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Inflammation, Complement Factor H, and Age-Related Macular Degeneration: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To describe the relationship of systemic inflammatory disease, complement factor H (*CFH*) Y402H (1277T→C) genotype status and age-related macular degeneration (AMD) prevalence in a multiethnic population of whites, blacks, Hispanics, and Chinese.

Design—Population-based, cross-sectional study.

Participants—We included 5887 persons aged 45 to 84 years with gradable AMD.

Methods—Digital fundus photographs were used to measure AMD. Two years earlier, biomarkers of inflammation were measured and history of inflammatory disease and use of antiinflammatory agents obtained.

Main Outcome Measure—Prevalence of AMD.

Results—While controlling for age, gender, race/ethnicity, and study site, there were no associations between systemic inflammatory factors and AMD severity. Higher levels of high-sensitivity C-reactive protein (odds ratio [OR] per standard deviation [SD] increase in natural log [*ln*] units, 2.34; 95% confidence interval [CI], 1.33–4.13) and interleukin-6 (OR per SD in *ln*, 2.06;

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95% CI, 1.21–3.49) were associated with geographic atrophy but not other AMD end points. History of periodontal disease (OR, 1.68; 95% CI, 1.14–2.47) was related to increased retinal pigment. A history of arthritis was associated with soft distinct drusen (OR, 1.24; 95% CI, 1.06–1.46). A history of oral steroid use was related to large drusen (OR, 2.13; 95% CI, 1.14–3.97) and soft distinct drusen (OR, 1.76; 95% CI, 1.00–3.10) and history of cyclooxygenase 2 inhibitor use were associated with large drusen (OR, 1.50; 95% CI, 1.10–2.04), soft indistinct drusen (OR, 1.84; 95% CI, 1.09–3.10), and large drusen area (OR, 1.66; 95% CI, 1.02–2.71). Whites, blacks, and Hispanics with *CFH* Y402H CC variant genotype had the highest frequency of early AMD compared with those with wild TT genotype. The frequency of *CFH* did explain some of the difference in AMD prevalence between Chinese and Hispanics compared with whites, but did not explain the difference in prevalence between whites and blacks.

Conclusions—This study confirmed associations of the Y402H *CFH* gene variant with AMD in nonwhite populations, but neither explained the lack of association between inflammatory factors and AMD in the cohort nor the basis for the observed differences in AMD prevalence across ethnic groups.

Inflammation has been hypothesized to have a role in the pathogenesis of age-related macular degeneration (AMD).[1–5] Drusen have been shown to contain proteins associated with immune-mediated processes and inflammation,[6] and chronic inflammatory cells have been found on the outer surface of Bruch's membrane in eyes with neovascular AMD.[7] These inflammatory cells are thought to cause microvascular injury by direct release of long-acting oxidants, toxic oxygen compounds, and proteolytic enzymes that damage Bruch's membrane.[8,9] However, data from clinical and epidemiologic studies to date regarding the relation of systemic inflammation, use of antiinflammatory drugs, presence of blood inflammatory biomarkers, or exposure to pathogens and AMD have been inconsistent.[10–31]

More recent studies have also shown that a Y402H polymorphism in the complement factor H (*CFH*) gene on chromosome 1q is strongly associated with AMD, suggesting a role of innate immunity and inflammation in its pathogenesis.[32–34] Furthermore, in 1 study, markers of inflammation, such as serum C-reactive protein (CRP), were found to be related to AMD only in carriers of *CFH* Y402H variants.[35] However, although a considerable body of information has been developed regarding the *CFH* gene and inflammatory factors in whites, less is known regarding the distribution of these genes and their relation to AMD in other racial/ethnic groups in the general population.[36]

Endothelial dysfunction and hemostatic factors, possibly related to inflammation, cigarette smoking, and other processes, have also been thought to be involved in the pathogenesis of AMD,[37] possibly via effects on choroidal blood flow.[38,39] However, epidemiologic studies have failed to show a consistent relation of systemic markers of endothelial dysfunction[23–26] or hemostatic or fibrinolytic biomarkers to AMD.[12–17,19,25,26] Again, most of the previous studies have been in whites.

In this report, we examine the relationship of diseases associated with systemic inflammation, use of antiinflammatory drugs, and specific markers of inflammation, for example, high-sensitivity CRP (hsCRP), interleukin (IL)-6, and *CFH* Y402H (1277T→C) genotype status with AMD in a multiethnic sample of whites, blacks, Hispanics, and Chinese in the United States. We hypothesized that systemic inflammation and this *CFH* variant and abnormalities in endothelial function and hemostasis are associated with higher risk of AMD and that these factors would explain, in part, differences in the prevalence of AMD among different racial/ethnic groups.

Methods

Study Sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of men and women aged 45–85 years without a history of clinical cardiovascular disease (CVD) living in 6 United States communities.[40] The study objectives of the MESA are to identify risk factors for subclinical CVD, progression of subclinical CVD, and transition from subclinical to clinical CVD. Selection of the study population has been reported in detail elsewhere.[40] At the first examination, carried out between July 17, 2000, and August 29, 2002, there were 6814 participants: 1086 from Baltimore, Maryland, 1164 from Chicago, Illinois, 1077 from Forsyth County, North Carolina, 1319 from Los Angeles County, California, 1102 from New York, New York, and 1066 from St. Paul, Minnesota. Tenets of the Declaration of Helsinki were followed, and institutional review board approval was granted at each study site. Written informed consent was obtained from each participant.

Retinal Photography and Measurement of Age-Related Macular Degeneration

Fundus photography using a 45-degree 6.3-mega pixel digital nonmydriatic camera was performed at the second examination immediately after the baseline examination, which was conducted between September 9, 2002, and February 7, 2004, at each site using a standardized protocol.[41,42] Two photographic fields were taken of each eye; the first centered on the optic disc (Early Treatment Diabetic Retinopathy Study field 1) and the second centered on the fovea (Early Treatment Diabetic Retinopathy Study field 2).[43] Images were obtained from 6176 participants.

Fundus Image Grading—Capture and grading of digital images and quality control have been described in detail elsewhere.[44,45] Each image was graded twice (a preliminary and a detail grade) on-line using a modification of the Wisconsin Age-related Maculopathy Grading scheme.[45] For the purposes of this report, 5887 (98.9%) of those photographed, those with ≥1 eye that could be evaluated for AMD (right eye [n = 211], left eye [n = 200], and both eyes [n = 5476]) are included in the analyses. There were no statistically significant differences for gradability for AMD among the 4 racial/ethnic groups in the study (data not shown).

Definitions of Variables—Among the AMD features evaluated were drusen size, type, and area, increased retinal pigment, retinal pigment epithelial (RPE) depigmentation, pure geographic atrophy, and signs of exudative macular degeneration (subretinal hemorrhage, subretinal fibrous scar, RPE detachment, and/or serous detachment of the sensory retina or laser or photodynamic treatment for neovascular AMD). Soft distinct drusen were defined by size (between 63 and 300 μm in diameter) and appearance (sharp margins and a round nodular appearance with a uniform density [color] from center to periphery). Soft indistinct drusen were the same size as the soft distinct, but have indistinct margins and a softer, less solid appearance. Increased retinal pigment appears as a deposition of granules or clumps of grey or black pigment in or beneath the retina. Depigmentation of the RPE is characterized by faint grayish-yellow or pinkish-yellow areas of varying density and configuration without sharply defined borders. Early AMD was defined by either the presence of any soft drusen (distinct or indistinct) and pigmentary abnormalities (either increased retinal pigment or RPE depigmentation) or the presence of a large soft drusen 125 μm in diameter with a large drusen area (≥500 μm in diameter circle) or large (≥125 μm in diameter) soft instinct drusen in the absence of signs of late AMD. Late AMD was defined by the presence of any of the following: geographic atrophy or pigment epithelial detachment, subretinal hemorrhage or visible subretinal new vessels, subretinal fibrous scar or laser treatment scar for AMD.

When 2 eyes of a participant were discrepant for the severity of a lesion, the grade assigned for the participant was that of the more severely involved eye. For example, in assigning the prevalence of soft drusen, if soft drusen were present in 1 eye but not in the other eye, the participant was considered to have soft drusen. When drusen or signs of AMD could not be graded in an eye, the participant was assigned a score equivalent to that in the other eye.

Assessment of Risk Factors

Participants underwent an interview and assessment of cardiovascular risk factors during the course of the study.[40,46] Variables for this analysis were based on data collected at the first examination when most of the systemic hematological tests were conducted. Resting blood pressure was measured 3 times with participants in the seated position (Dinamap model Pro 100 automated oscillometric sphygmomanometer; Critikon, Tampa, FL). The average of the last 2 measurements was used in analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medications. Height and weight were measured with participants wearing light clothing and no shoes; body mass index (BMI) was calculated as kg/m^2. Presence of diabetes was based on self-reported physician diagnosis, use of insulin and/or oral hypoglycemic agent, or a fasting blood glucose value ≥126 mg/dL at the MESA baseline examination.

A detailed questionnaire was used to obtain information about past medical history, such as hypertension, diabetes, asthma, arthritis, cancer, liver disease, emphysema, gum disease, hepatitis, cigarette smoking, alcohol consumption (defined as current or past/never), and medication use including antihypertensive and antidiabetic medications, lipid-lowering agents, diuretics, oral contraceptives, hormone replacement therapy, oral steroids, aspirin and nonsteroidal antiinflammatory agents, cyclooxygenase (COX) 2 inhibitors.

Assessment of Blood Factors

Fasting (>8 hours) venous blood samples were drawn from participants, and aliquots were prepared for central analysis and for storage at the University of Vermont and the University of Minnesota.[40] Standardized protocols were used to measure markers of systemic inflammation, hemostasis and fibrinolysis, endothelial cell function, and antibodies to various pathogens.[46]

In the total cohort, the following were analyzed in this study: serum high sensitivity hsCRP, plasma fibrinogen, IL-6, plasmin–antiplasmin complex, D-dimer, factor VIII, total homocysteine, and IgG antibody to *Chlamydia pneumoniae*. In a smaller, randomly selected subsample of 1000 MESA participants with CT scans, the following factors were also assayed: plasma plasminogen activator inhibitor-1 (PAI-1), plasma von Willebrand factor, serum soluble E-selectin, serum IL-2 soluble receptor α chain, serum matrix metalloproteinase-3 and -9, serum tumor necrosis factor-α, plasma-soluble tissue factor, plasma thrombin activatable fibrinolysis inhibitor, plasma tissue factor pathway inhibitor, plasma soluble thrombomodulin, serum antihuman heat shock protein 60, and antibodies for *Cytomegalovirus*, *Helicobacter pylori*, *Herpes simplex*, and hepatitis A virus. Plasma-soluble intercellular adhesion molecule-1 was run on the first 2400 participants examined and on the 1000 randomly selected participants not included in the first 2400 participants. Of persons with retinal images available (n = 6176), 2309 had data available for plasma-soluble intercellular adhesion molecule-1 and gradable photographs for AMD.

A subcohort of 2880 MESA subjects were selected for genetic studies from subjects who (1) gave informed consent for DNA extraction and genetic substudy and (2) had samples in the study DNA laboratory with sufficient DNA. Priority was given to subjects who participated in the MESA third examination, supplemented by random selection from remaining cohort to

fulfill balanced ethnic group representation (720 black, 720 Hispanic, 720 Chinese, and 720 Caucasian) and equality by gender. Of these, there were 2456 participants with AMD gradings with *CFH* gene polymorphism Y402H (1277T→C) measured.

Statistical Analysis

Logistic regression was used to estimate the odds ratio (OR) and its 95% confidence intervals (CI) for early and late AMD and specific AMD lesions associated with different risk factors. Each risk factor was entered into a separate model while adjusting for age (in 4 groups: 44–54, 55–64, 65–74, 75–84 years), gender, racial/ethnic group, and study site. Odds ratios for continuous variables are presented per standard deviation (SD) increase. Several of the variables (e.g., hsCRP, IL-6) were transformed to natural log to minimize skewness in the data. Tests of trend were done for categorical variables with several levels by considering the variable as a continuous ordered factor in logistic regression models. Interactions between race/ethnicity and inflammatory markers were tested by including an interaction term in the logistic regression models. Other interactions tested were between *CFH* and factors measured in the whole population. Models where a significant relation was found were additionally adjusted for education level, smoking status, alcohol use, and BMI to examine if the risk factor was independent of these other potentially confounding variables. Version 9.1 of SAS (Cary, NC) was used for all analyses.

Results

Selected characteristics and risk factors for the full cohort and each of the 4 racial/ethnic groups among participants who had gradable images for AMD (n = 5887) are shown in Table 1. There were 2321 (39.4%) whites, 699 (11.9%) Chinese, 1589 (27%) blacks, and 1278 (21.7%) Hispanics in the cohort. There were significant differences in the frequency and distribution of most risk factors among the racial/ethnic groups. For example, Hispanics and Chinese were more likely to have less than a high school education and blacks were more likely to have hypertension and to be current cigarette smokers. Blacks and Hispanics had higher levels of serum (hs)CRP, plasma fibrinogen, and plasma IL-6 than whites and Chinese; whites had higher levels of serum IL-2 than blacks and Hispanics. Other differences among biomarkers and racial/ethnic groups are found in Table 1. For the total cohort, early AMD was present in 4%, late AMD in 0.5%, large drusen in 9%, soft drusen in 15%, increased pigment in 2%, RPE depigmentation in 0.9%, exudative AMD in 0.3%, and geographic atrophy in 0.3%.

Distributions for the *CFH* Y402H (1277T→C) genotype varied among the different racial/ethnic groups, with whites and blacks having the highest frequency for homozygosity (CC genotype) and heterozygosity (CT genotype) of the variant and Hispanics and Chinese the lowest (Table 1).

Associations

Table 2 shows the association of biomarkers of inflammation with early and late AMD. There was not 1 statistically significant association of factors studied with early or late AMD (Table 2). There were no relationships of endothelial dysfunction and hemostasis and antibodies to *Helicobacter pylori* and *Herpes simplex* to early or late AMD (data not shown).

Relationships of inflammatory factors to specific AMD lesions were examined. Increasing levels of natural log serum hsCRP (OR, 2.34; 95% CI, 1.33–4.13; $P = 0.003$) and plasma IL-6 (OR, 2.06; 95% CI, 1.21–3.49; $P = 0.007$) were associated with geographic atrophy, history of arthritis with soft distinct drusen (OR, 1.24; 95% CI, 1.06–1.46; $P = 0.007$), history of gum disease with increased retinal pigment (OR, 1.68; 95% CI, 1.14–2.47; $P = 0.009$), history of use of oral steroids with large (OR, 2.13; 95% CI, 1.14–3.97; $P = 0.02$) and soft drusen (OR,

1.76; 95% CI, 1.00–3.10; $P = 0.05$), and history of use of COX 2 inhibitors with large drusen (OR, 1.50; 95% CI, 1.10–2.04; $P = 0.01$), soft distinct drusen (OR, 1.43; 95% CI, 1.10–1.87; $P = 0.008$), soft indistinct drusen (OR, 1.84; 95% CI, 1.09–3.10; $P = 0.02$), and large drusen area (OR, 1.66; 95% CI, 1.02–2.71; $P = 0.04$). As hypothesized, all significant associations were in a positive direction. None of the risk factors were associated with RPE depigmentation or neovascular AMD (data not shown). While controlling for age, gender, and other confounders, smoking status, BMI, education level, and history of alcohol consumption in multivariate models, the risk factors found to be associated with specific AMD lesions remained statistically significantly associated (data not shown) except for COX 2 inhibitors and large drusen area association, which were no longer statistically significant (OR, 1.58; 95% CI, 0.95–2.61; $P = 0.08$).

There were no statistically significant interaction effects for systemic inflammation factors in Table 1 and race/ethnicity with early AMD except for one with plasma fibrinogen (P for interaction = 0.04). Greater mean plasma fibrinogen level was directly associated with early AMD in blacks (OR per SD, 1.39; 95% CI, 1.02–1.89) and not associated in other racial/ethnic groups.

In a subset of the population with data available for the *CFH* Y402H (1277T→C) polymorphism and gradable AMD, whites, blacks, and Hispanics with *CFH* Y402H CC variant genotype had the highest frequency of early AMD compared with those with wild TT genotype (Table 3). The *CFH* Y402H SNP met Hardy–Weinberg equilibrium in each racial/ethnic group (all $P>0.01$; data not shown). One statistically significant interaction was found between this polymorphism and plasma fibrinogen in models for early AMD. Persons homozygous for the variant (CC) *CFH* Y402H SNP with higher levels of fibrinogen had increased odds of early AMD (OR per SD, 2.12; 95% CI, 1.16–3.89) whereas those heterozygous (CT; OR, 0.87; 95% CI, 0.61–1.26) and those with 2 wild copies (TT; OR, 0.81; 95% CI, 0.56–1.17) had nonsignificant effects for fibrinogen (P-interaction = 0.005). No other interactions with *CFH* polymorphism status were detected for other AMD lesions or other systemic inflammatory biomarkers (data not shown).

Finally, we examined the difference in the prevalence of early AMD among racial/ethnic groups (Table 4) in models that adjusted for potential explanatory risk factors that were measured in the whole cohort. After controlling for age, gender, and center, whites had significantly higher frequency of early AMD than other racial/ethnic groups. For example, compared with whites, blacks had a 61% lower odds of early AMD (OR, 0.39 for blacks vs. whites; $P = 0.005$). Adjustment for serum hsCRP, plasma fibrinogen, IL-6, plasmin–antiplasmin complex, total homocysteine, and IgG antibody to *C. pneumoniae* did not substantially alter these racial/ethnic differences between blacks and whites (OR 0.37 for blacks vs. whites; $P = 0.005$). While controlling for age, gender, and study site, adding *CFH* Y402H (1277T→C) genotype status also did not result in a change in the relationship of early AMD in whites and blacks (OR 0.39 for blacks vs. whites; $P = 0.005$).

Discussion

This study provided a unique opportunity to examine the relationship of a wide range of biomarkers of inflammation and related processes, systemic inflammatory diseases, and antiinflammatory medication use and *CFH* Y402H genotype status to AMD in a large, multiethnic cohort free from clinical CVD. After controlling for age, gender, race/ethnicity, and study site, we found few consistent associations between the factors studied and prevalent early or late AMD. These factors also did not explain differences in the prevalence of early AMD in whites and blacks. As in other studies, *CFH* Y402H genotype status was related to AMD end points.

We did find some associations between different inflammatory biomarkers and specific AMD signs. For example, both serum hsCRP and plasma IL-6 were associated with the prevalence of geographic atrophy although not with neovascular AMD or early AMD signs in the MESA cohort. Relationships between serum hsCRP and incident AMD or progression of AMD have been reported in case-control and cohort studies, but none have shown a specific association with geographic atrophy.[22,23,25] The findings of no association of serum hsCRP and serum tumor necrosis factor-*α*, plasma IL-6, and serum IL-2 with early AMD in MESA are consistent with data from the large, population-based Beaver Dam Eye and Blue Mountains Eye studies and the Cardiovascular Health Study, but not with data from the Rotterdam Study.[17,24,26,47] The reason for the differences among studies is not known. In some cases, such as the Age-Related Eye Disease Study, it may reflect a higher proportion of more advanced disease than in the population-based studies. In others, it may reflect a higher proportion of genetically susceptible (e.g., higher proportion of persons with *CFH* gene variants) and environmental exposures, such as smoking, than in other populations. It is possible that inflammation may play a larger role in the pathogenesis of progression to late rather than initiating the earlier stages of AMD. It is also possible that inflammation occurring earlier in life initiates processes involved in the pathogenesis of early AMD and this relationship is not detected in the cross-sectional examination of persons studied later in life.

It has been hypothesized that infectious agent activation of an aberrantly regulated alternative complement pathway might contribute to the development of AMD.[48] Earlier data from a sample of a cohort study showed an association of *C. pneumoniae* antibody titers with the 7-year progression of AMD.[49] Data from 2 small case control studies also showed an association with *C. pneumoniae*, but not other pathogens with AMD.[50,51] It was speculated that macrophages infected with *C. pneumoniae* may enter the circulatory system and spread to the choroid resulting in production of inflammatory cytokines such as tumor necrosis factor-*α*. It is possible that pathogen exposure is involved in advanced stages of AMD involving neovascularization of the choroid.[50] However, in MESA, there were no relationships of 5 biomarkers of previous pathogen exposure, including *C. pneumoniae*, and prevalent early or late AMD and there was no apparent interaction with *CFH* status. This is consistent with findings from the Beaver Dam and Blue Mountains Eye studies.[24,52]

We had previously reported racial/ethnic differences in the frequency of early AMD with decreasing overall frequencies found in whites (5.4%), Chinese (4.6%), Hispanics (4.2%), and blacks (2.4%) in MESA.[42] The reasons for these racial/ethnic differences, especially between whites and blacks, were not explained by known risk factors such as cigarette smoking, history of alcohol drinking, BMI, hypertension, diabetes status, and markers of subclinical CVD.[53] In the current analysis, we showed that a history of inflammatory diseases or use of antiinflammatory agents, or biomarkers of inflammation and related processes also did not explain racial/ethnic differences in prevalence of early AMD among the different racial/ethnic groups. Whites, blacks, and Hispanics who were all homozygous for the *CFH* Y402H CC variant genotype had the highest frequencies of early AMD compared with those with the *CFH* Y402H TT wild genotype. The *CFH* Y402H CC variant genotype distributions varied among the racial/ethnic groups and did explain some of the difference in early AMD prevalence for Chinese (after adjusting for *CFH* genotypes, *P* values changed from 0.02 to 0.19) and for Hispanics (after adjusting for *CFH* genotypes, *P* values changed from 0.05 to 0.12) but did not explain the difference in AMD prevalence between whites and blacks. It is possible that differences in distributions of other protective (*CFH*-related 1/3 deletions, C2/BF haplotype) and deleterious genotypes (e.g., LOC387715) not examined here and their interactions with environmental/host factors among the different racial/ethnic groups explain these differences in whites and blacks.[32–34,36,54]

Although our study has many strengths (objective grading of AMD and a large multiethnic cohort), caution must be exercised when interpreting the findings for several reasons. First, we examined many variables, some of which identified in previous studies as associated with AMD. This may have led to chance findings or type I error, particularly for associations that have not previously been reported, as is the case with COX 2 inhibitors. Second, the power to detect some associations may have been limited by the infrequency of AMD and its specific lesions and also some of the risk factors under study (e.g., emphysema, 1.3% prevalence). Many of the factors were also only measured in a sample of the population, further reducing the study power. Third, the period cross-sectional nature of the study (retinal examination 2 years after risk factors were measured) may have also limited our ability to detect associations with factors that may manifest subsequently as pathologic changes over time. Fourth, it is possible AMD may be misclassified because of the use of minified 45-degree nonstereoscopic fundus images as compared with 30-degree stereoscopic images. However, we have no reason to believe that this results in systemic biases. Finally, we cannot determine whether there were biases caused by nonparticipation or selective mortality that affected the relationships.

In summary, our study confirms the importance of *CFH* Y402H genotype status and AMD in different racial groups. However, we found few associations between systemic inflammatory disease, use of antiinflammatory agents, biomarkers of inflammatory disease, and related processes with AMD at a given point in time within the whole cohort. Overall, our data are consistent with other population-based studies and suggest that these factors are not strongly related to AMD in the general population. Additional investigations will be required to explain the ethnic differences in prevalence of AMD lesions.

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Table 1

Characteristics of the Multi-Ethnic Study of Atherosclerosis Cohort*

	All Persons		Whites		Chinese		Blacks		Hispanics	
Characteristic	***N***	***Mean ± SD***	***N***	***Mean ± SD***	***N***	***Mean ± SD***	***N***	***Mean ± SD***	***N***	***Mean ± SD***
Age, years	5887	61.5 ± 10.0	2321	62.0 ± 10.1	699	61.5 ± 10.1	1589	61.4 ± 9.7	1278	60.6 ± 10.1
High sensitivity CRP, mg/dL	5846	3.6 ± 5.4	2308	3.3 ± 4.8	697	1.7 ± 3.5	1568	4.6 ± 6.6	1273	4.1 ± 5.1
IL-6, pg/mL	5729	1.5 ± 1.2	2280	1.4 ± 1.2	690	1.2 ± 1.0	1518	1.7 ± 1.2	1241	1.6 ± 1.1
IL-2, pg/mL	886	0.93 ± 0.42	412	1.02 ± 0.44	87	0.69 ± 0.21	184	0.79 ± 0.32	203	0.98 ± 0.45
TNF-α, pg/mL	886	1.27 ± 0.35	412	1.34 ± 0.37	87	1.06 ± 0.28	184	1.22 ± 0.35	203	1.26 ± 0.28
Fibrinogen, mg/dL	5850	344 ± 72	2310	333 ± 69	699	328 ± 59	1569	358 ± 78	1272	356 ± 44
Homocysteine, μmol/L	5872	9.2 ± 3.7	2316	9.3 ± 4.0	698	8.8 ± 2.6	1581	9.6 ± 4.2	1277	8.9 ± 2.9
Gender, male	5887	47.8	2321	48.6	699	49.6	1589	45.6	1278	48.0
Education < high school	5870	16.5	2314	4.3	698	22.1	1580	10.8	1278	42.8
Hypertension	5886	43.0	2320	36.9	699	35.9	1589	57.4	1278	40.0
Current smoker	5856	12.8	2307	10.8	698	6.0	1576	18.0	1275	13.6
Current alcohol drinker	5847	57.0	2303	72.9	695	32.2	1572	50.9	1277	49.3
Chlamydia pneumonia, positive	5872	75.1	2315	69.2	699	84.8	1581	80.0	1277	74.5
Arthritis history	5821	34.7	2294	33.6	681	22.9	1579	41.7	1267	34.3
Gum disease history	5809	27.2	2290	25.5	672	41.4	1576	30.8	1271	18.2
Hepatitis history	5851	3.3	2306	2.7	693	8.1	1581	2.1	1271	3.3
Emphysema history	5880	1.3	2317	1.8	699	2.2	1587	1.0	1277	0.4
Aspirin ≥3 days/wk	5627	19.7	2177	27.4	689	13.9	1530	17.0	1231	12.7
NSAID use	5879	16.7	2320	22.4	699	4.2	1582	15.0	1278	15.5
COX 2 inhibitor use	5879	6.7	2320	7.0	699	4.7	1582	6.9	1278	6.3
Oral steroid use	5879	1.3	2320	1.4	699	0.3	1582	1.5	1278	1.3
CFH Y402H (1277 T→C)	2456		634		630		593		599	
CT genotype		33.1		45.4		9.7		45.0		33.1
CC genotype		8.2		13.3		0.5		12.1		7.2
Early AMD	5847	3.8	2303	4.8	691	3.6	1581	2.2	1272	4.0
Late AMD	5884	0.5	2319	0.6	699	1.0	1588	0.25	1278	0.23

AMD = age-related macular degeneration; *CFH* = complement factor H; COX = cyclooxygenase; CRP = C-reactive protein; IL = interleukin; NSAID = nonsteroidal antiinflammatory drugs; SD = standard deviation; TNF = tumor necrosis factor.

* Sample size for biochemical analytes vary owing to some being measured in whole cohort and some in a random sample of cohort with gradable fundus photographs for any of the AMD outcomes.

Table 2

Relation of Various Characteristics of Multi-Ethnic Study of Atherosclerosis Cohort to Early and Late Age-Related Macular Degeneration (AMD) Controlling for Age, Gender, Race/Ethnicity, and Study Site

	Presence of Early AMD			Presence of Late AMD		
Inflammatory Markers	**OR**	**95% CI**	***P*-Value**	**OR**	**95% CI**	***P*-Value**
High sensitivity CRP/1.20 *ln* units	0.99	0.85–1.15	0.88	1.46	0.94–2.27	0.09
IL-6/0.66 *ln* units	1.01	0.87–1.17	0.90	1.50	0.99–2.28	0.06
IL-2/0.37 *ln* units	1.02	0.71–1.46	0.92	1.06	0.28–4.01	0.93
TNF-α/0.26 *ln* units	1.11	0.77–1.62	0.57	0.54	0.11–2.60	0.44
*Chlamydia pneumonia (*positive vs negative)	1.25	0.89–1.76	0.20	0.51	0.21–1.23	0.13
Fibrinogen/73 mg/dL	1.04	0.90–1.20	0.58	1.33	0.89–1.99	0.17
Homocysteine/0.3 *ln* units	1.10	0.96–1.27	0.18	1.23	0.83–1.82	0.31
Arthritis history (present vs absent)	1.14	0.85–1.53	0.38	0.88	0.39–1.98	0.76
Gum disease history (present vs absent)	1.32	0.98–1.79	0.07	1.49	0.63–3.50	0.36
Hepatitis history (present vs absent)	1.44	0.74–2.82	0.29	CNE		
Emphysema history (present vs absent)	1.09	0.43–2.80	0.85	1.95	0.43–8.91	0.39
Aspirin (≥3 days/wk vs <3 days/wk)	1.10	0.79–1.52	0.58	1.47	0.65–3.37	0.36
NSAID use (present vs absent)	1.18	0.81–1.72	0.39	1.92	0.69–5.37	0.21
COX 2 inhibitor use (present vs absent)	1.49	0.95–2.33	0.08	0.35	0.05–2.59	0.30
Oral steroid use (present vs absent)	2.15	0.90–5.14	0.09	CNE		

CI = confidence interval; CNE = cannot estimate; COX = cyclooxygenase; CRP = C-reactive protein; IL = interleukin; *ln* = natural log; NSAID = nonsteroidal antiinflammatory drugs; OR = odds ratio; TNF = tumor necrosis factor.

Table 3

Prevalence of Early Age-Related Macular Degeneration (AMD) by Complement Factor H (*CFH*) Y402H Polymorphism and Racial/Ethnic Group

	White		Chinese		Black		Hispanic	
***CFH* Y402H Polymorphism**	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**
TT	262	3.8	560	3.9	254	2.8	358	2.0
CT	288	7.3	61	3.3	267	1.5	198	6.6
CC	81	8.6	2	0.0	71	4.3	43	7.0
P-value	0.05		0.74		0.90		0.006	

N = number with the polymorphism; % = percent with early AMD.

Table 4

Prevalence of Early Age-Related Macular Degeneration (AMD) Comparing Whites with Other Racial/Ethnic Groups, While Controlling for Other Factors*

	White	Chinese		Black		Hispanic		Any Difference
Adjusted for	**OR (95% CI)**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	***P***
Age, gender, and center	1.00 (ref)	0.46 (0.24–0.90)	0.02	0.39 (0.20–0.75)	0.005	0.53 (0.28–1.00)	0.05	0.01
Age, gender, center, and inflammatory factors†	1.00 (ref)	0.41 (0.20–0.82)	0.01	0.37 (0.19–0.74)	0.005	0.55 (0.29–1.05)	0.07	0.01
Age, gender, center, and *CFH* Y402 genotype	1.00 (ref)	0.62 (0.31–1.27)	0.19	0.39 (0.21–0.76)	0.005	0.60 (0.32–1.14)	0.12	0.04

CFH = complement factor H; CI = confidence interval; OR = odds ratio; ref = reference group.

*Analysis restricted to 2445 participants with data available for early AMD and *CFH* genotype.

†Factors include high sensitivity C-reactive protein, interleukin-6, fibrinogen, plasmin–antiplasmin complex, homocysteine, and *Chlamydia pneumonia*.