Associations of statin use with the onset and progression of open-angle glaucoma: A systematic review and meta-analysis

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Summary

Background Statins, the first-line therapy for hyperlipidemia, have received considerable attention as candidates for glaucoma treatments given its neuroprotective effects. In this systematic review and meta-analysis, we intended to assess the association of statin use with the onset and progression of open-angle glaucoma (OAG).

Methods Databases including PubMed, Embase and Web of Science Core Collection were searched for longitudinal studies reporting the association between statin use and OAG onset or progression on Feb 3, 2021. A meta-analysis was performed for the association between statin use and OAG onset. Relative risks (RRs) with 95% confidential intervals (CIs) were retrieved from included studies and pooled using random-effects models. Potential risks of bias were evaluated by the Newcastle-Ottawa Quality Assessment Scale for all eligible studies. This study had been registered on PROSPERO (CRD 42021232172).

Findings 515,788 participants (mean age 68.7 years, 62.3% female) from ten studies were included in the systematic review of the association between statin use and OAG onset, and 26,347 OAG patients (mean age 67.3 years, 52.2% female) from seven studies were included for the association between statin use and OAG progression. Potential risks of bias were detected in 12 studies, which were mainly attributed to selection and confounding bias. In addition, 515,600 participants from eight studies were included in the meta-analysis which collectively showed that statin use was associated with a reduced risk of OAG onset (Pooled RR: 0.95; 95%CI: 0.93−0.98; I^2=0.199;). No significant heterogeneity or publication bias was found for studies included in the meta-analysis. There were inconsistent evidences for the association between statin use and OAG progression.

Interpretation Statin use is associated with a slightly lower risk of OAG onset based on existing evidences from longitudinal observational studies, the association between statin use and OAG progression remains inconclusive. The included evidences were typically weak due to poor study design and under-powered studies. Current findings should be interpreted cautiously and still need to be validated in further research.

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Keywords: Open-angle glaucoma; 3-hydroxy-3-methyl glutaryl coenzyme a (hmg-coa) reductase inhibitors; meta-analysis

Abbreviations: OAG, open-angle glaucoma; IOP, intraocular pressure; HMG-COA, 3-hydroxy-3-methyl glutaryl coenzyme a; VF, visual field; WOS, web of science core collection; ORS, odds ratios; HRS, hazard ratios; PRS, relative risks; CIS, confidential intervals; ICD, international classification of diseases; NSLCM, non-statin lipid-controlling medications; RGC, retinal ganglion cell

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Research in context

Evidence before this study

We searched the PubMed, Embase and Web of Science Core Collection for longitudinal observational studies reporting the association between statin use and the onset or progression of open-angle glaucoma (OAG) from inception to February 3, 2021 using subject headings (MeSH and Emtree terms) and free texts (open-angle glaucoma, statins, HMG-CoA reductase inhibitors, etc.). We identified a total of 17 studies, of which 12 were with potential risks of bias. Two previous meta-analyses existed with one reporting a slightly reduced risk of OAG onset among statin users and the other one reporting no significant associations. Both studies were significantly limited by the glaucoma definition and statistical efficiency.

Added value of this study

This systematic review and meta-analysis suggested that use of statins, especially lovastatin, was associated with a lower risk of OAG onset (Pooled RR for statin use: 0.95; 95%CI: 0.93−0.98; I^2=0.199). The reduced risk of OAG onset was mainly observed in hyperlipidemic subjects, and could be larger for longer-term statin users. The association between statin use and OAG progression remains uncertain.

Implications of all the available evidence

Considering the potential neuroprotective effect, statins might be prospective candidates for convenient supplements to traditional anti-glaucoma treatments. Caution is required when interpreting current findings because most evidences about the association between statin use and OAG were weak and under-powered. Current findings should be further addressed in carefully-designed large cohorts and randomized trials.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide,[1] with global glaucoma cases projected to increase by 47% from 76 million in 2020 to 111.8 million in 2040.[2] Due to its chronic and progressive nature, the significant morbidity of glaucoma presents a remarkable health, societal and economic burden.[3] Open-angle glaucoma (OAG) is the most common type, responsible for 60−90% of glaucoma cases across different ethnic groups.[2,4] Although the link between OAG and elevated intraocular pressure (IOP) has been extensively characterized,[5−7] it is suggested that risk factors exist affecting the onset and progression of OAG, such as vascular dysfunction and neuroinflammation.[8,9] Indeed, patients with glaucomatous optic neuropathies may still show signs of progression despite optimal IOP control.[10] The recognition that IOP may not be the sole predictive factor of glaucoma progression has renewed interest in the role of alternative therapies for the prevention and treatment of OAG.[11]

Statins, or 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors, have been widely used for blood lipid control and cardiovascular disease prophylaxis.[12,13] In addition to the lipid-lowering effect, statins can improve blood supply and modulate immune responses in the nervous system,[14,15] which are potential biological mechanisms underlying OAG pathogenesis.[16−18] Therefore, oral statins may be considered as candidates for convenient supplements to traditional IOP-lowering treatments to improve patient prognosis.

The association between statin use and OAG onset was inconsistent in the literature.[19] Some studies suggested a reduced risk of OAG onset in statin users,[20,21] while others found no significant association.[22,23] The association between statin use and OAG progression also remains unclear.[24−27] In 2016, a systematic review and meta-analysis included 11 cross-sectional and longitudinal studies, supporting the reduced risk of glaucoma onset in statin users.[28] However, several recently published longitudinal studies provided contrary results.[22,23] Thus in this systematic review and meta-analysis, we aimed to summarize the most up-to-date evidences and assess the association between statin use and OAG onset. A systematic review of the association between statin use and OAG progression was also provided.

Methods

This study was conducted and reported based on the Meta-analysis of Observational Studies in Epidemiology Guideline (MOOSE),[29] and has been registered at the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO, registration no: CRD 42021232172).

Eligibility criteria

Studies were eligible for inclusion if they reported associations of statin use with OAG onset or progression among human participants and published in English language. If one cohort was analyzed in several studies, the study with the largest number of participants was selected for inclusion. The exclusion criteria included: 1. study outcomes rather than OAG; 2. studies investigating the association between statins and retinal structure or function among non-glaucomatous participants; 3. studies reporting the combined effect of statins with other systemic medications; 4. studies comparing the risk of OAG among users of different types of statins; 5.

letters, comments, editorials, reviews and meta-analyses; 6. cross-sectional studies, clinical trials or case-control studies (except nested case-control studies based on longitudinal cohorts). Studies with poor study quality as defined below were further excluded from the meta-analysis.

This systematic review focused on longitudinal observational studies including cohort studies and nested case-control studies. Of the included studies, participants with statin use based on questionnaires, interviews or medical records were selected as the exposure group, with participants without statin use as the control group. Specifically for studies assessing the association between statin and OAG onset, participants without established OAG were included and the study outcome was onset of OAG during the follow-up based on medical records or ocular examinations by ophthalmologists. With respect to OAG progression, OAG patients were included at baseline and the study outcome was progression of OAG determined by ophthalmologists.

Search strategy

We conducted the literature search using online databases including PubMed, Embase and Web of Science Core Collection (WOS) from inception to February 3, 2021. Both subject headings (MeSH and Emtree terms) and free texts (open-angle glaucoma, statins, HMG-CoA reductase inhibitors, etc.) were used to pick up relevant publications in PubMed and Embase respectively (Table S1). Only free texts were used in WOS. Reference lists of articles were also interrogated for additional relevant publications. Abstracts were also included.

Study selection and data extraction

After removal of duplicate publications, all titles and abstracts were preliminarily screened by two authors (YY and XH). Full texts of all relevant studies after title and abstract screening were also examined by YY and XH, independently. Only studies meeting the eligibility criteria were included in the systematic review. Essential data were extracted from eligible studies, including publication details (name of the first author and publication year), study population (country, eligibility criteria, duration, sample size, distribution of age and sex), definitions and details of statin use and outcomes, study design, confounding factors and effect sizes including regression coefficients (b), average changes of visual field (VF) results, odds ratios (ORs), relative risks (RRs), hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) or P values. All study selection and data extraction procedures were conducted by YY and XH, independently. A senior researcher (WW) was responsible for the comparison of results and the arbitration of discrepancies.

Risk of bias assessment

The Newcastle-Ottawa Quality Assessment Scale,[30] which is widely used for the quality assessment of non-randomized studies,[31] was employed to evaluate the potential risk of bias of included studies. It mainly assesses three categories, consisting of selection, comparability and exposure (case-control studies) or outcome (cohort studies). A total of nine stars were assigned to eight items in the three categories, with the item in comparability corresponding to two stars. The quality of studies was assessed by the number of awarded stars (0–9 stars). Only studies awarded >5 stars were included in the meta-analysis. The quality assessment was accomplished by YY and XH, with oversight from WW; details can be found in Tables S2 and S3.

Data synthesis and analysis

Given the limited number of eligible studies in each definition of OAG progression, only the association between statin use and OAG onset was evaluated in this meta-analysis. The fully-adjusted ORs and HRs in the multivariable model were considered equivalent to RRs based on the rare disease assumption.[32] In order to test the impact of potential overestimation, ORs were also converted to RRs in the sensitivity analyses[33] (Fig. S1). With respect to the time-dependent definition of statin use in some cohort studies, HRs for 1-year and 3-year statin use were calculated and included in the meta-analysis. Since a previous meta-analysis estimated that more than half of statin users were adherent to statin prescriptions in the first three years,[34] HRs for 1-year statin use were selected as conservative proxies for the assessment of the general association between statin use with OAG onset. Using the random-effects model, which is more conservative than the fixed-effects model, log-transformed RRs and standard errors were calculated for the combination of pooled effect sizes and assignment of weights using inverse weighted variance methods. Both the Cochrane Q statistics and I^2 value were used to evaluate between-study heterogeneity. A P value for Q statistics <0.1 or an I^2 value >50.0% was considered as significant heterogeneity between studies.[35] Egger's regression asymmetry test and Begg's test were used to examine publication bias. Additionally, we conducted the trim-and-fill analysis[36] to assess the impact of potential missing studies on this meta-analysis. We also conducted the study sequential analysis[37] based on a cumulative meta-analysis with all studies included in the random-effects model according to their publication years. O'Brien and Fleming methods[38] were used to construct monitoring boundaries which accounted for the risk of false positive findings related to random errors and repeated tests. A priori information size (APIS) was calculated to evaluate the least required information size under following conditions.[39]

It was assumed that both the relative risk reduction and the proportion of OAG onset were 0.05 in the study sequential analysis, which were consistent with the average level of previous studies. Two significant levels (0.05 and 0.01) were adopted to test the association between statin use and OAG onset, with the statistical efficiency maintained at 0.90. To test the robustness of this meta-analysis, we conducted a sensitivity analysis with only cohort studies included in the model. In addition, we also tested influence of individual studies on the overall estimation by removing each study from the meta-analysis in turn.

Subgroup analyses were conducted to estimate associations between statin use and OAG onset in the general population and hyperlipidemic patients, respectively. Associations between specific types of statins (atorvastatin, lovastatin, rosuvastatin, pravastatin and simvastatin) and OAG onset were also discussed in subgroup analyses. As for the duration, associations between different duration of statin use and OAG onset were divided into two categories (≤2-years and >2-years). Two-year was selected as the cut-off value since it was used by about half of the included studies.[20,22,40] In studies adopting time-dependent definitions of statin use, HRs for 1-year and 3-years statin exposure were allocated to the ≤2-years and >2-years categories. Pooled RRs were calculated in two categories using a random-effects model. All statistical analyses were performed using STATA software (Version 15.1, StataCorp, TX, USA). A P value of less than 0.05 was considered statistically significant for all tests except the Q statistics. Furthermore, the Bonferroni correction was used to control the rate of type I error in tests regarding specific types of statins.

Roel of the funding source

The sponsors or funding organizations had no role in the design or conduct of this research. The corresponding authors had full access to the data utilized in this study and had final responsibility for the decision to submit for publication.

Results

A total of 610 publications based on human participants and published in the English language were identified in the initial search. In addition, one eligible conference abstract identified in previous reviews[28] was included.[41] Details of the selection procedure are demonstrated in Figure 1. With 117 duplicate results removed, 494 publications were screened for titles and abstracts. 453 irrelevant publications were further excluded as per the aforementioned eligibility criteria. After a full-text review of the remaining 41 papers, one editorial,[42] one clinical trial[43] and three cross-sectional studies[44–46] were removed. One conference abstract was excluded since its full publication had already been included in this review.[47] Nine articles were excluded as the association between statin use and OAG was not specifically reported.[48–56] Nine articles were excluded since statin use was only adjusted as a confounding factor.[57–65] Two articles investigating the effect of statin use on ophthalmic examinations among non-glaucoma participants[66,67] and one article using participants taking low-potency statins as controls[68] were also excluded. Among the 14 eligible publications included in the systematic review, ten and seven studies explored associations between statin use with OAG onset[20–23,25,40,69–71] and progression,[21,24–27,41,72] respectively. Eight studies investigating the association between statin use and OAG onset were included in the meta-analysis.[20–23,40,69,70]

Characteristics of included studies

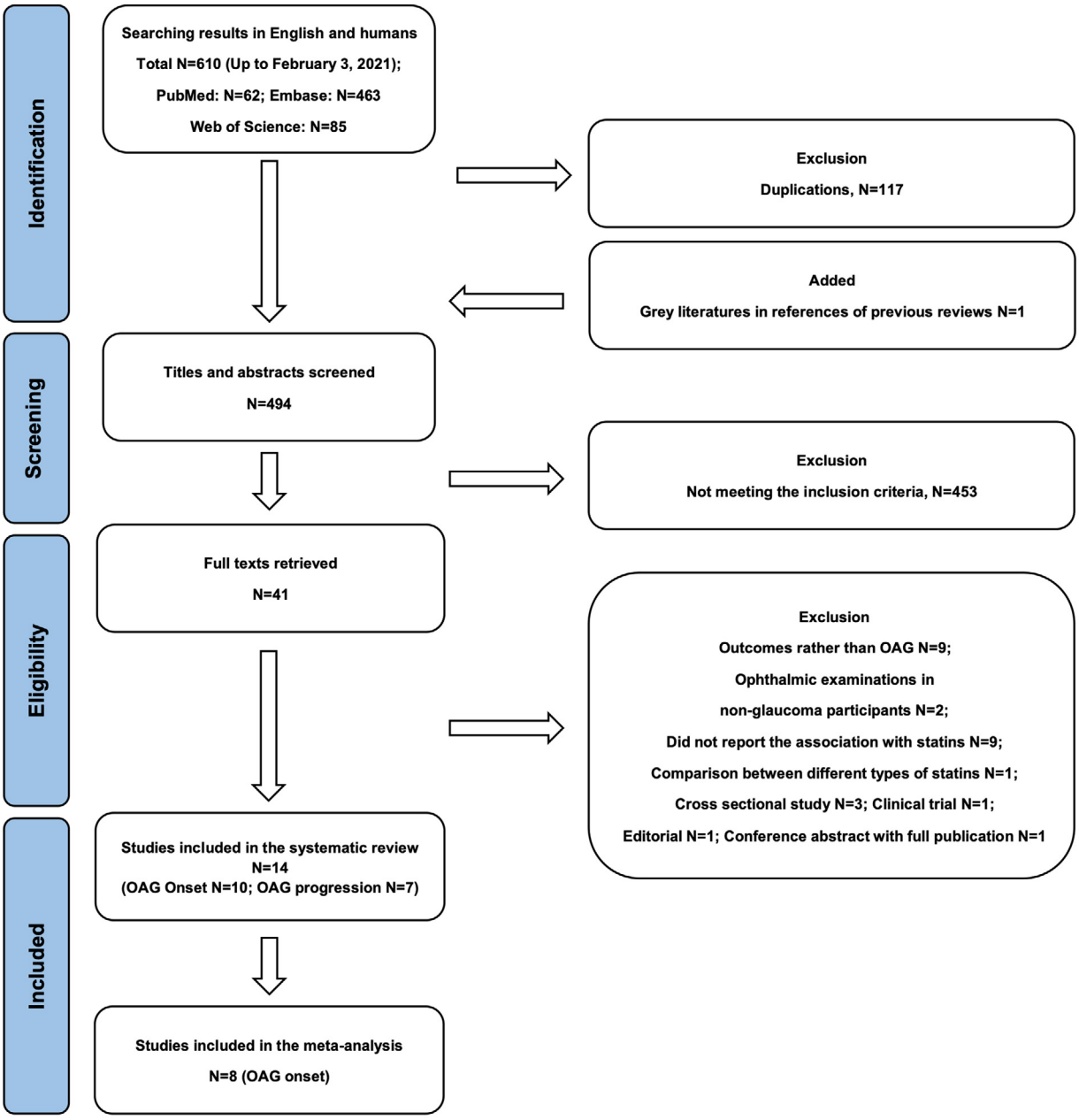
The features of studies investigating the associations between statin use and OAG onset are shown in Table 1. A total of 515,788 participants from ten studies were included in the systematic review. The average age was 68.7 years and 62.3% of all participants were female. Except for two studies in Europe[20,25] and one study in East Asia,[70] the remaining studies were all conducted in the United States. The duration ranged from 5 to 17 years with follow-ups taking place between 1991 and 2015. A total of 27,554 incident OAG patients were identified in these ten studies. The majority of these patients were identified by International Classification of Diseases (ICD) codes and 1063 patients were diagnosed by ophthalmic examinations.[20,22,25,71]

The characteristics of studies reporting the associations between statin use and OAG progression are also illustrated in Table 1. A total of 26,347 participants from seven studies were included. The average age was 67.3 years and 52.2% were female. Except for one study in Europe[25] and one study in East Asia,[24] all remaining studies were carried out in the United States. The duration of follow-up ranged from 3 to 15 years with follow-ups taking place between 1994 and 2015. Among all included OAG patients, 1,524 patients with OAG progression from two studies were identified based on claims records of OAG-related surgeries.[21,26] The remaining five studies defined progression as based on the deterioration of VF tests.[24,25,27,41,72]

Of the 17 studies included in this systematic review, potential risks of bias were identified in 12 studies (Table S2). Selection bias was identified in 11 studies, and confounding bias was recognized in three studies (Table S3). Among the ten studies regarding OAG onset, eight studies were included in the meta-analysis, with two studies graded less than six stars further excluded.

Systematic review

In terms of the association between statin use and OAG onset, five studies indicated that statin use was



Inclusion criteria:
Studies reporting associations of statin use with OAG onset or OAG progression among human participants in English language.
If one cohort was analyzed in several studies, the study with the largest number of participants was selected for inclusion

Exclusion criteria:
1. study outcomes rather than OAG;
2. studies investigating the association between statins and retinal structure or function among non-glaucomatous participants;
3. studies reporting the combined effect of statins with other systemic medications;
4. studies comparing the risk of OAG among users of different types of statins;
5. letters, comments, editorials, reviews and meta-analyses;
6. cross-sectional studies, clinical trials or case control studies (except nested case control studies based on longitudinal cohorts).

Additionally, studies with poor study quality as defined below were further excluded from the meta-analysis.

Figure 1. The flow diagram of study selection.

Author	Year	Country	Eligibility criteria	Duration	Sample size (persons)	Age*
OAG onset						
Kang[22]	2019	the U.S.	**Non-glaucoma individuals:** 1. ≥40y; 2. Completed baseline questionnaire; 3. No history of cancer; 4. Regular eye examinations	15y 15y; 17y	136783 NHS: 50710; HPFS: 23081; NHS2: 62992	POAG 68.6y(9.6y)
Pappelis[25]	2019	Netherlands	**POAG suspects:** 1. Ocular hypertension; 2. Positive family history of glaucoma; 3. Suspected optic disc; 4. Normal VF test results	Converted 4y-12y; 7y (mean) Non-converted 13y-18y; 16y (mean)	112	Converted 58.3y (10.0) y; Non-converted 55.4y(11.3y)
Zheng[23]	2018	the U.S.	**POAG patients:** 1. ≥45y; 2. Diagnosis of POAG; 3. Records of glaucoma-related surgeries between 2012/1/1 to 2013/12/31; 4. 5-y available records before index; **Cataract patients (controls):** 1.≥45y; 2. Diagnosis of cataract and cataract-related surgeries between 2012/1/1-2013/12/31; 3. No records of diagnosis or treatment of glaucoma; 4. 5-y available records before index	Follow-up 5y Identification 2y	POAG: 6130; Cataract: 30650	POAG 71.8y (11.3y); Cataract 71.7y(10.7y)
Talwar[69]	2017	the U.S.	**Non-OAG hyperlipidemic patients:** 1.≥60y; 2. Without diagnosis of OAG in first 2 years; 3. Diagnosis of hyperlipidemia; 4. Available records ≥2y	Follow-up 7y Identification 2y	25420	66.1y(5.8y)
Chen[70]	2015	Taiwan, China	**OAG patients:** 1. Diagnosis of OAG; 2. Diagnosis of hyperlipidemia; **Controls:** 1. Without diagnosis of OAG from 2004-2010; 2. Diagnosis of hyperlipidemia	8y	OAG: 1276; Controls: 12729	OAG 64.1y (12.6y); Controls 64.1y (12.4y)
Stein[21]	2012	the U.S.	**Hyperlipidemic glaucoma suspects:** 1. >60y; 2. Diagnosis of hyperlipidemia; ≥2y records and ≥2 visits for eye care; 3. Diagnosis of glaucoma suspects in first 2-year	Follow-up 7y Identification 2y	49628	OAG 69.3y (6.6y); Non-OAG 68.0y (6.6y)
Stein[21]	2012	the U.S.	**Hyperlipidemic Non-OAG patents:** 1. >60y; 2. Diagnosis of hyperlipidemia; 3. ≥2y records and ≥2 visits for eye care; 4. No diagnosis of OAG in first two year	Follow-up 7y Identification 2y	241711	OAG 69.7y (6.7y); Non-OAG 68.9y (6.7y)
Marcus[20]	2012	Netherlands	**Non- OAG patients:** 1. >55y; 2. No OAG at baseline; 3. No angle-closure or secondary glaucoma	9.8y (mean)	3939	OAG 68.4y(7.1y); Non-OAG 65.7y (6.8y)
DeDe Castro[71]	2007	the U.S.	**OAG suspects** 1. Diagnosis 0f OAG suspects; 2. HRT tests last longer than 12m; 3. IOP <22 mmHg through follow-up; 4. No VF defects at baseline; 5. Open angle on gonioscopy; 6. Baseline BCVA>6/12; 7. Reliable medication history; 8. Without other ocular comorbidities; 9. Without statins or aspirin use less than 23 months	5y	76 (149 eyes)	54.6y

Table 1 *(Continued)*

Author	Year	Country	Eligibility criteria	Duration	Sample size (persons)	Age*
McGwin[40]	2004	the U.S.	**OAG patients:** 1.≥50y; 2. Male; 3. Diagnosis of glaucoma **Controls:** 1.≥50y; 2. Male; 3. Without glaucoma from 1997 to 2001;	Life time follow up Identification 5y	Total: 7334; OAG: 667; Controls: 6667	OAG 69y (mean); Controls 69y (mean)
OAG progression						
Wang[26]	2019	the U.S.	**OAG patients** 1.≥35y; 2. OAG patients; 3. History of medical or laser treatments; 4. At least 1-year medical records before and after the initiation of statins or FAD; 5. No history of any glaucoma-related surgeries or diagnosis of other types of glaucoma.	12y 11y 10y	Statins/FAD Truven; 7977/7974 PACE/PAAD 268/572	Truven 65.6y (11.8y) PACE/PAAD 78.4y (6.3y)
Pappelis[25]	2019	Netherlands	**POAG patients** 1. Two consecutive VF tests with defects; 2. Without pseudo-exfoliate, pigment dispersion, angle-closure or secondary glaucoma.	9y-15y; 12y (mean)	250	61.8y (9.9y)
Whigham[27]	2018	the U.S.	**OAG patients** 1. Diagnosis of OAG; 2. Dispensing history of glaucoma medications; 3. Regular eye examinations for at least 3-y; No history of incisional glaucoma surgeries; 4. Reproducible VF defects.	Follow-up 43.7m Identification 6y	392	Statins 63.7y (11.2y); Non-statins 63.2y (11.9y)
Stein[21]	2012	the U.S.	**Hyperlipidemic non-surgical treated OAG patients** 1. >60y; 2. Diagnosis of hyperlipidemia; ≥2y records and ≥2 visits to eye care providers; 3. Diagnosis of OAG during follow-up period; 4. No records of glaucoma surgeries before OAG.	Follow-up 7y Identification 2y	8236	Surgical treated 69.5y (6.3y); Non-glaucoma surgery treated 69.8y (6.7y)
Leung[24]	2010	Hongkong, China	**NTG patients** 1. Diagnosis of NTG; 2. >18y; 3. At least 2 systemic diseases; 4. No history of statins other than simvastatin use; 5. No history of glaucoma treatment; 6. No history of ocular surgeries; 7. Without diseases interfering the measurement.	3y	256	Statins: 68.3y(9.2y); Non-statin: 67.5y(12.6y)
De[41]	2006	the U.S.	**Cases:** 1. Diagnosis of OAG; 2. At least three VF tests records; 3. Records of aspirin or statin use for at least 23m. **Controls:** 1. Diagnosis of OAG; 2. ≥3 VF records; 3. No records of aspirin or statin use.	N/A	315	Not mentioned
Phan[72]	2005	the U.S.	**Cases:** 1. Diagnosis of OAG; 2. At least three VF tests records; 3. Records of aspirin or statin use for at least 23m **Controls:** 1. Diagnosis of OAG; 2. ≥3 VF records; 3. No records of aspirin or statin use.	8y	214 eyes	Not mentioned

Females (proportion)	Definition of statin use	Details of statin use	Outcome definition	Study design	Confounding factor	Effect size**
NHS, NHS2 1.00; HPFS 0	History of statin use after index (Biennial questionnaires)	Types: A/F/L/R/P/Pi/S Duration: ≤2y, 2-4y, ≥5y	**POAG** (Self-reported POAG confirmed with slit lamp, gonioscopes and VF tests by ophthalmologists)	Retrospective cohort	age, calendar time, cohort, race, family history of glaucoma, self-reported diabetes, body mass index, hypertension, history of β-blocker use, history of diuretic use, history of other blood-pressure lowering medication use, cigarette smoking, cumulative mean caffeine intake, cumulative mean alcohol intake, physical activity, any cardiovascular disease, duration of statin use, and current use of other cholesterol-lowering drugs, age at menopause and postmenopausal hormone status.	Statin use 313/443419; HR 0.930 (0.800-1.100) Statin use ≤2y 76/99368; HR 0.950 (0.740-1.220) Statin use 2-4y 90/134742; HR 0.930 (0.730-1.170) Statin use ≥5y 147/209309; HR 0.930 (0.750-1.150) Rosuvastatin user current 19/32722; HR 0.930 (0.570-1.500) Lovastatin use current 13/15608; HR 1.130 (0.640-1.990) Simvastatin use current 52/87649; HR 0.930 (0.680-1.270) Pravastatin use current 29/40961; HR 0.950 (0.640-1.410) Atorvastatin use current 67/100805; HR 0.940 (0.710-1.240) References: (Cases/person-years) No cholesterol-lowering treatment 574/1041763;
Converted 0.57; Non-converted 0.54	Use of statins during follow-up (Semi-structured interview; medical files; letters)	Types: N/A Durations: N/A	**POAG suspect conversion** (≥2 abnormal VF for at least one eye	Retrospective cohort	None	Statin use 8/32; non-statin use 45/80; OR 0.260 (0.100-0.650)
POAG 0.52; Cataract 0.52	Statin prescriptions ≥90d during 5 years to 30 days before POAG (Uniform System of Classification codes and generic names in claims records)	Types: A/L/P/R/S Durations: N/A	**POAG receiving surgery treatment** (ICD-9CM and CPT codes in claims records)	Nested case-control	age, gender, geographic region of residence, employment status, and insurance plan type, the total number of drugs each individual patient submitted claims for during the pre-identification period	Statin/non-statin use in cases 3366/2764 in controls 17195/13455; OR 0.960 (0.900-1.020) Atorvastatin/non-atorvastatin use in cases 1276/4854 in controls 6718/23932; OR 0.930 (0.860-1.000) Simvastatin/non-simvastatin use in cases 1720/4410 in controls 8546/22104; OR 1.020 (0.960-1.090) Rosuvastatin/non-rosuvastatin use in cases 530/5600 in controls 2742/27908; OR 0.970 (0.870-1.080) Lovastatin/non-lovastatin use in cases 214/5916 in controls 1335/29315; OR 0.830 (0.710-0.970) Pravastatin/non-pravastatin use in cases 598/5532 in controls 3067/27853; OR 1.000 (0.900-1.110)

Table 1 (Continued)

Females (proportion)	Definition of statin use	Details of statin use	Outcome definition	Study design	Confounding factor	Effect size[60]
0.55	History of statin use after index (Generic names in claims records)	Types: A/C/F/P/S/L/R Durations: N/A	**OAG** (ICD-9CM codes in claims records)	Retrospective cohort	age, sex, race, household net worth, education level, region of residence, hypotension, obesity, sleep apnea, migraine, diabetes, hypertension, cataract, pseudophakia/ aphakia, macular degeneration, diabetic retinopathy, and comorbidity scores	Statin use 746/15898; Non-statin use 472/9,522; HR (month) 0.990 (0.983-0.998)
OAG 0.50; Controls 0.50	History of statin use before OAG diagnosis (ATC codes in claims records)	Types: A/F/P/S/L/R Durations: N/A	**OAG** (ICD-9CM codes in claims records)	Nested case-control	age, gender, diabetes, year of hyperlipidemia, hypertension, depression, Charlson Comorbidity Index scores, number of visits to eye care, Acipimox, Gemfibrozil, Fenofibrate, Inositol niacinate, and Xanthinol niacinate.	Statin/non-statin use in cases 704/572; in controls 6812/5917; OR 1.020 (0.900-1.150) Atorvastatin: No details; OR 0.900 (0.780-1.050) Lovastatin: No details; OR 0.860 (0.740-1.010) Simvastatin: No details; OR 1.090 (0.930-1.270) Rosuvastatin: No details; OR 0.930 (0.740-1.170) Pravastatin: No details; OR 1.190 (0.980-1.440)
OAG 0.57; Non-OAG 0.58	History of statin use after index (Generic names in claims records)	Types: A/C/F/P/S/L/R Durations: 1m, 1y, 2y	**OAG** (ICD-9CM codes in claims records)	Retrospective cohort	age, gender, race, intraocular pressure, central corneal thickness, refractive error, and history of hypertension, diabetes mellitus, migraine headaches, cancer, dyslipidemia, hypothyroidism, autoimmune disease, vasculitis	HR (month) 0.996 (0.993–0.999) HR (year) 0.952 (0.920–0.986) HR (2 years) 0.907 (0.846–0.973)
OAG 0.56; Non-OAG 0.57	History of statin use after index (Generic names in claims records)	Types: A/C/F/P/S/L/R Durations: 1m, 1y, 2y	**OAG** (ICD-9CM codes in claims records)	Retrospective cohort	age, gender, race, intraocular pressure, central corneal thickness, refractive error, and history of hypertension, diabetes mellitus, migraine headaches, cancer, dyslipidemia, hypothyroidism, autoimmune disease, vasculitis	HR (month) 0.997 (0.994–0.999) HR (year) 0.960 (0.933–0.988) HR (2 years) 0.922 (0.870–0.976)
OAG 0.49; Non-OAG 0.59	History of statin use during follow-up period (ATC codes in pharmacy network)	Types: A/C/F/P/S/R Durations: ≤2y, >2y	**OAG** (Repeated VF defects in HFA or perimetry tests; Open anterior chamber angle in gonioscopes)	Prospective cohort	age and gender, baseline IOP and IOP-lowering treatment, the family history of glaucoma, and myopia	Statin use 16/811; non-statin use 92/3128; HR 0.540 (0.310-0.960) Statin use ≤2y (no details); non-statin use 92/3128; HR 0.890 (0.410-1.940) Statin use >2y (no details); non-statin use 92/3128; HR 0.460 (0.230-0.940)
0.65	History of statin use more than 23 months (Medical records)	Types: N/A Durations: N/A	**OAG suspect conversion** (VF defects outside normal limits in HRT tests)	Retrospective cohort	age, gender, race, intraocular pressure, central corneal thickness, refractive error, and history of hypertension, diabetes mellitus, migraine headaches, cancer, dyslipidemia, hypothyroidism, autoimmune disease, vasculitis, coronary artery disease, stroke, and peripheral vascular disease	Stain use only 1/12; non-statin or aspirin use 9/39; statin and aspirin use 2/12; aspirin only 3/13 P for Fisher's exact test=0.833

Table 1 (Continued)

Females (proportion)	Definition of statin use	Details of statin use	Outcome definition	Study design	Confounding factor	Effect size**
OAG 0; Controls 0	History of statin use before glaucoma diagnosis (Medical records)	Types: A/C/F/P/S/L Durations: <12m, 12-23m, >23m	**OAG** (ICD-9CM codes in medical records)	Nested case-control	age, diabetes, lipid metabolism disorders, hypertension, cardiovascular disease, cerebrovascular disease, and arterial disease	Statin/non-statin use in cases 119/548; in controls 1004/5663; OR 0.850 (0.660-1.090); <12m Statin/non-statin use in cases 68/548; in controls 507/5663; OR 1.030 (0.770-1.390); 12m-23m Statin/non-statin use in cases 21/548; in controls 191/5663; OR 0.750 (0.460-1.230); >23m Statin/non-statin use in cases 30/548; in controls 306/5663; OR 0.600 (0.390-0.920)
Truven 0.50 PACE/PAAD 0.76	Statins dispensing after at least 365d wash-out (Claims records)	Types: A/F/L/R/P/Pi/S Durations: N/A	**Filtration surgery for OAG** (CPT and ICD-9 procedure codes in claims records)	Retrospective cohort	age, gender, race, region, duration of OAG prior exposure to each of the medications and comparators from the other four pairs, ocular-related comorbidities, comorbidity scores, inflammatory bowel disease, antidiabetic agents, antihypertensive agents, antidepressants, rheumatoid arthritis drugs, and measures of frailty	Truven MarketScan; (Cases/person-years) Intention-to-treat; Statins use 250/26318; FAD use 242/27477; (9.50% vs. 8.80%; P>0.05) PACE/PAAD; (Cases/person-years) As treated; Statins use 8/907; FAD use 15/1839; (8.60% vs. 8.20%; P>0.05)
0.46	Use of statins during follow-up (Semi-structured interview; medical file; letters)	Types: N/A Durations: N/A	**Progression of VF defects** (Slope of the MD in VF tests over at least 5y)	Retrospective cohort	age, gender, BMI, IOP, central corneal thickness, number of glaucoma medications, angiotensin receptor blocker	-0.083 (P=0.086)
0.04	Statin use before the last VF test in the study period (Prescription files)	Types: N/A Durations: N/A	**Glaucoma severity** (Progression, No progression and Intermittent classified by binocular VF tests)	Retrospective cohort	age, gender, race, baseline severity of glaucoma, and medical conditions (diabetes, cardiovascular diseases; coronary artery disease and renal insufficiency)	Statins use 52/196; non-statin use 89/196 (0.265 vs. 0.454; p<0.001)
Surgical treated 0.57; Non-glaucoma surgery treated 0.56	History of statin use after index (Generic names in claims records)	Types: N/A Durations: 1m, 1y, 2y	**Laser or incisional** glaucoma surgery (CPT codes in claims records)	Retrospective cohort	age, gender, race, intraocular pressure, central corneal thickness, refractive error, and history of hypertension, diabetes mellitus, migraine headaches, cancer, dyslipidemia, hypothyroidism, autoimmune disease, vasculitis	HR (month) 1.002 (0.994–1.010) HR (1 year) 1.021 (0.925–1.127) HR (2 year) 1.042 (0.856–1.269)
Statin users: 0.36; Non-statin users:0.46	Use of simvastatin during follow-up (Clinical records)	Types: S Durations: N/A	**NTG progression** (Two consecutive enlarged defects or new defects or innermost defects in VF tests)	Prospective cohort	age, central corneal thickness, history of disc hemorrhage, history of cardiovascular diseases, and hypercholesterolemia	Simvastatin use 8/31; Non-simvastatin use 113/225; RR 0.360 (0.140-0.910)
Not mentioned	History of statin use more than 23 months	Types: N/A Durations: N/A	**OAG progression** (MD of VF defects)	Retrospective chart review	None	Stain use only –0.048 dB/y; Non-statin or aspirin use 0.277 dB/y; d=0.325

Table 1 (Continued)

Females (proportion)	Definition of statin use	Details of statin use	Outcome definition	Study design	Confounding factor	Effect size**
Not mentioned	History of statin use more than 23 months (Medical records)	Types: N/A Durations: N/A	**OAG progression** (MD of VF defects)	Retrospective chart review	None	Stain use only −0.307 dB/y; Non-statin or aspirin use −0.009 dB/y; d=0.298 (0.099-0.498)

***Table 1*: Features and results of included studies investigating the associations between statin use with the onset and progression of OAG.**

* Presented as mean (standard deviation)

** Effect sizes were presented with corresponding 95% confidential intervals.A(atorvastatin); ATC(anatomical therapeutic chemical classification system); BCVA(best-corrected visual acuity); BMI(body mass index); C(cerivastatin); CDR(cup-disc ratio); CPT(current procedural terminology); F(fluvastatin); FAD(fibric acid derivates); HRs(hazard ratios); HRT(Heidelberg Retinal Tomograph II); HPFS(Health Professionals Follow-up Study); ICD-9CM(the International Classification of Diseases, Ninth Revision, Clinical Modification); IOP(intraocular pressure); L(lovastatin); LDL(low-density lipoprotein); MD(mean deviation); NHS(Nurses Health Study); NTG(normal tension glaucoma); N/A (Not mentioned or invalid); OAG(open-angle glaucoma); ORs(odds ratios); P(pravastatin); Pi(pitavastatin); POAG(primary open-angle glaucoma); RRs(relative risks); S(simvastatin); PACE/PAAD(medicare and pharmaceutical benefits data from Pennsylvania/ medicare and pharmaceutical benefits data from New Jersey); VF(visual field); y(years).

significantly associated with the reduced risk of OAG onset.[20,21,25,69] One retrospective cohort study[22] and three nested case-control studies[23,40,70] reported insignificant associations between statin use and OAG onset. One cohort study[71] did not conduct statistical analysis because of insufficient cases of OAG onset (Table 1). With respect to OAG progression, three studies suggested that statin use significantly delayed VF progression in OAG patients.[24,27,72] Two studies based on VF tests[25,41] and two studies involving OAG-related surgeries[21,26] suggested that the association between statin use and OAG progression was insignificant (Table 1).

Meta-analysis of the association between statin use and OAG onset

Among eight studies included in the meta-analysis,[20–23,40,69,70] a total of 27,486 cases of OAG onset were identified from 515,600 participants during the follow-up period. Compared with participants without exposure to statins, the risk of OAG onset was significantly lower in statin users in the random-effects model (Pooled RR: 0.95; 95%CI: 0.93–0.98; I^2=0.199; Figure 2), indicating an inverse association between statin use and OAG onset. No significant heterogeneity was demonstrated among studies. Although the distribution of studies with larger standard errors seemed asymmetrical in the funnel plot (Figure 3), neither the Egger's regression (P=0.13) nor the Begg's test (P=0.11) found significant publication bias among the included studies. Despite two missing studies detected, the trim-and-fill analysis showed similar results (Pooled RR: 0.95; 95%CI: 0.92–0.98; I^2=0.331; Figure 3). Study sequential analyses found that the number of included participants was larger than the estimated APIS when the significant level and the statistical efficiency were 0.05 and 0.90, respectively. The cumulative Z-score curve crossed the monitoring boundaries before APIS, firmly suggesting a reduced risk of OAG onset in statin users. Further analysis confirmed this association at a stricter significant level of 0.01 (Figs S2 and S3). Sensitivity analyses showed that removal of nested case-control studies or any single study from the analysis did not affect the significant negative association between statin use and OAG onset, supporting the reliability and robustness of this finding (Figs.S4 and S5).

The inverse association between statin use and OAG onset was significant among hyperlipidemic patients (Pooled RR: 0.95; 95% CI: 0.93–0.98; I^2=0.229; Figure 4). However, this association failed to reach statistically significant level when both hyperlipidemic patients and healthy participants were included (Pooled RR: 0.92; 95%CI: 0.82–1.02; I^2=0.366; Figure 4). As for specific statin types, the effects of atorvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin were summarized in the subgroup analysis (Figure 5). Use of

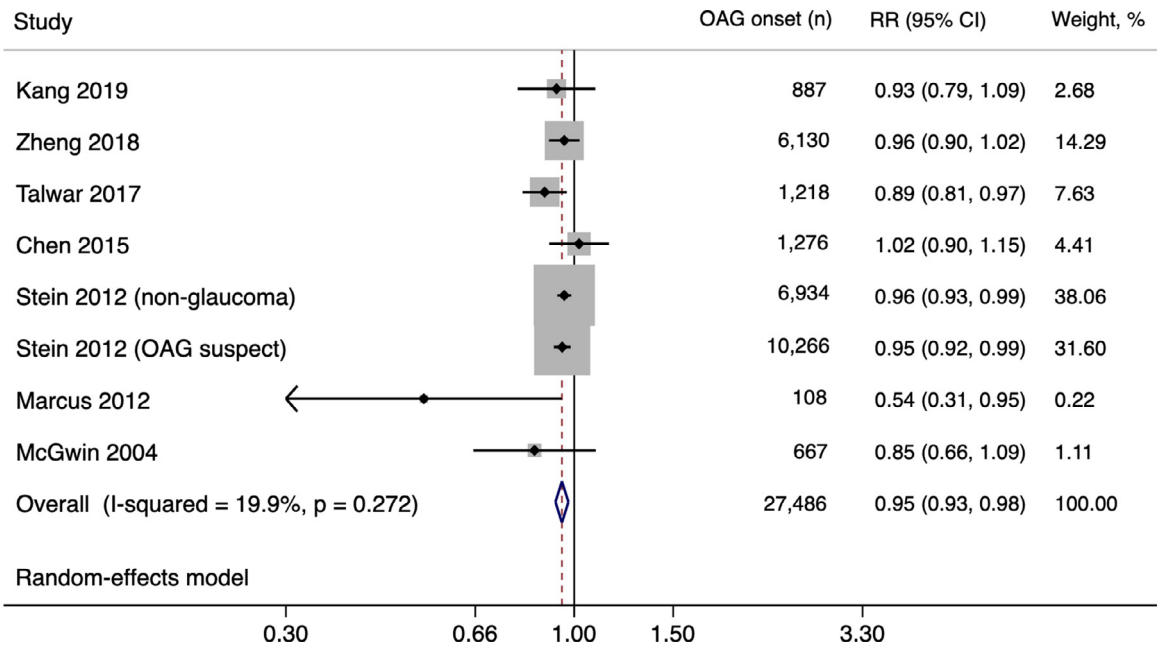


Figure 2. Forest plot of the association between statin use and OAG onset.

* RR (95%CI) represents the relative risks and corresponding 95% confidential intervals compared with participants without statin exposure.

** The diamond represents pooled estimates from the random-effects model.

*** OAG (Open-angle glaucoma), RR (Relative risks).

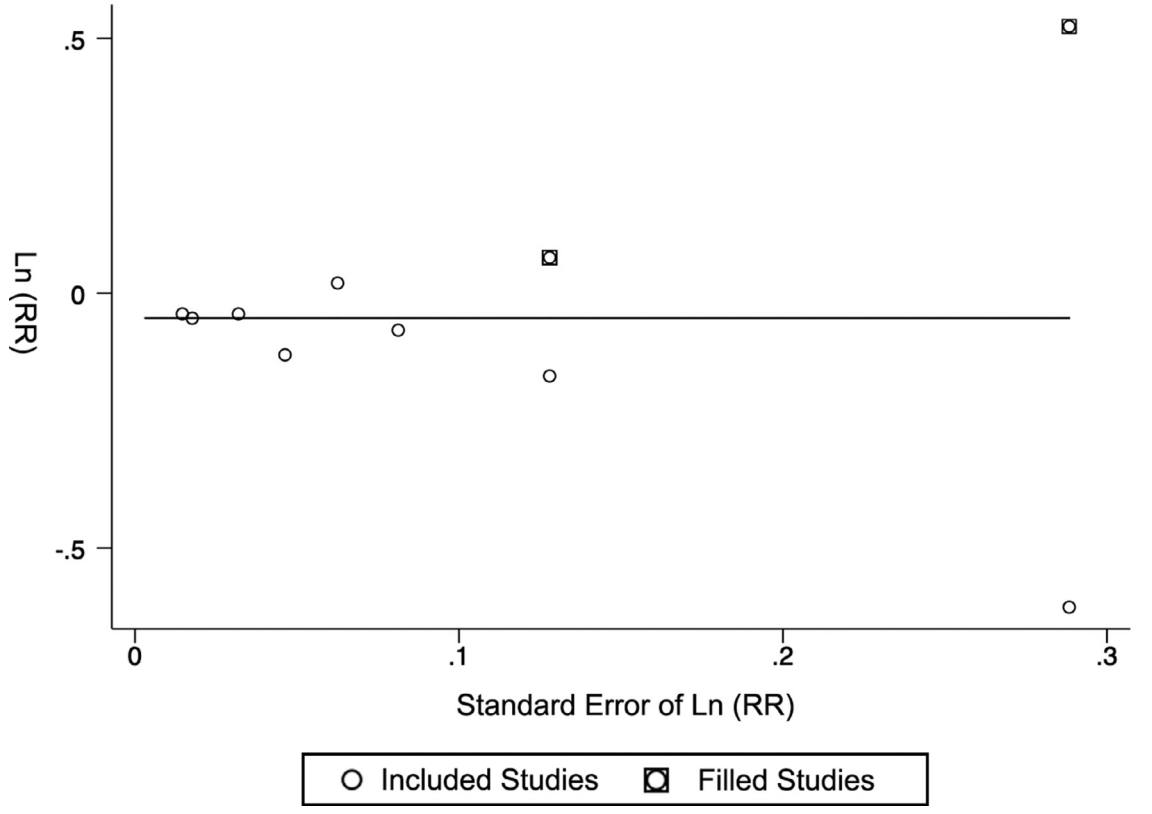


Figure 3. Funnel plot of eight included studies and two filled missing studies about the association between statin use and OAG onset.

* The horizontal line represented the pooled effect size (RR=0.95).

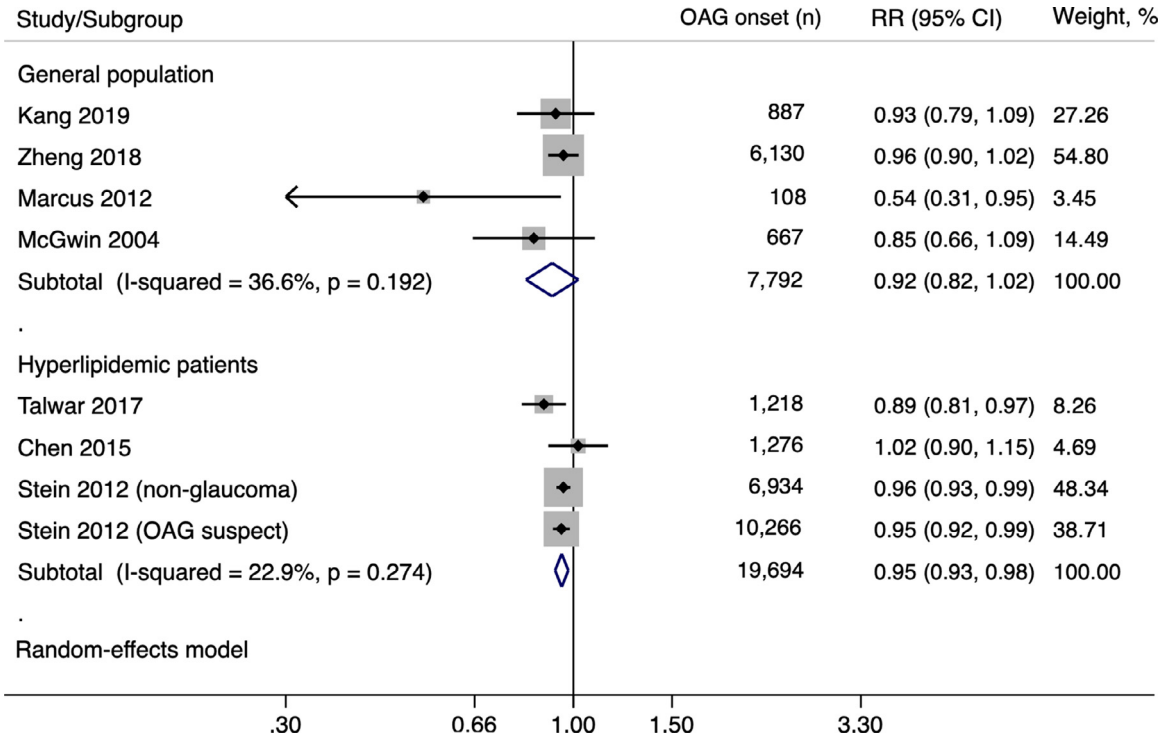


Figure 4. Forest plot of the association between statin use and OAG onset in the general population and hyperlipidemic participants.

* RR (95%CI) represents the relative risks and corresponding 95% confidential intervals compared with participants without statin exposure.

** The diamonds represent pooled estimates from the random-effects model.

*** OAG (Open-angle glaucoma), RR (Relative risks).

atorvastatin (Pooled RR: 0.93; 95%CI: 0.87–0.99; I^2=0) and lovastatin (Pooled RR: 0.85; 95%CI: 0.77–0.95; I^2=0) were found to be associated with reduced risks of OAG onset, with only the association between use of lovastatin and OAG onset remained significant after Bonferroni correction ($P < 0.01$). No significant association with OAG onset was found for other statin types. Compared with participants without exposure to statins, both ≤2-years and >2-years of statin use were significantly associated with reduced risks of OAG onset (Figure 6). A larger reduced risk of OAG onset was observed in those with longer duration of statin use (Pooled RR for ≤2-years and >2-years: 0.95 and 0.85). No significant between-study heterogeneity was found (I^2 for ≤2-years and >2-years of statin use: 0 and 0.362). Sensitivity analyses using converted RRs also showed similar results (Fig. S1).

Discussion

This systematic review provided updated evidence regarding the association of statin use with OAG onset and progression based on longitudinal observational studies. The meta-analysis demonstrated a reduced risk of OAG onset among statin users, especially among patients with hyperlipidemia. Among five specific types of statins, only lovastatin was found to be significantly associated with a reduced risk of OAG onset. Both ≤2 years and >2 years of statin use were found to be associated with reduced risks of OAG onset, with larger effect in the latter group. The association between statin use and OAG progression in the literature was inconsistent and more studies are needed in the future. It should be noted that most included evidences were weak and under-powered, with potential selection bias and confounding bias identified in about 70% of studies in this systematic review.

The reduced risk of OAG onset in short-term statin users reported in this study was consistent with the preceding systematic review by McCann et al.[28] They indicated that the risk of glaucoma onset decreased by 4% in participants who used statins for ≤2 years. However, they did not find significantly reduced risk for participants using statins for a longer duration given the insufficient statistical efficiency. Another earlier published meta-analysis trying to link statin use with glaucoma onset suggested an insignificant association.[73] In

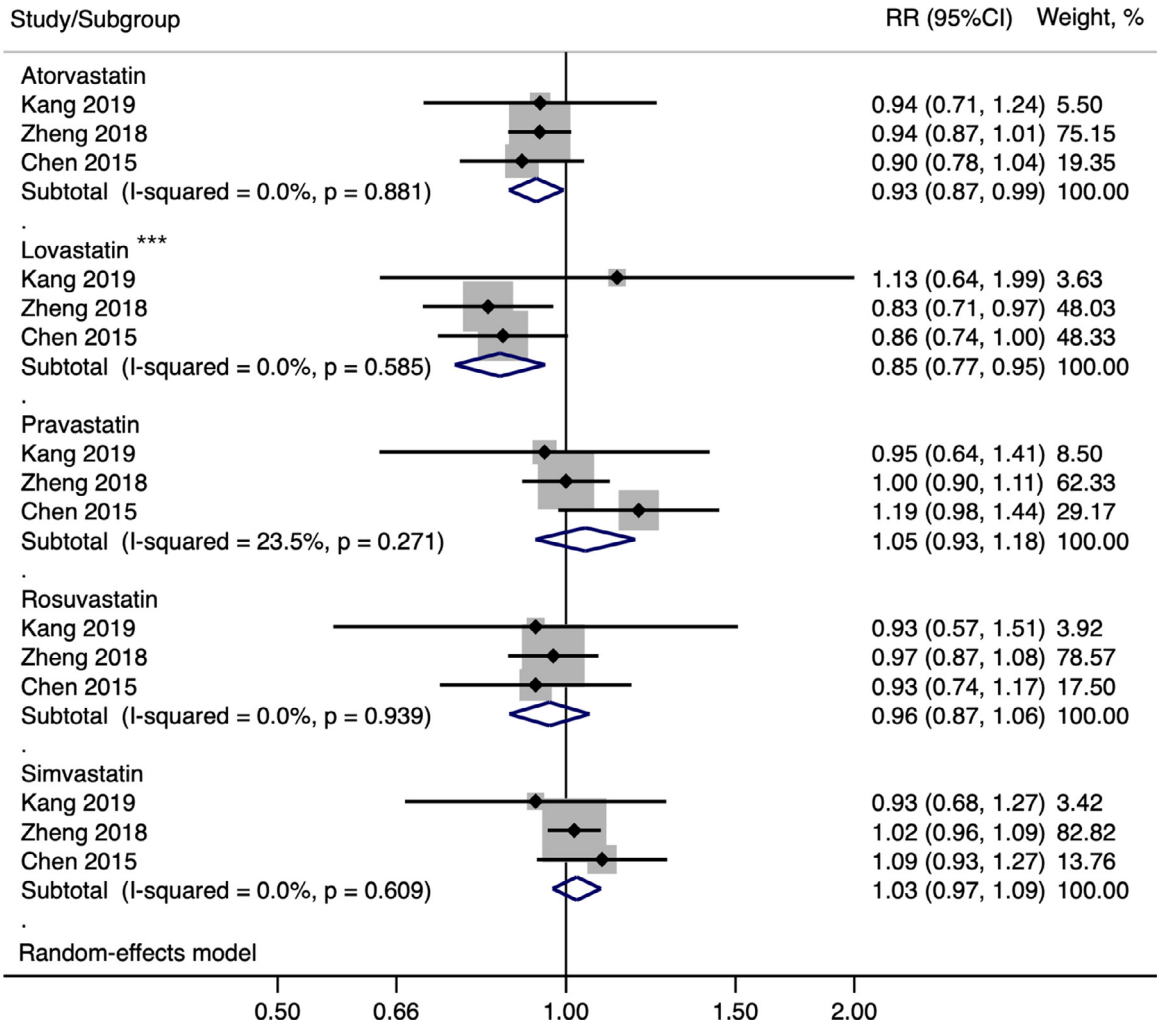


Figure 5. Forest plot of the association between statin use and OAG onset by specific statin types.

* RR (95%CI) represents the relative risks and corresponding 95% confidential intervals compared with participants without statin exposure.

** The diamonds represent pooled estimates from the random-effects model.

*** Significant associations after Bonferroni corrections.

contrast to previous reviews, our study focused on OAG and adopted a more precise definition of OAG onset according to current guidelines,[74] which further included the conversion from glaucoma suspects to OAG. In a re-analysis, McCann et al. also adopted this definition and found that >2 years statin use was related to a 12% reduced risk of glaucoma onset.[75] In addition, our study only included longitudinal studies, which provided higher-level epidemiological evidences. It should be noted that patients with ocular hypertension[51] were not excluded in both previous reviews, which also potentially biased the results.[76]

The association between statin use and glaucoma progression remains inconsistent based on existing literature. Although some studies showed that statin use had the potential to delay VF deterioration and improve retinal blood supply,[14,24,27] another study indicated that statin use was not associated with the reduced risk of glaucoma progression.[53] Current evidences indicated that the risk of progression to status requiring OAG-related surgeries did not reduce significantly in statin users.[21,26] A possible explanation was that the protective effect of statins on the retinal circulation and VF was insufficient to control the progression and prevent adverse outcomes in glaucoma patients. Cross-sectional[46] and longitudinal studies[71] also provided conflicting evidences of the association between statin use and retinal nerve fiber defects. The discrepancies between study outcomes and potential confounding factors may contribute to the conflicting study findings.

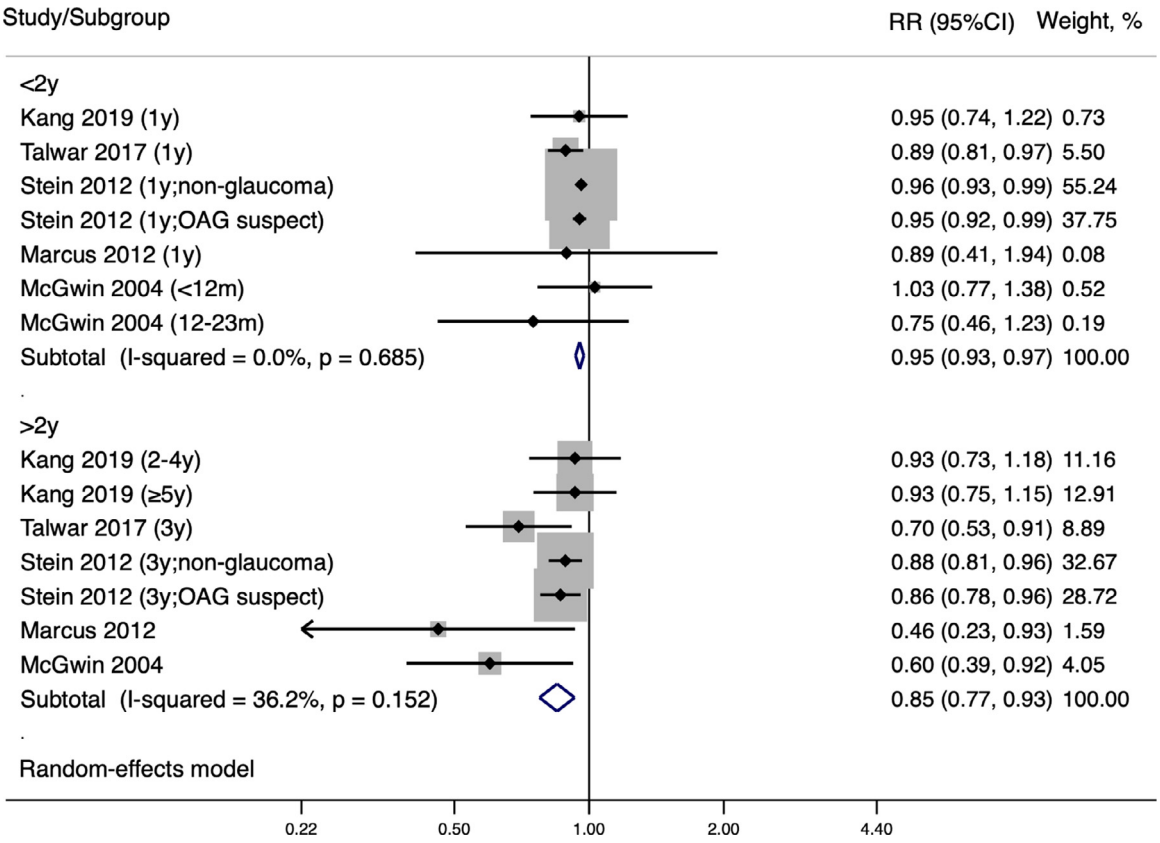


Figure 6. Forest plot of the association between statin use and OAG onset by duration of statin use.

* RR (95%CI) represents the relative risks and corresponding 95% confidential intervals compared with participants without statin exposure.

** The diamonds represent pooled estimates from the random-effects model.

Additionally, previous cross-sectional[43,44,50] and longitudinal[20,24] studies failed to show a consistent association between statin use and IOP.

Hyperlipidemia, the most important confounder in the statin-glaucoma association, was suggested to be associated with an increased risk of glaucoma in previous meta-analyses.[77] It is possible, therefore, that statin use only mitigated the increased risk of glaucoma secondary to hyperlipidemia. However, caution should be taken here since effects of statins and non-statin lipid-controlling medications (NSLCM) on OAG were inconsistent between studies. Most included studies investigated the effects of NSLCM on OAG onset in conjunction with statins, nevertheless, the reduced risks of OAG onset in users of NSLCM was only found to be significant in two studies by Zheng et al.[23] and McGwin et al.[40] The other studies suggested that statins might protect from OAG onset by lipid-independent mechanisms.[21,22,70] In this meta-analysis, the association between statin use and reduced risks of OAG onset was only found to be significant in hyperlipidemic patients. The insignificant pooled RR in the general population may be attributed to the relatively small sample size, as reflected by the wide 95% confidential interval. Besides hyperlipidemia, use of antihypertensive medications was more prevalent in statin users compared with non-statin users. The reduced risk of OAG onset in statin users may be partly attributed to the IOP-lowering effect of antihypertensive medications, especially Beta-blockers.[78,79] Additionally, confounding factors including socioeconomic status which were related to access to medications and surgeries were also emphasized in most studies. Appropriate control of these potential confounding bias was expected in further research.

Several mechanisms have been posited in earlier studies for association between statin use and OAG. Statins not only directly control the synthesis of lipids, but also modulate the subcellular localization and transportation of intracellular proteins[80] by regulating lipid-related intermediates[81] and pathways.[82] Firstly, statins enhance expression of endothelial nitric oxide synthetase through activation of Rho and Akt pathways.[14] As a result, elevated level of endothelial nitric oxide protects

the functions and structures of retinal vasculatures, which improves retinal blood supply and reduces risks of retinal damages secondary to chronic ischemia.[14,83] Secondary, statins can suppress the activation of immune cells and the release of inflammatory factors, both of which are implicated in the dysfunction of retinal ganglion cells (RGC).[18,84] The anti-inflammatory effect of statins may ameliorate the vulnerability of RGC and protect RGC from IOP assaults.[15] In addition, some studies suggest that statins could elevate nitric oxide levels in the trabecular meshwork, which may increase aqueous outflow and reduce IOP.[85] With respect to specific types of statins, the reduced risk of OAG onset was mainly observed in lovastatin users, probably due to its high lipophilicity[86] which facilitate crossing through the blood-retina barrier. It should also be noted that lovastatin is one of medium-intensity lipid-lowering medications. Most of its users who have mild or moderate hyperlipidemia[87] are at a lower risk of OAG onset than those with severe hyperlipidemia. Additional studies are still required to validate the protective effect of statins, especially lovastatin, under physiological status.

This systematic review provided by far the most comprehensive summary of evidences regarding the association between statin use and OAG based on longitudinal observational studies. The cumulative information size in the meta-analysis delivered sufficient statistical efficiency to support a precise estimation of the association between statin use and OAG onset. Multiple sensitivity analyses, including the study sequential analysis and trim-and-fill analysis, indicated that the significantly reduced risk of OAG onset in statin users was unlikely to be a false positive finding due to the inflated sample size or publication bias. Random-effects models were used in this meta-analysis to compensate for the unavoidable heterogeneity, and the discrepancies between included studies were further assessed in subgroup analyses. Although only modest effect in risk reduction was identified, our findings supported that statin use could be considered as a very promising factor for clinical OAG management in further research. However, there were still some limitations. The main limitation came from the definitions of OAG in most included studies. OAG identified by ICD codes based on records of insurance databases or hospital systems conferred a higher risk of misdiagnosis and underdiagnoses, as compared to diagnosis confirmed by clinical examinations.[74] Secondly, measurements required for the diagnosis and monitoring of OAG including IOP, anterior chamber angle and other ocular comorbidities were not discussed in this systematic review as most included studies did not elaborate on these details. Thirdly, confounding bias related to socioeconomic factors and systemic health status from observational studies is inevitable in this systematic review. Furthermore, different dosage and duration of statin use (especially long-term statin use) were rarely analyzed in previous studies, limiting our ability to perform a reliable dose-response analysis. Last but not least, most evidences summarized in this systematic review were weak and under-powered, which was attributed to the observational design and the considerable risk of bias. The association between statin use and OAG should be further validated in high-quality large cohorts and randomized clinical trials.

In summary, this systematic review and meta-analysis suggested that use of statins, especially lovastatin, was associated with a lower risk of OAG onset. The reduced risk of OAG onset was mainly observed in hyperlipidemic subjects, and could be larger for longer-term statin users. The association between statin use and OAG progression remains uncertain. Considering the limited evidence, the study findings should be interpreted with caution. Carefully-designed and adequately-powered studies are needed to further address this research question and better guide clinical practice.

Contributors

Yixong Yuan: conceptualization, formal analysis, writing – original draft; Ruilin Xiong: conceptualization, writing – review & editing; Yi Wu: conceptualization; Jason Ha: writing – review & editing; Wei Wang: conceptualization, formal analysis, supervision; Xiaotong Han: conceptualization, writing – original draft, supervision; Mingguang He: writing – review & editing, supervision. The corresponding authors (XTH and WW) had full access to the data utilized in this study and had final responsibility for the decision to submit for publication. All authors are aware of and agree with the decision to submit for publication.

Data sharing statement

All the data utilized in this study are available in the manuscript and Table 1.

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Declaration of interests

No conflicting association exists for any author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101364.

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