Global Incidence, Progression, and Risk Factors of Age-Related Macular Degeneration and Projection of Disease Statistics in 30 Years: A Modeling Study

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Keywords

Age-related macular degeneration · Incidence · Progression · Risk factors

Abstract

Objective: Age-related macular degeneration (AMD) has become a major cause of visual impairment worldwide, especially in the elderly. Estimates of incidence, progression rates, and risk factors of AMD vary among studies, complicating the understanding of its epidemiology. **Methods:** For this systematic review and meta-analysis, literature published up to March 1, 2021, was searched in both English and Chinese databases. Hierarchical Bayesian approaches were used to estimate pooled incidence, progression, and 95% credible intervals (CrIs). **Results:** Thirty studies were included. The pooled annual early and late AMD incidence rates were 1.59 (95% CrI: 1.18–2.11) and 0.23 (95% CrI: 0.14–0.34) per 100 person-years, respectively. The annual progression

rate of AMD was 5.5 (95% CrI: 2.3–8.8) per 100 person-years. Smoking was an independent risk factor for both early and late AMD, whereas age, high-density lipoprotein cholesterol, and alcohol consumption were risk factors for early AMD incidence only. The projected number of new cases of early and late AMD in 2050 would be 39.05 million (95% CrI: 23.12–63.57) and 6.41 million (95% CrI: 3.37–13.22), respectively. **Conclusion:** The prediction the number of new cases of AMD is not equal across the globe. Our findings indicate the need for more rigorous control and prevention measures in AMD focus on its risk factors for early intervention. The epidemiological estimates reported in this study could inform to identify effective strategies for preventing AMD worldwide.

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Introduction

Age-related macular degeneration (AMD) has become the most common cause of blindness among people over 60 years old, particularly in developed countries [1, 2]. As the population of older persons in the world is expected to double by 2050, it is important to examine how AMD occurs over time and what contributes to its development to point the way for related health services and protocol. Previously, there were several meta-analyses focused on the prevalence of AMD [3–6], which measures the proportion of the disease in the population. However, incidence is a key measure to examine new cases over time, allowing for forecasting of current demands for related health care services. Additionally, progression is an important indicator of the stage and severity of the disease. In particular, there is no systematic review of both incidence and progression of AMD despite multiple individual studies. Interpreting incidence data from such different studies is challenging because of wide variation in estimates between countries and regions, due to differences in study methods, diagnosis criteria, and time trends. Generally, according to the grading protocol of the Wisconsin Age-Related Macular Degeneration Grading System (WAMDGS) [7] and international classification and grading system (IGS) [8], early AMD can be defined by the presence of signs of any size drusen and pigmentary abnormalities, or by the presence of a large size drusen over 125 μm in diameter but without signs of late AMD. Late AMD can be defined as follows: geographic atrophy of the retinal pigment epithelium or pigment epithelial detachment, subretinal hemorrhage or subretinal new vessel, or subretinal scar or photocoagulation treatment scar. There is little summarized data on AMD incidence or progression to guide global strategies for disease management. A prior meta-analysis reported that annual incidence of late AMD in white Americans was 3.5 per 1,000 aged >50 years, equivalent to 293,000 new cases in white Americans per year [9]. However, there is a lack of robust estimates of the worldwide incidence and progression of both early and late AMD in the general population.

Besides, in order to better understand of etiology and provide pathways to AMD prevention, it is necessary to analyze the risk factors. Risk factors can be divided into demographic factors, such as age, sex and ethnicity, and lifestyle factors, such as smoking and alcohol consumption [10]. However, numerous risk factors on AMD have been reported but the evidence and strength of association varies. Currently, little is known about the risk factors of AMD based on longitudinal cohort studies providing strong evi-

dence worldwide, which are very important for clinical or public healthy staff to intervene and prevent as soon as possible and reduce the incidence of ophthalmological carries. Generally, robust data on incidence, progression and risk factors of both early and late AMD and their burden are important for development of major public health strategies, such as screening and prevention programs.

Methods

This systematic review was conducted and reported in accordance with the Reporting Checklist for Meta-analyses of Observational Studies (MOOSE). The completed MOOSE checklist is available in the online suppl. material (for all online suppl. material, see www.karger.com/doi/10.1159/000518822). Further, this study is registered with PROSPERO, number CRD42019118832.

Search Strategy and Selection Criteria

For this systematic review and meta-analysis, 2 authors (Y.W. and L.L.) independently searched PubMed, Web of Science, EM-BASE, China National Knowledge Infrastructure (CNKI), Wanfang, and ViP databases for relevant articles published up to March 1, 2021. Detailed search terms (formatted for PubMed search): {"Macular Degeneration" [Mesh] AND ("Incidence" [Mesh] OR "Epidemiology" [Mesh] OR "Longitudinal Studies" [Mesh] OR "Cohort Studies" [Mesh]); {"age-related maculopathy" [All Fields] OR "age-related maculopathy" [All Fields] OR "age-related macular degeneration" [All Fields] OR "age-related macular degeneration" [All Fields] OR "macular degeneration" [All Fields]) AND ("incidence" [All Fields] OR "progression" [All Fields] OR "epidemiology" [All Fields] OR "risk factors" [All Fields])}, without language restrictions. Additionally, reference lists of identified articles were also searched to identify other relevant literatures. Two reviewers (Y.W. and Y.Z.) evaluated all included studies independently. Disagreements were discussed with another investigator (L.L.) and resolved by consensus.

Inclusion criteria were: (1) longitudinal or cohort studies on incidence or progression of AMD diagnosed by retinal photographs and standardized grading classifications (WAMDGS [7], IGS [8], or the Barbados Eye Studies Grading Protocol [BISEDP] [11]), (2) AMD reported as an individual entity, and (3) the data included crude figures or enabled crude calculation of AMD incidence or progression. Studies with a greater amount of person-years or more sophisticated case-finding methods that reported on similar study populations but not conducted during the same time periods were also included. There were no restrictions regarding publication year. Exclusion criteria were as follows: (1) duplicated articles; (2) reports not written in English or Chinese; (3) reports number of eyes with AMD as opposed to number of individuals; (4) dynamic population; and (5) not population based or longitudinal cohort study.

Data Extraction and Quality Assessment

A data extraction spreadsheet was used to collect information on the study and participant characteristics from each of the included studies. Relevant information was extracted from the included studies by 2 researchers (Y.W. and L.L.). Publication authors were contacted for missing data on incidence or progression of AMD when necessary. We assessed the quality of included stud-

Fig. 1. Flowchart: study identification and selection. AMD, age-related macular degeneration.

ies using an assessment scale based on the Newcastle-Ottawa Scale (NOS, details in online suppl. Method) [12, 13]. From this, studies were judged to be at low risk of bias (≥ 3 points) or high risk of bias (< 3 points). Data were double-checked and reviewed by a statistician (L.Z.). In the event of any disagreement on extracted data, the article was assessed again and discussed between the 3 reviewers (Y.W., Y.Z., and L.L.) until an agreement was achieved.

Incidence of AMD was defined as the development of early AMD or late AMD [14]. Progression of AMD was defined as development of advanced AMD in one or both eyes with early AMD at baseline of the study [15].

Statistical Analysis

Hierarchical Bayesian approach was used to estimate the pooled AMD annual incidence of the population along with 95% credible intervals (CrIs). Projections of AMD were estimated based on the World Population Prospects of the United Nations [16]. Age group-specific annual incidence rates were assumed to be constant over the next 30 years for our global projection for the year 2050, since Bayesian hypothesis testing of the study baseline year covariate (Bayes factor [BF] is 0.17 for early AMD and 0.19 for late AMD) in our review showed no trend for incidence from year 1987 to 2010, whereas BF describes level of statistical evidence: negative evidence (BF < 1), weak (BF 1–3), substantial (BF 3–10), strong (BF 10–30), very strong (BF 30–100), and decisive (BF > 100) [17]. Bayesian meta-regression models were generated to assess the association between incidence of AMD and relevant factors. Since studies varied in length of follow-up, annual inci-

dence was calculated based on exponential assumptions and the formula used by a previous systematic review [9]: $-\ln(1-S)/t$, where $\ln()$ is the natural logarithm function, S is the cumulative incidence over years and t is the duration of years of follow-up.

In order to investigate the demographic, lifestyle, and health-related factors related to AMD incidence, Hierarchical Bayesian approach was used to calculate the pooled effect estimates. Since the incidences of both early and late AMD were very low ($< 10\%$), the 3 measures (hazard ratio, relative risk, and odds ratio [OR]) of association were expected to yield similar estimates of OR [18]. Therefore, we put together all the OR estimates as appropriately as possible to ensure the comprehensiveness of the analysis and maximize the statistical power [18, 19]. Forest plots are used to display statistical analysis results.

Standard χ^2 test with I^2 statistics (the percentage of variability in incidence estimation due to heterogeneity rather than sampling error or chance) and p values were used to assess between-study heterogeneity. Funnel plot and Egger test for funnel plot asymmetry were used to assess study publication bias.

Results

Characteristics of Included Studies regarding

As shown in Figure 1, the initial literature search returned 732 citations from enrolled bibliographic databases-

Fig. 2. a Forest plot for annual incidence of early AMD by region. AMD, age-related macular degeneration; CI, confidence interval. **b** Forest plot for annual incidence of late AMD by region. AMD, age-related macular degeneration; CI, confidence interval. (Figure continued on next page.)

es. Finally, 30 studies involving 82,973 individuals from 12 countries and 5 continents were included in the current analysis. Among all included longitudinal population-based observational studies, 19 [20–38] were con-

ducted before year 2000 and 11 [39–49] were conducted after year 2000. The age of the study participants ranged from 30 [35] to 98 [33] years old and follow-up duration ranged from 2 years [29] to 15.6 years [20]. Sample sizes

Fig. 3. a Forest plot for annual incidence of early AMD by observed duration. AMD, age-related macular degeneration; CI, confidence interval. **b** Forest plot for annual incidence of late AMD by observed duration. *Long duration: observed duration ≥ 10 years; short duration: observed duration < 10 years. AMD, age-related macular degeneration; CI, confidence interval. (Figure continued on next page.)

ranged from 313 in the Copenhagen City Eye Study/Denmark (CCES) [22, 23] to 20,196 in the Nationwide Population-Based Study (NPBS) [47], while response rates ranged from 50.1% in the Nakuru Eye Disease Cohort

Study (NEDCS) [45] to 97.3% in the CCES [22, 23]. Overviews of studies regarding AMD incidence or progression are listed in online suppl. Table 1 and studies included for analysis are shown in online suppl. Table 2.

Fig. 4. a Forest plot for annual incidence of early AMD by AMD grading methods. AMD, age-related macular degeneration; CI, confidence interval; WAMDGS, Wisconsin Age-Related Macular Degeneration Grading System; IGS, international classification and grading system; BISEDGP, Barbados Eye Studies Grading

Protocol. **b** Forest plot for annual incidence of late AMD by AMD grading methods. AMD, age-related macular degeneration; CI, confidence interval; WAMDGS, Wisconsin Age-Related Macular Degeneration Grading System; IGS, international classification and grading system. (Figure continued on next page.)

Subgroup Analysis by Region on AMD Incidence

Figure 2a, b shows the annual incidence of early AMD and late AMD stratified by region, respectively. For early AMD, the overall annual incidence was 1.59 (95% CI,

1.18–2.11) per 100 person-years ($I^2 = 90.3\%$, $p < 0.0001$). The annual incidence was 1.79 (95% CrI, 1.08–3.88) per 100 person-years in Europe [25, 39, 41, 48], 1.46 (95% CrI, 0.81–2.30) per 100 person-years in Asia [28, 40, 44,

Fig. 5. Age trend of annual incidence of early AMD by country. **a** Overall age trend of annual incidence of early AMD by country. AMD, age-related macular degeneration. **b** Male-specific age trend of annual incidence of early AMD by country. AMD, age-related macular degeneration. **c** Female-specific age trend of annual incidence of early AMD by country. AMD, age-related macular degeneration

Fig. 6. Age trend of annual incidence of late AMD by country. **a** Overall age trend of annual incidence of late AMD by country. AMD, age-related macular degeneration. **b** Male-specific age trend of annual incidence of late AMD by country. AMD, age-related macular degeneration. **c** Female-specific age trend of annual incidence of late AMD by country. AMD, age-related macular degeneration.

49], 1.67 (95% CrI, 1.06–2.86) per 100 person-years in Oceania [20, 32–34], and 1.45 (95% CrI, 0.87–2.20) per 100 person-years in North America [27, 30, 31, 38, 43], where Europe had the highest annual incidence. For late AMD, the overall annual incidence was 0.23 (95% CrI, 0.14–0.34) per 100 person-years ($I^2 = 95.7\%$, $p < 0.0001$). The annual incidence was 0.18 (95% CrI, 0.06–0.35) per 100 person-years in Europe [24, 25, 39, 41, 48], 0.25 (95% CrI, 0.13–0.52) per 100 person-years in Asia [28, 40, 44, 47, 49], 0.25 (95% CrI, 0.13–0.48) per 100 person-years in Oceania [20, 32–34] and 0.23 (95% CrI, 0.12–0.47) per 100 person-years in North America [30, 31, 43], where Asia and Oceania had the highest annual incidence.

Subgroup Analysis by Observed Duration on AMD Incidence

When classified by duration of observation, 6 studies [20, 22, 23, 26, 30, 34] were in the long duration group (≥ 10 years), and 24 studies [21, 24, 25, 27–29, 31–33, 35–49] were in the short duration group (< 10 years). Of the 30 included studies, 9 had a 5-year observation period [25, 28, 31–33, 35, 37, 41, 42]. Annual incidences in studies with long duration were lower for both early AMD and late AMD (Fig. 3a, b).

Subgroup Analysis by AMD Grading Methods on AMD Incidence

Of the total number of included studies, 14 graded AMD using the WAMDGS [20, 22, 23, 26, 30–32, 34, 37,

Table 1. Projection of number of people (aged 45–85, in millions) who will have developed early AMD by regions

Region	2030	2040	2050
Europe	5.97 (3.72, 12.64)	6.06 (3.77, 12.83)	5.73 (3.56, 12.12)
Asia	23.93 (13.95, 37.01)	28.23 (16.46, 43.66)	30.44 (17.75, 47.09)
Oceania	0.26 (0.17, 0.45)	0.30 (0.20, 0.51)	0.34 (0.22, 0.56)
Northern America	2.28 (1.41, 3.39)	2.45 (1.52, 3.64)	2.55 (1.58, 3.80)
World	32.44 (19.25, 53.48)	37.04 (21.95, 60.64)	39.05 (23.12, 63.57)

AMD, age-related macular degeneration.

Table 2. Projection of number of people (aged 45–85, in millions) who will have developed late AMD by regions

Region	2030	2040	2050
Europe	0.65 (0.23, 1.21)	0.66 (0.23, 1.23)	0.62 (0.22, 1.16)
Asia	4.17 (2.29, 8.73)	4.92 (2.70, 10.30)	5.31 (2.91, 11.11)
Oceania	0.04 (0.02, 0.08)	0.05 (0.03, 0.09)	0.05 (0.03, 0.10)
Northern America	0.38 (0.19, 0.76)	0.40 (0.21, 0.81)	0.42 (0.22, 0.85)
World	5.24 (2.73, 10.78)	6.04 (3.16, 12.44)	6.41 (3.37, 13.22)

AMD, age-related macular degeneration.

40, 41, 43, 44, 49]. For early AMD, the annual incidence was highest when using BISEDGP [27, 38], with an overall incidence of 1.86% (95% CrI, 1.08–3.66) per 100 person-years, followed by 1.83 (95% CrI 1.07–3.49) when using WAMDGS & IGS [25, 28], 1.64 (95% CrI, 0.97–2.69) when using IGS [33,39,48], and 1.50 (95% CrI, 1.05–2.09) when using WAMDGS [20, 30–32, 34, 40, 41, 43, 44, 49]. For late AMD, the annual incidence was 0.20 (95% CrI, 0.05–0.74) when using WAMDGS & IGS [25, 28], 0.21 (95% CrI, 0.08–0.52) per 100 person-years when using WAMDGS [20, 30–32, 34, 40, 41, 43, 44] and 0.20 per 100 person-years when using IGS [24, 33, 39] on its own (95% CrI, 0.06–0.61) (Fig. 4a, b).

Forest plots for annual incidence of early and late AMD by response rate, baseline year, and sample size are provided in the online suppl. Figures 1a, b, 2a, b, and 3a, b. Analysis of annual incidence on country after adjusted by age and gender are shown in the online suppl. Table 3.

Age Trend of Annual Incidence of Late AMD by Regions

As the figure shows, the annual incidence of AMD increased with age. Compared with the total trend, the incidence of early AMD in Oceania, followed by Europe, was above the overall incidence when age was over 75 years old (Fig. 5a). For either males (Fig. 5b) or females (Fig. 5c), the incidence of early AMD increased most rapidly in Europe after age 75. In the age trend of annual incidence of late AMD, Oceania had the highest incidence while Europe had the lowest incidence. Compar-

ing with early AMD, the incidence of late AMD changed less (Fig. 6a). For males, incidence in Asia was the highest in most age groups (Fig. 6b), while the incidence was higher and increased most rapidly in Europe after 75 years of age for females (Fig. 6c). Besides, age trend of annual incidences of early and late AMD by country and sex are also presented in the online suppl., in which there is a difference between male and female (online suppl. Fig. 4a–f).

Projection Estimates of AMD for 2020–2050 by Regions

Tables 1 and 2 show the estimated number of people who will develop early or late AMD from 2030 to 2050 in decades stratified by regions. For the year 2030, the global projected new cases of early AMD would be 32.44 million (95% CrI, 19.25–53.48), rising to 39.05 million (95% CrI, 23.12–63.57) by 2050, with the largest number of people in Asia (30.44 million by 2050). Europe is expected to be second to Asia for early AMD (5.73 million by 2050), followed by Northern America (2.55 million), and then Oceania (0.34 million). For late AMD, the incidence is much lower than that of early AMD, with the same ranking of regions. In the year 2020, the global projected new cases for late AMD would be 5.24 million (95% CrI 2.73–10.78), rising to 6.41 million (95% CrI 3.37–13.22) by 2050, with the largest number of people in Asia (5.31 million by 2050), followed by Europe (0.62 million), Northern America (0.42 million), and Oceania (0.05 million).

Table 3. Risk factors for global incidence of early AMD

Factor	Studies, <i>n</i>	OR (95% CrI)	<i>p</i> value
Age	6	1.09 (1.05–1.13)	<0.001
Female gender	5	0.99 (0.63–1.56)	0.975
Smoking	7	1.59 (1.17–2.17)	0.003
Alcohol consumption	2	1.92 (1.04–3.57)	0.038
Diabetes mellitus	3	1.13 (0.80–1.60)	0.484
Hypertension	2	0.89 (0.72–1.10)	0.286
CVDs	2	1.21 (0.69–2.12)	0.499
Pulse pressure	2	1.00 (0.99–1.01)	0.999
HDL-C	2	1.35 (1.01–1.81)	0.040
DBP	2	1.02 (1.00–1.04)	0.052

CVDs, cardiovascular diseases; HDL-C, high-density lipoprotein cholesterol; DBP, diastolic blood pressure; OR, odds ratio; CrIs, credible intervals; AMD, age-related macular degeneration.

Progression Rate on AMD

The annual progression rate of AMD was 5.5 (95% CrI: 2.3–8.8) per 100 person-years. Studies that have been included in the progression rate analysis were the Age and Gene/Environment Susceptibility Study (AGES) [41], the Barbados Eye Studies II (BISED II) [27], the Los Angeles Latino Eye Study (LALES) [43], and the Rotterdam Study (RTES) [29].

Risk Factors for Occurrence of Early and Late AMD

We summarized variables related to AMD incidence that were reported in the included studies. After pooling these factors, we found that age (OR: 1.09; 95% CrI: 1.05–1.13) [20, 21, 28, 40–42], high-density lipoprotein cholesterol (HDL-C) (1.35; 95% CrI: 1.01–1.81) [39, 41], smoking (1.59; 95% CrI: 1.17–2.17) [20, 21, 27, 28, 37, 40, 41], and alcohol consumption (1.92; 95% CrI: 1.04–3.57) [37, 44] could be considered as pooled risk factors of early AMD incidence. For late AMD, only smoking [20, 27, 37] was investigated among 3 studies, and its risk toward late AMD incidence was 2.32 (95% CrI: 1.04–5.18). A relative table of risk factors is shown in Tables 3 and 4.

Discussion

Principle Findings

To our knowledge, this is the first meta-analysis to summarize the global incidence rates and risk factors for both early and late AMD. In addition, we investigated progression rates of AMD among population-based longitudinal cohorts. In this systematic review and meta-analysis of 30 longitudinal population-based observa-

Table 4. Risk factors for global incidence of late AMD

Factor	Studies, <i>n</i>	OR (95% CrI)	<i>p</i> value
Smoking	3	2.32 (1.04–5.18)	0.040

AMD, age-related macular degeneration; OR, odds ratio; CrIs, credible intervals.

tional studies [20–47], the main findings aimed to estimate the global incidence and progression of AMD and were as follows: First, the global annual incidence of AMD was different when stratified by different subgroups including regions, countries, observation durations, AMD grading methods, response rates, baseline years, and sample size. Second, in the year 2020, the estimated global new cases would be 32.44 million for early AMD and 5.24 million for late AMD, rising to 39.05 million and 6.41 million by 2050, respectively. Third, the global annual incidence of both early and late AMD increased with age. Fourth, smoking was considered to be a risk factor for both early and late AMD, while age, HDL-C, and alcohol consumption were risk factors for early AMD only.

Meaning of the Study and Comparison with Other Studies

This meta-analysis included only 1 study from Africa [45] to examine cumulative incidence of AMD which might be caused by low income and limited infrastructure [45, 50]. Since AMD is more prevalent among whites than blacks [51] and developed countries [10], more studies were conducted in Europe, North America, and Australia. Moreover, as presented in the Supplement, the annual incidence of early and late AMD increased with age, in which trends in females were more obvious than males. As Tables 1 and 2 shows, globally, the incidence of AMD is increasing in decades, with >75% of new cases in Asia by 2050. Compared with Europe, the annual incidence of early AMD is lower in Asia. However, Asia has a large population base, and hence we will see the largest projected number of people with AMD. Besides, incidence of AMD in Asia is expected to increase more rapidly than other regions over the years [52], as age is a risk factor for AMD and the problem of the aging population in Asia is serious while the incidence in Europe being flat in the last 40 years according to our projection. The above points suggest that we should focus on prevention and control of AMD in Asia.

Age [20, 21, 28, 40–42], HDL [39, 41], alcohol consumption [37, 44], and smoking [20, 21, 27, 28, 37, 40,

41] are risk factors after analysis of results. Many factors such as gender [20, 21, 40, 45, 47], hypertension [27, 41], diabetes [27, 41, 45], and cardiovascular disease [27, 44] are no longer considered risk factors as their ORs were inconsistent across studies. For example, being female was considered to be a risk factor in the AGES [41], the Blue Mountains Eye Study III (BMES III) [20], the Singapore Malay Eye Study (SIMES) [40], and the NEDCS [45], while being male was considered as a risk factor in the Hisayama Study (HS) [21]. Ethnicity might partly explain the difference. The relationship between smoking and late AMD could be explained by shared risk factors (e.g., hypertension) or by potential unmeasured confounders (e.g., physical status) [53]. Although only 10 studies are included, all of risk factors are relative to incidence which overall results have not been reported till now. For further analysis, future studies should be performed in other regions and population such as Africa and Africans to obtain a more comprehensive understanding of how incidence can provide insight to time of exposure to risk factors.

Results from this study also showed that the annual progression rate [27, 29, 41, 43] of AMD was 5.5 per 100 person-year with 95% CrI from 2.3% to 8.8%. As only 4 studies were included, the results of the stratified analysis were not very reliable. This implies that more research is needed to better understand progression and facilitate progression analysis.

The assessment of the quality of the studies was performed in order to provide additional evidence of the internal and external validity of the data. According to NOS (online suppl. Tables 4, 5a, b), 27 of 30 studies included in our analysis were judged to be of low risk of bias probably because of that large, population-based, cohort studies had the advantage over other study designs in which they eliminate any temporal or causal ambiguity as exposure is before the onset of disease [53, 54]. Furthermore, the result funnel plot indicated evidence of significant publication bias (online suppl. Fig. 5a, b).

Strengths and Limitations of the Study

Strength of current study is that it comprises geographically and chronologically dispersed epidemiological data on global AMD incidence and progression specifically derived from longitudinal cohort studies to date. We had strict inclusion criteria to ensure including studies focus on incidence or progression rather than prevalence. Furthermore, our meta-analysis quantified global AMD incidence and its risk factors, enabling us to provide a contemporary estimation of AMD epidemiology.

This study was not without limitations. There were limited prospective epidemiological data on AMD incidence for some large populations, including India and Russia and nations from the continents of Africa and South America. We included cohort studies published in English and Chinese databases. However, variations in AMD incidence reported in a different language may exist, which may not have been included in this analysis. Another notable limitation of such a meta-analysis would be the significant heterogeneity, and this may have led to an overestimation or underestimation of incidences. Finally, in all included studies, AMD were diagnosed based on photographs. In clinic, a consensus group has recently recommended a multimodal image approach, including optical coherence tomography features, so that it may have led to an underestimation of the actual disease incidence. Notably, it may be unlike that this limitation in the study design inherent to almost any population- or community-based study might be involving these devices on site investigation. Future studies may further explore this topic.

Unanswered Questions and Future Research

Based on this systematic review, we recommend further studies of developing countries such as those in Africa and South America in order to obtain precise estimates of either early or late AMD across all regions. This is especially needed for studies pertaining to late AMD. Additionally, to avoid heterogeneity and facilitate meta-analysis, future studies should consider following a standardized method of reporting, including variables such as age and sex.

Conclusions

In summary, this systematic review provided an overview of the global incidence, progression, and risk factors of AMD over the past few decades and projected estimates of the number of people who will develop the disease from 2020 to 2050 across several regions in the world. Country-specific data are needed because of the varying population compositions and socioeconomic levels across different countries and cultures. Continued growth of the aging population will result in increasing numbers of cases of visual impairment related to AMD. Slowing the incidence of AMD, along with controlling its risk factors and developing future therapies, is required to reduce potential visual impairment burdens. Overall, this review provides useful information for the conceptualization

and development of major public health strategies, such as prevention programs for AMD based on risk factors analysis.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The original idea for the research was developed by L.L. and L.Z. L.Z. conducted the analysis with input from Y.W. and L.L. Y.Z., Y.W., and L.L. conducted the searches, study selection, quality assessments, and other data extraction. Q.W., Y.T., T.H.R., C.C., J.W., H.L., H.Y., X.Y., and D.M.K. wrote the manuscript. All authors interpreted the findings and contributed to critical revision of the manuscript. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. L.L. is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Availability Statement

No additional data are available.

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