Effect of cataract surgery on the progression of age-related macular degeneration
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Abstract
Background: Cataracts and age-related macular degeneration (AMD) are common causes of decreased vision and blindness in individuals over age 50. Although surgery is the most effective treatment for cataracts, it may accelerate the progression of AMD, so this study further evaluated the influence of cataract surgery for AMD through a systematic review and meta-analysis.

Methods: The Cochrane Systematic Evaluation method was adopted, and computer searches were conducted for the China Knowledge Network, Wanfang, Vipul, SinoMed, PubMed, SpringerLink, Clinicalkey, Medline, Cochrane Library, Web of Science, OVID, and Embase databases of cohort studies on the impact of cataract surgery on AMD, with search timeframes up to May 2022. Meta-analysis was performed using Stata/12.0.

Results: A total of 8 cohort studies were included in the study. The results showed that the relative risk (RR) of AMD progression after cataract surgery was not significantly different, RR 1.194 [95% credibility interval (CI) 0.897‐1.591]; the risk remained increased more than 5 years after surgery, RR 1.372 (95% CI 1.062‐1.772).

Conclusion: There is still a significant positive correlation between cataract surgery and increase the risk of worsening of AMD progression, and faster progression of early-to-late AMD found in cataract surgery with longer follow-up of patients.

Abbreviations: AMD = age-related macular degeneration, CI = credibility interval, HR = hazard ratio, NOS = Newcastle-Ottawa scale, OR = odds ratio, RCT = randomized controlled trial, RR = relative risk.

Keywords: age-related macular degeneration, cataract, meta-analysis, surgery, systematic review

1. Introduction
Cataracts and age-related macular degeneration (AMD) are common causes of decreased vision and blindness in individuals over age 50. By 2020, the number of people with AMD globally is expected to be approximately 200 million, increasing to nearly 300 million by 2040. For the past few decades, vision has been an important criterion for cataract surgery, and cataracts can improve vision by removing the opaque lens. Surgery is the most effective operation in cataract patients to improve visual function, but some professor’s suspect it increase the risk of worsening of underlying AMD and vision. This potential problem has not been resolved for a long time. Prospective or retrospective studies have reported a higher frequency of AMD progression in surgical eyes than in nonoperated eyes. However, some studies have also shown that there is no significant correlation between cataract surgery and AMD. A cross-sectional study also explored this topic, but it is still inconclusive. The truth is that cataracts and AMD often coexist, and there may be adverse effects between AMD and cataract surgery. However, delaying cataract surgery can also negatively impact a patient’s vision. Therefore, this study further evaluated the influence of cataract surgery for AMD through a systematic review and meta-analysis.

2. Materials and Methods
2.1. Search strategy
A meta-analysis was performed according to the PRISMA guidelines. We independently searched PubMed, SpringerLink, Clinicalkey, Medline, the Cochrane library, Web of Science, OVID, Embase, and SinoMed from their earliest dates up to May 2022. The final search string was “macular degeneration,” “wet macular degeneration,” “choroidal neovascularization,” “geographic atrophy,” “age-related macular degeneration” and “randomized controlled trial.”

2.2. Inclusion criteria
Cohort study comparing visual acuity in AMD patients with or without cataract surgery.
2.3. Research objects
Age-related cataract patients who underwent cataract emulsification surgery or suffered from both cataracts and AMD were included. Those who had cataract history may affect postoperative visual acuity and were therefore excluded.

2.4. Outcome measures
To describe whether cataract surgery increases the risk of worsening of underlying AMD and vision (relative risk (RR)).

2.5. Data extraction
For each study, 2 reviewers independently evaluated the retrieved literature against the inclusion and exclusion criteria. In case of disagreement, adjudicate by consultation or with the aid of a 3rd commentator. To ensure the consistency of the data collection of each study, we conform to the conditions of the study of the following information into a structured Excel data table: first author, year of publication, study design, number of control and case groups, location, patients’ age, AMD classification, duration of follow-up, RR, odds ratio (OR) and hazard ratio (HR) with corresponding 95% CI [credibility interval (CI)]. The one that adjusts the most variables was used when there were multiple estimates.

2.6. Quality evaluation and statistical analysis
The risk of bias of nonrandomized studies was assessed using the Newcastle-Ottawa scale (NOS). In consideration of the low prevalence of AMD, the distinction between RR/OR/HR can generally be ignored. We used Stata 12.0 to derive pooled effect estimates such as risk ratios (RR) using a fixed-effects model or a random-effects model. Heterogeneity test: The $\chi^2$ test was used to analyze the statistical heterogeneity between studies with an $\alpha$ level of 0.1, and the magnitude of heterogeneity was quantitatively estimated according to $I^2$. If there was statistical heterogeneity between studies ($P > .1$ and $I^2 < 50\%$), a fixed effect model was used; if $P < .1$ and $I^2 > 50\%$, but when it was clinically judged that the research indicators of each group were consistent and needed to be merged, a random effect model was selected to merge the effect values. We use sensitivity analyses to assess the impact of individual studies on the outcome, funnel plots quantified by Egger and Begg tests to observe potential publication bias, and region, duration of follow-up, and AMD classification to performed subgroup analyses. $P < .05$ was considered statistically significant.

3. Results
3.1. Literature search
After inclusion and exclusion screening and reducing the repeated synthesis of the same control group and the same study population, 8 studies were finally included in the meta-analysis. The screening flowchart is shown in Figure 1.

3.2. Basic characteristics of the included studies
Among the 8 studies, 2 studies were conducted in Europe; 2 studies were conducted in Asia; and the others were from the Americas and Oceania. Patients in all studies were
older than 42 years and were followed for 3 months to 20 years (Table 1).

3.3. Quality assessment

Cohort studies were assessed using the cohort study coding manual. If the NOS score was equal to or higher than 8 points, the article was considered high quality. All articles were high-quality literature (Table 1).

3.4. Efficacy analysis

There was no significant publication bias in the studies (Egger test $P = .323$; Begg test $P = .373$). The data had high heterogeneity ($I^2 = 72.7\%$). In the random-effects model, cataract surgery and progression of AMD were not significantly associated (RR 1.194, 95% CI 0.897-1.591), and the difference was not statistically significant ($Z = 1.21, P = .225$) (Fig. 2).

3.5. Sensitivity analysis

Sensitivity analysis indicated that the sensitivity was low, and the results were relatively stable and credible (Fig. 3). We excluded the effects of the included studies on outcomes one by one, and found that none of them would lead to the reversal of results or significant increase in heterogeneity. The subgroup analysis can be divided into four groups by region, namely, Asia, Europe, Oceania, and America. Asia RR 2.855 (95% CI 1.704-4.781), Europe RR 1.271 (95% CI 0.914-1.769), Oceania RR 1.017 (95% CI 0.607-1.703), Americas RR 0.997 (95% CI 0.621-1.601) (Fig. 4). Cataract surgery in Asia was significantly associated with AMD progression by subgroup analysis (Fig. 5).

### Table 1

| Author         | Year  | Type       | Area                          | Sample size | Male (%) | Age   | AMD     | Follow-up time | Quality assessment (NOS) | OR/RR/HR | 95% CI          | $P$  |
|----------------|-------|------------|-------------------------------|-------------|----------|-------|---------|----------------|--------------------------|----------|-----------------|-----|
| Pollack        | 1996  | Cohort study | Asia                          | 47          | 42.5     | 80.4  | Early AMD | 1 year         | 8                       | RR = 4.500 | 1.027-19.726 | .054|
| Lintje Ho      | 2008  | Cohort study | Europe                        | 454/11548   | 40.3/42.9 | >55   | AMD      | 5.7 year       | 9                       | OR = 1.26   | 0.85-1.86   | NR  |
| Jie Jin Wang,  | 2003  | Cohort study | Oceania, North America        | 6019        | 42.9     | 43-86 | Late AMD  | 5 year         | 9                       | OR = 5.7    | 2.4-13.6    | NR  |
| Sudha Cugati   | 2006  | Cohort study | Oceania                       | 1952        | 39.95    | >49   | Dry AMD   | 10 year        | 8                       | OR = 4.5    | 1.4-14.7    |    |
| Jau-Der Ho     | 2018  | Cohort study | Asia                          | 3465/10395  | 45.5/45.5 | 70.2 ±9.6 | AMD      | 14 year      | 8                       | OR = 1.3    | 0.7-2.4     | NR  |
| Helena Buch    | 2005  | Cohort study | Europe                        | 359         | 36.2     | 82.4 ±4.63 | AMD      | 14 year      | 8                       | OR = 1.6    | 0.8-3.2     |    |
| Emily Y. Chew  | 2009  | Cohort study | America                       | 6037        | NR       | 55-80 | AMD      | 5 year        | 9                       | OR = 0.76   | 0.44-1.30   | .31 |
| Jie Jin Wang,  | 2012  | Cohort study | Oceania                       | 1711/348    | NR       | >65   | Late AMD  | 3 year        | 8                       | OR = 0.74   | 0.23-2.36   | NR  |
| Jie Jin Wang,  | 2016  | Cohort study | Oceania                       | 2029        | 39.8     | >65   | Early AMD | 5 year        | 8                       | OR = 0.7    | 0.4-1.2     | NR  |
| Ronald         | 2002  | Cohort study | North America                 | 2764        | NR       | 43-86 | AMD      | 10 year       | 8                       | RR = 1.97   | 1.29-3.02   | <.01|
| Klein, B. E.   | 2012  | Cohort study | North America                 | 3275        | NR       | 43-86 | Early AMD | 20 year       | 9                       | OR = 1.96   | 0.82-2.23   | .23 |
| Ronald         | 1998  | Cohort study | North America                 | 3684        | NR       | 43-86 | Early AMD | -             | 8                       | OR = 1.73   | 0.93-3.21   | .08 |
| Klein          |       |            |                               |             |          |       | Dry AMD   |               |                         | OR = 2.80   | 1.03-7.63   | .04 |

NA = not reported.
Figure 2. Relationship between cataract surgery and age-related macular degeneration.

Figure 3. Sensitivity analysis.

4. Discussion

Many large-scale epidemiological studies have not clearly identified whether cataract surgery is such an intervention can increase the risk of worsening of AMD progression. Our results show that worsening of AMD progression after cataract surgery are the most common in Asia patients, which is similar to Wang JJ’s study published in 2012,[20] it showed that the incidence of neovascular AMD within 5 years after cataract surgery was 2-3 times higher than that of nonsurgical patients (HR 2.68; 95% CI 1.55-4.66; P < .001). In a cross-sectional study of North Africans, Lazreg et al.[12] found that patients with cataract surgery were more likely to develop AMD than those without surgery (OR: 2.69; 95% CI 1.96-3.70; P < .0001). Darker iris color can increase the risk of worsening of AMD progression too.[24]

We divided AMD into early AMD and advanced AMD (including wet AMD and dry AMD) thought severity, and it was found that cataract surgery did not exacerbate all types of AMD.

The studies included differed significantly in the duration of follow-up, and no selection date was proposed. When the
Figure 4. Subgroup analysis (region).

Figure 5. Subgroup analysis (age-related macular degeneration type).
follow-up time was >5 years, there was a significant positive association between cataract surgery and increase the risk of worsening of AMD progression. Studies have found that the risk of neovascular AMD differs in different clinical subtypes of AMD. Combining the findings of Beaver Dam and Blue Mountain, cataract surgery was found to be associated with an increased 5-year incidence of neovascular AMD. Klein et al also found that the OR value of advanced AMD is higher in patients with cataract surgery more than 5 years. Epidemiological studies have provided the incidence of AMD after up to 20 years of follow-up, while clinical trials have been followed for no more than 1 year.

In general, the studies included varied widely in study populations and study durations, which were limited in comparability. However, this study included only cohort studies, and the association between cataract surgery and AMD progression became stronger with follow-up beyond 5 years. Many studies with long-term follow-up of AMD patients found that patients who underwent cataract surgery had a higher risk of AMD progression than those who did not. In a cross-sectional study combining 3 population studies, those who reported surgery at 5 years or more had a 2.1-fold (95% CI 1.0 vs 4.6) chance of developing advanced AMD compared with those who had surgery less than 5 years. The odds of developing advanced AMD were slightly increased, but the increase was not statistically significant (OR 1.4, 95% CI 0.7 2.6). A population-based cohort of older Australians reported that the long-term (10-year) risk of developing advanced AMD in the eye undergoing surgery was significantly higher than baseline. Ferris et al found that the risk of advanced AMD progression in patients with moderate AMD was as high as 30% within 3 years. In conclusion, AMD patients need regular fundus examinations no matter with or without cataract surgery.

Both cataracts and AMD are strongly age-related, and multiple studies have found that cataracts and AMD may share the same epidemiological risk factors, but this study did not find that cataract surgery and the risk of worsening of AMD progression are directly related or have a clear connection. Although most of the included observational studies did control for different familiar confounders, but cataract status is still residual confounding for the possible interactions of AMD, cataract, and cataract surgery do not all appear to be consistent. However, all of these are insufficient to explain the association between cataract surgery and the risk of worsening of AMD progression in this study.

This review has the following limitations: First, Persuading cataract patients to randomize surgery is difficult, so it’s hard to conduct randomized controlled trials (RCTs), which with the highest level of evidence, prospective or retrospective studies can provide the most powerful evidence under the circumstances with a series of obstacles of RCTs. In addition, there are some less standardized studies, the incidence of AMD was artificially reduced for some patients with unclear fundus cataracts cause were excluded. Therefore, all those may affect the statistical analysis of the association of AMD with other parameters.

In conclusion, there is still a significant positive correlation between cataract surgery and increase the risk of worsening of AMD progression, and faster progression of early-to-late AMD found in cataract surgery with longer follow-up of patients. However, based on the result of this review, we cannot draw conclusions about the effect of cataract surgery on the risk of worsening of AMD progression. In conclusion, the studies we included were highly heterogeneous in terms of study population and study period, and were highly heterogeneous, so their comparability was limited. More clinical trials (with sufficient statistical power) are needed, which should ideally be able to adequately control for confounding variables such as age and cataract severity, and subgroup analyses can be set up to make the study more precise. Regarding the need for more clinical trials (with sufficient statistical power) to demonstrate this hypothesis by adequately controlling for confounding variables such as age and cataract severity.

**Author contributions**

ZYC conceived and designed the experiments. YZ and FYT performed the experiments and data analysis. YZ and ZYC...
provided the reagents, materials and analysis tools. ZYC wrote the manuscript. ZYC revised the work critically for important intellectual content. All authors have read and approved the final version of the manuscript.

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