Systemic Dyslipidemia in Age-related Macular Degeneration

An Updated Systematic Review and Meta-analysis

Brandon Li,[1,2] Deborah Goss,[1] Joan W. Miller, MD,[1] Jonathan B. Lin, MD, PhD,[1]
Demetrios G. Vavvas, MD, PhD[1]

Topic: Though lipid and cholesterol dyshomeostasis is thought to contribute to the pathogenesis of age-related macular degeneration (AMD), there is no consensus regarding which elements of systemic lipid homeostasis are perturbed in AMD. In this systematic review and meta-analysis, an update to that performed by Wang et al in 2016, we characterized serum lipoprotein profiles in patients with AMD and its various stages.

Clinical Relevance: These findings may identify novel therapeutic approaches for AMD, a leading cause of blindness among older adults in the industrialized world.

Methods: We used MEDLINE, Embase, and Web of Science to identify articles from database inception to May 2022 that reported blood/serum levels of lipid subspecies (triglycerides [TGs], total cholesterol [TC], low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) in patients with AMD compared with controls. We meta-analyzed the data by generating multilevel random-effects models using restricted maximum likelihood estimation.

Results: Our updated meta-analysis included 56 studies, almost 3 times as many studies as the 2016 meta-analysis with a total of 308 188 participants. There were no significant differences in serum TG, TC, LDL, or HDL between patients with AMD and non-AMD controls. Given significant heterogeneity, we performed subanalyses specifically in patients with early to intermediate nonexudative AMD, advanced nonexudative AMD, and advanced exudative AMD. Compared with non-AMD controls, patients with early to intermediate nonexudative AMD had significantly lower serum TG (standardized mean difference [SMD]: −0.03; 95% confidence interval [95% CI]: −0.06 to −0.01) and higher serum HDL (SMD: 0.07; 95% CI: 0.04−0.11). Patients with advanced exudative AMD had significantly higher serum LDL (SMD: 0.33; 95% CI: 0.04−0.62) compared with non-AMD controls. There were no other significant differences identified.

Conclusion: We found that there is significant heterogeneity in systemic lipoproteins in patients with AMD compared with non-AMD controls. The specific pattern of lipid dyshomeostasis appeared to be distinct based on AMD stage. These findings highlight both the underlying heterogeneity of AMD as well as the presence of distinct pathophysiological mechanisms involved at different stages or subtypes of AMD and may inform the development of novel therapeutic approaches.

Financial Disclosure(s):   Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2024;4:100341 © 2023 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyscience.org.

Age-related macular degeneration (AMD) is a leading cause of blindness in the industrialized world. Over 19 million Americans > 40 years of age have AMD, and of those, approximately 1.5 million Americans have vision-threatening forms of AMD.[1] Though we have therapies for advanced exudative disease targeting VEGF and a newly approved drug targeting the complement pathway that may have some role for slowing growth of geographic atrophy lesions,[2] there are no treatments available to prevent progression to advanced disease. As

the disease burden of AMD will likely increase with the aging population, there is a need for further research to uncover the pathophysiology underlying AMD to aid in the development of novel therapeutic approaches.[3]

Numerous studies in preclinical models have suggested that lipid dyshomeostasis likely contributes to the pathophysiology of AMD, though the relationship between AMD and lipid homeostasis, as studied in humans, is incompletely understood.[4−9] Furthermore, there is no consensus regarding which elements of systemic lipid homeostasis are

perturbed in AMD.[6] We recently showed that high-dose statin therapy, which is known to lower levels of systemic low-density lipoprotein (LDL), may contribute to the regression of some high-risk features of AMD.[10] Additionally, a meta-analysis in 2016 found that patients with elevated systemic triglycerides (TGs), total cholesterol (TC), and LDL had a lower prevalence of AMD, whereas patients with elevated high-density lipoprotein (HDL) had a higher prevalence of AMD.[11] Given a large number of new studies investigating this question since 2016, the goal of this systematic review and meta-analysis was to provide an updated characterization of systemic lipid homeostasis in AMD. These findings will not only improve our understanding of the relationship between lipid dyshomeostasis and AMD pathogenesis but may also contribute to the development of novel therapeutic strategies.

Methods

Protocol and Registration

We designed and executed a systematic literature search guided by a medical librarian (D.G.), following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[12] The review protocol was not registered prior to publication. This meta-analysis of published group-level data did not require institutional review board approval and informed consent was not applicable. The study adhered to the tenets of the Declaration of Helsinki.

Search Strategy and Information Sources

We performed a comprehensive literature search using Ovid MEDLINE (1946-), Embase.com (1947-), and Web of Science (Core Collection 1900-). Each search utilized a combination of controlled vocabulary and keywords focused on risk factors of AMD and dyslipidemia. The full search syntax used for each database is provided in Appendix A (available at https://www.ophthalmologyscience.org). The Cochrane filter for human studies was used for MEDLINE and Embase, and the English language database filters were used for all databases. We did not apply any restrictions based on study design, date of publication, or country of origin. The final searches were executed on May 31, 2022. This search identified a total of 9349 articles after duplicates were removed. We exported references into Endnote 7.8 for deduplication and then to Covidence for study screening, selection, and data extraction.

Eligibility Criteria, Study Selection, and Screening

The titles and abstracts for each of the manuscripts identified by our comprehensive search strategy were reviewed by one of 2 authors (B.L. or J.B.L.). Articles were omitted at this stage if they were clearly not relevant to the present study or if they were review articles. The full texts of the remaining 251 manuscripts were obtained and assessed for inclusion by 2 authors (B.L. and J.B.L.). We included all studies that quantitatively described the association between serum lipid species (TG, TC, HDL, or LDL) and AMD with an odds ratio (OR) or relative risk or provided group-level data (i.e., mean or median with standard deviation or interquartile range) comparing AMD and non-AMD groups. Studies were included if they investigated $\geq$ 1 serum lipid species. Studies that analyzed serum lipid species data in a categorical fashion (i.e., serum TG are normal [< 150 mg/dl], borderline high [150−199 mg/dl], or high [> 200 mg/dl]) rather than in a continuous fashion were excluded due to inability to meta-analyze this data. Conflicts were resolved by discussion at the end of each stage.

Data Extraction and Quality Assessment

We created a data extraction form to extract the study characteristics and outcomes from each of the included studies (Appendix B; available at https://www.ophthalmologyscience.org). We used a modified Newcastle−Ottawa scale to assess the quality of included studies (Appendix C; available at https://www.ophthalmologyscience.org).

Summary Measures and Synthesis of Results

We performed statistical analysis with R 4.2.1 and RStudio Desktop using the *meta*,[13] *metafor*,[14] *effectsize*,[15] *compute.es*,[16] *tidyverse*,[17] and *esc*[18] packages. For studies reporting group-level serum lipid values in patients with AMD versus control, we calculated standardized mean differences (SMDs) using Hedges' *g*. For studies reporting ORs to describe the association between serum lipid levels and AMD, we converted ORs to SMD using Hedges' *g* using the *compute.es* package.[16] Four studies[19−22] reported a median and/or interquartile range due to nonnormal data, which we converted to an estimated mean/standard deviation using established formulas.[23] With all data represented as SMD, we ran a multilevel (nested), random-effects model to allow for the inclusion of multiple SMDs from individual studies (e.g., if a study reported data separately for early/intermediate AMD, advanced dry AMD, and advanced wet AMD). For one study,[24] the confidence interval (CI) of the OR was estimated to be OR = 1.00, 95% CI [0.996, 1.004] to account for likely rounding error in the published OR = 1.00, 95% CI [1.00, 1.00] since the corresponding authors (K.S.W. and P.S.J.) did not respond to our request for clarification. We also performed subgroup analysis based on AMD stage. Given the heterogeneity of AMD classification criteria used, we subdivided AMD into the following categories: early to intermediate nonexudative AMD (e.g., presence of medium to large drusen, pigmentary changes), advanced nonexudative AMD (i.e., presence of geographic atrophy), and advanced exudative AMD (i.e., presence of choroidal neovascularization). Studies that reported data for patients with "advanced AMD" but without specifying further details were unable to be included in subgroup analysis.

Assessment of Heterogeneity, Outliers, and Publication Bias

We assessed between-study heterogeneity using Higgin's and Thompson's I^2. We defined outliers as those with 95% confidence intervals (95% CIs) of their SMD that did not overlap with the 95% CI of the pooled effect size. Because of the significant between-study heterogeneity in the "all AMD" models and the fact that no significant differences were found in these comparisons, we performed sensitivity analyses in the subgroup analyses only, rerunning these models after omitting outliers, and not in the overall "all AMD" models. For all these analyses, removal of outliers did not significantly change the pooled effect size (Table S1; available at https://www.ophthalmologyscience.org). Additionally, we reanalyzed data after omitting data from the study of lower quality[20] based on the modified Newcastle−Ottawa scale and for the study[24] where the OR was adjusted to account for rounding error and found that this did not significantly change the observed results. Finally, to ensure that conversion of data from ORs to SMD did not introduce bias, we performed subgroup analyses using a mixed-effects model and

found that there were no significant differences between the pooled effect of studies that underwent data conversion and ones that did not.

We analyzed publication bias with a funnel plot and tested for asymmetry with the rank correlation test. Most models showed no evidence of significant publication bias. The exception was the LDL and all AMD models ($\tau = 0.4058$, $P < 0.0001$), though this was unlikely to introduce problematic bias, as we would expect publication bias to bias us toward a significant result while we found a null result instead.

Results

Study Characteristics

Our initial electronic search identified 9349 unique articles. After omitting articles that were clearly not relevant based on their title and abstract, we assessed the full texts of 251 articles. Of these, 81 (41%) were excluded for being the wrong publication type (e.g., conference abstracts), 72 (37%) were excluded since they did not quantify an association between lipids and AMD, 23 (12%) were excluded for being the wrong study design (e.g., inappropriate case definition), and 19 (10%) were excluded for not being relevant to this topic (e.g., not studying AMD). In total, this process yielded 56 articles for inclusion (Figure 1).

The meta-analysis included 308 188 patients, of which 265 477 were controls and 42 711 were patients with AMD. Of the patients with AMD, 13 060 were patients with early to intermediate nonexudative AMD, 146 were patients with advanced nonexudative AMD, and 319 were patients with advanced exudative AMD. The mean proportion of females was 54%, and the mean age was 66. The Wisconsin Age-Related Maculopathy Grading System[25] was used in 18 studies, the International Classification and Grading System[26] in 11 studies, the Age-Related Eye Disease Study[27] scale in 5 studies, the Rotterdam classification system[28] in 3 studies, the Three Continent Consortium[29] method in 3 studies, the Beckman classification system[30] in 2 studies, other nonstandardized classification criteria in 6 studies, and nonspecified methods in 8 studies. The most common countries in which the included studies were performed included 7 from the United States (13%),[31-37] 5 from Germany (9%),[19,38-41] and 4 from Australia (7%).[42-45] A summary of study characteristics is provided in Table 2.

Quality Assessment of Included Studies

We assessed the quality of included studies based on a modified Newcastle−Ottawa scale (Appendix C; available at https://www.ophthalmologyscience.org). One study[20] had a score of 4, due to a lack of specific case definition, no information provided regarding the method used to obtain AMD diagnosis, and no measures performed to increase comparability between case and control groups. Otherwise, all other included studies scored ≥ 7, indicating acceptable study quality (Table S3; available at https://www.ophthalmologyscience.org). The removal of this low-scoring study from the models did not significantly impact any of the pooled effect sizes.

Systemic TGs in AMD

By meta-analyzing 53 effect sizes from 43 studies,[19-22,24,31,34-37,40-52,56-63,66-69,71-73,75-77,79-81] we found that there was no significant difference between systemic TGs in patients with AMD versus controls (SMD: −0.03; 95% CI: −0.06 to 0.01) (Figure 2). Because there was significant interstudy heterogeneity ($I^2 = 99.3\%$), we also performed subgroup analysis based on AMD stage, though heterogeneity remained high in the early to intermediate dry AMD ($I^2 = 88.8\%$) and advanced wet AMD groups ($I^2 = 96.0\%$). With this caveat in mind, subgroup analysis revealed a statistically significantly lower level of systemic TGs in patients with early to intermediate AMD versus controls (SMD: −0.03; 95% CI: −0.06 to −0.01). No significant difference in systemic TGs was found for patients with advanced dry AMD (SMD: −0.03; 95% CI: −0.94 to 0.88) or for patients with advanced wet AMD (SMD: −0.19; 95% CI: −0.89 to 0.51).

Systemic TC in AMD

By meta-analyzing 74 effect sizes from 52 studies,[19,20,22,24,31-33,35-37,40-81] we found that there was no significant difference in systemic TC levels in patients with AMD versus controls (SMD: −0.01; 95% CI: −0.02 to 0.00) (Figure 3). There was moderate to high heterogeneity ($I^2 = 75.4\%$) among meta-analyzed studies. Similarly, after subgroup analysis, there were no significant differences in systemic TC levels when examining patients with early to intermediate dry AMD (SMD: −0.01; 95% CI: −0.03 to 0.00), patients with advanced dry AMD (SMD: −0.01; 95% CI: −0.01 to 0.00), or patients with advanced wet AMD (SMD: 0.08; 95% CI: −0.04 to 0.20) when compared with controls.

Systemic LDL in AMD

By meta-analyzing 49 effect sizes from 38 studies,[19,20,22,31,33,34,36-39,41,43,46-53,56-59,61-63,66-68,71-73,76,77,79-81] we found no significant difference in systemic LDL in patients with AMD versus controls (SMD: −0.00; 95% CI: −0.01 to 0.00) (Figure 4). Again, because of significant interstudy heterogeneity ($I^2 = 84.9\%$), we also performed subgroup analysis based on AMD stage, which improved the extent of heterogeneity. This subgroup analysis revealed that there was significantly higher LDL among patients with advanced wet AMD versus control (SMD: 0.33; 95% CI: 0.04−0.62; $I^2 = 53.3\%$). In contrast, patients with early to intermediate dry AMD (SMD: −0.01; 95% CI: −0.02 to 0.00; $I^2 = 90.0\%$) or with advanced dry AMD (SMD: −0.10; 95% CI: −1.72 to 1.52; $I^2 = 0.0\%$) did not exhibit a significant difference in systemic LDL when compared with controls.

Systemic HDL in AMD

By meta-analyzing 69 effect sizes from 49 studies,[19,20,22,24,32,34,36-44,46-54,56-68,70-81] we found no significant difference in systemic HDL in patients with AMD compared with controls (SMD: 0.19; 95% CI: −0.10 to 0.48)

Identification of studies via databases and registers

Identification

Records identified from:
Medline (Ovid) (n=4,221)
Embase.com (n=5,604)
Web of Science (n=4,336)
Total (n=14,161)

→ Records removed *before screening*:
Duplicate records removed
Endnote X7.8 (n=4,778)
Covidence (n=31)
Manual (n=3)

Screening

Records screened
(n=9,349)

→ Records excluded
(n=9,098)

Reports sought for retrieval
(n=251)

→ Reports not retrieved
(n=0)

Reports assessed for
eligibility
(n=251)

→ Reports excluded:
Wrong publication type (n=81)
No outcome reported on lipid and
AMD association (n=72)
Wrong study design (n=23)
Not topical (n=19)

Included

Studies included in review
(n=56)
Total patients: 308,188

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing citations identified, screened, included, and excluded. AMD = age-related macular degeneration.

(Figure 5). There was high heterogeneity among meta-analyzed studies (I^2 = 100.0%). Even after subgroup analysis, heterogeneity remained high in the early to intermediate dry AMD (I^2 = 99.0%). With this caveat in mind, patients with early to intermediate dry AMD exhibited significantly higher systemic HDL compared with controls (SMD: 0.07; 95% CI: 0.04−0.11). There was no significant difference in systemic HDL when comparing patients with advanced dry AMD (SMD: 0.01; 95% CI: −0.04 to 0.07; I^2 = 0.0%) or with advanced wet AMD (SMD: −0.06; 95% CI: −0.18 to 0.06; I^2 = 23.6%) to controls.

Discussion

Here, we performed a comprehensive systematic review with guidance from an experienced medical librarian (D.G.) to update our understanding of the association between systemic lipoprotein profiles and AMD. Our meta-analysis included 58 studies and 308 188 patients, almost 3 times as many compared to the prior 2016 meta-analysis by Wang et al,[11] which included 19 studies and 104 270 patients. When analyzing all patients with AMD regardless of stage of disease, we found no differences in systemic TGs, TC, LDL, or HDL compared to controls (Table 4). On the other hand, when analyzing patients with early to intermediate AMD separately, there were significantly lower levels of TGs and higher levels of HDL but no differences in the levels of TC or LDL. Patients with advanced dry AMD had no significant differences in TGs, TC, LDL, or HDL. Finally, patients with advanced wet AMD had significantly higher systemic LDL but no differences in TGs, TC, or HDL. Taken together, our results highlight the significant heterogeneity of AMD and suggest that the specific aspects of lipid homeostasis that are perturbed may depend on the underlying stage or subtype of disease.

These findings may explain, in part, why there is a discrepancy in the literature published to date with respect to the specific facets of lipid dyshomeostasis that are associated with the pathophysiology of AMD.[6] We speculate that

Table 2. Study Characteristics for Studies Included in This Meta-analysis

Study; Country/Countries [reference]	Study Design	Mean Age	AMD Classification	Outcomes Data Type	Lipids Investigated	Number of Participants				
						Control	All AMD	Early/Int dry AMD	Adv Dry AMD	Adv Wet AMD
Abalain et al (2022); France[46]	Case-control	76.2	WARMGS	Means	TG, TC, LDL, HDL	62	84	-	33	-
Ambreen et al (2014); Pakistan[47]	Case-control	63.7	ICGS	Means	TG, TC, LDL, HDL	100	90	-	-	-
AnandBabu et al (2016); India[48]	Case-control	59.1	AREDS	Means	TG, TC ,LDL, HDL	30	48	-	-	-
Arifoglu et al (2016); Turkey[49]	Case-control	63.8	Other	Means	TG, TC, LDL, HDL	24	20	-	-	20
Baker et al (2009); US[37]	Cross-sectional	78.3	WARMGS	Means	TG, TC, LDL, HDL	1737	351	-	-	-
Bikbov et al (2020); Russia[50]	Cross-sectional	58.5	Beckman	OR	TG, TC, LDL, HDL	4412	520	-	-	-
Blumenkranz et al (1986); US[36]	Case-control	76.0	Not specified	Means	TG, TC, LDL, HDL	26	23	-	-	-
Brandl et al (2016); Germany[38]	Cross-sectional	47.5	AREDS	OR	LDL, HDL	2208	343	270	-	-
Brandl et al (2022) - KORA-FF4; Germany[39]	Cohort	61.9	3CC	OR	LDL, HDL	172	122	122	-	-
Brandl et al (2022) - KORA-Fit; Germany[39]	Cohort	44.6	3CC	OR	LDL, HDL	172	122	122	-	-
Cackett et al (2008); Singapore[51]	Cross-sectional	58.7	WARMGS	OR	TG, TC, LDL, HDL	3075	190	169	-	-
Cezario et al (2015); Brazil[52]	Case-control	64.8	Not specified	Means	TG, TC, LDL, HDL	30	30	-	-	-
Cheung et al (2007); US[35]	Cross-sectional	59.8	WARMGS	Means	TG, TC	9500	454	454	-	-
Cheung et al (2012); Singapore[53]	Cross-sectional	53.7	AREDS	Means	TC, LDL, HDL	2961	211	-	-	-
Cheung et al (2013) - Central Indians; Singapore and India[54]	Cross-sectional	57.8	WARMGS	OR	TC, HDL	3213	209	209	-	-
Cheung et al (2013) - Singaporeans; Singapore and India[54]	Cross-sectional	57.8	WARMGS	OR	TC, HDL	3149	188	188	-	-
Cheung et al (2014); Singapore[55]	Cross-sectional	59.7	WARMGS	OR	TC	3046	266	-	-	-
Colak et al (2011); Serbia[56]	Cross-sectional	69.8	AREDS	Means	TG, TC, LDL, HDL	80	82	-	-	-
Colijn et al (2019); France, Germany, Italy, Netherlands, Norway, Portugal, UK[57]	Cross-sectional	69.5	Rotterdam	OR	TG, TC, LDL, HDL	19 539	5374	3768	-	-
Cougnard-Gregoire et al (2014); France[58]	Cross-sectional	80.2	ICGS	OR	TG, TC, LDL, HDL	630	308	247	-	-
Davari et al (2013); Iran[59]	Case-control	75.0	Other	Means	TG, TC, LDL, HDL	32	32	-	-	-
Delcourt et al (2001); France[60]	Cross-sectional	70.1	ICGS	OR	TG, TC, HDL	1415	768	730	-	-
Erke et al (2014); Norway[61]	Cohort	72.3	ICGS	OR	TG, TC, LDL, HDL	2048	727	635	-	-
Fan et al (2017); Several; US and non-US[34]	Case-control	-	Other	OR	TG, LDL, HDL	23 107	18 363	-	-	-
Fauser et al (2011); Germany, Netherlands[40]	Case-control	74.9	Other	Means	TG, TC, HDL	521	792	-	-	-
Fernandez et al (2012); US[33]	Cohort	62.0	WARMGS	Means	TC, LDL	5338	895	893	-	-
Hashemi et al (2018); Iran[62]	Case-control	-	Not specified	Means	TG, TC, LDL, HDL	15	15	-	-	-
Javadzadeh et al (2007); Iran[63]	Case-control	70.0	Not specified	Means	TG, TC, LDL, HDL	60	60	-	-	60
Joachim et al (2015); Australia[42]	Cohort	62.2	WARMGS	Means	TG, TC, HDL	2425	534	534	-	-
Jonasson et al (2014); Iceland[64]	Cross-sectional	74.7	WARMGS	OR	TC, HDL	2540	328	-	-	-
Kawasaki et al (2008); Japan[65]	Cross-sectional	60.4	WARMGS	Means	TC, HDL	1559	66	58	-	-
Klein et al (1993); US[32]	Cross-sectional	61.7	WARMGS	OR	TC, HDL	1746	773	745	11	17
Klein et al (2003); US[31]	Cohort	78.5	WARMGS	OR	TG, TC, LDL	1995	366	366	-	-
Koller et al (2022); Germany[41]	Cohort	78.2	3CC	Means	TG, TC, LDL, HDL	1635	627	-	-	-
Ludtke et al (2019); Germany[19]	Cohort	-	Rotterdam	Means	TG, TC, LDL, HDL	1088	753	745	-	-
Mao et al (2019); China[66]	Cohort	51.0	WARMGS	OR	TG, TC, LDL, HDL	4823	214	214	-	-
McCarty et al (2008); Australia[43]	Cross-sectional	73.9	ICGS	Means	TG, TC, LDL, HDL	160	160	-	-	-

(Continued)

Study; Country/Countries [reference]	Study Design	Mean Age	AMD Classification	Outcomes Data Type	Lipids Investigated	Number of Participants				
						Control	All AMD	Early/Int dry AMD	Adv Dry AMD	Adv Wet AMD
Neethu et al (2020); India[20]	Cross-sectional	62.0	not specified	Means	TG, TC, LDL, HDL	39	39	-	-	-
Ngai et al (2011); UK[67]	Cohort	71.1	ICGS	Means	TG, TC, LDL, HDL	843	91	-	-	-
Nordestgaard et al (2021); Denmark[21]	Cohort	58.0	Not specified	Means	TG	104 916	1787	-	-	-
Ornek et al (2016); Turkey[68]	Case-control	73.0	Not specified	Means	TG, TC, LDL, HDL	78	98	-	-	47
Park et al (2014); Korea[24]	Cross-sectional	55.1	ICGS	OR	TG, TC, HDL	12 667	1046	958	22	66
Paunksnis et al (2005); Lithuania[69]	Cross-sectional	-	ICGS	Means	TG, TC	84	84	84	-	-
Peiretti et al (2014); Italy[70]	Cross-sectional	76.2	AREDS	OR	TC, HDL	38	136	98	-	-
Pertl et al (2016); Austria[22]	Cross-sectional	76.7	Other	Means	TG, TC, LDL, HDL	26	29	-	-	29
Qin et al (2014); UK[71]	Case-control	58.0	WARMGS	Means	TG, TC, LDL, HDL	14	14	-	-	-
Raman et al (2016); India[72]	Cross-sectional	72.0	ICGS	OR	TC, LDL, HDL	3805	986	893	-	-
Roh et al (2008); Korea[73]	Cross-sectional	52.7	Rotterdam	Means	TG, TC, LDL, HDL	9082	235	-	-	-
Semba et al (2019); Iceland[74]	Case-control	79.7	Not specified	Means	TC, HDL	80	160	-	80	80
Smith et al (1998); Australia[44]	Cross-sectional	62.2	WARMGS	OR	TG, TC, HDL	3342	312	240	-	-
Song et al (2009); Korea[75]	Cross-sectional	57.2	ICGS	Means	TG, TC, HDL	10 551	339	318	-	-
Taniguchi et al (2013); Japan[76]	Case-control	71.3	ICGS	Means	TG, TC, LDL, HDL	40	88	-	-	-
Tsang et al (1992); Australia[45]	Case-control	73.9	Other	Means	TG, TC	86	80	-	-	-
Ulas et al (2013); Turkey[77]	Cross-sectional	71.0	Not specified	Means	TG, TC, LDL, HDL	141	142	-	-	142
Vingerling et al (1995); Netherlands[78]	Case-control	71.0	WARMGS	Means	TC, HDL	1324	96	-	-	-
Wang et al (2012); China[79]	Cross-sectional	60.4	WARMGS	OR	TG, TC, LDL, HDL	2865	161	-	-	-
Xue et al (2021); China[80]	Cross-sectional	60.5	Beckman	OR	TG, TC, LDL, HDL	6112	1607	-	-	-
Yip et al (2015); UK[81]	Cohort	67.4	WARMGS	Means	TG, TC, LDL, HDL	4671	673	-	-	-

3CC = Three Continent Consortium; Adv = advanced; AMD = age-related macular degeneration; AREDS = Age-Related Eye Disease Study; HDL = high-density lipoprotein; ICGS = International Classification and Grading System; Int = intermediate; LDL = low-density lipoprotein; OR = odds ratio; TC = total cholesterol; TG = triglyceride; UK = United Kingdom; US = United States; WARMGS = Wisconsin Age-Related Maculopathy Grading System.

Figure 2. Forest plot for systemic triglycerides (TG) in patients with age-related macular degeneration (AMD) versus non-AMD controls. Blue diamonds denote the 95% confidence interval (95% CI); dashed lines denote the 95% prediction interval. SMD = standardized mean difference.

among patients with AMD, there may be facets of lipid dyshomeostasis that are specific to certain stages of the disease process. In fact, recent studies have shown that patients with soft drusen are distinct from those with subretinal drusenoid deposits (SDDs) on the basis of their systemic associations, serum profiles, and genetic risk

profiles and provided evidence that high HDL was associated with classic soft drusen, whereas low HDL was associated with SDDs.[82,83] Interestingly, these authors also found an association between SDDs and the presence of coexisting systemic vascular disease (e.g., aortic stenosis, myocardial infarction) and suggest that both of these (i.e.,

Author Year	Sample Size Ctrl	AMD		SMD	[95% CI]
All AMD					
Yip 2015	4671	673		-0.06	[-0.14, 0.02]
Xue 2021	6112	1607		0.01	[-0.02, 0.04]
Wang 2012	2865	161		-0.02	[-0.12, 0.07]
Vingerling 1995	1324	96		-0.34	[-0.55, -0.14]
Tsang 1992	86	80		0.09	[-0.21, 0.40]
Taniguchi 2013	40	88		0.16	[-0.21, 0.54]
Roh 2008	9082	235		0.00	[-0.13, 0.13]
Qin 2014	14	14		0.69	[-0.08, 1.45]
Ngai 2011	843	91		0.08	[-0.13, 0.30]
Neethu 2020	39	39		0.19	[-0.26, 0.63]
McCarty 2008	160	160		-0.05	[-0.27, 0.17]
Koller 2022	1635	627		-0.02	[-0.11, 0.07]
Jonasson 2014	2540	328		-0.03	[-0.09, 0.04]
Hashemi 2018	15	15		0.52	[-0.21, 1.25]
Fauser 2011	521	792		0.04	[-0.07, 0.15]
Davari 2013	32	32		0.91	[0.40, 1.43]
Colak 2011	80	82		0.68	[0.37, 1.00]
Cheung 2012	2961	211		-0.11	[-0.25, 0.02]
Cheung 2014	3046	266		-0.01	[-0.08, 0.07]
Cezario 2015	30	30		-0.28	[-0.79, 0.22]
Blumenkranz 1986	26	23		-0.24	[-0.80, 0.33]
Bikbov 2020	4412	520		-0.01	[-0.04, 0.03]
Baker 2009	1737	351		-0.09	[-0.20, 0.03]
AnandBabu 2016	30	48		0.88	[0.40, 1.36]
Ambreen 2014	100	90		0.28	[-0.01, 0.56]
Song 2009 (advanced dry and wet)	10551	21		-0.09	[-0.52, 0.34]
Smith 1998 (advanced dry and wet)	3342	72		0.04	[-0.05, 0.13]
Raman 2016 (advanced dry and wet, rural)	3805	52		-0.01	[-0.02, 0.00]
Raman 2016 (advanced dry and wet, urban)	3805	41		0.01	[-0.01, 0.02]
Ludtke 2019 (advanced dry and wet)	1088	8		0.38	[-0.31, 1.08]
Kawasaki 2008 (advanced dry and wet)	1559	8		-0.30	[-0.99, 0.40]
Erke 2014 (advanced dry and wet, male)	2048	44		-0.05	[-0.22, 0.11]
Erke 2014 (advanced dry and wet, female)	2044	48		-0.05	[-0.20, 0.11]
Delcourt 2001 (advanced dry and wet)	1415	38		-0.02	[-0.19, 0.15]
Cackett 2008 (advanced dry and wet)	3075	21		-0.10	[-0.30, 0.11]
Song 2009 (early/intermediate dry)	10551	318		0.07	[-0.04, 0.18]
Early/intermediate dry AMD					
Smith 1998 (early/intermediate dry)	3342	240		-0.03	[-0.10, 0.04]
Raman 2016 (early/intermediate dry, rural)	3805	565		-0.01	[-0.01, -0.00]
Raman 2016 (early/intermediate dry, urban)	3805	328		-0.01	[-0.01, -0.00]
Peiretti 2014	38	136		-0.78	[-1.14, -0.41]
Paunksnis 2005	84	84		-0.15	[-0.46, 0.15]
Park 2014 (early/intermediate dry)	12667	958		0.00	[-0.00, 0.00]
Mao 2019	4823	214		-0.02	[-0.10, 0.07]
Ludtke 2019 (early/intermediate dry)	1088	745		0.10	[0.00, 0.19]
Klein 2003	1995	366		-0.02	[-0.04, -0.01]
Klein 1993 (early/intermediate dry, male group1)	1746	75		0.00	[-0.12, 0.12]
Klein 1993 (early/intermediate dry, male group2)	1746	96		-0.05	[-0.09, -0.00]
Klein 1993 (early/intermediate dry, male group3)	1746	92		0.01	[-0.11, 0.13]
Klein 1993 (early/intermediate dry, male group4)	1746	79		-0.23	[-0.38, -0.08]
Klein 1993 (early/intermediate dry, female)	1746	403		-0.06	[-0.12, -0.01]
Kawasaki 2008 (early/intermediate dry)	1559	58		-0.10	[-0.36, 0.17]
Joachim 2015	2425	534		0.04	[-0.06, 0.13]
Fernandez 2012	5338	895		-0.04	[-0.11, 0.03]
Erke 2014 (early/intermediate dry)	2000	635		-0.02	[-0.06, 0.03]
Delcourt 2001 (soft drusen)	1415	506		0.04	[-0.01, 0.09]
Delcourt 2001 (pigmentary abnormalities)	1415	224		0.02	[-0.06, 0.09]
Cougnard-Gregoire 2014	630	308		0.02	[-0.07, 0.10]
Colijn 2019	20555	5538		0.00	[-0.01, 0.01]
Cheung 2007	9500	454		-0.04	[-0.13, 0.05]
Cheung 2013 (Central Indians)	3213	209		0.07	[-0.07, 0.20]
Cheung 2013 (Singaporeans)	3149	188		-0.12	[-0.21, -0.04]
Cackett 2008 (early/intermediate dry)	3075	169		-0.06	[-0.13, 0.02]
Advanced dry AMD					
Semba 2019 (advanced dry)	80	80		-0.09	[-0.40, 0.22]
Park 2014 (advanced dry)	12667	22		-0.01	[-0.01, 0.00]
Klein 1993 (advanced dry)	1746	11		0.00	[-0.21, 0.21]
Abalain 2022	62	84		0.02	[-0.31, 0.35]
Advanced wet AMD					
Ulas 2013	141	142		0.33	[0.10, 0.57]
Semba 2019 (advanced wet)	80	80		0.10	[-0.21, 0.41]
Pertl 2016	26	29		0.20	[-0.33, 0.73]
Park 2014 (advanced wet)	12667	66		0.01	[0.00, 0.01]
Ornek 2016	78	98		0.07	[-0.22, 0.37]
Klein 1993 (advanced wet)	1746	17		0.06	[-0.07, 0.20]
Javadzadeh 2007	60	60		0.18	[-0.18, 0.54]
Arifoglu 2016	24	20		0.10	[-0.50, 0.69]
TC (all AMD), I^2=75.39%				-0.01	[-0.02, 0.00]
TC (early/intermediate dry), I^2=93.73%				-0.01	[-0.03, 0.00]
TC (advanced dry), I^2=0.00%				-0.01	[-0.01, 0.00]
TC (advanced wet), I^2=43.27%				0.08	[-0.04, 0.20]

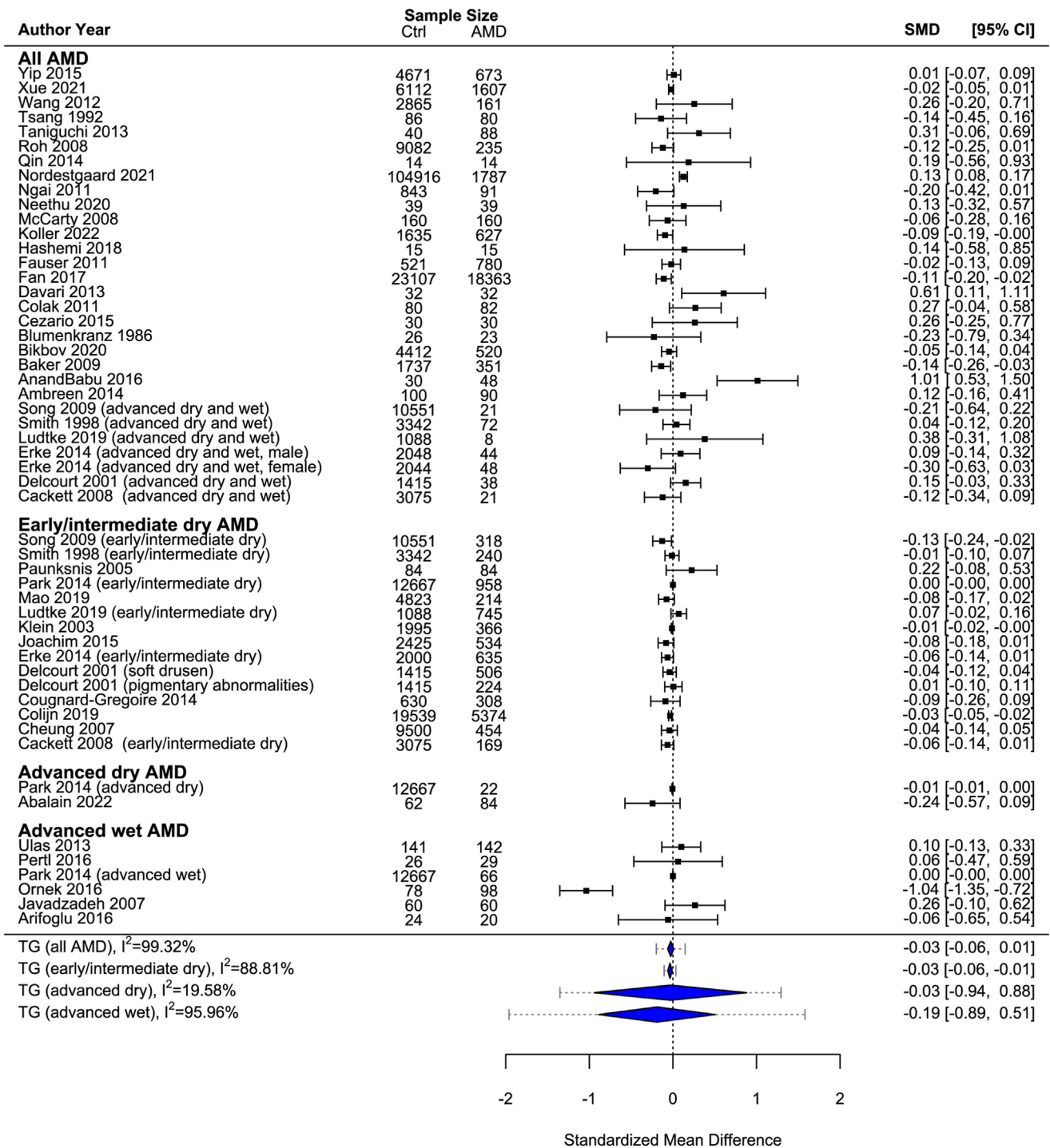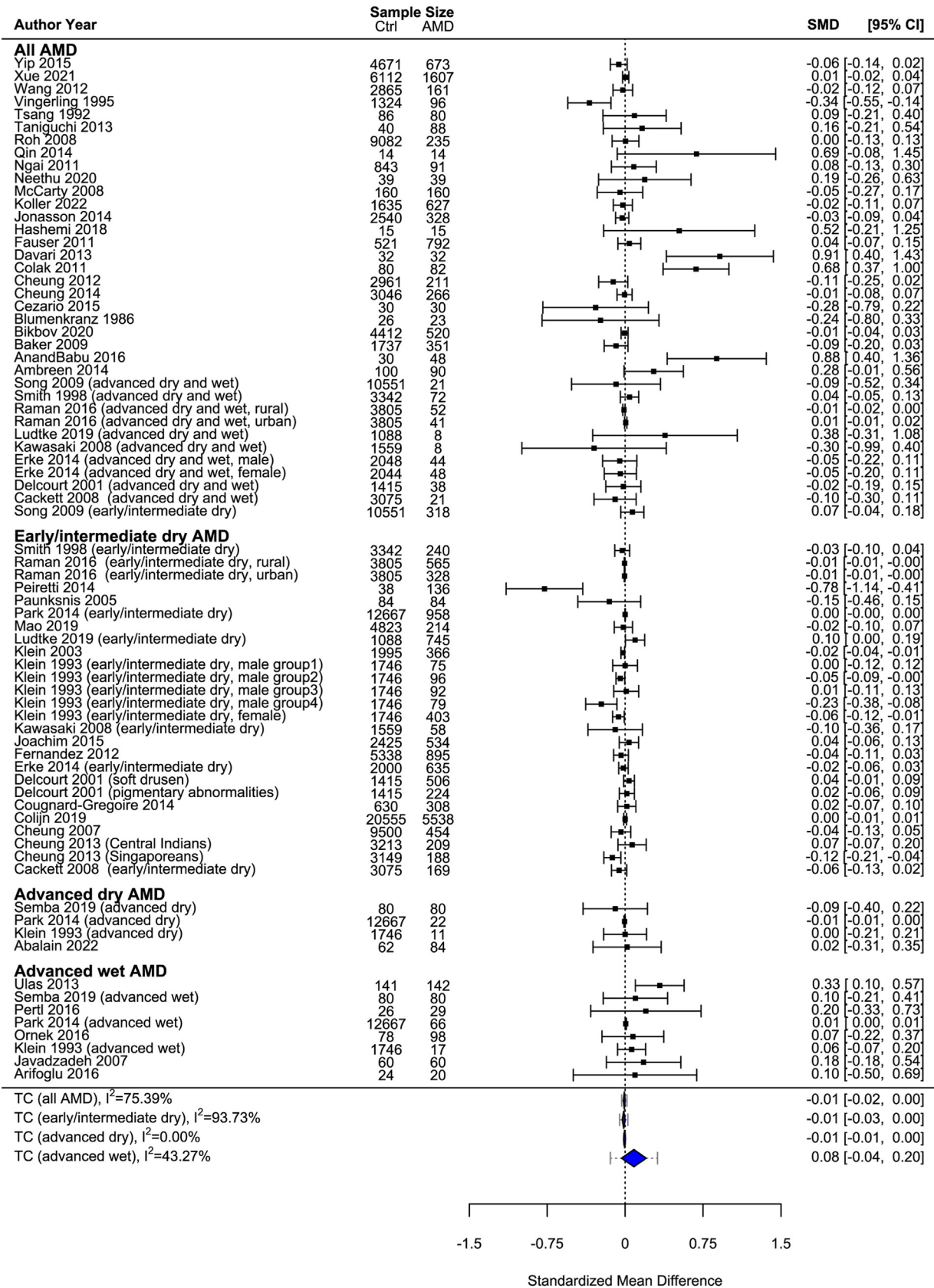Standardized Mean Difference (axis: -1.5, -0.75, 0, 0.75, 1.5)

Figure 3. Forest plot for systemic total cholesterol (TC) in patients with age-related macular degeneration (AMD) versus non-AMD controls. Blue diamonds denote the 95% confidence interval (95% CI); dashed lines denote the 95% prediction interval. SMD = standardized mean difference.
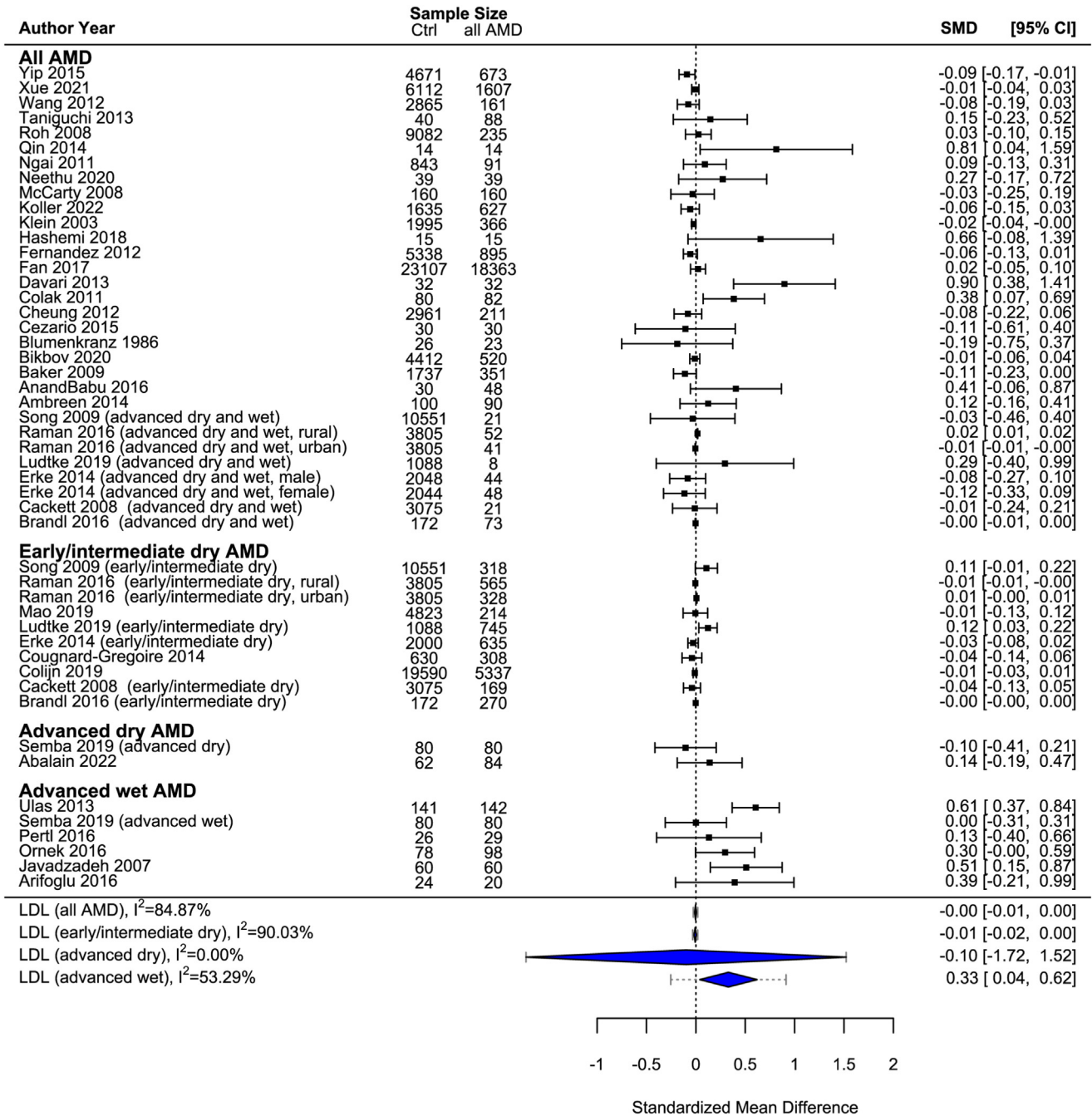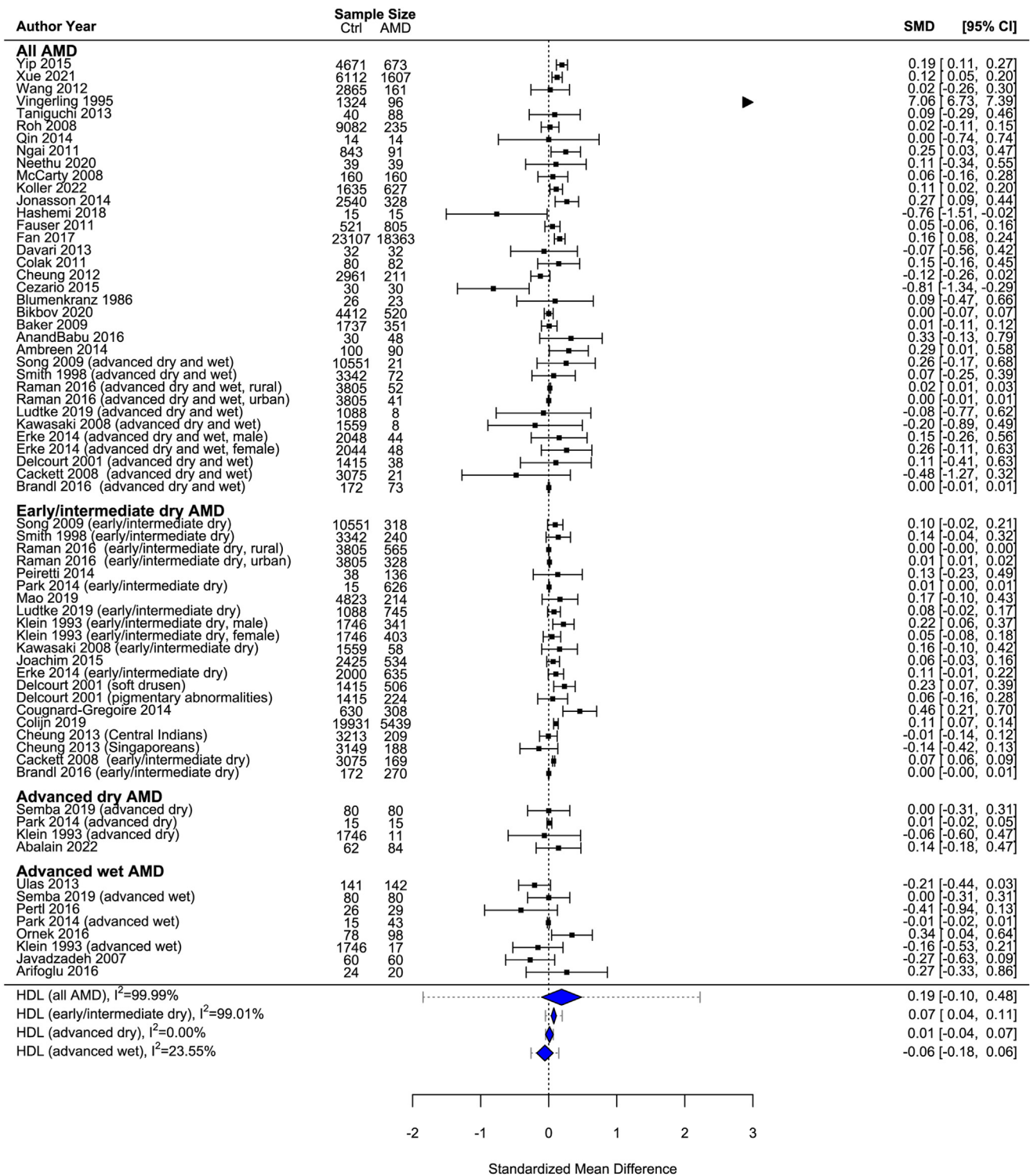
Figure 4. Forest plot for systemic low-density lipoprotein (LDL) in patients with age-related macular degeneration (AMD) versus non-AMD controls. Blue diamonds denote the 95% confidence interval (95% CI); dashed lines denote the 95% prediction interval. SMD = standardized mean difference.

low HDL and presence of SDDs) may be related to systematic atherosclerosis.

Further research is necessary to explore this heterogeneity within patients with AMD. It may be necessary to tailor therapy for these disparate underlying pathophysiologies. We have previously shown in a small pilot study that high-dose statin therapy may lead to reduction in progression to advanced exudative AMD in high-risk patients.[10] Similarly, in a study of commercially insured patients, no patients taking very-high-dose lipophilic statins progressed

to exudative AMD.[84] These findings correspond well with the findings of this meta-analysis, as statins are most known for lowering systemic LDL, and elevated LDL was found to be most prominent in patients with advanced wet AMD. Lipid-based therapies may be efficacious if used in the appropriate patient population. Future studies investigating the association between systemic dyslipidemia and AMD should include careful characterization of patients with AMD. Some factors that would be important to consider are AMD stage (i.e., early/intermediate vs. late),

Figure 5. Forest plot for systemic high-density lipoprotein (HDL) in patients with age-related macular degeneration (AMD) versus non-AMD controls. Blue diamonds denote the 95% confidence interval (95% CI); dashed lines denote the 95% prediction interval. SMD = standardized mean difference.

intermediate AMD subtype (i.e., drusen vs. SDDs), demographic factors (e.g., age, sex, ethnicity), presence of coexisting systemic vascular disease, and genetic variants in genes related to lipid pathways such as cholesteryl ester transfer protein, apolipoprotein E, and hepatic lipase.[85] These detailed studies may identify subtypes of AMD and thereby partially explain the heterogeneity found within the present study.

Our meta-analysis had several limitations. The most prominent limitation was the moderate to high heterogeneity

Table 4. Summary of SMDs with 95% Confidence Intervals and Measure of Heterogeneity (I^2) in Triglycerides, Total Cholesterol, LDL, and HDL between Patients With AMD or Specific Stages of AMD Compared with Controls

	SMD [95% Confidence Interval]; I^2			
	All AMD	*Early/Intermediate Dry AMD*	*Advanced Dry AMD*	*Advanced Wet AMD*
Triglycerides	−0.03 [−0.06, 0.01]; 99.3%	−0.03 [−0.06, −0.01]; 88.8%	−0.03 [−0.94, 0.88]; 19.6%	−0.19 [−0.89, 0.51]; 96.0%
Total cholesterol	−0.01 [−0.02, 0.00]; 75.4%	−0.01 [−0.03, 0.00]; 93.7%	−0.01 [−0.01, 0.00]; 0.0%	0.08 [−0.04, 0.20]; 43.3%
LDL	−0.00 [−0.01, 0.00]; 84.9%	−0.01 [−0.02, 0.00]; 90.0%	−0.10 [−1.72, 1.52]; 0.0%	0.33 [0.04, 0.62]; 53.3%
HDL	0.19 [−0.10, 0.48]; 100.0%	0.07 [0.04, 0.11]; 99.0%	0.01 [−0.04, 0.07]; 0.0%	−0.06 [−0.18, 0.06]; 23.6%

AMD= age-related macular degeneration; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SMD = standardized mean difference.

of the meta-analyzed effect sizes ($I^2 > 90\%$), which affects the precision and reliability of the pooled effect size estimate. In many cases, heterogeneity remained high even after subgrouping the patients by AMD stage. This interstudy heterogeneity was likely related to underlying differences with respect to the studies' country of origin, the AMD classification criteria used, the types of outcome data presented, and the study design, among other factors. However, they could also reflect the significant heterogeneity of AMD as a disease process and suggest that there is a need for improved, more precise AMD classification criteria based on our improving understanding of its underlying pathophysiological mechanisms at the cellular and molecular level.

Additionally, there were much less data from patients with advanced dry AMD (N = 146) or advanced wet AMD (N = 319) compared to those from patients with early to intermediate dry AMD (N = 13 060), leading to reduced statistical power in these associated meta-analyses. Finally, because studies differed in terms of how they reported their outcomes (e.g., reporting means of various groups vs. reporting ORs), we had to convert all of these outcomes to SMDs to allow for an estimate of the pooled effect size. Though we used validated mathematical formulas for these conversions, they could have introduced bias due to their underlying assumptions.

Overall, our findings support that there is systemic dyshomeostasis in patients with AMD compared with non-AMD controls and that the specific pattern of impaired lipid homeostasis appears to depend on AMD stage. We propose that these findings reflect the underlying heterogeneity of AMD, the presence of distinct pathophysiological mechanisms involved at different stages of AMD, and may even suggest the existence of distinct AMD subtypes that should be investigated further to inform novel therapeutic approaches.

Footnotes and Disclosures

[1] Massachusetts Eye and Ear and Harvard Medical School, Boston, Massachusetts.

[2] Boston University School of Medicine, Boston, Massachusetts.

Demetrios Vavvas, an editor of this journal, was recused from the peer-review process of this article and had no access to information regarding its peer-review.

Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The authors made the following disclosures:

J.B.L.: Supported by the VitreoRetinal Surgery Foundation and the Gragoudas-Folkman Award. D.G.V. was supported by the Monte J. Wallace Chair in Retina, the Solman and Libe Friedman OHMS Ophthalmology Chair, the Ines and Fred Yeatts Retina Research lab fund, the MLS Foundation, and the American Macular Degeneration Foundation. The sponsor or funding organization had no role in the design or conduct of this research. The remaining authors have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: Human subjects were included in this study. This meta-analysis of published group-level data did not require institutional review board approval and informed consent was not applicable. The study adhered to the tenets of the Declaration of Helsinki. No animal subjects were included in this study.

Author Contributions:

Conception and design: Li, Lin, Vavvas

Data Collection: Li, Goss, Lin

Analysis and interpretation: Li, Miller, Lin, Vavvas

Obtained funding: N/A; Study was performed as part of regular employment duties at Mass Eye and Ear/Harvard Medical School.

Overall responsibility: Li, Goss, Miller, Lin, Vavvas

Abbreviations and Acronyms:
3CC = Three Continent Consortium; **AMD** = age-related macular degeneration; **AREDS** = Age-Related Eye Disease Study; **CI** = confidence interval; **HDL** = high-density lipoprotein; **ICGS** = International Classification and Grading System; **LDL** = low-density lipoprotein; **OR** = odds ratio; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **SDD** = subretinal drusenoid deposits; **SMD** = standardized mean difference; **TC** = total cholesterol; **TG** = triglycerides; **WARMGS** = Wisconsin Age-Related Maculopathy Grading System.

Keywords:
Age-related macular degeneration, Lipids, Meta-analysis, Cholesterol.

Correspondence:
Demetrios G. Vavvas, MD, PhD, 243 Charles Street, Boston, MA 02114. E-mail: demetrios_vavvas@meei.harvard.edu; and Jonathan B. Lin, MD, PhD, 243 Charles Street, Boston, MA 02114. E-mail: jonathan_lin@meei.harvard.edu.

References

1. Rein DB, Wittenborn JS, Burke-Conte Z, et al. Prevalence of age-related macular degeneration in the US in 2019. *JAMA Ophthalmol*. 2022;140:1202−1208.
2. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: a randomized phase 2 trial. *Ophthalmology*. 2020;127:186−195.
3. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Global Health*. 2014;2:e106−e116.
4. Kishan AU, Modjtahedi BS, Martins EN, et al. Lipids and age-related macular degeneration. *Surv Ophthalmol*. 2011;56: 195−213.
5. Vanderbeek BL, Zacks DN, Talwar N, et al. Role of statins in the development and progression of age-related macular degeneration. *Retina*. 2013;33:414.
6. Lin JB, Halawa OA, Husain D, et al. Dyslipidemia in age-related macular degeneration. *Eye (Lond)*. 2022;36:312−318.
7. Choudhary M, Ismail EN, Yao P-L, et al. LXRs regulate features of age-related macular degeneration and may be a potential therapeutic target. *JCI Insight*. 2020;5:e131928.
8. Ban N, Lee TJ, Sene A, et al. Impaired monocyte cholesterol clearance initiates age-related retinal degeneration and vision loss. *JCI Insight*. 2018;3:e120824.
9. Lin JB, Moolani HV, Sene A, et al. Macrophage microRNA-150 promotes pathological angiogenesis as seen in age-related macular degeneration. *JCI Insight*. 2018;3:e120157.
10. Vavvas DG, Daniels AB, Kapsala ZG, et al. Regression of some high-risk features of age-related macular degeneration (AMD) in patients receiving intensive statin treatment. *EBio-Medicine*. 2016;5:198−203.
11. Wang Y, Wang M, Zhang X, et al. The association between the lipids levels in blood and risk of age-related macular degeneration. *Nutrients*. 2016;8:663.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
13. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22:153−160.
14. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36:1−48.
15. Ben-Shachar MS, Lüdecke D, Makowski D. effectsize: estimation of effect size indices and standardized parameters. *J Open Source Softw*. 2020;5:2815.
16. Del Re A. Calculate effect sizes. https://www.acdelre.com/calculate-effect-sizes.html. Accessed February 24, 2023.
17. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4:1686.
18. Lüdecke D. *esc: Effect Size Computation for Meta Analysis*. 2018.
19. Lüdtke L, Jürgens C, Ittermann T, et al. Age-related macular degeneration and associated risk factors in the population-based study of health in Pomerania (ship-trend). *Med Sci Monit*. 2019;25:6383−6390.
20. Neethu A, Jayashree K, Senthilkumar GP, et al. Circulating adropin and vascular endothelial growth factor receptor-2 levels in age-related macular degeneration and T2DM patients-a cross-sectional study. *J Fam Med Prim Care*. 2020;9:4875−4879.
21. Nordestgaard LT, Tybjærg-Hansen A, Frikke-Schmidt R, Nordestgaard BG. Elevated apolipoprotein A1 and HDL cholesterol associated with age-related macular degeneration: 2 population cohorts. *J Clin Endocrinol Metab*. 2021;106: E2749−E2758.
22. Pertl L, Kern S, Weger M, et al. High-density lipoprotein function in exudative age-related macular degeneration. *PLoS One*. 2016;11:e0154397.
23. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:1−10.
24. Park SJ, Lee JH, Kang SW, et al. Age-related macular degeneration: prevalence and risk factors from Korean National Health and Nutrition Examination Survey, 2008 through 2011. *Ophthalmology*. 2014;121:1756−1765.
25. Klein R, Davis MD, Magli YL, et al. The Wisconsin age-related maculopathy grading system. *Ophthalmology*. 1991;98:1128−1134.
26. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol*. 1995;39: 367−374.
27. A simplified severity scale for age-related macular degeneration. *Arch Ophthalmol*. 2005;123:1570−1574.
28. Thee EF, Meester-Smoor MA, Luttikhuizen DT, et al. Performance of classification systems for age-related macular degeneration in the Rotterdam study. *Transl Vis Sci Technol*. 2020;9:26.
29. Klein R, Myers CE, Buitendijk GHS, et al. Lipids, lipid genes, and incident age-related macular degeneration: the three continent age-related macular degeneration consortium. *Am J Ophthalmol*. 2014;158:513−524.e3.
30. Ferris FL, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120:844−851.
31. Klein R, Klein BEK, Marino EK, et al. Early age-related maculopathy in the cardiovascular health study. *Ophthalmology*. 2003;110:25−33.
32. Klein R, Klein BEK, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy: the Beaver Dam Eye study. *Ophthalmology*. 1993;100:406−414.
33. Fernandez AB, Wong TY, Klein R, et al. Age-related macular degeneration and incident cardiovascular disease: the multiethnic study of atherosclerosis. *Ophthalmology*. 2012;119: 765−770.
34. Fan Q, Maranville JC, Fritsche L, et al. HDL-cholesterol levels and risk of age-related macular degeneration: a multiethnic genetic study using Mendelian randomization. *Int J Epidemiol*. 2017;46:1891−1902.
35. Cheung N, Liao D, Islam FMA, et al. Is early age-related macular degeneration related to carotid artery stiffness? The Atherosclerosis Risk in Communities study. *Br J Ophthalmol*. 2007;91:430−433.
36. Blumenkranz MS, Russell SR, Robey MG. Risk factors in age-related maculopathy complicated by choroidal neovascularization. *Ophthalmology*. 1986;93:552−558.
37. Baker ML, Wang JJ, Rogers S, et al. Early age-related macular degeneration, cognitive function, and dementia: the cardiovascular health study. *Arch Ophthalmol*. 2009;127: 667−673.

38. Brandl C, Breinlich V, Stark KJ, et al. Features of age-related macular degeneration in the general adults and their dependency on age, sex, and smoking: results from the German KORA study. *PLoS One*. 2016;11:e0167181.

39. Brandl C, Gunther F, Zimmermann ME, et al. Incidence, progression and risk factors of age-related macular degeneration in 35-95-year-old individuals from three jointly designed German cohort studies. *BMJ Open Ophthalmol*. 2022;7:e000912.

40. Fauser S, Smailhodzic D, Caramoy A, et al. Evaluation of serum lipid concentrations and genetic variants at high-density lipoprotein metabolism loci and TIMP3 in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2011;52:5525−5528.

41. Koller A, Brandl C, Lamina C, et al. Relative telomere length is associated with age-related macular degeneration in women. *Invest Ophthalmol Vis Sci*. 2022;63:30.

42. Joachim NDL, Mitchell P, Kifley A, Jinwang J. Incidence, progression, and associated risk factors of medium drusen in age-related macular degeneration findings from the 15-year follow-up of an Australian cohort. *JAMA Ophthalmol*. 2015;133:698−705.

43. McCarty CA, Dowrick A, Cameron J, et al. Novel measures of cardiovascular health and its association with prevalence and progression of age-related macular degeneration: the CHARM study. *BMC Ophthalmol*. 2008;8:25.

44. Smith W, Mitchell P, Leeder SR, Wang JJ. Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye study. *Arch Ophthalmol*. 1998;116:583−587.

45. Tsang NCK, Penfold PL, Snitch PJ, Billson F. Serum levels of antioxidants and age-related macular degeneration. *Doc Ophthalmol*. 1992;81:387−400.

46. Abalain JH, Carre JL, Leglise D, et al. Is age-related macular degeneration associated with serum lipoprotein and lipoparticle levels? *Clin Chim Acta*. 2002;326:97−104.

47. Ambreen F, Khan WA, Qureshi N, Qureshi IZ. Assessment of serum lipids in patients with age related macular degeneration from Pakistan. *J Pak Med Assoc*. 2014;64:664−669.

48. AnandBabu K, Bharathidevi SR, Sripriya S, et al. Serum paraoxonase activity in relation to lipid profile in age-related macular degeneration patients. *Exp Eye Res*. 2016;152:100−112.

49. Arifoglu HB, Karatepe Hashas AS, Atas M, et al. Systemic endothelial function in cases with wet-type age-related macular degeneration. *Aging Clin Exp Res*. 2016;28:853−856.

50. Bikbov MM, Zainullin RM, Gilmanshin TR, et al. Prevalence and associated factors of age-related macular degeneration in a Russian population: the Ural Eye and Medical study. *Am J Ophthalmol*. 2020;210:146−157.

51. Cackett P, Wong TY, Aung T, et al. Smoking, cardiovascular risk factors, and age-related macular degeneration in Asians: the Singapore Malay Eye study. *Am J Ophthalmol*. 2008;146:960−967.e1.

52. Cezario SM, Calastri MC, Oliveira CI, et al. Association of high-density lipoprotein and apolipoprotein E genetic variants with age-related macular degeneration. *Arq Bras Oftalmol*. 2015;78:85−88.

53. Cheung CMG, Tai ES, Kawasaki R, et al. Prevalence of and risk factors for age-related macular degeneration in a multi-ethnic Asian cohort. *Arch Ophthalmol*. 2012;130:480−486.

54. Cheung CMG, Li X, Cheng CY, et al. Prevalence and risk factors for age-related macular degeneration in Indians: a comparative study in Singapore and India. *Am J Ophthalmol*. 2013;155:764−773.

55. Cheung CMG, Li X, Cheng CY, et al. Prevalence, racial variations, and risk factors of age-related macular degeneration in Singaporean Chinese, Indians, and Malays. *Ophthalmology*. 2014;121:1598−1603.

56. Colak ES, Majkic-Singh NT, Stankovic SS, et al. Gender associated lipid and apolipoprotein profile in patients with age-related macular degeneration. *EJIFCC*. 2011;22:16−23.

57. Colijn JM, Verzijden T, Meester-Smoor MA, et al. Increased high-density lipoprotein levels associated with age-related macular degeneration: evidence from the EYE-RISK and European Eye Epidemiology Consortia. *Ophthalmology*. 2019;126:393−406.

58. Cougnard-Grégoire A, Delyfer MN, Korobelnik JF, et al. Elevated high-density lipoprotein cholesterol and age-related macular degeneration: the Alienor study. *PLoS One*. 2014;9:e90973.

59. Davari MH, Gheitasi H, Yaghobi G, Heydari B. Correlation between serum lipids and age-related macular degeneration: a case-control study. *J Res Health Sci*. 2013;13:98−101.

60. Delcourt C, Michel F, Colvez A, et al. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. *Ophthalmic Epidemiol*. 2001;8:237−249.

61. Erke MG, Bertelsen G, Peto T, et al. Cardiovascular risk factors associated with age-related macular degeneration: the Tromsø study. *Acta Ophthalmol*. 2014;92:662−669.

62. Hashemi R, Bandarian M, Abedi-Taleb E, et al. The association between blood vitamins D and E with age-related macular degeneration: a pilot study. *Interv Med Appl Sci*. 2018;10:127−132.

63. Javadzadeh A, Ghorbanihaghjo A, Rashtchizadeh N, et al. Enhanced susceptibility of low-density lipoprotein to oxidation in wet type age-related macular degeneration in male patients. *Saudi Med J*. 2007;28:221−224.

64. Jonasson F, Fisher DE, Eiriksdottir G, et al. Five-year incidence, progression, and risk factors for age-related macular degeneration: the age, gene/environment susceptibility study. *Ophthalmology*. 2014;121:1766−1772.

65. Kawasaki R, Wang JJ, Ji G, et al. Prevalence and risk factors for age-related macular degeneration in an adult Japanese population. The Funagata study. *Ophthalmology*. 2008;115:1376−1381.e2.

66. Mao F, Yang X, Yang K, et al. Six-year incidence and risk factors for age-related macular degeneration in a rural Chinese population: the Handan Eye study. *Invest Ophthalmol Vis Sci*. 2019;60:4966−4971.

67. Ngai LY, Stocks N, Sparrow JM, et al. The prevalence and analysis of risk factors for age-related macular degeneration: 18-year follow-up data from the Speedwell Eye study, United Kingdom. *Eye*. 2011;25:784−793.

68. Ornek N, Ornek K, Aydin S, et al. Serum vascular endothelial growth factor receptor-2 and adropin levels in age-related macular degeneration. *Int J Ophthalmol*. 2016;9:556−560.

69. Paunksnis A, Cimbalas A, Cerniauskiene LR, et al. Early age-related maculopathy and risk factors of cardiovascular disease in middle-aged Lithuanian urban population. *Eur J Ophthalmol*. 2005;15:255−262.

70. Peiretti E, Mandas A, Abete C, et al. Age-related macular degeneration and cognitive impairment show similarities in changes of neutral lipids in peripheral blood mononuclear cells. *Exp Eye Res*. 2014;124:11−16.

71. Qin L, Mroczkowska SA, Ekart A, et al. Patients with early age-related macular degeneration exhibit signs of macro- and micro-vascular disease and abnormal blood glutathione levels. *Graefes Arch Clin Exp Ophthalmol*. 2014;252:23−30.

72. Raman R, Pal SS, Ganesan S, et al. The prevalence and risk factors for age-related macular degeneration in rural-urban

India, Sankara Nethralaya Rural-Urban Age-related Macular Degeneration Study, Report No. 1. *Eye (Lond)*. 2016;30: 688−697.

73. Roh MI, Kim JH, Byeou SH, et al. Estimated prevalence and risk factor for age-related maculopathy. *Yonsei Med J*. 2008;49:931−941.

74. Semba RD, Moaddel R, Cotch MF, et al. Serum lipids in adults with late age-related macular degeneration: a case-control study. *Lipids Health Dis*. 2019;18:7.

75. Song SJ, Youm DJ, Chang Y, Yu HG. Age-related macular degeneration in a screened South Korean population: prevalence, risk factors, and subtypes. *Ophthalmic Epidemiol*. 2009;16:304−310.

76. Taniguchi H, Shiba T, Takahashi M, et al. Cardio-ankle vascular index elevation in patients with exudative age-related macular degeneration. *J Atheroscler Thromb*. 2013;20:903−910.

77. Ulaş F, Balbaba M, Özmen S, et al. Association of dehydro-epiandrosterone sulfate, serum lipids, C-reactive protein and body mass index with age-related macular degeneration. *Int Ophthalmol*. 2013;33:485−491.

78. Vingerling JR, Dielemans I, Bots ML, et al. Age-related macular degeneration is associated with atherosclerosis - the Rotterdam study. *Am J Epidemiol*. 1995;142:404−409.

79. Wang S, Xu L, Jonas JB, et al. Dyslipidemia and eye diseases in the adult Chinese population: the Beijing Eye study. *PLoS One*. 2012;7:e26871.

80. Xue CC, Cui J, Gao LQ, et al. Peripheral monocyte count and age-related macular degeneration. The Tongren Health Care study. *Am J Ophthalmol*. 2021;227:143−153.

81. Yip JL, Khawaja AP, Chan MP, et al. Cross sectional and longitudinal associations between cardiovascular risk factors and age related macular degeneration in the EPIC-Norfolk Eye study. *PLoS One*. 2015;10:e0132565.

82. Ledesma-Gil G, Otero-Marquez O, Alauddin S, et al. Subretinal drusenoid deposits are strongly associated with coexistent high-risk vascular diseases. *BMJ Open Ophth*. 2022;7: e001154.

83. Thomson RJ, Chazaro J, Otero-Marquez O, et al. Subretinal drusenoid deposits and soft drusen: are they markers for distinct retinal diseases? *Retina*. 2022;42:1311−1318.

84. Ludwig CA, Vail D, Rajeshuni NA, et al. Statins and the progression of age-related macular degeneration in the United States. *PLoS One*. 2021;16:e0252878.

85. Lambert NG, Singh MK, ElShelmani H, et al. Risk factors and biomarkers of age-related macular degeneration. *Prog Retin Eye Res*. 2016;54:64−102.