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Risk Factors and Global Prevalence of Neovascular Age-Related Macular Degeneration: Protocol for A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Neovascular age-related macular degeneration (nAMD) is the most prevalent cause of blindness among individuals over 50 years old in developed countries. nAMD can result in vision loss due to the degeneration of the retinal pigment epithelium or the formation of abnormal blood vessels called choroidal neovascular membranes (CNVM) beneath the macula. These CNVM can leak fluid and blood, leading to the formation of a scar that can cause severe vision impairment.

Methods: A comprehensive search was conducted on various databases including PubMed, Cochrane Library, Web of Science, Embase, OVID MEDLINE, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedicine Literature Database (CBM-SinoMed), and VIP to gather research literatures on the risk factors and global prevalence of nAMD. The search strategy Headings (MeSH) terms and free-text terms, and Stata12.0 software was utilized for meta-analysis of the collected data.

Results: This study is ongoing and the results will be submitted to a peer-reviewed journal for publication.

INTRODUCTION

Age-related macular degeneration (AMD) is a prevalent eye condition that impacts the macula, which is responsible for central vision. It is a major cause of visual impairment and blindness among the elderly globally and primarily affects individuals aged 50 and above. With a global prevalence rate of 8.7%, the projected number of cases of AMD) was 196 million worldwide in 2020 Wong et al. (2014). It is expected to increase to 288 million by 2040, with the majority of cases occurring in Asia (113 million in 2040) Ng et al. (2019) and it is predicted that the prevalence and incidence of AMD in European countries will increase by 15% and 75% respectively in the aging population until 2050 li et al. (2020). During the initial phases of AMD, drusen may be detected in the macular region, and as AMD progresses, it can present as either non-neovascular or neovascular and impose a substantial burden on individuals, families, communities, and societies, resulting in significant detrimental effects.

Neovascular age-related macular degeneration (nAMD), which is characterized by choroidal neovascularization, subretinal fluid accumulation, hemorrhage and fibrosis Geltzer et al. (2013). It occurs when pathological blood vessels grow from the choroid layer towards the retina. The abnormal growth and leakage of these vessels can result in exudation and hemorrhage, causing damage to the layers of the retina and consequent vision loss Bourla et al. (2006), Pauleikhoff et al. (2005). Although nAMD only represents 4-7% of the total AMD cases, it is responsible for more than 90% of severe visual loss or legal blindness in individuals with AMD Wang et al. (2018), Moschos et al. (2018), Colijn et al. (2017). The pathogenesis of nAMD involves complex mechanisms, including inflammation, oxidative stress, genetic predisposition, and environmental factors.

The risk factors of nAMD are numerous and complex, contributing to the progression of the disease from asymptomatic stages to irreversible vision loss. Despite efforts, effectively preventing visual impairment caused by nAMD remains challenging and difficult. Therefore, further research is necessary to identify the global prevalence the risk factors of nAMD and develop effective preventive measures. Implementing interventions targeted at high-risk factors is crucial for preventing the occurrence and progression of nAMD, as well as for early vision preservation before irreversible damage occurs. The latest estimates of incidence and

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prevalence of nAMD is a epidemiological study in a population-based cohort in Finland. The findings from it indicate a 1.2-fold and 2.4-fold rise in the occurrence of nAMD over the past 15 years in the Finnish population aged 75-84 and 85-96 years, respectively. Additionally, the prevalence of nAMD in 2020 was estimated to be around 3% Korva-Gurung et al. (2023). The development of nAMD is influenced by multiple factors. Several studies have suggested a correlation between nAMD and factors such as hyperopia, black ethnicity, and atherosclerosis Lazreg et al. (2016). However, the research findings regarding the relationship between smoking, alcohol consumption, BMI, diet, and nAMD have shown inconsistent results Anastasopoulos et al. (2018), Chen et al. (2019).

Systematic reviews and meta-analysis can offer empirical evidence for healthcare choices and can also contribute to the development of evidence-based recommendations in clinical guidelines McKenzie et al. (2017), Gao et al. (2019). The objective of the present study is to conduct a comprehensive review and meta-analysis in order to obtain updated estimates of the risk factors and global prevalence of nAMD. These findings will provide valuable insights for the development, implementation, and assessment of preventive interventions for nAMD, ultimately aiming to reduce its impact on morbidity. Based on the existing evidence, we aimed to: (1) pool the overall global prevalence of nAMD; (2) estimate the effects of demographic and geographic variables on the prevalence of nAMD; (3) assess the major risk factors associated with nAMD.

METHODS AND ANALYSIS

Study registration

The review's methods have been defined in advance following the Prepared Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines;this protocol has been formulated in accordance with the PRISMA-P checklist.

The study has been registered on the PROSPERO (https:// www.crd. york.ac.uk /PROSPERO/), the registration number is CRD42023470864

Study inclusion and exclusion criteria

Only studies that present original data will be considered for inclusion in the review. We will include studies that had to be population-based and reported the risk factors and prevalence of nAMD.

Types of studies: Inclusion: (1) Randomized controlled trial; (2) cohort studies; (3) case-control studies;(4) cross-sectional studies. Exclusion: (1) Literature not written in Chinese or English; (2) Research data that is incomplete or missing; (3) Original documents that cannot be obtained; (4) Duplicate publications of literature; (5) Editorials; (6) Commentaries.

Types of participants: Any study that includes at least one participant with nAMD.

Risk factors: age, male gender, genetic factors, smoking, cardiovascular diseases, surgery, total cholesterol [TC], triglyceride [TG], body mass index [BMI], systolic blood pressure [SBP].

Types of outcomes measures: Incidence and prevalence, risk factors of nAMD.

Search scheme and strategy

The following databases were searched: PubMed, Cochrane Library, Web of Science, Embase, OVID MEDLINE, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Biomedicine Literature Database (CBM-SinoMed) and VIP. Our comprehensive search strategies combined terms of diabetic retinopathy, epidemiology (incidence, prevalence, morbidity, mortality, epidemiology). The literatures will be searched from the establishment of the database to September 21, 2023, with "Macular Degeneration", "Retinal Degeneration","Choroidal Neovascularization", "prevalen*" and "Risk Factors"and so on were used as keywords for the search. The specific search strategy is presented in Table 1 (PubMed was used as an example). To supplement the electronic database search, reference lists of eligible publications and related reviews were also scanned to identify other potentially pertinent studies. No language restrictions were imposed on searches or search results.

Study selection

Studies retrieved from the different data sources will be grouped together and duplicated records will be removed using a reference management software package (EndNote 2020, Clarative Analytics). Identified studies will be independently reviewed for eligibility by two authors (LJ, GD) in a two-step process; a first screen will be performed based on title and abstract while full texts will be retrieved for the second screen. At both stages intercoder agreement will be assessed using Cohens' k. A minimum k value of 0.75 will be taken to represent high agreement Landis et al. (1977). Disagreements between reviewers will be resolved by discussion and consultation with a third author (WY), irrespectively of the k value. The studies' selection process will be graphically reported in a PRISMA flow diagram Moher et al. (2010).

Data extraction

With a predefined data-collection form, data will be extracted by one author (GE) supervised by a second author (XZL) using a standardised data extraction spreadsheet. The following information was extracted from the included studies:1) Characteristics of the study: authors' names and affiliations, publication year, country of publication, study design, study period, study year, study setting and location, geographic region and so on.

Table 1: Search strategy used in PubMed database.

Number	Search terms
#1	"Macular Degeneration"[Mesh]
#2	((((((((((Macular Degeneration[Title/Abstract]) OR (Maculopathy[Title/Abstract])) OR (Maculopathies[Title/Abstract])) OR (Macular Dystrophy[Title/Abstract])) OR (Macular Dystrophies[Title/Abstract])) OR (Age-Related Macular Degeneration[Title/Abstract])) OR (Age Related Macular Degeneration[Title/Abstract])) OR (Age-Related Macular Degenerations[Title/Abstract])) OR (Age-Related Maculopathies[Title/Abstract])) OR (Age Related Maculopathies[Title/Abstract])) OR (Age-Related Maculopathy[Title/Abstract])) OR (Age Related Maculopathy[Title/Abstract])
#3	#1 OR #2
#4	"Retinal Degeneration"[Mesh]
#5	retinal degeneration [Title/Abstract]
#6	#4 OR #5
#7	"Choroidal Neovascularization"[Mesh]
#8	"Retinal Drusen"[Mesh]
#9	"Macula Lutea"[Mesh]
#10	#7 OR #8 OR #9
#11	((((Choroidal Neovascular [Title/Abstract]) OR (Choroidal Neovascularization [Title/Abstract])) OR (exudative [Title/Abstract])) OR (degener*[Title/Abstract])) OR (Choroid Neovascularization [Title/Abstract])
#12	((((macul*[Title/Abstract]) OR (retina*[Title/Abstract])) OR (choroid*[Title/Abstract])) OR (wet [Title/Abstract])) OR (degener*[Title/Abstract])
#13	(((macul*[Title/Abstract]) OR (retina*[Title/Abstract])) OR (choroid*[Title/Abstract])) AND (neovasc*[Title/Abstract])
#14	(maculopath*[Title/Abstract]) OR (drusen*[Title/Abstract])
#15	((macul*[Title/Abstract]) AND (lutea*[Title/Abstract])) OR (syndrome [Title/Abstract])
#16	(macul*[Title/Abstract]) AND (dystroph*[Title/Abstract])
#17	((macul*[Title/Abstract]) OR (geographic*[Title/Abstract])) AND (atroph*[Title/Abstract])
#18	((AMD[Title/Abstract]) OR (ARMD[Title/Abstract])) OR (nAMD[Title/Abstract])
#19	((retina*[Title/Abstract]) AND (angiomat*[Title/Abstract])) AND (prolif*[Title/Abstract])
#20	#3 OR #6 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	acid mine drainage
#22	#20 NOT #21
#23	"Risk Factors"[Mesh]
#24	(risk factor [Title/Abstract]) OR (risk)
#25	#23 OR #24
#26	"Epidemiologic Studies"[Mesh]
#27	(((((((((prevalen*[Title/Abstract]) OR (Inciden*[Title/Abstract])) OR (Percent*[Title/Abstract])) OR (epidemiol*[Title/Abstract])) OR (frequenc*[Title/Abstract])) OR (occurrenc*[Title/Abstract])) OR (morbidit*[Title/Abstract])) OR (rate*[Title/Abstract])) OR (Probabilit*[Title/Abstract])) OR (Population*[Title/Abstract])
#28	#26 OR #27
#29	#22 AND #25 AND #28

2) Characteristics of the sample (general population and people with nAMD): sample size, sampling method, demographic characteristics of study participants (age, gender, ethnicity, etc), duration of nAMD, age (age range, mean or median age), gender (male, female or mixed);

3) Prevalence data: the number of people with nAMD and the number of participants who had been tested for nAMD, by age, nAMD duration, gender, setting;

4) Risk factor data: other behavioural and clinical risk factors (ie, smoking habits, BMI, blood pressure, lipid profile, current use of medications), OR and corresponding confidence intervals (CIs).

Risk of bias assessment

The quality assessment of the included studies will be conducted using three different assessment tools and two reviewers will independently assess the quality of included studies.(1)The ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions), specifically developed for NRS I (Non-randomised studies of the effects of interventions)[r].The seven domains of the ROBINS-I tool were categorized as having low, moderate, serious, or critical risk of bias, or having no available information. After the evaluation of the seven domains, the overall Risk of Bias (RoB) for each study was assessed. (2) A Briggs Institute's critical appraisal checklist is a specific method for assessing the quality of studies reporting prevalence data to be included in systematic reviews and meta-analysis[s]. The Joanna Briggs Institute's checklist will be used as a reference when conducting sensitivity analysis restricted to high quality studies and, as recently proposed by Tracey et al[t], methodological quality will be considered 'low', 'moderate' and 'high' if three or less, four to six, and seven to nine criteria will be met, respectively. (3) The Cochrane bias risk assessment tool was used to evaluate the final included RCTs: random allocation method; allocation plan concealment; blinding of research subjects and experimenters; blinding of outcome evaluators; completeness of result data; selective reporting of studies Results; other sources of bias, including potential bias related to the specific research design of the study[u].For each of the above items, make a judgment of "low risk of bias", "high risk of bias" and "uncertain risk of bias". Disagreement will be solved by discussion or by consulting the third person (SLS).

Data synthesis

We will perform descriptive analysis and report the characteristics of included studies in summary tables and narrative text. Statistical analysis was performed on the extracted data using Stata 12.0 software. For measurement data, the weighted mean difference (WMD) is used as the combined effect size; for binary variable data, the odds ratio (OR) is used as the combined effect size.

Assessment of heterogeneity

To test the heterogeneity of the combined literature, we can use the statistics I2 and P values. If $P \geq 0.1$, $I2 < 50\%$, it indicates that there is homogeneity among the studies or the heterogeneity is within an acceptable range. In this case, the fixed effects model can be used to calculate the effect size for merging the data. On the other hand, if $P < 0.1$, $I2 > 50\%$, it suggests the there is heterogeneity between the studies. In such cases, additional methods like Egger's method and Begg's method can be employed to assess publication bias.

Assessment of reporting biases

An assessment of reporting bias will be conducted to validate the study findings. If the number of included studies is greater than 10, the symmetry of the funnel plot will be evaluated using Begg and Egger tests with the aid of Stata 14.0 software.

Subgroup analysis

If there is considerable heterogeneity observed across the studies included in our analysis, we conducted subgroup analyses to further investigate potential factors influencing the results. These factors may include age, gender, race, treatment duration, sample size, disease classification, and other relevant variables. If substantial evidence is available, we subgroup analyses to examine the impact of specific factors on the results.

CONCLUSIONS

Taking into account the rapidly changing patterns in nAMD epidemiology there is a strong rationale for updating current available evidence on global nAMD prevalence and risk factors. We strongly believe our data will be of crucial importance for both research and policy. Indeed, the data can assist in identifying specific settings or population subgroups that are at a higher risk of developing nAMD. This information can then be used to prioritize prevention efforts, allocate resources effectively, and guide future research to address any gaps in our understanding of the disease.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Ethics and dissemination

Ethical approval is not applicable, since this is an overview based on published articles.

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