

Contributions of Lipid-Related Metabolites and Complement Proteins to Early and Intermediate Age-Related Macular Degeneration

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Objective: Our objective was to determine the effects of lipids and complement proteins on early and intermediate age-related macular degeneration (AMD) stages using machine learning models by integrating metabolomics and proteomic data.

Design: Nested case–control study.

Subjects and Controls: The analyses were performed in a subset of the Singapore Indian Chinese Cohort (SICC) Eye Study. Among the 6753 participants, we randomly selected 155 Indian and 155 Chinese cases of AMD and matched them with 310 controls on age, sex, and ethnicity.

Methods: We measured 35 complement proteins and 56 lipids using mass spectrometry and nuclear magnetic resonance, respectively. We first selected the most contributing lipids and complement proteins to early and intermediate AMD using random forest models. Then, we estimated their effects using a multinomial model adjusted for potential confounders.

Main Outcome Measures: Age-related macular degeneration was classified using the Beckman classification system.

Results: Among the 310 individuals with AMD, 166 (53.5%) had early AMD, and 144 (46.5%) had intermediate AMD. First, high-density lipoprotein (HDL) particle diameter was positively associated with both early and intermediate AMD (odds ratio [OR]_{early} = 1.69; 95% confidence interval [CI], 1.11–2.55 and OR_{intermediate} = 1.72; 95% CI, 1.11–2.66 per 1-standard deviation increase in HDL diameter). Second, complement protein 2 (C2), complement C1 inhibitor (IC1), complement protein 6 (C6), complement protein 1QC (C1QC) and complement factor H-related protein 1 (FHR1), were associated with AMD. C2 was positively associated with both early and intermediate AMD (OR_{early} = 1.58; 95% CI, 1.08–2.30 and OR_{intermediate} = 1.56; 95% CI, 1.04–2.34). C6 was positively (OR_{early} = 1.41; 95% CI, 1.03–1.93) associated with early AMD. However, IC1 was negatively associated with early AMD (OR_{early} = 0.62; 95% CI, 0.38–0.99), whereas C1QC (OR_{intermediate} = 0.63; 95% CI, 0.42–0.93) and FHR1 (OR_{intermediate} = 0.73; 95% CI, 0.54–0.98) were both negatively associated with intermediate AMD.

Conclusions: Although both HDL diameter and C2 levels show associations with both early and intermediate AMD, dysregulations of IC1, C6, C1QC, and FHR1 are only observed at specific stages of AMD. These findings underscore the complexity of complement system dysregulation in AMD, which appears to vary depending on the disease severity.

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Supplemental material available at www.opthalmologyscience.org.

Age-related macular degeneration (AMD) is an important cause of irreversible blindness in Asia and worldwide.^{1,2} The spectrum of AMD comprises stages that are classified as early, intermediate, and late. The early and intermediate AMD stages are characterized by drusen in the outer retinal layers causing none or minimal reductions in visual

function. However, the late manifestation of geographic atrophy (GA), which is a confluent atrophy of the outer retinal layers or the presence of neovascular complexes (macular neovascularization [MNV]) lead to severe central visual loss.² Age-related macular degeneration is known to be a multifactorial disease caused by a combination of

lifestyle and genetic factors.^{3–6} Several pathways are involved in the pathogenesis of AMD, such as complement system activation and lipid dysregulation.^{7–11} Although progress has been made in the understanding of these pathways, treatment options to prevent AMD onset and progression remain limited because the etiology and pathogenesis of AMD are remain incompletely understood.

Dysregulation of the complement system is a significant driver of AMD pathogenesis. Mutations in complement genes account for up to 60% of AMD heritability,¹² with the main mutations identified in complement factor H (CFH),¹³ and some others in complement protein 3 (C3), complement protein 5 (C5), complement protein 9 (C9), and complement factor D genes,^{4,14} indicating that multiple complement components are dysregulated in patients with AMD. Higher levels of complement activation (C3d/C3 ratio) have been found in patients with intermediate AMD and late dry AMD, compared with both controls and early AMD groups,¹⁵ suggesting that this excessive activation of the complement cascade is at play after the onset of the disease. It is essential to further determine the contributions of the different complement components according to the disease severity, especially at the early stages.

Lipid dysregulation, which hitherto been given less prominence, has also been identified as playing a fundamental role in AMD pathogenesis. The accumulation of very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) containing esterified cholesterol-rich apolipoprotein B within Bruch membrane, and accumulations of drusen, which are the hallmark of AMD, have led researchers to suggest that these metabolites are involved in the pathogenesis of AMD specific lesions.¹⁶ Recent large epidemiologic studies have reported that elevated high-density lipoprotein (HDL) cholesterol is associated with a higher risk of AMD, whereas triglycerides (TGs) confer lower risk.^{17–20} Interestingly, these associations are reversed in other diseases of chronicity such as cardiovascular disease. Furthermore, both lipid classes exhibit higher magnitude effects for early than for late AMD, suggesting an initiating role for lipids at the early phase of disease rather than a potentiating role in terms of progression to late stages.¹⁷ The precise contributions of the subclasses of lipids to disease evolution and stage remain poorly understood.

We proposed here to integrate metabolomics and proteomic data to disentangle the effects of lipids and complement proteins in the pathogenesis of early and intermediate AMD stages. Machine learning models were used to account for the complex characteristics of the data. Our objective was to determine the relative contributions of lipids and complement proteins in terms of association with early and intermediate AMD stages.

Methods

Study Design and Participants

The analyses were performed in a subset of the Singapore Indian Chinese Cohort (SICC) Eye Study. The Singapore Indian Chinese

Cohort is a prospective population-based study of 6753 subjects aged ≥ 40 years.²¹ Participants underwent a standardized interview and laboratory investigations. Informed, written consent was obtained from participants, and ethical approval was obtained from the Institutional Review Board of SingHealth.

We selected among the SICC participants those of Indian ($n = 3400$) and Chinese ($n = 3353$) ancestry. We excluded the following individuals: (1) those with incomplete clinical data ($n = 662$), or with missing information on lipid levels ($n = 616$) and (2) those with any retinopathy ($n = 385$), any cataract ($n = 1964$), or any type of glaucoma ($n = 133$; Fig S1, available at www.opthalmologyscience.org). Among the remaining population ($n = 3206$), we randomly selected 200 Indian and 200 Chinese individuals with early or intermediate AMD at the baseline examination. Then, we selected our control population (individuals without features of any of the stages of AMD in both eyes) matched based on age (5-year categories), sex, and ethnicity. This iterative process yielded 197 and 196 pairs of cases and controls among the Indian and the Chinese populations, respectively (3 Indians and 4 Chinese cases did not have any control with the same age category and sex). Finally, we selected 155 pairs of Indian participants ($n = 310$) and 155 pairs of Chinese participants ($n = 310$) who had enough serum stored (if the case or the control within a pair did not have enough blood, then the entire pair was excluded).

AMD Grading

In SEED, color fundus photographs were graded by the Singapore National Eye Centre Ocular reading center. Features of AMD were identified, and the severity of AMD was determined according to the Beckman classification system.²² In brief, an individual was considered free of any AMD if pigmentary abnormalities (hyperpigmentation or depigmentation) and drusen ($>63 \mu\text{m}$) were absent in both eyes. Early AMD was defined as the presence of drusen $\geq 63 \mu\text{m}$ and $\leq 125 \mu\text{m}$ in at least 1 eye and without pigmentary abnormalities (Fig S2, available at www.opthalmologyscience.org). Intermediate AMD was defined as the presence of large drusen ($\geq 125 \mu\text{m}$) or the presence of pigmentary abnormalities in at least 1 eye (Fig S3, available at www.opthalmologyscience.org). The analyses were performed at the individual level with the Beckman grading of the more severe eye considered for each individual.

Proteomics Data

A targeted liquid chromatography–mass spectrometry proteomics technique was used to quantify protein's serum concentrations. This technique allows the simultaneous measurement of many proteins in a single experiment. We used 20 μL of stored serum samples at the baseline visit. A Reference Peptide Mix standard was added to the reconstituted peptide sample according to manufacturer's protocol (PlasmaDive Reference Peptides kit, Biognosys AG). The reconstituted peptide samples were then analyzed on an EASY-nLC 1200 system coupled to Orbitrap Exploris 480 mass spectrometer (ThermoFisher Scientific). Orbitrap Exploris 480 mass spectrometer was operated in data-independent and positive ionization mode. The resulting tandem mass spectrometry data were processed using Spectronaut (Biognosys AG) DIA analysis. Among the 313 proteins quantified, we selected 35 complement proteins. Individuals with missing values ($n = 7$) were imputed by the minimum value divided by 5 (because they were below the detection threshold). The distributions were log transformed and standardized (centered and scaled). Finally, individuals with values lower than -5 and higher than $+5$ standard deviations (SDs) were excluded ($n = 24$).

Metabolomics Data

A high-throughput proton nuclear magnetic resonance metabolomics platform (Nightingale Health Ltd) was used to measure each metabolite's serum concentrations. Details of the methodology and applications of the nuclear magnetic resonance metabolomics platform have been described.²³ This method provides simultaneous quantification of the following 150 blood lipid-related metabolites: total and subfractions of cholesterol, triglyceride, phospholipid, cholesterol ester, and free cholesterol in HDL, LDL, and VLDL particles; phosphoglyceride; choline, apolipoproteins; and S/M/L/XL and XXL HDL, LDL, and VLDL lipoprotein subclasses. Moreover, in each subclass, the concentrations of lipids, triglycerides, cholesterol esters, free cholesterol, and phospholipids were quantified. Because the correlations among these 150 lipid-related metabolites were very high, we did not consider the levels of these subfractions in each lipoprotein subclass, thus including a total of 56 lipid-related metabolites. The distributions were log transformed and standardized (centered and scaled). Finally, individuals with values lower than -5 and higher than $+5$ SDs were excluded ($n = 31$).

Statistical Analyses

The statistical analyses were conducted in 3 steps. First, we tested each of the 56 lipids and 35 complement proteins in separate logistic models adjusted on age (5-year category), sex, ethnicity, lipid-lowering medication, hypertension, diabetes, and body mass index (BMI). Separate analyses were performed for early and intermediate AMD. To address multiple testing issues, we used the method developed by Gao et al,²⁴ which account for the multicollinearity between the variables. This method uses principal component analysis to reduce dimensionality of the data considered (i.e., lipids and complement proteins) and identify the number of independent components. We have chosen the first 8 components that explain 99.2% of the variance. The P value considered for significance was thus equal to $0.05/8 = 0.00625$.

Second, to account for possible nonlinearity and interactions between the variables, we used random forest models to select lipids and complement proteins with highest contributions. Here, all the variables were included in the model to allow the estimations of their effects independently of each other's. The variable contributions were estimated using the variable importance (VI) metric. The higher the VI value, the higher the contribution. For the number of variables to be randomly

selected at each split in each tree, we used the square root of the total number of variables (10). One thousand trees were run. One separate model was run for early AMD, and 1 was run for intermediate AMD. The same confounders as the ones previously considered were included in the model. We selected the 20 lipids and complement proteins with the highest VI values for each outcome.

Third, we built a multinomial model with the 2 sets of 20 variables selected in step 1, minus the overlapping ones selected (selected in both models). We combined the 2 sets of variables because the multinomial model allows to determine the effects of these variables on early and intermediate AMD in a single model. The same adjustment variables as the first 2 steps were considered. Finally, we tested the possible interactions between the lipids and complement proteins with the ethnic group (those who were Indian vs. those who were Chinese). The same multinomial model was used to test these possible interactions, with the ethnicity considered as an interaction variable with each lipid and complement protein (instead of an adjustment variable). All the analyses were done using R software version 4.0.4.²⁵

Results

Study Population

Among the 310 individuals with AMD, 166 (53.5%) had early AMD, and 144 (46.5%) intermediate AMD (Table 1). The age and sex distribution were similar, as a result of the matching between cases and controls, as well as other possible confounders such as BMI and diabetes status. However, more intermediate AMD cases were reported in the Chinese population than in the Indian population (56.9% vs. 43.1%).

Selection of Lipids and Complement Proteins

The effects of each lipid and complement protein were first tested separately in logistic models. Regarding lipids, several HDL subfractions (cholesterol, phospholipids, cholesterol ester, and free cholesterol), average HDL diameter, apolipoprotein A1 (ApoA1), and concentrations of large and medium HDL particles were associated with both early and intermediate AMD. The apolipoprotein

Table 1. Characteristics of the Study Population According to AMD Severity Stage

	No AMD n = 310	Early AMD n = 166	Intermediate AMD n = 144	P Value
Age (yrs), n (%)				0.179
(40–50)	93 (30)	56 (33.7)	37 (25.7)	
(50–60)	132 (42.6)	74 (44.6)	58 (40.3)	
(60–85)	85 (27.4)	36 (21.7)	49 (34)	
Female, n (%)	157 (50.6)	85 (51.2)	72 (50)	0.978
Body mass index, median (IQR)	24.6 (22.1–27.1)	25.4 (22.8–27.7)	24.6 (21.9–27.5)	0.312
Hypertension, n (%)	157 (50.6)	79 (47.6)	83 (57.6)	0.194
Diabetes, n (%)	54 (17.4)	34 (20.5)	32 (22.2)	0.441
Lipid-lowering medication, n (%)	70 (22.6)	37 (22.3)	36 (25)	0.818
Ethnic group, n (%)				0.075
Chinese	155 (50)	73 (44)	82 (56.9)	
Indian	155 (50)	93 (56)	62 (43.1)	

AMD = age-related macular degeneration; IQR = interquartile range.

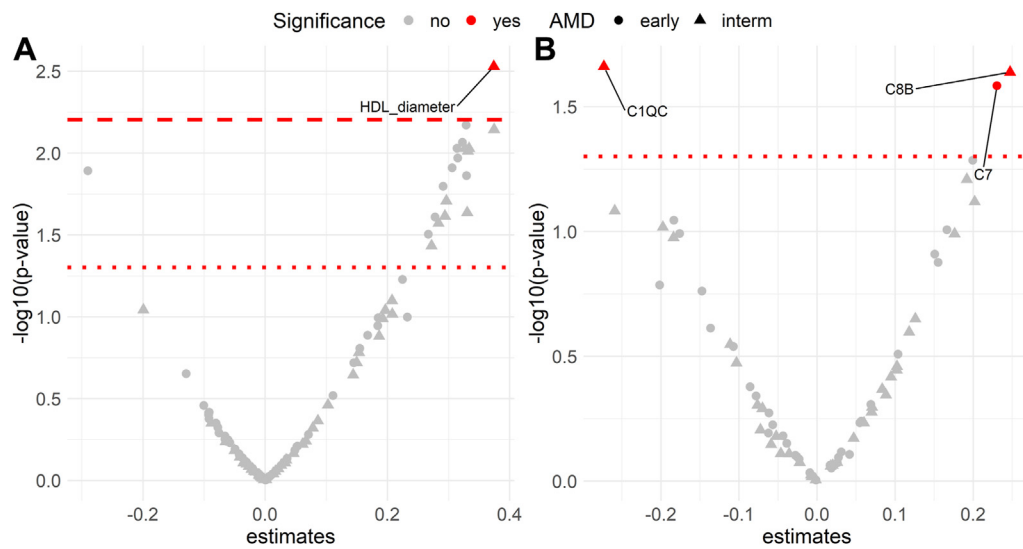


Figure 4. Effects of lipids and complement proteins on early and intermediate AMD (β estimates from logistic regression models). Each lipid and complement protein were tested separately in a model adjusted for age, sex, ethnicity, lipid-lowering medication, hypertension, diabetes, and body mass index. The red horizontal lines correspond to a significant threshold at 0.05 (dotted line) and 0.006 (dashed line). The latter threshold was calculated by dividing 0.05 by the number of components that explained 99.2% of the variance of the lipids ($0.05/8 = 0.006$). AMD = age-related macular degeneration; C1QC = complement protein 1QC; C7 = complement protein 7; C8B = complement protein 8B; HDL = high density lipoprotein.

B/ApoA1 ratio was associated with early AMD, and very large HDL particles were associated with intermediate AMD. However, after correcting for multiple testing, only the HDL diameter was significantly associated with intermediate AMD (Fig 4). Among complement proteins, complement protein 7 (C7) was associated with early

AMD, and complement protein 1QC (C1QC) and complement protein 8B were associated with intermediate AMD, but these associations lost significance after accounting for multiple testing.

Then, we used random forests models to select the 20 most contributing lipids and complement proteins for each

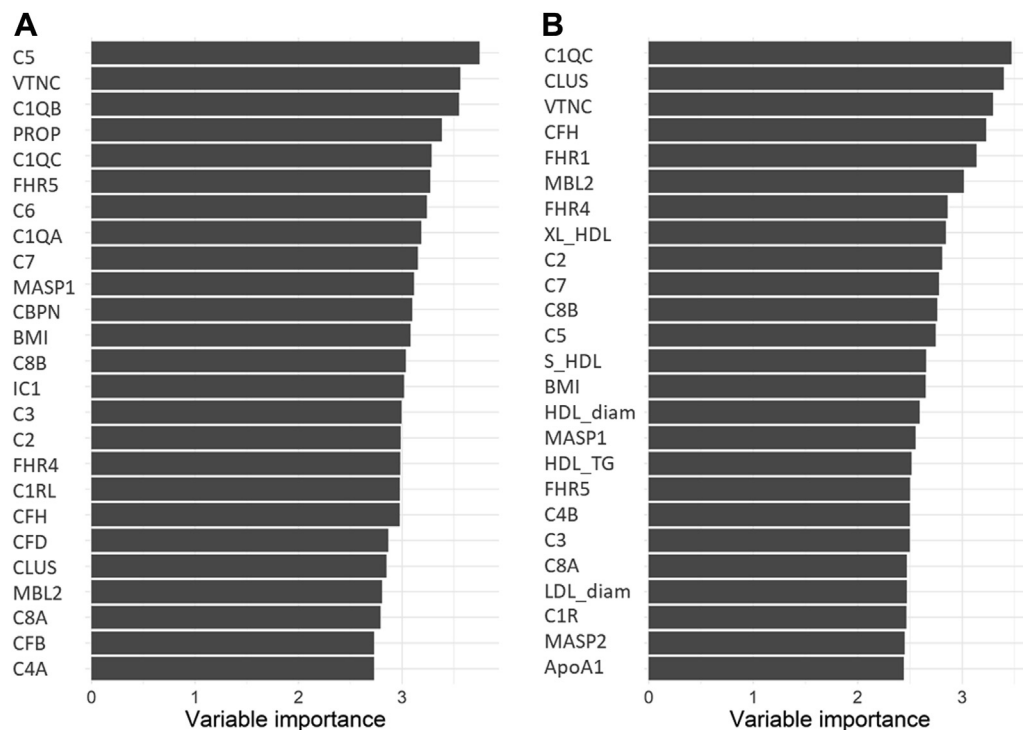


Figure 5. Top 25 lipids and complement proteins selected by a random forest model for (A) early and (B) intermediate age-related macular degeneration.

Table 2. Contributions of Lipids and Complement Proteins, Expressed as Odds Ratios per 1-SD Increase with their 95% Confidence Intervals, to Early and Intermediate AMD.

		Early AMD		Intermediate AMD	
		OR (95% CI)	P Value	OR (95% CI)	P Value
Lipid Protein	HDL diameter	1.69 (1.11–2.55)	0.013	1.72 (1.11–2.66)	0.016
	C1QC	0.77 (0.53–1.12)	0.177	0.63 (0.42–0.93)	0.021
	C6	1.41 (1.03–1.93)	0.032	1.06 (0.76–1.47)	0.739
	IC1	0.62 (0.38–0.99)	0.047	0.61 (0.37–1.01)	0.055
	C2	1.58 (1.08–2.30)	0.017	1.56 (1.04–2.34)	0.030
	FHR1	0.93 (0.68–1.26)	0.621	0.73 (0.54–0.98)	0.039

C1QC = complement protein 1QC; C2 = complement protein 2; C6 = complement protein 6; FHR1 = complement factor H-related protein 1; HDL = high-density lipoprotein; IC1 = complement C1 inhibitor.

The 6 variables presented in this figure correspond to the significant variables tested in the multinomial model adjusted for age, sex, ethnicity, lipid-lowering medication, hypertension, diabetes, and body mass index.

outcome (Fig 5). Given that 12 variables were selected in both models (early and intermediate), the final set of variables considered was composed of 28 variables, including 4 lipids and 24 complement proteins.

Contribution of Lipids and Complement Proteins

The set of 28 lipids and complement proteins were included in a multinomial model adjusted on confounders. Among these variables, 1 lipid and 4 complement proteins were significantly associated with early or intermediate AMD or both. Larger HDL diameter (OR = 1.69; 95% confidence interval [CI], 1.11–2.55 and OR = 1.72; 95% CI, 1.11–2.66 per 1-SD increase in HDL diameter) and higher levels of complement protein 2 (C2; OR = 1.58; 95% CI, 1.08–2.30 and OR = 1.56; 95% CI, 1.04–2.34) were associated with higher odds of both early and intermediate AMD. Higher levels of complement protein C6 were associated with higher odds of early AMD (OR = 1.41; 95% CI, 1.03–1.93). Furthermore, a higher level of complement protein 1 inhibitor (IC1) was associated with lower odds of early AMD (OR = 0.62; 95% CI, 0.38–0.99). Finally, higher levels of C1QC (OR = 0.63; 95% CI, 0.42–0.93) and FHR1 (OR = 0.73; 95% CI, 0.54–0.98) were associated with lower odds of intermediate AMD (Table 2; Figs 6 and 7). The raw distributions of the significant lipids and complement proteins according to AMD features (pigmentary abnormalities and drusen size) are presented Figures S8 and S9 (available at www.opthalmologyscience.org). The effects of all the 28 variables tested are presented in Figure S10 and Table S3 (available at www.opthalmologyscience.org).

Interactions between Lipids and Complement Proteins with Ethnic Group

Finally, we tested the interactions between the 28 selected lipids and complement proteins and the ethnic group. No interaction was found with the 6 lipids and complement proteins associated with AMD. However, the effect of triglycerides subfraction in HDL on early AMD was significant only in the Chinese population (OR_{Chinese} = 1.92; 95% CI, 1.26–2.93; OR_{Indian} = 0.8; 95% CI,

0.57–1.13), and the effect of C4B on intermediate AMD was only significant in the Indian population (OR_{Chinese} = 1.35; 95% CI, 0.93–1.96; OR_{Indian} = 0.56; 95% CI, 0.33–0.94; Fig S11, available at www.opthalmologyscience.org).

Discussion

In this study, we used a combination of metabolomics and proteomics data to determine the effects of lipids and complement proteins according to AMD severity. We used random forest models to identify the most contributing

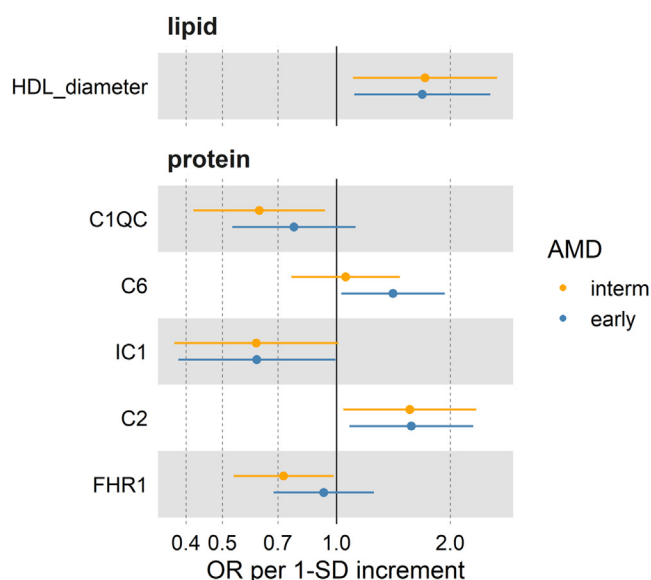


Figure 6. Effects of lipids and complement proteins, expressed in ORs with their 95% confidence intervals, on early and intermediate AMD. The 6 variables presented in this figure correspond to the significant variables tested in the multinomial model adjusted for age, sex, ethnicity, lipid-lowering medication, hypertension, diabetes, and body mass index. AMD = age-related macular degeneration; C1QC = complement protein 1QC; C2 = complement protein 2; C6 = complement protein 6; FHR1 = complement factor H-related protein 1; HDL = high density lipoprotein; IC1 = complement C1 inhibitor; OR = odds ratio.

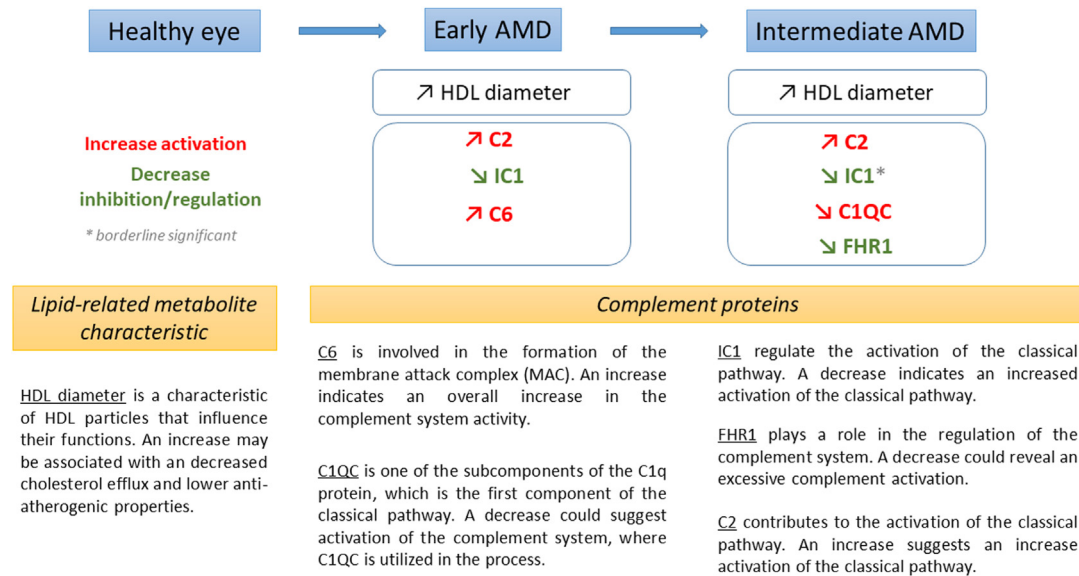


Figure 7. Overview of the effects of lipids and complement proteins to early and intermediate AMD. AMD = age-related macular degeneration; C1QC = complement protein 1QC; C2 = complement protein 2; C6 = complement protein 6; FHR1 = complement factor H-related protein 1; HDL = high density lipoprotein; IC1 = complement C1 inhibitor.

variables and further tested them using a multivariable multinomial model. We found that, among 56 lipid-related metabolites and lipoprotein characteristics and 35 complement proteins, only the average HDL particle diameter and 5 complement proteins (i.e., C6, IC1, C1QC, FHR1, and C2) were associated with early or intermediate AMD stages. Larger HDL particle diameter and a higher level of C2 were similarly associated with higher odds of early or intermediate AMD. However, a higher level of C6 and a lower level of IC1 were associated with higher odds of early AMD; and lower levels of C1QC and FHR1 were associated with higher odds of intermediate AMD.

Our data suggest that dysregulation of lipid metabolism is likely involved at both early and intermediate stages with the same magnitude of effect. Notably, we observed that, compared with individuals with no AMD, those with early and intermediate AMD had higher ORs. In this context, mean HDL diameter can be regarded as an integrative measure of HDL heterogeneity and particle profile.²⁶ High-density lipoprotein consists of many different particles which are heterogeneous in structure, size, composition, and biological activity. These characteristics define HDL functionality. The 2 main types of HDL are the large HDL2 and the smaller HDL3. The smaller HDL3 particles are highly efficient in promoting cholesterol efflux via the ABCA1 transporter, which in turn has numerous effects including anti-inflammatory and antioxidant properties.²⁷ By contrast, the association seen with the larger HDL diameter particles in individuals with features of AMD is in accord with the view that higher risk of disease exists when there is reduced anti-inflammatory and antioxidant activity.

We identified 5 complement proteins that were associated with AMD. Although C2 and IC1 were associated with both early and intermediate AMD (albeit borderline significant for IC1 in intermediate AMD), C6 was specifically

associated with early AMD, and C1QC and FHR1 were associated with intermediate AMD. Higher levels of C2 and lower levels of IC1 were found in individuals with early and intermediate AMD. Polymorphism in the C2 gene is associated with AMD.^{4,28} Although C2 contributes to the activation of the classical pathway, IC1 regulates its activation; therefore, it can be surmised that their respective increase and decrease might be associated with an increased level of inflammation. Moreover, we found C6 to be increased specifically in early AMD, and C1QC and FHR1 were found to be decreased in intermediate AMD. C6 is involved in the formation of the membrane attack complex. This protein has been found in AMD donors' drusen.²⁹ Its increase might indicate an overall increase in the complement system activity. Furthermore, C1QC is 1 of the subcomponents of the C1Q protein, which is the first component of the classical pathway. C1Q has been identified as a key driver of complement activity in AMD and as a candidate therapeutic target for GA.³⁰ A decrease could suggest an activation of the complement system, where C1QC is utilized in the process. Finally, FHR1 plays a role in the regulation of the complement system as an inhibitor involved in the regulation of complement factor C3b turnover. Therefore, its decrease could reveal an excessive complement activation. Taken together, our results suggested that, although an overall increase activation of the complement system occurs in early and intermediate stages through variations C2 and IC1, specific modulations may happen at specific stages, i.e., C6 in early and C1QC and FHR1 in intermediate, either related to an increased activity or a decreased regulation of the system.

Some known associations involving lipids and complement proteins have not been evidenced in our study. First, regarding lipids, no association between AMD and lipids such as

triglycerides or LDL cholesterol was found. This absence of effect could be due to our limited sample size. Second, complement proteins known to be associated with AMD, such as CFH or C3, were not significant in our study. However, both CFH and C3 proteins were selected by the random forest models, and non-significant trends were found in the multinomial model ($OR_{C3} = 1.42$; 95% CI, 0.97–2.09; $P = 0.075$ for intermediate AMD and $OR_{CFH} = 0.76$; 95% CI, 0.54–1.05; $P = 0.093$ for early AMD) suggesting that this could be due to a lack of statistical power owing to the limited sample size.

The principal strength of this study is its combination of metabolomics and proteomic data to identify the contributions of lipid-related metabolites and complement proteins to AMD severity. Moreover, we have used both machine learning and classical statistical models to filter possible contributors to AMD risk while accounting for complex patterns in the data and further test their associations independently of the main confounders. Our study also suffers from limitations. First, the sample size was limited and only included individuals of Indian and Chinese ancestries. Therefore, further studies are needed with larger sample sizes including other ethnicities to investigate the generalizability and reproducibility of our results in different populations and geographic locations where cultural factors

influence diet and consequently lipid metabolism. Nevertheless, the absence of interaction between ethnicity and the lipids and proteins associated with AMD suggest that our results are robust in our 2 ethnic groups. Second, we did not include individuals with late AMD, limiting our ability to investigate the separate contributions of lipids and complement proteins to the late stage of the disease. Finally, because of the limited sample size, only the average HDL diameter reached significance after correction for multiple testing. Larger studies are needed to confirm our findings.

To summarize, we identify and determine the contribution of lipids and complement proteins on early and intermediate AMD stages using a combination of metabolomics and proteomics data. First, our findings suggest that dysregulation of the lipid metabolism via HDL particles is likely involved at both early and intermediate stages with same magnitude of effect. Second, we found increased activation of the complement system via C6 protein and decreased levels of inhibition via IC1 for individuals with early AMD; and an increased activation of the classical pathway via C1QC and decreased levels of inhibition via FHR1 in individuals with intermediate AMD. These findings underscore the complexity of complement system dysregulation, which appears to vary depending on the disease severity.

Footnotes and Disclosures

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Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

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No animal subjects were included in this study.

Author Contributions:

Conception and design: Nusinovici, Chakravarthy, Cheng

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Analysis and interpretation: Nusinovici, Zhou, Xinyue Wang, Tham, Xiaomeng Wang, Wong, Chakravarthy, Cheng

Obtained funding: Nusinovici, Cheng

Overall responsibility: Nusinovici, Zhou, Xinyue Wang, Tham, Xiaomeng Wang, Wong, Chakravarthy, Cheng

Abbreviations and acronyms:

AMD = age-related macular degeneration; **ApoA1** = apolipoprotein A1; **BMI** = body mass index; **C1QC** = complement protein 1QC; **C2** = complement protein 2; **C3** = complement protein 3; **C5** = complement protein 5; **C6** = complement protein 6; **C7** = complement protein 7; **C9** = complement protein 9; **CFH** = complement factor H; **CI** = confidence interval; **FHR1** = complement factor H-related protein 1; **GA** = geographic atrophy; **HDL** = high-density lipoprotein; **IC1** = complement protein 1 inhibitor; **LDL** = low-density lipoprotein; **MNV** = macular neovascularization; **OR** = odds ratio; **SD** = standard deviation; **SICC** = Singapore Indian Chinese Cohort; **TG** = triglyceride; **VI** = variable importance; **VLDL** = very low-density lipoprotein.

Keywords:

Multi-omics, Lipids, Complement proteins, Age-related macular degeneration, Severity.

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