020.100858
6. Romdhoniyyah D, Harding S, Cheyne C, Beare N. Metformin, a potential role in age-related macular degeneration: a systematic review and meta-analysis. Ophthalmol Ther. 2021;10:245-60. doi: 10.1007/s40123-021-00344-3
7. Saisho Y. Metformin and inflammation: its potential beyond glucose-lowering effect. Endocr Metab Immune Disord Drug Targets. 2015;15:196-205. doi: 10.2174/1871530315666150316124019
8. Campbell J, Bellman S, Stephenson M, Lisy K. Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: a systematic review and meta-analysis. Ageing Res Rev. 2017:31-44. doi: 10.1016/j.arr.2017.08.003
9. Shu C, Tsen C, Li M, Bee Y, Lin S, Sheu S. Metformin and rapamycin protect cells from vital dye–induced damage in retinal pigment epithelial cells and in vivo. Graefes Arch Clin Exp Ophthalmol. 2020;258:557-64. doi: 10.1007/s00417-019-04548-z
10. Qu S, Zhang C, Liu D, Wu J, Tian H, Lu L, et al. Metformin protects ARPE-19 cells from glyoxal-induced oxidative stress. Oxid Med Cell Longev. 2020;2020:1740943. doi: 10.1155/2020/1740943
11. Liu D, Wu Q, Zhu Y, Liu Y, Xie X, Li S, et al. Co-delivery of metformin and levofloxacin hydrochloride using biodegradable thermosensitive hydrogel for the treatment of corneal neovascularization. Drug Deliv. 2019:522-31. doi: 10.1080/10717544.2019.1609623
12. Fan Y, Wu C, Lin J, Hsiung C, Liu H, Lai J, et al. Metformin treatment is associated with a decreased risk of nonproliferative diabetic retinopathy in patients with type 2 diabetes mellitus: a population-based cohort study. J Diabetes Res. 2020;2020:9161039. doi: 10.1155/2020/9161039
13. Ying Y, Ueta T, Jiang S, Lin H, Wang Y, Vavvas D, et al. Metformin inhibits ALK1-mediated angiogenesis via activation of AMPK. Oncotarget. 2017;8:32794-806. doi: 10.18632/oncotarget.15825
14. Fontana L, Partridge L, Longo V. Extending healthy life span—from yeast to humans. Science. 2010:321-6. doi: 10.1126/science.1172539
15. Anisimov V. Metformin for cancer and aging prevention: is it a time to make the long story short? Oncotarget. 2015;6:39398-407. doi: 10.18632/oncotarget.6347
16. Inzucchi S, Bergenstal R, Buse J, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55:1577-96. doi: 10.1007/s00125-012-2534-0
17. Gokhale K, Adderley N, Subramanian A, Lee W, Han D, Coker J, et al. Metformin and risk of age-related macular degeneration in individuals with type 2 diabetes: a retrospective cohort study. Br J Ophthalmol. 2023:980-6. doi: 10.1136/bjophthalmol-2021-319641
18. Lee H, Jeon H, Park S, Shin J. Effect of statins, metformin, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers on age-related macular degeneration. Yonsei Med J. 2019;60:679-86. doi: 10.3349/ymj.2019.60.7.679
19. Aggarwal S, Moir J, Hyman M, Kaufmann G, Flores A, Hariprasad S, et al. Metformin Use and Age-Related Macular Degeneration in Patients Without Diabetes. JAMA Ophthalmol. 2024 Jan 142:53-7. doi: 10.1001/jamaophthalmol.2023.5478
20. Khanna S, Shaw L, Hyman M, Zhang J, Hariprasad S, Soo J, et al. Association of metformin use with risk of newly onset neovascular age-related macular degeneration development. Retina. 2024;44:205–13. doi: 10.1097/IAE.0000000000003968
21. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4:1.
22. Von Elm E, Altman DG, Egger M, Pocock S, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344-9. doi: 10.1016/j.jclinepi.2007.11.008.
23. Huang K, Chang Y, Lee C, Gau S, Tsai T, Chung N, et al. Dose-response association of metformin use and risk of age-related macular degeneration among patients with type 2 diabetes mellitus: a population-based study. Front

Pharmacol. 2023:1275095. doi: 10.3389/fphar.2023.1275095
24. Kaufmann G, Hyman M, 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;64:22. doi: 10.1167/iovs.64.11.22
25. Tseng C. The Risk of Age-Related Macular Degeneration Is Reduced in Type 2 Diabetes Patients Who Use Metformin. Pharmaceuticals (Basel). 2023;16:224. doi: 10.3390/ph16020224.
26. Domalpally A, Whittier S, Pan Q, Dabelea D, Darwin C, Knowler W, et al. Association of metformin with the development of age-related macular degeneration. JAMA Ophthalmol. 2023;141:140-7. doi: 10.1001/jamaophthalmol.2022.5567
27. Vergroesen J, Thee E, Ahmadizar F, van Duijn C, Stricker B, Kavousi M, et al. Association of diabetes medication with open-angle glaucoma, age-related macular degeneration, and cataract in the Rotterdam study. JAMA Ophthalmol. 2022:674-81. doi: 10.1001/jamaophthalmol.2022.1435
28. Jiang J, Chen Y, Zhang H, Yuan W, Zhao T, Wang N, et al. Association between metformin use and the risk of age-related macular degeneration in patients with type 2 diabetes: a retrospective study. BMJ Open. 2022:e054420. doi: 10.1136/bmjopen-2021-054420
29. Eton E, Wubben T, Besirli C, Hua P, McGeehan B, VanderBeek B. Association of metformin and development of dry age-related macular degeneration in a US insurance claims database. Eur J Ophthalmol. 2022;32:417-23. doi: 10.1177/1120672121997288
30. Blitzer A, Ham S, Colby K, Skondra D. Association of metformin use with age-related macular degeneration: a case-control study. JAMA Ophthalmol. 2021;139:302-9. doi: 10.1001/jamaophthalmol.2020.6331
31. Stewart J, Lamy R, Wu F, Keenan J. Relationship between oral metformin use and age-related macular degeneration. Ophthalmol Retina. 2020;4:1118-9. doi: 10.1016/j.oret.2020.06.003
32. Brown E, Ball J, Chen Z, Khurshid G, Prosperi M, Ash J. The common antidiabetic drug metformin reduces odds of developing age-related macular degeneration. Invest Ophthalmol Vis Sci. 2019;60:1470-7. doi: 10.1167/iovs.18-26422
33. Chen Y, Shen Y, Lai Y, Wang C, Lin K, Feng S, et al. Association between metformin and a lower risk of age-related macular degeneration in patients with type 2 diabetes. J Ophthalmol. 2019;2019:1649156.doi:10.1155/2019/1649156
34. Holtz J, Thinggaard B, Grauslund J, Subhi Y. Association between oral metformin use and the risk of age-related macular degeneration: A systematic review with meta-analysis. Acta Ophthalmol. 2023;101:595-605. doi: 10.1111/aos.15655
35. Mauschitz M, Verzijden T, Schuster A, Elbaz H, Pfeiffer N, Khawaja A, et al. Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans. Br J Ophthalmol. 2023;107:1880-6. doi: 10.1136/bjo-2022-321985
36. Liang K, Chen C, Tsai H, Chang C, Chen T, Hsu W. 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;63:10. doi: 10.1167/iovs.63.13.10
37. Dang K, Wu T, Hui Y, Du H. Newly-found functions of metformin for the prevention and treatment of age-related macular degeneration. Int J Ophthalmol. 2021;14:1274-80. doi: 10.18240/ijo.2021.08.20
38. Kim H, Lee W, Ryu I, Kim J, Kim H, Yoo T. Association between metformin use and the risk of developing open-angle glaucoma among patients with diabetes: a retrospective cohort study and meta-analysis. Int Ophthalmol. 2024;44:6. doi: 10.1007/s10792-024-02945-w
39. Tan L, Wang Z, Okoth K, Toulis K, Denniston A, Singh B, et al. Associations of antidiabetic drugs with diabetic retinopathy in people with type 2 diabetes: an umbrella review and meta-analysis. Front Endocrinol (Lausanne). 2024;14:1303238. doi: 10.3389/fendo.2023.1303238
40. O'connor L, Bailey-Whyte M, Bhattacharya M, Butera G, Hardell K, Seidenberg A, et al. Association of metformin use and cancer incidence: a systematic review and meta-analysis. J Natl Cancer Inst. 2024 6:518-29. doi: 10.1093/jnci/djae021
41. Zhang J, Zhang X, Sun Y, Lv R, Chen M, Li M. Metformin use is associated with a reduced risk of cognitive impairment in adults with diabetes mellitus: A systematic review and meta-analysis. Front Neurosci. 2022:984559. doi: 10.3389/fnins.2022.984559
42. Campbell J, Stephenson M, De Courten B, Chapman I, Bellman S, Aromataris E. Metformin use associated with reduced risk of dementia in patients with diabetes: a systematic review and meta-analysis. J Alzheimers Dis. 2018;65:1225-36. doi: 10.3233/JAD-180263