J Nephropharmacol. 2025; 14(1): e12754.

https://jnephropharmacology.com DOI: 10.34172/npj.2025.12754

Journal of Nephropharmacology

Association between statins administration and glaucoma; a systematic review and meta-analysis of observational studies

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ARTICLE INFO

Article Type:
Meta-analysis

Article History:
Received: 5 Nov. 2024
Accepted: 28 Dec. 2024
ePublished: 30 Dec. 2024

Keywords:
Hydroxymethylglutaryl-CoA reductase inhibitors, Glaucoma, HMG CoA reductase inhibitor, Statin

ABSTRACT

Introduction: Glaucoma is the leading cause of irreversible visual impairment in the world. Statins, primarily through their lipid-lowering effects, have been suggested to play a potential role in influencing the incidence of glaucoma. Consequently, this study aimed to examine the relationship between statins and the risk of developing glaucoma.

Materials and Methods: This investigation adhered to PRISMA guidelines and employed systematic review and meta-analysis methodologies. The databases Cochrane, ProQuest, PubMed, Web of Science, and the search engine Google Scholar were searched up to March 4, 2024. STATA 14 software was used to analyze the data, and statistical significance was determined at $P<0.05$.

Results: The findings indicated no statistically significant association between statin consumption and the incidence of glaucoma overall (OR: 0.97, 95% CI: 0.92, 1.02). The lack of statistical significance persisted across different study designs, including case-control research (OR: 0.99, 95% CI: 0.96, 1.02), cross-sectional studies (OR: 0.98, 95% CI: 0.81, 1.19), and cohort studies (OR: 0.91, 95% CI: 0.79, 1.06). Furthermore, the association between specific statins, including simvastatin (OR: 1.04, 95% CI: 0.98, 1.10), lovastatin (OR: 0.89, 95% CI: 0.76, 1.03), pravastatin (OR: 1.05, 95% CI: 0.96, 1.15), fluvastatin (OR: 1.05, 95% CI: 0.86, 1.28), atorvastatin (OR: 1.04, 95% CI: 0.94, 1.15), and rosuvastatin (OR: 1.05, 95% CI: 0.99, 1.11), and the incidence of glaucoma was not statistically significant. However, a reduced risk of glaucoma was observed among individuals aged 60 to 69 years (OR: 0.89, 95% CI: 0.82, 0.97) and in specific geographical regions, notably the United States (OR: 0.92, 95% CI: 0.88, 0.96) and the Netherlands (OR: 0.41, 95% CI: 0.21, 0.82).

Conclusion: Statin consumption in individuals aged 60-69 years and in the United States and the Netherlands reduced the risk of developing glaucoma.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024521496) and Research Registry (UIN: reviewregistry1909) website.

Implication for health policy/practice/research/medical education:
Statin administration in individuals aged 60-69 years and in the United States and the Netherlands reduced the risk of developing glaucoma; therefore, it is recommended that future studies compare the correlation between statin take and the risk of developing glaucoma based on different ages, ethnicities, and even different doses and durations of statin consumption.

Please cite this paper as: Fakhri M, Nowroozpoor Dailami K, Ahmadi H, Ramezanpour M. Association between statins administration and glaucoma; a systematic review and meta-analysis of observational studies. J Nephropharmacol. 2025;14(1):e12754. DOI: 10.34172/npj.2025.12754.

Meta-analysis

Introduction

Globally, glaucoma is the primary cause of permanent blindness, and its prevalence is steadily increasing (1,2). It affects 64.3 million individuals worldwide and is the second most common cause of blindness and this burden will reach up to 111.8 million in 2040 without

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intensified intervention (2). This disease brings about a heavy burden not only on human health but also on social life and economic costs (3). In relation to the underlying mechanism, primary glaucoma is subdivided into open-angle and angle-closure types (4). The primary open-angle type represents the most common form of primary glaucoma, with over two-thirds of all cases manifesting this type (5). Primary open-angle glaucoma (POAG) is a well-known age-dependent form that increases with intraocular pressure (IOP) and myopia (4).

While the highest attributable risk factor for the development of glaucoma is elevated IOP (6), other factors, such as lipids, are implicated in the disease. They involve the association of polymorphisms in genes coding for proteins with key roles in lipid metabolism, such as ABCA1, GAS7, and ATXN2 (7). Furthermore, other studies have indicated that some systemic diseases (8, 9) and the use of drugs (10) might be correlated with the risk of occurrence or progression to glaucoma. Patients with diabetes mellitus and hypertension are the most frequent among those coming to the clinic for patients with glaucoma (11-13). Statins lower lipid levels with additional biochemical effects, including anti-inflammatory and neuroprotection activities pharmacologically (14).

Since there is a wide prevalence of statin use, recent concerns and research have been directed toward studying the adverse effects of statins in non-cardiovascular diseases, including eye diseases (15,16). Statins are considered a new approach for managing eye diseases because of pleiotropic effects, a good safety record, and low-costs (17). Given that some studies suggest statins reduce the risk of developing glaucoma (18,19). In contrast, others find no statistically significant correlation between statins and glaucoma incidence (20,21). Considering that previous meta-analyses have only examined the correlation between statins and the likelihood of open-angle glaucoma, reviewing studies published up to 2019 (22), this current study aims to systematic review and meta-analysis of the correlation between statin use and the risk of developing glaucoma.

Materials and Methods

The current research is available according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines (23). This review protocol was registered in the PROSPERO (International Prospective Register of Systematic Reviews) under.

Search strategy

We conducted searches through Cochrane, ProQuest, PubMed, Web of Science, and Google Scholar. The search was performed without language, time, or place restrictions until March 4th, 2024. MeSH (Medical Subject Headings) terms and their synonyms were conducted in the search strategy to enhance comprehensiveness. Keywords were then combined logically (AND, OR). We reviewed the reference lists of identified studies. The search strategy in the Web of Science database Hydroxymethylglutaryl-CoA Reductase Inhibitors OR HMG CoA Reductase Inhibitor OR Statin (All Fields) AND Glaucoma (All Fields).

PICO elements

- Population: Research that investigated the link between statin intake and glaucoma risk.
- Intervention: The specific intervention was the use of statins.
- Comparison: The comparison group consists of those without statins or using the lowest doses.
- Outcomes: Determine the effect of statins on the risk of glaucoma.

Inclusion and exclusion criteria

Observational research that assessed the correlation between statin consumption at any dose or duration and the risk of glaucoma were included. Research that was duplicated, review studies, systematic reviews, or meta-analysis, studies of poor quality in the qualitative assessment phase, studies that simultaneously examined the effect of statins and another drug, studies with incomplete abstract data or inaccessible full texts, and non-observational studies were removed.

Quality assessment

Two authors used the Newcastle Ottawa Scale (NOS) to assess the quality of included studies in a non-biased, comprehensive way. The star rating scale had one maximum of one-star question per item (except for comparison questions, which could receive two stars). These ratings ranged from zero (indicating the lowest quality) to ten (indicating the highest quality). We conducted two meta-analyses of the studies with a quality score >5 (24).

Data extraction

Data extraction was independently carried out by two authors. The extracted data included the author's name, age, location where the study was conducted, year(s) during which patients were sampled for each study group (studies vs. control), type of study design, total sample size per category (statin use or not), statin used if mentioned, described explicitly by INN and branding when available, along with the maximum daily doses given, the diagnosis definition applied for glaucoma, the number specifics allowed to evaluate the risk factor, and the exact association statistics related to statin treatment exposure. The relative effect estimate was derived from studies with a 95% CI.

Statistical analysis

The logarithms of the odds ratios (ORs) and relative risks (RRs) were utilized for data analysis, and the studies were subsequently aggregated. A random-effects model was applied in current research. Data analysis was conducted

using STATA 14 software, with a significance level set at $P<0.05$.

Results

A total of 997 articles were retrieved. Of these, 456 were withdrawn due to redundancies. Then, we evaluated the abstracts of 541 articles, excluding 23 studies with incomplete or unsupported information in their abstract and no full text. After retrieving the full text for these 518 articles, the reasons behind exclusion were as follows: lack of data (59 studies). Of the 459 articles that entered title and abstract screening, an additional 444 after full-text review were excluded according to other exclusion criteria, yielding 15 studies (Figure 1).

This study reviewed 15 observational studies between 2004 and 2023, including eight cohort researches, five case-control researches, and two cross-sectional researches (Table 1).

The present meta-analysis of all studies (Figure 2) showed no significant difference in the development of glaucoma between statin users and non-users (OR: 0.97, 95% CI: 0.92 to 1.02).

However, there was no significant relationship of statins with glaucoma in case-control researches (OR: 0.99, 95% CI: 0.96-1.02), cross-sectional researches (OR: 0.98, 95% CI: 0.81-1.19), and cohort researches (OR: 0.91, 95% CI: 0.79-1.06) (Figure 3).

Additionally, subgroup analysis revealed that the consumption of statins was not statistically significantly associated with a risk reduction for glaucoma development in Japan (OR: 1.00, 95% CI: 0.92-1.09), Australia (OR: 1.04, 95% CI: 0.97-1.11), the UK (OR: 1.02, 95% CI: 0.96-1.09), and Taiwan (OR: 1.20, 95% CI: 0.84-1.72). However, a significant risk reduction was observed in the USA (OR: 0.92, 95% CI: 0.88-0.96) and the Netherlands (OR: 0.41, 95% CI: 0.21-0.82) (Figure 4).

In this study, statin use was not associated with the development of glaucoma in individuals aged 50-59 (OR: 1.08, 95% CI: 0.87-1.33) and those aged 70-79 (OR: 0.97, 95% CI: 0.92-1.02). On the other hand, statin administration among patients aged 60-69 was associated with a lower risk of developing glaucoma (OR: 0.89, 95% CI: 0.82-0.97) (Figure 5).

Figure 6 shows no statistically significant relationship between simvastatin and glaucoma (OR: 1.04, 95% CI: 0.98-1.10).

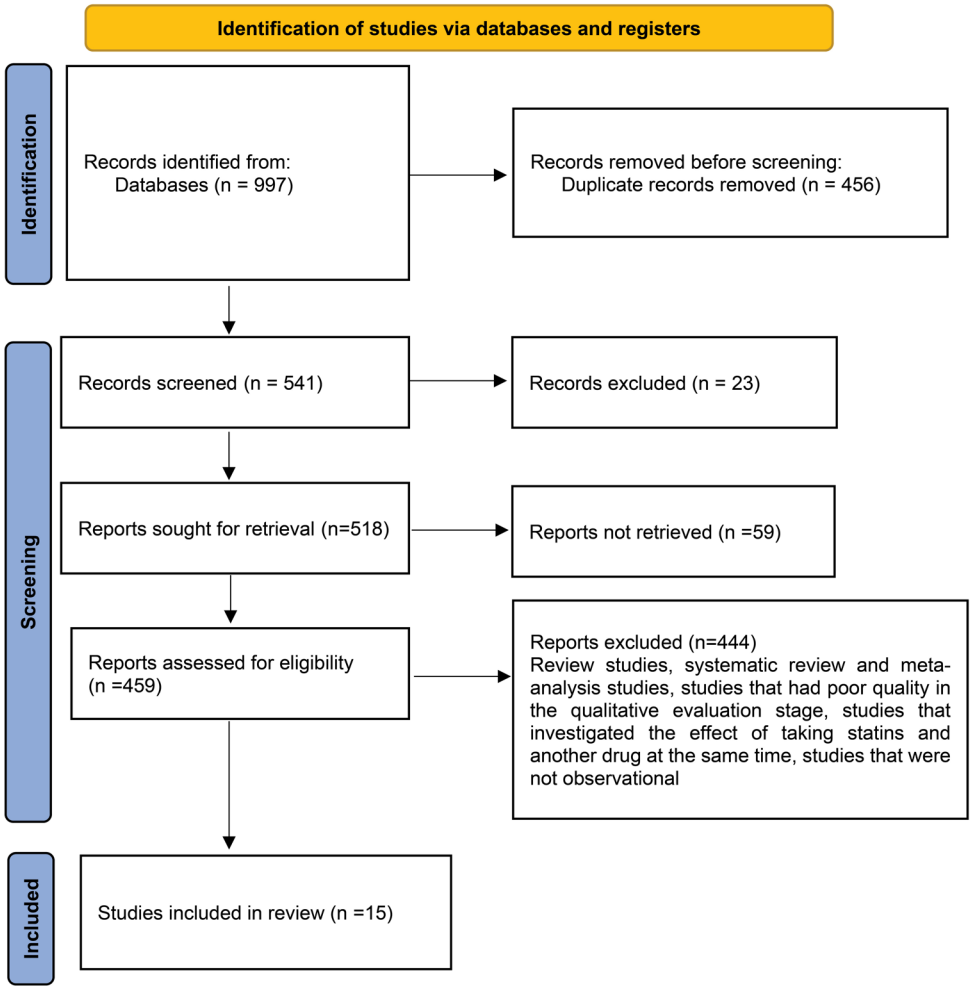

Figure 1. The PRISMA flow chart of study selection.

Table 1. Summary of studies included in the systematic review and meta-analysis

Author, year	Country	Type of study	No. of all participants	Average age of all participants	Average age of people taking statins	Average age in comparison group	Duration of study	Type of glaucoma
Yokoyama S, 2023 (21)	Japan	Case-control	207944	NR	NR	NR	2005-2020	Open-angle glaucoma
Yuan Y, 2023 (20)	Australia	Case-control	27179	>45	>45	>45	2009-2016	NR
Kim J, 2022 (25)	UK	Cross-sectional	118153	56.5	55.9	61.4	2006-2010	NR
Lee S, 2022 (26)	USA	Cohort	5489	NR	NR	NR	2005-2008	NR
Chien CC, 2021 (27)	Taiwan	Cohort	NR	NR	54.57	52.34	between 2000 and 2013	NR
Ooba N, 2020 (28)	Japan	Cohort	117036	NR	51.2	51.6	between Jan 1, 2005 and Mar 31, 2014	Open-angle glaucoma
Kang JH, 2019 (18)	USA	Cohort	121700	68.5	NR	NR	2000 to 2014	Primary open-angle glaucoma
Pappelis K, 2019 (19)	Netherlands	Cohort	112	56.77	NR	NR	2000-2015	Primary open-angle glaucoma
Zheng W, 2018 (10)	USA	Case-control	NR	NR	71.8	71.7	from Jan 1, 2007, to Dec 31, 2014	Open-angle glaucoma
Talwar N, 2017 (29)	USA	Cohort	25420	66.1	NR	NR	from Jan 2001 to Dec 2009	Open-angle glaucoma
Chen HY, 2015 (30)	Taiwan	Case-control	NR	NR	64.1	64.1	2004 to 2011	Open-angle glaucoma
Marcus MW, 2012 (31)	Netherlands	Cohort	3939	NR	68.4	65.7	1997-2006	Open-angle glaucoma
Stein JD, 2012 (32)	USA	Cohort	524109	68.1	NR	NR	between 2001 and 2009	Open-angle glaucoma
Owen CG, 2010 (33)	UK	Case-control	NR	NR	70	70	between 2000 and 2007	NR
McGwin G, 2004 (34)	USA	Cross-sectional	NR	NR	69	69	Janu 1997 through Dec 2001	Open-angle glaucoma

NR: Not reported.

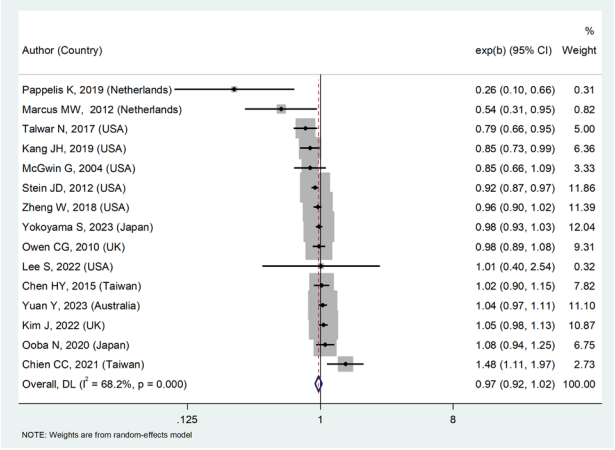

Figure 2. Forest plot showing the relationship between statins and glaucoma.

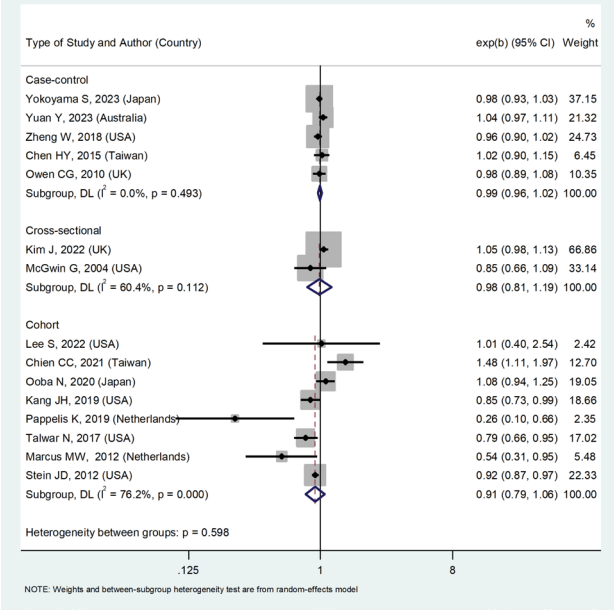

Figure 3. Forest plot showing the relationship between statins and glaucoma by type of study.

Figure 7 shows the absence of such an association between lovastatin use and the susceptibility to glaucoma (OR: 0.89, 95% CI: 0.76-1.03).

As shown in Figure 8, pravastatin use was not significantly associated with the development of glaucoma (OR: 1.05, 95% CI: 0.96-1.15).

Regarding fluvastatin, Figure 9 confirmed that the risk of exposure was not associated with glaucoma (OR: 1.05, 95% CI: 0.86-1.28).

Similarly, no significant correlation was found between atorvastatin treatment and the occurrence of glaucoma (OR: 1.04, 95% CI: 0.94-1.15) (Figure 10).

Additionally, rosuvastatin use had no significant impact on glaucoma development (OR: 1.05, 95% CI: 0.99-1.11) (Figure 11).

Using meta-regression, Figures 12 and 13 failed to show

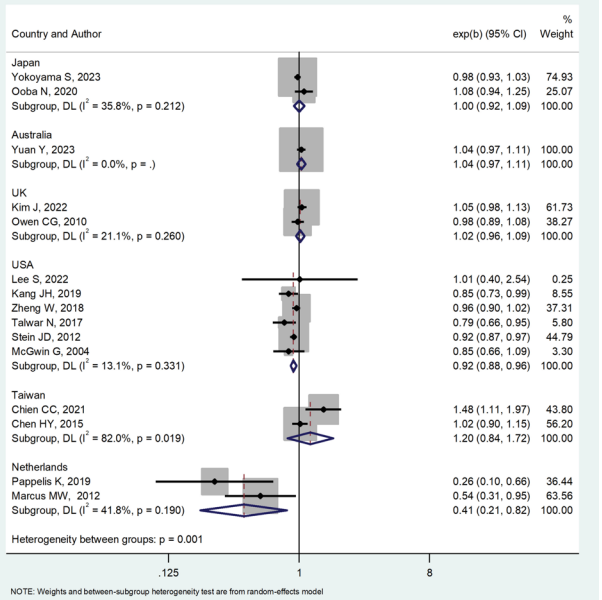

Figure 4. Forest plot showing the relationship between statins and glaucoma by countries.

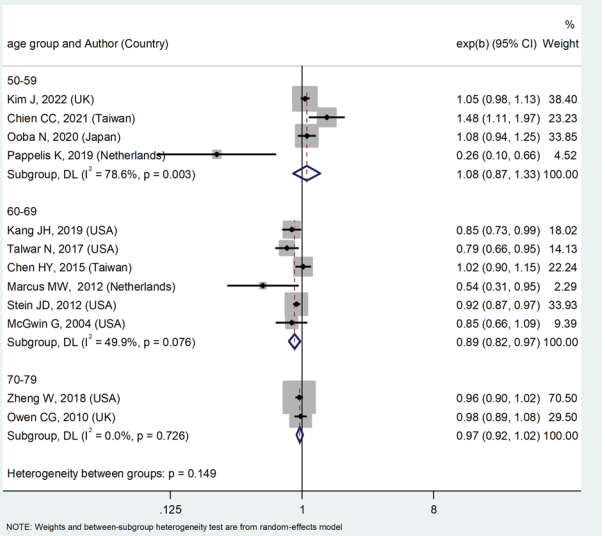

Figure 5. Forest plot showing the relationship between statins and glaucoma by age group.

a significant association between "statins and glaucoma" and the year of study publication ($P = 0.179$). Additionally, there was no significant association between the sample size of studies and the development of glaucoma by statin use ($P = 0.811$).

Figure 14 showed no significant publication bias ($P = 0.371$). Thus, all the sources in this area were searched and reviewed without bias, ensuring that the source search stage was fully completed.

Discussion

Using simvastatin, lovastatin, pravastatin, fluvastatin,

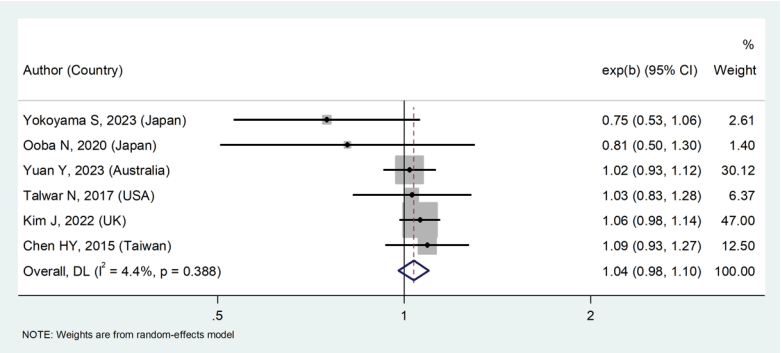

Figure 6. Forest plot showing the relationship between simvastatin and glaucoma.

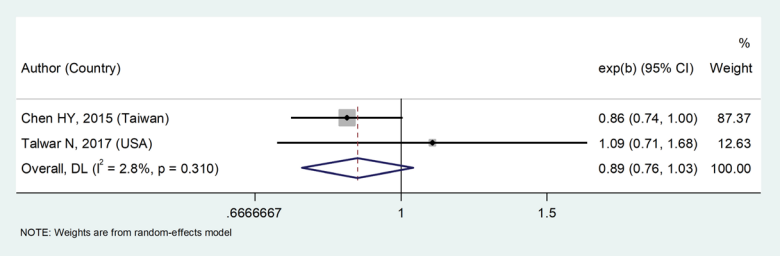

Figure 7. Forest plot showing the relationship between lovastatin and glaucoma.

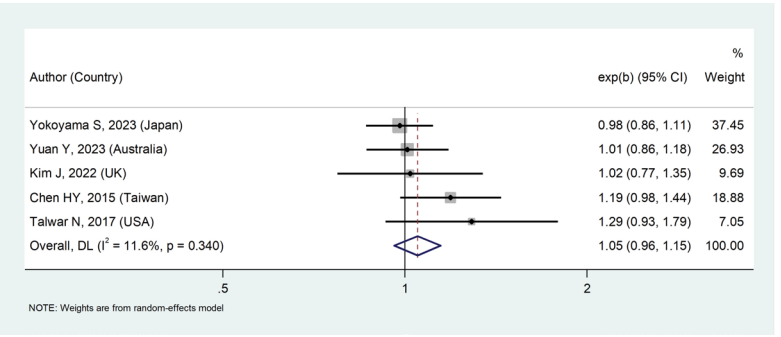

Figure 8. Forest plot showing the relationship between pravastatin and glaucoma.

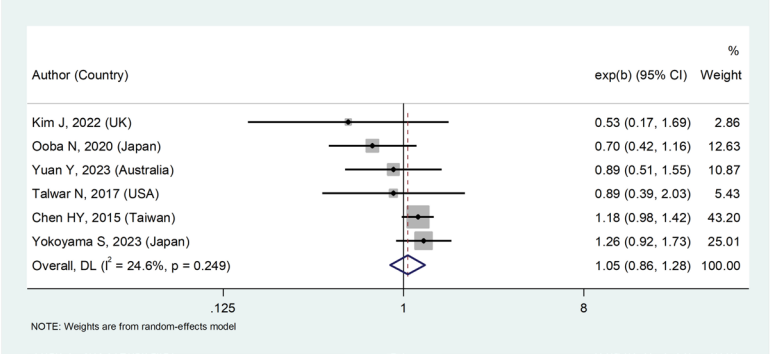

Figure 9. Forest plot showing the relationship between fluvastatin and glaucoma.

atorvastatin, and rosuvastatin revealed no statistically significant correlation with the development of glaucoma. Nevertheless, statin use in the population aged between 60 and 69 years significantly decreased the risk of developing glaucoma, and its use in this age group is safe. Statins were also associated with a reduced risk of glaucoma in

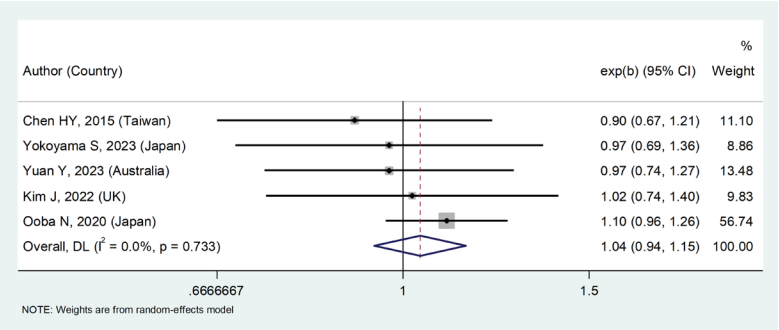

Figure 10. Forest plot showing the relationship between atorvastatin and glaucoma.

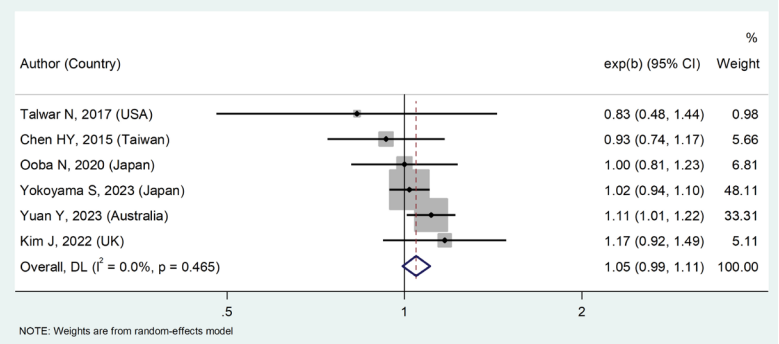

Figure 11. Forest plot showing the relationship between rosuvastatin and glaucoma.

patients from the United States and the Netherlands; thus, ethnicity may be responsible for the "association between statin administration and the development of glaucoma". In a meta-analysis by Yuan et al on eight researches, researchers found that statin use reduced the risk of developing open-angle glaucoma (RR: 0.95, 95% CI: 0.93, 0.98) (22). The findings of our study did not align with the results of the previous meta-analysis. However, the previous meta-analysis examined the association between statin use and open-angle glaucoma. In contrast, our meta-analysis included all types without any restrictions on the type of glaucoma. Additionally, the number of studies reviewed in the current meta-analysis is nearly double that of the previous meta-analysis. These differences may have contributed to the discrepancies in the final results of the two studies.

Another meta-analysis by McCann et al concluded that Patients who had taken statins for less than 2 years had a reduced risk of glaucoma (OR: 0.96, 95% CI: 0.94, 0.99). However, in patients who had taken statins for more than 2 years, statin use had no significant correlation with the risk of glaucoma (35). The results of this study indicated

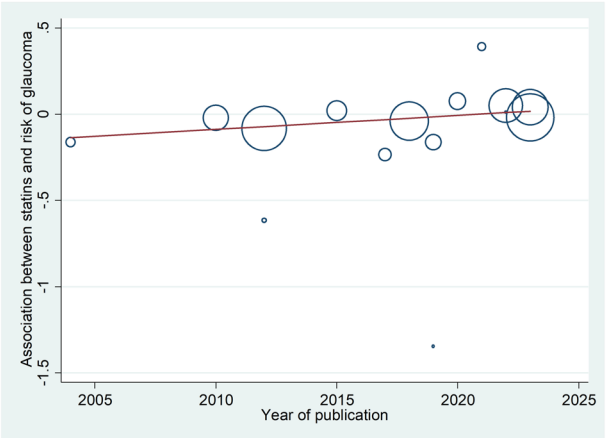

Figure 12. The meta-regression diagram showing the association between statins and glaucoma by year of publication.

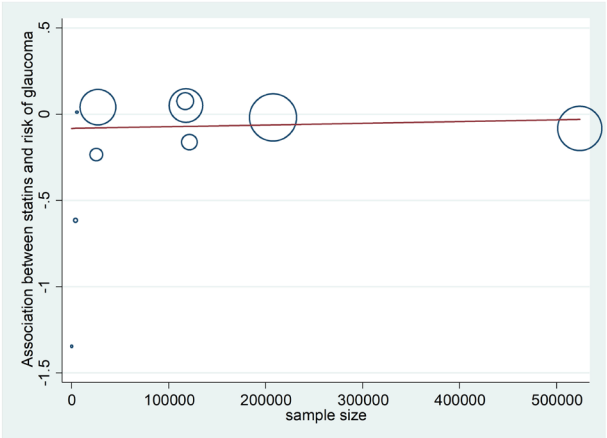

Figure 13. The meta-regression diagram showing the association between statins and glaucoma by sample size.

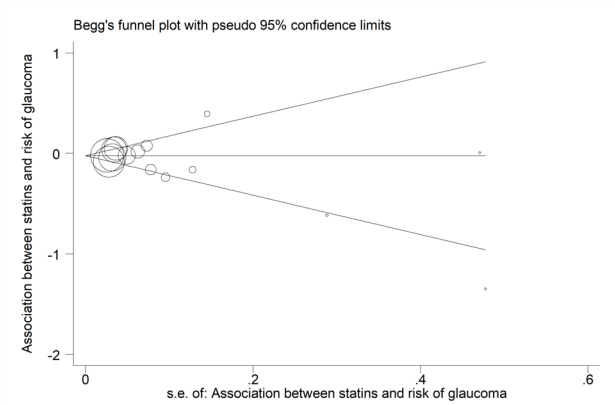

Figure 14. Chart of publication bias.

that long-term statin use was ineffective in reducing the incidence of glaucoma, which is consistent with the final results of the current research. In our research, we concluded that no correlation between statin and the development of glaucoma was existed. Since the duration and dosage of statin use varied among the studies reviewed in our research, this may have caused heterogeneity between the studies, ultimately leading to the conclusion that statin use does not affect the development of glaucoma.

Lymperopoulou et al conducted a systematic review to examine statins' effects on ocular disorders. They suggested that statin administration might prevent the formation of cataracts, age-related macular disease, the progression of diabetic retinopathy, and non-infectious uveitis (36). Conversely, the results of a meta-analysis by Alves et al indicated that statin use could increase the risk of developing cataracts (OR: 1.11, 95% CI: 1.02, 1.21) (37). These studies presented conflicting evidence regarding the association between statin use and ocular diseases such as cataract formation. One of these studies was a systematic review, while the other was a meta-analysis. This distinction might be one of the reasons for the differing results concerning the correlation between statin and the risk of developing cataracts.

Meanwhile, the meta-analysis by Liu et al stated that the relative risk between adiposity and increased IOP was (RR: 1.73, 95% CI: 1.18, 2.54), while the relative risk between adiposity and open-angle glaucoma was (RR: 0.97, 95% CI: 0.83, 1.13). The combined relative risk between abdominal adiposity and glaucoma was (RR: 1.28, 95% CI: 1.15, 1.41), whereas the relative risk between general adiposity and glaucoma was (RR: 1.09, 95% CI: 0.87, 1.37) (38). In this regard, this meta-analysis's results were consistent with our study's findings.

Moreover, Wang et al stated that hyperlipidemia significantly increased the risk of developing glaucoma (OR: 1.37, 95% CI: 1.16 to 1.61) (39). Huang et al stated that dyslipidemia increases the risk of POAG (OR: 1.25, 95% CI: 1.23 to 1.26) (40). The inference, therefore, can be drawn that if hyperlipidemia increases the risk of developing glaucoma, a drug like statin, known to reduce blood lipids, may find some application in reducing the risk of glaucoma under certain conditions. As we concluded in the present meta-analysis, statins used among the age group of 60-69 years can prevent glaucoma development; however, our study findings can be reasonably justified based on the evidence cited in the above two meta-analysis.

Conclusion

Statin administration in individuals aged 60-69 years and in the United States and the Netherlands reduced the risk of developing glaucoma; therefore, it is recommended that future studies compare the correlation between statin take and the risk of developing glaucoma based on different ages, ethnicities, and even different doses and durations of statin consumption. This will help determine the role of these essential variables in the correlation between statin consumption and the risk of developing glaucoma and reduce heterogeneity as much as possible.

Limitations of the study

Some studies did not specify the type of glaucoma, making it impossible to examine statins' effect on different types of glaucoma. The studies reviewed in our meta-analysis did not evaluate the impact of statins on glaucoma by gender. The dosage of statins in the reviewed studies was not specified, making it impossible to compare the effect of high and low statins on the development of glaucoma. The number of eligible studies was not significant.

Authors' contribution

Conceptualization: Moloud Fakhri.
Data curation: Kiumars Nowroozpoor Dailami, Hanieh Ahmadi.
Formal analysis: Hanieh Ahmadi.
Funding acquisition: Moloud Fakhri.
Investigation: Melina Ramezanpour.
Methodology: Moloud Fakhri.
Project administration: Hanieh Ahmadi.
Resources: Moloud Fakhri.
Software: Melina Ramezanpour.
Supervision: Moloud Fakhri.
Validation: Hanieh Ahmadi.
Visualization: Kiumars Nowroozpoor Dailami.
Writing–original draft: All authors.
Writing–review & editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the

PROSPERO website with (ID: CRD42024521496,) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1909). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Funding/Support

Mazandaran University of Medical Sciences sponsored the research project of this article.

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