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Review Article

The Relationship between Age-Related Macular Degeneration and Cardiovascular Disease: A Meta-Analysis

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Abstract

Background: Age-related macular degeneration (AMD) and cardiovascular disease (CVD) share pathogenic mechanisms, and their lead-lag relationship remains unclear. We performed a meta-analysis of data from longitudinal studies to evaluate the interactive association between age-related macular degeneration (AMD) and cardiovascular disease (CVD).

Methods: A literature search was performed in PubMed, Embase, and Cochrane Library up to Feb 2019. Estimates were pooled by study quality and type of AMD and CVD. Publication bias was assessed by Begg's test.

Results: We identified nine studies for the risk of AMD in CVD and ten studies for the risk of CVD in AMD. Overall, evidence for the risk of CVD in AMD patients was most robust. Both early and late AMD preceded CVD, but more solid significance existed in late AMD. Among the types of CVD, stroke was more tightly associated with AMD than coronary heart disease. Publication bias was not significant in either direction.

Conclusion: AMD is a risk factor for CVD, which is primarily driven by the increased risk of stroke in patients with late AMD. Moreover, these results suggested that AMD treatment and screening for CVD in AMD patients may have unexplored clinical benefits.

Keywords: Age-related macular degeneration; Cardiovascular disease; Meta-analysis; Stroke

Introduction

Age-related macular degeneration (AMD) is a major public concern and a leading cause of blindness (1). Despite advancements in medical and surgical intervention, AMD is considered an epidemic, with the global prevalence predicted to rise to 288 million by 2040 (2). The blindness resulting from AMD causes many health problems, including falls (3), fractures (4), and loss of independence (5, 6). The economic burden of AMD is also substantial: analyses of US medical claims data have estimated the annual cost of AMD to be $575–733 million (7).

AMD is a multifactorial disease (8). Risk factors for AMD include cigarette smoking, lack of physical exercise, nutritional factors, genetic markers, and cardiovascular risk factors (1). Nutritional and behavioral modifications can reduce incident AMD and progression to advanced forms, and genetic counseling may aid in the early detection of AMD. Although the current evidence suggested that there are multiple similarities between the pathogenic mechanisms of AMD and cardiovascular disease (CVD) (e.g., advancing age, smoking, obesity, C-reactive protein, apo-lipoprotein E

gene, and complement factor H), the relationship between AMD and CVD has not been clearly elucidated (9, 10). Of note, it remains unclear which condition follows or precedes the other, and the implications of this chronological order are likely to differ considerably.

To date, associations between AMD and CVD have been investigated by many researchers, but a consensus has yet to be reached. Many studies examining this relationship have been cross-sectional. Prior meta-analyses of longitudinal studies reported that AMD is predictive of a small (11) or absent increase (12) in risk of future CVD. Other systematic reviews focused on the specific types of AMD (13) or CVD (14). Theses analyses lacked some relevant papers and included studies with a specific disease setting (15), mortality (12), or multiple papers that were published using the same database (16, 17).

The purpose of this study was to conduct a systematic review and meta-analysis of longitudinal studies to investigate the chronological sequence between AMD and CVD by examining their associations in both directions.

Methods

We followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines to conduct our review and analysis of associations between AMD and CVD (18). Ethical approval was waived, as this study used data extracted from published literature.

Literature Search and Selection

We performed a systematic literature search of all studies published with PubMed, Embase, and the Cochrane Library from inception to Feb 01, 2019, without language restrictions. Search terms were related to AMD and CVD (Appendix 1). Citations were first scanned at the title and abstract level. The bibliographies of the full text articles were examined for congruent but uncaptured references.

Literatures with a cross-sectional nature in which the order of occurrence of AMD and CVD was unknown were excluded *a priori* to ensure causal inference. The inclusion criteria were as follows: 1) a population-based cohort study published as original research; 2) the baseline study group was the general population (i.e., excluding studies of disease-specific populations, such as diabetes patients); and 3) relative risks, odds ratios, or hazard ratios (HRs) with 95% confidence intervals (CIs) were provided. If there was more than one study with an overlapping cohort, we selected the latest or most complete study. One of primary outcomes was overt CVD, not subclinical CVD or CV risk factors. When possible, we limited our search to ischemic stroke, because hemorrhagic stroke is relatively rare and has different biological mechanisms than atherosclerosis (16).

The following information was extracted from each of qualified study: 1) the first author's name; 2) publication year; 3) study design with follow-up duration; 4) study setting (number of participants); 5) types/assessment of AMD and CVD; 6) covariates adjusted; and 7) the greatest adjusted estimates with 95% CIs. In general, CVD includes coronary heart disease (CHD) and any stroke; CHD includes myocardial infarction and any angina. The AMD classification systems used in each study were recorded with the Wisconsin age-related maculopathy grading system (19) or the international classification (20). Early AMD is defined as either any soft drusen and pigmentary abnormalities or large soft drusen 125 μm or more in diameter with a large drusen area (>500 μm diameter circle) or large soft indistinct drusen in the absence of signs of late AMD. Late AMD is categorized as either pure geographic atrophy involving the foveal center (e.g., dry) or neovascular (e.g., wet; nAMD). Study selection and data collection were performed independently by two authors (JL and HSS), and inconsistences were resolved by consensus with the third author (ICH).

Analytical Methods

Estimates reported in individual studies were pooled for analysis. The models used for analysis was dependent on heterogeneity quantified with

the I^2-statistic (21). Specifically, if substantial heterogeneity (I^2>50%) was observed, the random-effect model with the DerSimonian and Laird method (22) was used. Forest plots were produced to assess visually each HR and corresponding 95% CI across studies. In addition, we conducted subgroup analyses using a minimum of three studies and stratified by specific types of AMD and/or CVD and quality of studies. The quality of the studies was assessed with the Newcastle-Ottawa Scale (NOS, 0–9). Overall, prospective studies with longer follow-up duration or consideration of conventional CV risk factors received high NOS scores (mean score=7.22; Appendix 2). Studies with ≥8 points according to the NOS were classified as high quality. Publication bias was assessed using Begg's test. STATA version 12.1 (Stata Corp., College Station, TX, USA) was used for analyses. All reported probabilities were two-sided, and P values<0.05 were considered statistically significant.

Results

Literature Search Results and Study Characteristics

An outline of the literature search conducted is depicted in Fig. 1. Of the 2,254 articles retrieved, 75 underwent abstract screening, and 26 met the eligibility criteria. After reviewing the full text of these studies, 11 articles were excluded, and four studies were added following identification by manual search. In total, 19 articles were included in the final analysis.

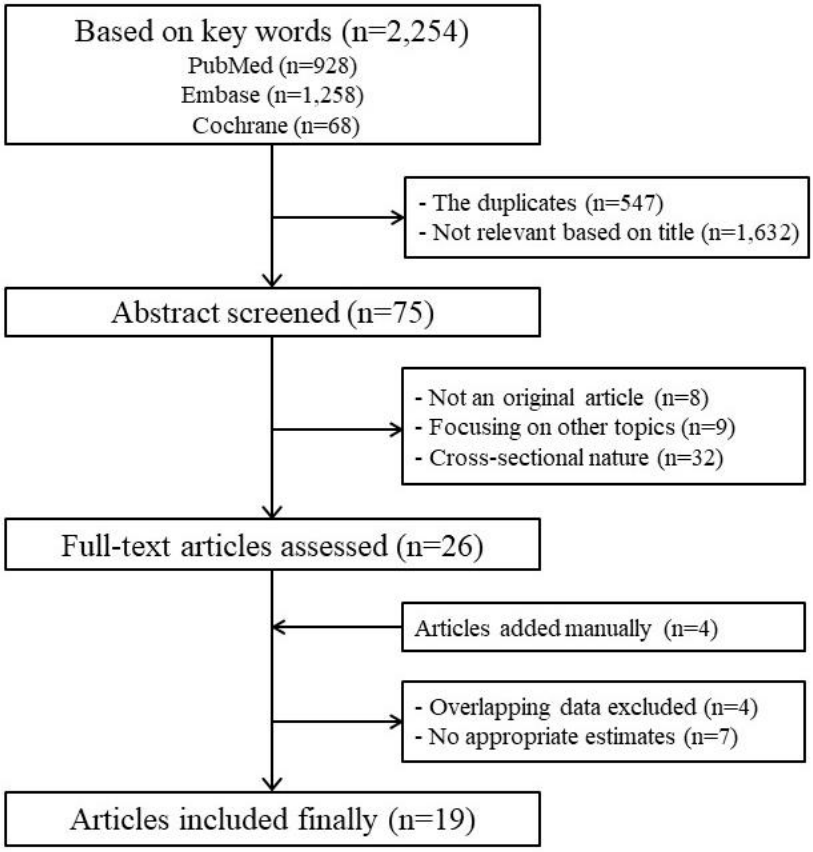

Fig. 1: Flow diagram of the identification of relevant articles

Table 1 summarizes the characteristics of the studies included in the analyses. Nine studies investigated the risk of AMD in patients with CVD, and ten studies explored the reverse association. Studies were published between 2003 and 2018 and included seven nested case-control studies and 12 prospective studies. Most studies were conducted in Western countries (n=16), and many studies reported multiple exposures and outcomes. We used data from each study in each analysis as appropriate. Non-neovascular AMD, cited in two studies (23, 24), was treated as early AMD based on the prevalence rate.

Table 1: Characteristics of studies reporting the association between AMD and CVD

Reference No.	*Country*	*Design (F/U years)*	*Types of AMD*	*CVD*	*NOS*
Risk of AMD in CVD					
(44)	Singapore	Prospective (6)	Early	All CVD	7
(45)	UK	Nested case-control (6)	All	CHD (MI)	7
(46)	USA	Nested case-control (NR)	All	CHD	6
(28)	USA	Prospective (10)	Early Late (neo/non-neo)	MI, angina All stroke All CVD	8
(47)	Australia	Prospective (4.9)	Early/Late	MI, angina All stroke All CVD	6
(48)	Barbados	Prospective (9)	Early/Late	All CVD	5
(49)	Denmark	Prospective (14)	Early/Late	All CVD	5
(50)	USA Australia Netherlands	Prospective (5–6)	Late (neo/non-neo)	MI Al stroke	6
(51)	USA	Prospective (10)	Early Late (neo)	MI All stroke	7
Risk of CVD in AMD					
(16)	Taiwan	Nested case-control (4.7)	Neo	MI All stroke (ischemic) All CVD	8
(17)	USA	Prospective (13)	All (early)	All stroke (ischemic)	9
(52)	USA	Prospective (5.4)	All (early/late)	CHD All CVD	8
(25)	Netherland	Prospective (13.6)	Neo/non-neo	All stroke (ischemic)	9
(53)	Israel	Nested case-control (11)	All	MI	7
(54)	USA	Prospective (6–7)	Early/Late	CHD All stroke	8
(26)	USA	Nested case-control (3.5)	Neo	MI All stroke	7
(23)	USA	Nested case-control (2)	All (early/neo)	All stroke (ischemic)	7
(55)	USA	Prospective (8)	Early	CHD	8
(24)	USA	Nested case-control (2)	All (early/neo)	MI	7

AMD, age-related macular degeneration; CVD, cardiovascular disease; F/U, follow-up; NR, not reported; neo, neovascular; CHD, coronary heart disease; MI, myocardial infarction; NOS, Newcastle-Ottawa Scale

Quantitative Synthesis

Figure 2 shows the impact of AMD type on the risk of CVD. Patients with CVD are at risk of early AMD (HR, 1.28; 95% CI, 1.04–1.58, whereas incidental CVD occurred in patients with both early AMD (HR, 1.20; 95% CI, 1.03–1.40) and late AMD (HR, 1.20; 95% CI, 1.18–1.22) (Fig. 3).

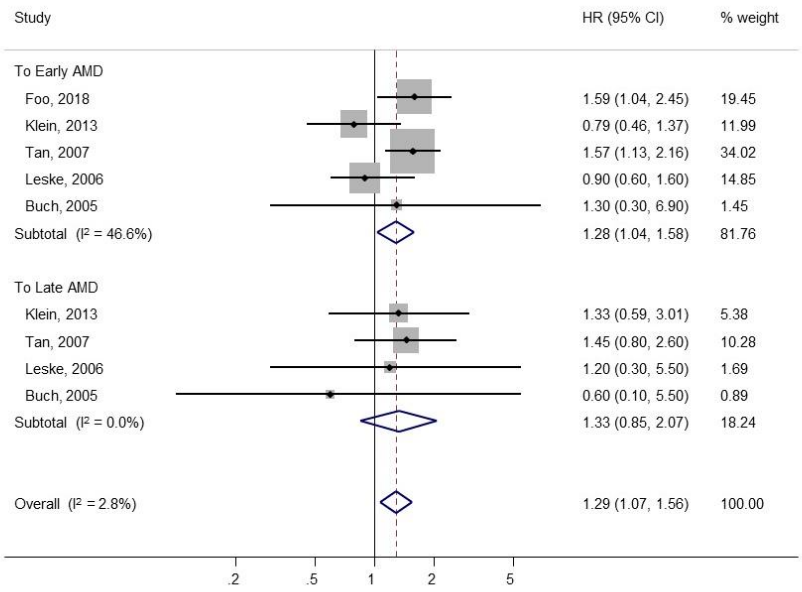

Fig. 2: Forest plots of the impact of AMD types on the association with CVD. HR, hazard ratio; CI, confidence interval (Studies on the AMD risk in CVD)

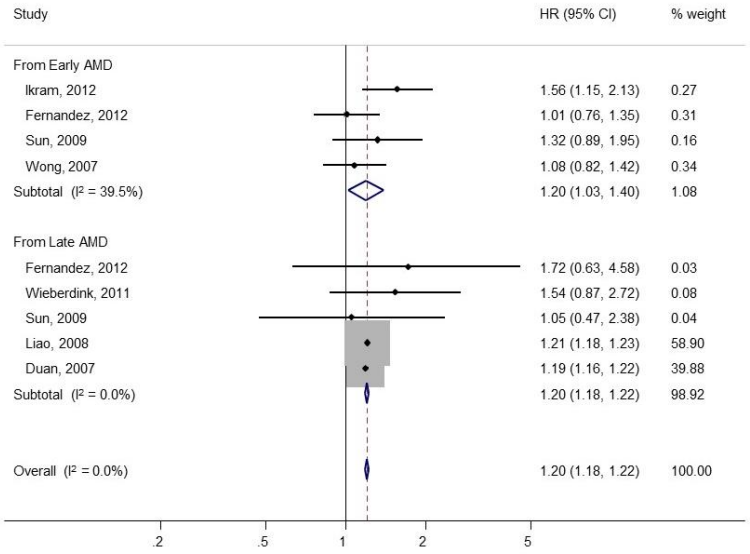

Fig. 3: Forest plots of the impact of studies on the CVD risk in AMD. HR, hazard ratio; CI, confidence interval

The results of the subgroup analyses, which were stratified by AMD type and/or CVD type, are presented in Table 2. Overall, studies concerning the risk of CVD in AMD were more prominently significant, and this remained true among high-quality studies. Additionally, the associations with incident CVD demonstrated higher HRs and/or narrower 95% CIs in late AMD compared to early AMD. Interestingly, stroke occurrence was more tightly associated with AMD than CHD in both directions.

Among studies of CVD risk in nAMD (five studies of any CVD, four studies of stroke, three studies of CHD), high heterogeneity was detected (I^2 = 96.6%, 94.9%, and 96.4%, respectively).

Table 2: Subgroup analyses[a] of the associations between AMD and CVD

Variable	*No.*	*Summary HR (95% CI)*	*Heterogeneity (%), I^2*	*Model*
Risk of AMD in CVD				
Overall				
AMD risk in CVD (28, 47-49)	4	1.23 (0.99–1.52)	1.4	Fixed
Early AMD risk in CVD (28, 44, 47-49)	5	1.28 (1.04–1.58)	46.6	Fixed
Late AMD risk in CVD (28, 47-49)	4	1.33 (0.85–2.07)	0	Fixed
Early AMD risk in MI (28, 47, 51)	3	1.02 (0.75–1.40)	0	Fixed
Late AMD risk in MI (28, 47, 50, 51)	4	0.95 (0.59–1.50)	0.3	Fixed
Early AMD risk in stroke (28, 47, 51)	3	1.56 (1.04–2.34)	0	Fixed
Late AMD risk in stroke (47, 50, 51)	3	1.39 (0.78–2.47)	0	Fixed
Risk of CVD in AMD				
Overall				
Any CVD in AMD (17, 23, 24, 52-54)	6	1.20 (1.18–1.22)	34.0	Fixed
Stroke in AMD (17, 23, 54)	3	1.21 (1.19–1.24)	0	Fixed
Any CVD in early AMD (17, 24, 52, 54, 55)	5	1.18 (1.15–1.22)	41.2	Fixed
Any CVD in late AMD (23-25, 52, 54)	5	1.26 (1.17–1.35)	74.3	Random
Stroke in late AMD (23, 25, 54)	3	1.31 (1.26–1.36)	20.0	Fixed
In high-quality studies (NOS≥8)				
Any CVD in AMD (17, 52, 54)	3	1.27 (1.08–1.48)	33.1	Fixed
Any CVD in early AMD (17, 52, 54, 55)	4	1.24 (1.01–1.51)	50.6	Random
Any CVD in late AMD (25, 52, 54)	3	1.53 (1.12–2.09)	0	Fixed

AMD, age-related macular degeneration; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; NOS, Newcastle-Ottawa Scale; MI, myocardial infarction.
[a]Subgroup analyses involving a minimum of three studies

Thus, a descriptive review was conducted (data not shown). Briefly, in the five studies concerning risk of any CVD, three reported a significant positive association (23-25); one reported a significant negative association (26); and one reported a nonsignificant positive association (16). All but one (26) study of the risk of stroke reported a significant positive association with nAMD (16, 23, 25). Finally, of the studies involving CHD, one reported a significant positive association (24); one reported a significant negative associa-

tion (26); and one reported a nonsignificant positive association (16).

Begg's test showed no evidence of significant small-study effect for the analyses in either direction (P_{bias}=0.216 for AMD risk in CVD, P_{bias}=0.553 for CVD risk in AMD). Figure 4 depicts funnel plots for publication bias.

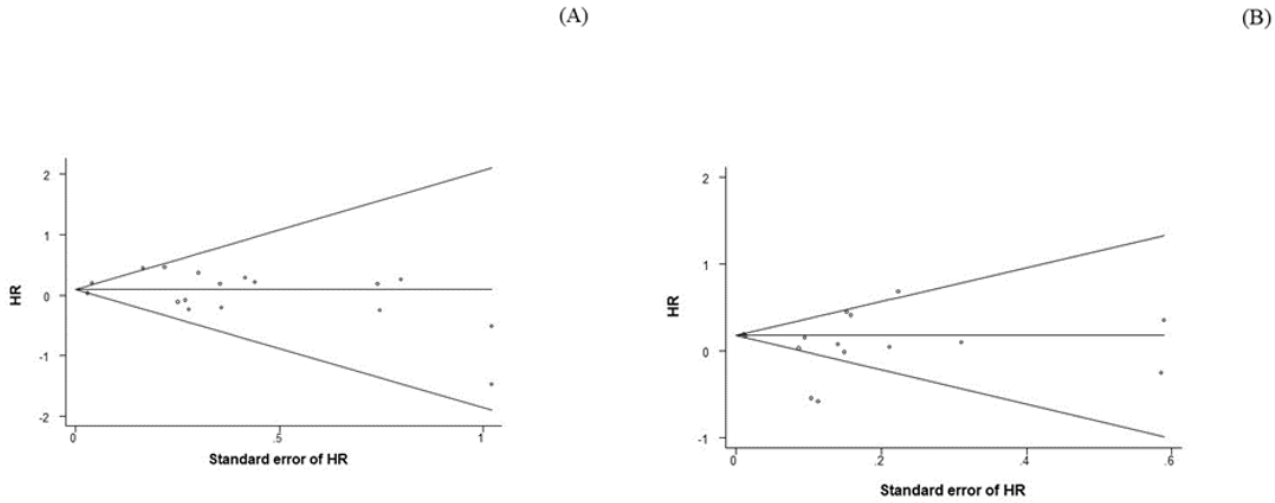

Fig. 4: Begg's funnel plots for publication bias. HR, hazard ratio. (A) Studies on the AMD risk in CVD, (B) Studies on the CVD risk in AMD

Discussion

Similarities between AMD and CVD at the pathophysiologic and genetic levels have been reported; however, the clinical evidence linking these conditions remains inconclusive. Thus, a comprehensive summary is necessary to characterize fully the cause-and-effect relationship between AMD and CVD. By confining our analyses to longitudinal studies, the effect of temporality was greatly reduced, providing insight into causation. The main finding of our study was that AMD is a potential risk factor of CVD. The causative direction identified in this study was supported by the evidence that progression of subclinical CVD is greater in AMD patients compared to controls (27) but not vice versa (28). It is reasonable that the ultimate ischemic events of atherosclerosis, overt CVDs, are not a direct cause of AMD.

In addition, we investigated the association of AMD and CVD according to the specific types of each condition separately. The pooled analyses were needed for the relatively low prevalence of specific disease types. For example, most prospective cohort studies lacked the power to assess the association of late AMD with CVD, let alone with CVD subtypes. Our further analysis revealed as follows: 1) late AMD is a more potent predictor for CVD than early AMD; and 2) stroke is more tightly associated with AMD than CHD.

As patients with CVD, especially stroke, were more likely to develop early AMD, we hypothesized that individuals with a strong genetic predisposition to AMD may have an earlier age of onset and may be prone to preexisting CVD due to genetic or other factors. Another explanation for the relatively weak association of CVD and AMD occurrence was a selection bias. For example, nonparticipants at baseline were more likely to be fragile due to a serious sequela of CVD or be already deceased. Thus, removing these individuals who are most likely to develop future AMD may attenuate the association. In the overt CVD cohort, additional longitudinal studies examining incident AMD (especially early type) according to secondary CVD attack would assist in

clarifying this association. Nevertheless, the underlying cause of the association of AMD in CVD patients remains unknown.

According to our results, when AMD manifests first, it may serve as a useful indicator of increased risk for future CVD events. In addition, the increasing magnitude of association with future CVD from early to late AMD is biologically plausible and implies that CV risk assessment for AMD patients may be clinically useful for early detection of underlying CVD. Additional research is warranted to understand the usefulness of CVD screening among patients with AMD. Moreover, as AMD is actively treated (i.e., anti-vascular endothelial growth factor [VEGF]) to delay progression, our results highlight additional clinical considerations for CVD prevention.

In this study, the risk of stroke in AMD patients was much higher than the risk of CHD. Both AMD and CVD are associated with atherosclerosis, inflammation, and a local up-regulation of VEGF (9). Therefore, generalized atherosclerosis is unlikely to account fully for the association of stroke occurrence with AMD. It has also been reported that pathological mechanisms of lipid deposition are similar in the vessel wall and in the eye (29). All of these are true in stroke (30), and complement activation in both stroke and AMD seems to suggest a further link (31, 32). On the other hand, higher levels of high-density lipoprotein cholesterol (HDL-C) detected in AMD patients (33) may protect more strongly against CHD compared to stroke (34).

Despite high heterogeneity, the association between nAMD and stroke observed in this study was noteworthy. Our qualitative review suggested that nAMD could predict future CVD, especially stroke (positive significance in three of four studies). In contrast to other types of AMD, a diagnosis of nAMD is unlikely to be misclassified by different doctors due to the classical clinical signs (presence of exudates, hemorrhages, or retinal detachment). Potential mechanisms underlying the risk of stroke among patients with nAMD include an imbalance in matrix metalloproteinase-9 (35), deposition of the complement membrane attack complex (36, 37), and homocysteinemia (38). Furthermore, recent epidemiologic studies supported a stronger association for hemorrhagic stroke than for ischemic stroke in patients with AMD (17), late AMD (25), and nAMD (16). Thus, specific types of AMD, such as nAMD, may be useful clinical predictors of CVD, and especially stroke.

Our study has several limitations. First, most studies were conducted in Western societies, limiting the generalization of our results to other ethnic groups. CVD incidence and CVD-prone behaviors varied across cultures (39), and the AMD types observed in Asians differed from those observed in Caucasians (40). Second, high heterogeneity was observed in several analyses. In general, heterogeneity depends on the study design, length of follow-up, covariates, and accuracy of the definitions of exposure and outcome (41). Although most of these variables were accounted for by the NOS, ascertainment of exposure and/or outcome could not be regulated satisfactorily. The types of AMD in each study were diverse, and CVD outcomes in some studies encompassed a spectrum of conditions, from asymptomatic angina to myocardial infarction. Finally, we were unable to account for dietary factors, genetic factors, or current treatment for AMD and CVD (42). This is concerning because nAMD patients being treated with anti-VEGF agents may be at increased risk for thromboembolic events (43). Additional studies are necessary to clarify the link between AMD and CVD by accounting for the effect of such treatments.

Despite the limitations, this study has both research and clinical implications. Our meta-analysis, based on the best-available evidence from longitudinal studies, indicates that AMD carries a higher risk for the development of CVD, especially stroke. Moreover, this association is even stronger in late AMD. Based on these findings, a cross-disciplinary awareness of the link between these two conditions is warranted among ophthalmologists, optometrists, cardiologists, and family physicians. Specifically, ophthalmologists should be alerted to the risk of CV events when treating patients with AMD, especially if the patient has underlying CV risk fac-

tors. In addition to further exploration of the underlying biological processes of AMD, our findings supported the need for additional observational studies examining whether treatments that delay the progression of AMD may also prevent the development of CVD.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Appendix 1

Search strategy
#1: (macular degeneration)
#2: maculopathy
#3: (retinal degeneration)
#4: #1 OR #2 OR #3
#5: cerebrovascular
#6: apoplexy
#7: (brain vascular accident)
#8: stroke
#9: cardiovascular
#10: (coronary artery disease)
#11: (coronary heart disease)
#12: (myocardial infarction)
#13: (ischemic heart disease)
#14: #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15: ratio
#16: risk
#17: incidence
#18: #15 OR #16 OR #17
#19: #4 AND #14 AND #18

Appendix 2: Methodological quality of the included studies, as assessed by the Newcastle-Ottawa Scale

	Selection				***Compa-rability***	***Outcome***			
Cohort studies	Repre-senta-tiveness of ex-posed cohort	Selection of non-exposed cohort	Ascer-tainment of expo-sure	Presen-tation of outcome at start	Control for im-portant factor	Assess-ment of outcome	Enough follow-up	Ade-quate follow-up	To tal
Foo, 2018	1	1	0	1	2	1	0	1	7
Klein, 2013	1	1	0	1	2	1	1	1	8
Ikram, 2012	1	1	1	1	2	1	1	1	9
Fernan-dez, 2012	1	1	1	1	2	1	0	1	8
Wieber-dink, 2011	1	1	1	1	2	1	1	1	9
Sun, 2009	1	1	1	1	2	1	0	1	8
Wong, 2007	1	1	1	1	2	1	0	1	8
Tan, 2007	1	1	0	1	1	1	0	1	6
Leske, 2006	1	1	0	1	0	1	0	1	5
Buch, 2005	0	1	0	1	0	1	1	1	5
Tomany,	1	1	0	1	1	1	0	1	6

2004									
Klein, 2003	1	1	0	1	1	1	1	1	7
		Selection			Comparability		Exposure		
Case-control	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of control	Control for important factor	Ascertainment of exposure (blinding)	Same method of ascertainment	Non-response rate	Total
Lee, 2017	1	1	1	1	2	1	1	0	8
Vassilev, 2015	1	1	1	1	1	1	1	0	7
Thomas, 2015	1	1	1	1	0	1	1	0	6
Golan, 2011	1	1	1	1	1	1	1	0	7
Nguyen-Khoa, 2008	1	1	1	1	1	1	1	0	7
Liao, 2008	1	1	1	1	1	1	1	0	7
Duan, 2007	1	1	1	1	1	1	1	0	7