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The Relationship of Atherosclerosis to the 10-Year Cumulative Incidence of Age-Related Macular Degeneration: The Beaver Dam Studies

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Abstract

Objective—To describe the relationships of intima-media layer thickness (IMT), plaque in the carotid artery, angina, myocardial infarction (MI), and stroke to the 10-year cumulative incidence of early and late age-related macular degeneration (AMD) and progression of AMD.

Design—Cohort study.

Participants—1700 persons aged 53–96 years who participated in both the Epidemiology of Hearing Loss Study and the Beaver Dam Eye Study in 1998–2000, with photographs gradable for AMD at a 5- (2003–2005) and/or 10-year (2008–2010) follow-up examination.

Methods—IMT and presence of plaque were assessed using B-mode ultrasonography of the carotid artery. Presence of angina, MI, and stroke were defined based on a self-reported history of physician diagnosis. Presence and severity of AMD were determined by systematic grading of stereoscopic color fundus photographs.

Main Outcome Measures—AMD.

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Results—The 10-year cumulative incidence of early AMD was 15.7% and the 10-year cumulative incidence of late AMD was 4.0%. Adjusting for age, sex, body mass index, smoking status, *Age-Related Maculopathy Susceptibility 2* and *Complement Factor H* genotypes and other factors, mean IMT was associated with the 10-year incidence of early AMD (odds ratio per 0.1 mm IMT 1.11, 95% confidence interval 1.00–1.21, P value=0.03) and late AMD (1.27, 1.10–1.47, P=0.001). Mean IMT was associated with the 10-year incidence of pure geographic atrophy (1.31, 1.05–1.64, P=0.02) but not exudative AMD (1.14, 0.97–1.34, P=0.11). Similar associations were found for maximum IMT. The number of sites with plaque was related to the incidence of late AMD (2.79 for 4–6 sites vs. none, 1.06–7.37, P=0.04) but not to early AMD. A history of angina, MI, or stroke was not related to any incident AMD outcome.

Conclusions—In these population-based data, carotid artery IMT and carotid plaques had a weak relationship to the incidence of late AMD, independent of systemic and genetic risk factors. Angina, MI, and stroke were not related to AMD. It is unclear whether the carotid IMT is a risk indicator of processes affecting Bruch's membrane and the retinal pigment epithelium, or a measure of atherosclerosis affecting susceptibility to AMD.

Atherosclerotic cardiovascular disease (CVD), through a postulated effect on blood flow in the choroidal circulation, has been hypothesized to be a pathogenetic factor for the development of age-related macular degeneration (AMD).¹ Alternatively, it has been hypothesized that atherosclerotic processes such as inflammation and lipid deposition directly affect Bruch's membrane and the retinal pigment epithelium resulting in the development of AMD in genetically susceptible persons.² However, history of myocardial infarction (MI) and stroke and markers of subclinical atherosclerosis such as carotid artery intima-media thickness (IMT) and plaques have not been consistently associated with AMD.^{3–16} Most of the studies that have examined this relationship have been cross-sectional. The purpose of our report is to examine the relationship of IMT, the presence of plaque in the carotid artery, and history of MI and stroke to the 10-year cumulative incidence of early and late AMD in a large population-based cohort.

METHODS

Population

Analyses included data from persons aged 53–96 years participating in both the Epidemiology of Hearing Loss Study (EHLS) and the Beaver Dam Eye Study (BDES). The 1998–2000 examination included 2609 persons who participated in both the BDES and EHLS examinations; this is considered the baseline examination for the current investigation.^{17,18} Follow-up examinations were conducted in 2003–2005 and 2008–2010.¹⁹ Of the 2609 persons, 909 were excluded (50 persons with exudative AMD at the 1998–2000 examination, 293 persons who died or did not participate at any follow-up examination, 118 persons who did not have fundus photographs that were gradable for AMD at the 1998–2000 or any follow-up examination, and 458 persons with no carotid artery ultrasonography data at the 1998–2000 examination). This left 1700 persons who had fundus photographs gradable for AMD at baseline and follow-up and carotid artery ultrasonography scans.

Approval for these studies was obtained from the Institutional Review Board at the University of Wisconsin. Informed consent was obtained from each participant before every examination. The work performed was compliant with the Health Insurance Portability and Accountability Act (HIPAA). The study adhered to the tenets of the Declaration of Helsinki.

Procedures

Similar procedures were used at baseline and follow-up eye examinations.^{20–29} Participants underwent a standardized interview and examination at each visit. Information on

demographic characteristics, smoking, physical activity, medication and vitamin use, and history of being told by a physician that they had angina, MI, or stroke were obtained at all examinations. Blood pressure was measured using the Hypertension Detection and Follow-up Protocol.³⁰ Weight and height were determined. Casual blood specimens were obtained at the time of each examination. An aliquot of serum was used immediately to determine serum total and high-density lipoprotein (HDL) cholesterol levels. Serum total and HDL cholesterol were measured by reflectance spectrophotometry.^{24–27} Blood glycosylated hemoglobin was determined by affinity chromatography.^{24–27} Because blood was not tested for white blood cell count or serum C-reactive protein at the baseline exam, an aliquot of blood from the visit preceding the baseline visit by 5 years was used to determine the white blood cell count by the Coulter counter method.^{24–27} Remaining serum was stored without preservative at -80°C in cryogenic vials with O-rings for up to 17 years until the vials were shipped on dry ice to the University of Minnesota laboratory for analysis of C-reactive protein. Serum C-reactive protein from the visit preceding the baseline visit by 10 years was measured in EDTA plasma by a latex particle-enhanced immunoturbidimetric assay kit (Kamiya Biomedical Company, Seattle, Washington, USA) on the Hitachi 911 Automatic Analyzer (Roche Diagnostics, Indianapolis, Indiana, USA).^{24–27}

Genetic Measurements

DNA was extracted from buffy coat specimens collected at the baseline and follow-up examinations. The 2 most common AMD-associated single nucleotide polymorphisms, A69S in *ARMS2* and Y402H in *CFH*, were used in this study. The A69S variant was genotyped in 5188 individuals using two different platforms, Taqman (Applied Biosystems, Foster City, California, USA) and Illumina (San Diego, California, USA). Assays were performed at two separate times in 2248 and 2940 samples, respectively. Five hundred and eighty-eight samples were genotyped with both platforms, with a genotype concordance rate of 99.7%. The genotype calls from each assay were combined to create a single dataset for analysis. The Y402H variant was directly genotyped using a Taqman assay in 3015 samples in the BDES, which is described elsewhere.^{31,32} To increase sample size for the Y402H variant, we used data imputation techniques (MACH program version 1.0) on 2940 samples genotyped for 70 markers in the *CFH* region using a custom Illumina array. Using the surrounding linkage disequilibrium structure at *CFH*, we inferred genotypes at Y402H in both typed and untyped samples, keeping only genotypes that could be imputed with a high probability ($r^2 \geq 0.9$). A concordance rate of 99.8% was observed among 1476 samples for which both genotyped and imputed data were available.³³

Fundus Photography and Grading

Stereoscopic 30° color fundus photographs centered on the macula (Diabetic Retinopathy Study standard field 2) were taken of each eye.^{20,28,29} Two gradings were performed for the pair of photographs of each macula at each examination using the Wisconsin Age-Related Maculopathy Grading System.^{20–22,28,29} Graders were masked as to any information related to the participant and to the fellow eye. A preliminary and detail grading was performed for each eye. Graders were randomly selected from two groups, the first consisting of 2 senior graders who performed a preliminary grading and the second consisting of 3 other experienced graders who performed either detailed or edit gradings on a specific eye. A series of edits and reviews was performed next. The preliminary and detailed gradings were compared for the presence and severity of specific lesions at each examination (e.g., maximum drusen size, type, area, and pigmentary abnormalities). Standardized edit rules were used to adjudicate disagreements.^{20–23} A longitudinal side-by-side comparison of photographs for eyes that showed change for AMD lesions was performed. All eyes newly classified with early and late AMD were also confirmed at this time. Additional information on gradability at previous examinations can be found elsewhere.^{22–25}

Carotid Artery Ultrasonography

High resolution B-mode carotid artery ultrasound images (Biosound AU4, Biosound Esaote, Indianapolis, Indiana, USA) were obtained using a modification of the Atherosclerosis Risk In Communities (ARIC) study ultrasound scanning protocol.³⁴ The areas of focus were the 1 cm of the distal common carotid artery (CCA) closest to the bifurcation, the bifurcation, and 1 cm of the proximal internal carotid artery (ICA) closest to the flow divider. IMT and plaque measurements were made by certified graders using a custom program interfaced with Image Pro Plus version 4.1 (Media Cybernetics, Silver Spring, Maryland, USA), and a modified version of the ARIC protocol.^{34,35} Mean IMT at the person level was defined as the overall mean of the near and far walls of the CCA, the bifurcation, and the ICA on both the left and right sides, a total of 12 sites for each participant. EHLS IMT measures were highly reproducible, with a mean inter-grader difference of 0.03 mm. Plaque assessment was based on a protocol used in the ARIC study.^{36,37} Plaque was determined by evaluating change in wall shape, change in wall texture, and wall thickness (≥ 1.5 mm). Plaque was considered to be present at the person level if one of these was present with acoustic shadowing, or if two were observed in an area without acoustic shadowing. The number of sites (left and right CCA, ICA, and bifurcation) with plaque was categorized: 0, 1–3 and 4–6 sites. For side-specific analyses, mean IMT on the right side was defined as the mean of the near and far walls of the CCA, the bifurcation, and the ICA on the right side (6 sites). Presence of plaque on the right side was evaluated in the same way as at the person level but was categorized as 0 or 1–3 sites (the maximum number of sites possible on a single side). Definitions of mean IMT and presence of a plaque were similar for the left side. Inter-grader reliability for number of sites with plaque was excellent; kappa scores averaged 0.76 and percent agreement averaged 90%.

Definitions

The severity of AMD was determined using the modified 5-step BDES AMD Severity Scale.³⁸ The definitions of each step are as follows.

10 (No AMD): Hard drusen or small soft drusen (<125 μm in diameter only) regardless of area of involvement and no pigmentary abnormalities (defined as increased retinal pigment or retinal pigment epithelial [RPE] depigmentation present); or no definite drusen with any pigmentary abnormality.

20 (Minimally severe early AMD): Hard drusen or small soft drusen (<125 μm in diameter), regardless of area of involvement, with any pigmentary abnormality; or soft drusen (≥ 125 μm in diameter) with drusen area $<331,820$ μm^2 (equivalent to O_2 , a circle with a diameter of 650 μm) and no pigmentary abnormalities.

30 (Moderately severe early AMD): Soft drusen (≥ 125 μm in diameter) with drusen area $<331,820$ μm^2 (equivalent to O_2) and with any pigmentary abnormality; or soft drusen (≥ 125 μm in diameter) with drusen area $\geq 331,820$ μm^2 (equivalent to O_2) with or without increased retinal pigment but no RPE depigmentation.

40 (Severe early AMD): Soft drusen (≥ 125 μm in diameter) with drusen area $\geq 331,820$ μm^2 (equivalent to O_2) and RPE depigmentation present, with or without increased retinal pigment.

50 (Late AMD): Pure geographic atrophy (GA) in the absence of exudative macular degeneration; or exudative macular degeneration with or without GA present.

Presence of AMD was evaluated both at the person level and at the eye level. In the person-level analyses, data from both eyes were combined. When data for one eye were missing, it was assumed to have the same AMD severity as the fellow eye. Persons at risk for developing early AMD were those without any lesion defining early or late AMD at the

baseline examination. Incidence of early AMD was defined by developing step 20, 30, or 40 in at least 1 eye when both eyes were step 10 at the previous examination. Similarly, persons at risk for developing late AMD were those without late AMD at baseline who developed late AMD in one or both eyes at follow-up. To be at risk for incidence of pure GA, an individual must have been free of any late AMD lesion at baseline; however, individuals with pure GA were considered at risk for exudative AMD as long as no exudative lesions were present at baseline. The progression of AMD was defined as transitioning by one or more steps to a more severe AMD step in one or both eyes in persons with step 20–40 at the baseline examination.

In the eye-level analyses, data were analyzed for each eye separately. An eye at risk for developing early AMD was one without any lesion defining early or late AMD at the baseline examination regardless of the presence or absence of AMD in the fellow eye. Incidence of early AMD was defined by developing step 20, 30, or 40 in at an eye when that eye was step 10 at the baseline examination. Incidence of late AMD, its subtypes, and the progression of AMD were defined similarly. Quality assurance procedures were employed throughout the study.

Participants were considered to have a history of CVD if they self-reported physician-diagnosed angina, MI, or stroke. Mean arterial blood pressure was defined as $(\text{systolic blood pressure} + [2 \times \text{diastolic blood pressure}]) \div 3$. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, and/or physician diagnosis of hypertension and current use of hypertension medication. Smokers were defined as persons having smoked 100 or more cigarettes in their lifetime who had not stopped smoking by the time of examination. Nonsmokers were defined as individuals who had either never smoked or who smoked in the past but had stopped by the time of examination. Diabetes presence was defined by a self-report of physician diagnosis of same with or without use of hypoglycemic medications or elevated glycosylated hemoglobin level ($\geq 6.5\%$). Body mass index (BMI) was calculated by dividing a participant's weight in kilograms by their height in meters squared. Participants were considered sedentary if they reported that they did not engage in a regular activity long enough to work up a sweat at least once per week.

Statistical Methods

All analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina, USA). Persons included in analyses were compared to persons not included using a general linear model adjusting for age. Cumulative incidence of AMD was estimated by the product-limit method,³⁹ accounting for the competing risk of death.⁴⁰ Discrete logistic hazard regression⁴¹ was used to estimate odds ratios (ORs) for associations between mean and maximum IMT and presence of plaque with AMD outcomes. We first modeled the relationship of each risk factor to the incidence of each AMD outcome at the person level adjusting only for age and sex; in a second model, we further adjusted for BMI, smoking status, history of current use of multivitamins, physical activity, serum HDL cholesterol, history of current statin use, hypertension, diabetes, C-reactive protein, white blood cell count, and *ARMS2* and *CFH* genotypes. We then repeated these analyses in a third model examining carotid IMT and plaque on one side of the body to the AMD outcome on the same side (e.g., mean IMT thickness on a person's right side to incidence of AMD in the right eye), accounting for correlation between the sides using a generalized estimating equation sandwich variance estimator.

RESULTS

Persons included in the analyses were more likely to be younger (mean age 66.8 vs. 71.8 years) than those excluded (Table 1). While adjusting for age, persons excluded were more

likely to lead a sedentary lifestyle, more likely to have a history of stroke or CVD, and have higher serum C-reactive protein levels and white blood cell counts. There were no statistically significant differences between persons included and persons excluded by sex, mean arterial blood pressure, body mass index, history of smoking, history of taking multivitamins, and distributions of *Complement Factor H* (*CFH*, rs1061170) and *Age-Related Maculopathy Susceptibility 2* (*ARMS2*, rs10490924) single nucleotide polymorphisms.

In this substudy, the mean carotid IMT and maximum IMT were 0.87 mm (standard deviation=0.22) and 1.5 mm (standard deviation=0.70), respectively at the 1998–2000 examination. Carotid artery plaques were present in 66.8% of the cohort, of whom 77% had 1–3 sites affected and 23% had 4–6 sites affected. Mean IMT thickness increased with age from 0.80 mm in persons aged 53–64 years to 1.06 mm in persons aged 85 years or older, and while adjusting for age was thicker in men than in women (Figure 1A). Prevalence of plaques also increased with age from 52.8% in persons aged 53–64 years to 91.1% in persons aged 85 years or older, and while adjusting for age was more frequent in men than in women (Figure 1B).

The 10-year cumulative incidence of early AMD was 15.7% and the 10-year cumulative incidence of late AMD was 4.0%. In 39.3% of persons with AMD step 20–40, AMD severity progressed by 1 or more steps. The 10-year cumulative incidence of early AMD, late AMD, and progression of AMD varied with age from 10.4%, 0.8%, and 28.6%, respectively in persons aged 53–64 years to 26.0%, 12.2%, and 24.0%, respectively in persons aged 85 years or older (Figure 2). After adjusting for age, there was no difference in the incidence of early, late, and progression of AMD between men and women.

After adjusting for age and sex, mean IMT was associated with higher incidence of early and late AMD (Table 2, Model 1); maximum IMT was associated with incidence of early, late, GA, and exudative AMD. Further adjustment for BMI, smoking status, history of multivitamin use, physical activity, high-density lipoprotein cholesterol, history of statin use, hypertension, diabetes, C-reactive protein, white blood cell count, *ARMS2* and *CFH* did not change these relationships, though the effect sizes for mean IMT and incidence of late AMD and GA were slightly larger (Table 2, Model 2). There were no statistically significant associations of any factor with progression of AMD in Models 1, 2 or 3 (data not shown). Adjusting for age, sex, and other factors, mean IMT was associated with the incidence of large drusen and soft indistinct drusen but not the incidence of pigmentary abnormalities (data not shown).

The presence of 4–6 sites with carotid plaque was associated with the incidence of late AMD and exudative AMD, adjusting for age and sex, but the latter association became non-significant when adjusting for other factors (Table 2). History of angina, MI, and history of CVD were not related to the incidence of any AMD outcome (Table 2). The analyses of history of stroke were limited to incidence of early AMD (Table 2, Models 1 and 2) and progression of AMD (data not shown) and history of stroke were not statistically significantly associated with either. There were no interactions of IMT or carotid plaque with age, sex, smoking status, *CFH* or *ARMS2* with any incident or progressed AMD outcome. Sex specific associations of IMT and presence of plaque to incident and progressed AMD outcomes were similar to outcomes reported for the whole cohort (data not shown).

In analyses by right/left side, maximum IMT was associated with the 10-year cumulative incidence of late AMD, and mean IMT was associated with the risk of pure GA; no other associations were statistically significant (Table 2, Model 3).

DISCUSSION

In the Beaver Dam Eye Study and Epidemiology of Hearing Loss cohort, carotid IMT was associated with the 10-year cumulative incidence of early AMD and late AMD in the worse eye, and having a greater number of carotid plaques was associated with late but not early AMD in the worse eye. Neither a history of angina nor MI nor CVD was associated with incidence of any of the late AMD outcomes.

Data from earlier studies have been inconsistent regarding the relationship of history of CVD and AMD.^{3–6} Hyman and colleagues⁴² reported that persons with AMD had a higher risk of stroke and CVD (OR 1.7; 95% confidence interval [CI] 1.1–2.7) than persons without AMD. Data from the National Health and Nutrition Examination Survey also show that persons with a history of atherosclerotic vascular disease had a higher prevalence of AMD (OR 4.6; 95% CI 1.4–15.3) than persons without.⁴³ In a study involving a Colorado cohort, the presence of angina was associated with the presence of soft indistinct drusen (OR 2.7; 95% CI 1.1–6.7).¹² In the BDES, after adjusting for age and sex, higher pulse pressure, a presumed indicator of atherosclerotic vascular disease, was associated with a 30% increased 5-year incidence (95% CI 1.0–1.7 per 10 mmHg of pulse pressure) and 25% increased progression (95% CI 1.01–1.53 per 10 mmHg of pulse pressure) of exudative AMD in persons aged 65 years or older.¹⁵ In addition, persons with a history of stroke at baseline had an increased incidence of exudative AMD (OR 2.6, 95% CI 0.7–9.7), which did not reach statistical significance. In the Beaver Dam Offspring Study, carotid IMT was not associated with the prevalence of early AMD.⁴⁴

Our data in the present study are consistent with the findings from the Multi-Ethnic Study of Atherosclerosis, a study performed in a cohort free of clinical CVD at baseline. In that study, two signs of subclinical atherosclerosis, an increased Agatston calcium score of the coronary artery (OR per increasing category 1.2, 95% CI 1.0–1.5, $P=0.04$), and greater mean carotid artery IMT (OR per 0.83 μm [=1 standard deviation] 1.2, 95% CI 1.0–1.5, $P=0.02$) were cross-sectionally associated with early AMD in whites.¹³ In a small case-control study, while adjusting for serum C-reactive protein levels, lipid levels, and other risk factors, IMT was associated with an OR of 3.9 in persons with both cataract and AMD compared to persons with neither.¹⁴

Our study findings are also consistent with those from the Rotterdam Study.⁸ In that cross-sectional study, persons younger than age 85 years who had plaques at the carotid bifurcation were 4.7 times as likely to have late AMD (95% CI 1.8–12.2) as persons without these plaques.⁸ They did not find a relationship between increased IMT of the common carotid artery in persons with early or late AMD versus those without. The ARIC study showed an association of carotid plaque with pigmentary abnormalities but no association with carotid artery stiffness or IMT with early AMD, soft drusen, or pigmentary abnormalities.^{9,10}

There are few prospective studies that have examined the relation of carotid artery IMT or plaque with the incidence and progression of AMD. Our findings are inconsistent with data from one such study, the Cardiovascular Health and Age-Related Maculopathy study,⁴⁵ which found that while adjusting for age, smoking, and other CVD risk factors, there was no significant relationship of carotid artery IMT with prevalent AMD, late AMD, or progression of AMD. While this may be due to selective survival, the authors speculated that atherosclerosis and reduced arterial compliance might protect an individual from developing AMD.

The association of carotid artery IMT and plaque may possibly reflect reduced blood flow in choroidal blood vessels that may have an effect on outer retinal/choroidal function resulting

in higher risk of developing AMD. However, earlier cross-sectional studies have not consistently shown decreased blood volume and blood flow in early AMD.^{46–48} Alternatively, greater carotid artery IMT and carotid plaque may be risk indicators of local lipid and inflammatory processes directly affecting the Bruch's membrane and retinal pigment epithelium that are not reflected by systemic measures (e.g., serum lipid levels, white blood cell count, serum C-reactive protein levels). Curcio and colleagues² have hypothesized that deleterious processes (e.g., inflammation, macrophage recruitment, neovascularization) that occur in atherosclerosis may also occur in eyes at risk for AMD. It is also not clear why markers of carotid artery plaque, but not other measures of severe stages of atherosclerotic disease such as angina, stroke, or MI are related to incident late AMD outcomes. It is possible that the acute ischemic effects of atherosclerosis manifest as an MI or stroke may not be a direct cause of AMD. It is also possible that the lack of a statistically significant relation among these severe stages of atherosclerotic vascular disease and the incidence and progression of AMD may be due, in part, to selective survival or limited power to detect an association with these conditions.

Among the strengths of our study are its population-based design, the standardized fundus grading system, and its long-term follow-up. There are some limitations that may have affected the results. First, the main potential source of bias in this cohort study is selection bias. Of the original 4926 persons identified at the BDES baseline examination in 1988–1990, by 1998–2000 when the carotid IMT was first measured there were 2609 persons, 1700 of whom had both fundus photographs gradable for AMD and IMT measures and who participated in a 5- or 10-year follow-up. The characteristics of the people included and excluded from the analyses are presented in Table 1. Persons excluded were older and more likely to have a history of CVD. In order for selection bias to explain these findings, there would have to have been differential follow-up that is related to exposure and outcome. For example, the observed findings could occur if people with atherosclerosis and/or AMD had a higher rate of follow-up or if people without atherosclerosis or AMD had a lower follow-up rate. In our study, we have found that among individuals with no AMD at baseline, those with a history of CVD were more likely to be lost to follow-up due to death than individuals without a history of CVD ($P=0.01$, data not shown). However, we have no evidence that people with a history of CVD who developed AMD were more likely to die or participate compared to people with CVD who did not develop AMD, suggesting that selection bias is less likely to explain our findings.⁴⁹ Second, there is limited power to determine relationships of some risk factors (e.g., stroke) and some outcomes (e.g., incident late AMD, exudative AMD, GA). Third, the population is almost entirely white, limiting the generalizability of our findings to other racial/ethnic groups. Last, although we adjusted our models for several common risk factors for AMD and subclinical atherosclerosis, the relationships we observed could be the result of uncontrolled confounding.

In conclusion, we show a weak relation of greater carotid IMT and carotid plaques but not angina, MI, or stroke to the incidence of AMD outcomes. There is a need for further exploration of underlying biological processes explaining the relationship of carotid IMT and carotid plaques and the incidence of AMD.

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Fig 1A

Fig 1B

Figure 1.

A. Mean carotid artery intima-media thickness (IMT) and B. frequency of presence of any carotid artery plaques by age group and sex. In both, $P < 0.01$ for increase in age group, and while adjusting for age $P < 0.01$ for men vs. women.

Figure 2. 10-year cumulative incidence of early age-related macular degeneration (AMD), late AMD, and progression of AMD by age group. $P < 0.01$ for increase in age group for all outcomes.

Table 1

Characteristics of Participants of the Epidemiology of Hearing Loss Study and Beaver Dam Eye Study Included and Excluded from Analyses.

Risk Factor	Included N=1700 Mean (SD) or %	Excluded N=909 Mean (SD) or %	Age-adjusted P value
Age (years)	66.9 (8.7)	71.9 (10.7)	<0.001
Sex (male)	42.7	40.5	0.94
Mean arterial blood pressure, mmHg	93.1 (11.5)	93.1 (12.5)	0.26
Hypertension present	55.8	64.6	0.08
Current smoker	10.9	7.9	0.79
Serum total cholesterol, mg/dL	213.8 (38.8)	210.7 (42.7)	0.21
Serum HDL cholesterol, mg/dL	50.9 (17.0)	49.5 (15.9)	0.09
History of statin use	20.1	17.3	0.20
History of MI present	8.1	10.7	0.66
History of stroke present	2.7	8.2	<0.001
History of CVD present	15.0	22.8	0.04
History of angina present	9.7	11.4	0.51
History of multivitamin use	68.2	66.2	0.19
Diabetes present	14.3	16.7	0.56
Body mass index, kg/m ²	30.0 (5.9)	29.7 (5.9)	0.41
Sedentary lifestyle	71.4	78.3	0.05
Serum C-reactive protein, mg/L	3.2 (5.5)	3.9 (7.9)	0.04
White blood cell count, 1000/ μ L	7.2 (1.9)	7.4 (2.1)	0.004
<i>CFH</i> genotype			0.52
C/T	47.24	45.5	
C/C	13.38	13.5	
<i>ARMS2</i> genotype			0.39
G/T	36.78	35.0	
T/T	4.44	5.8	

ARMS2, age-related maculopathy susceptibility 2; *CFH*, complement factor H; CVD, cardiovascular disease; HDL, high density lipoprotein; MI, myocardial infarction; SD, standard deviation.

Table 2
Risk Factors Associated With the Incidence and Progression of Age-Related Macular Degeneration.

AMD Outcome	Model 1*			Model 2*			Model 3*		
	N at risk [†] (N events)	OR (95% CI)	P value	N at risk [†] (N events)	OR (95% CI)	P value	N at risk [†] (N events)	OR (95% CI)	P value
Early AMD	1284 (192)			1060 (161)			3324 (270)		
Mean IMT, per 0.1 mm		1.10 (1.02, 1.18)	0.01		1.11 (1.01, 1.21)	0.03		1.05 (0.99, 1.12)	0.11
Maximum IMT, per 0.1 mm		1.02 (1.00, 1.05)	0.03		1.02 (1.00, 1.05)	0.09		1.01 (0.99, 1.03)	0.23
Plaque sites, 1–3 vs. none		0.96 (0.66, 1.40)	0.85		0.99 (0.66, 1.49)	0.96		1.13 (0.84, 1.53)	0.42
Plaque sites, 4–6 vs. none		1.29 (0.77, 2.17)	0.33		1.15 (0.63, 2.07)	0.65			
History of MI present		1.44 (0.87, 2.39)	0.16		1.13 (0.60, 2.14)	0.69			
History of stroke present		0.92 (0.35, 2.38)	0.86		1.25 (0.46, 3.38)	0.66			
History of CVD present		0.92 (0.59, 1.44)	0.72		0.79 (0.46, 1.37)	0.40			
History of angina present		1.14 (0.69, 1.86)	0.61		0.90 (0.48, 1.71)	0.78			
Late AMD	1677 (63)			1400 (54)			2682 (69)		
Mean IMT, per 0.1 mm		1.18 (1.05, 1.31)	0.004		1.27 (1.10, 1.47)	0.001		1.17 (1.00, 1.37)	0.05
Maximum IMT, per 0.1 mm		1.04 (1.01, 1.08)	0.005		1.06 (1.02, 1.10)	0.002		1.05 (1.01, 1.09)	0.02
Plaque sites, 1–3 vs. none		1.27 (0.60, 2.67)	0.54		1.11 (0.49, 2.52)	0.80		1.62 (0.77, 3.44)	0.21
Plaque sites, 4–6 vs. none		2.56 (1.12, 5.87)	0.03		2.79 (1.06, 7.37)	0.04			
History of MI present		0.97 (0.41, 2.27)	0.94		1.04 (0.36, 3.02)	0.94			
History of stroke present		‡			‡				
History of CVD present		1.19 (0.63, 2.26)	0.60		1.33 (0.59, 3.01)	0.49			
History of angina present		0.89 (0.40, 1.95)	0.76		0.89 (0.32, 2.50)	0.82			
Pure Geographic Atrophy	1673 (21)			1397 (18)			2719 (28)		
Mean IMT, per 0.1 mm		1.19 (1.00, 1.42)	0.05		1.31 (1.05, 1.64)	0.02		1.19 (1.03, 1.38)	0.02
Maximum IMT, per 0.1 mm		1.05 (1.00, 1.10)	0.04		1.06 (1.00, 1.12)	0.03		1.05 (0.99, 1.11)	0.10
Plaque sites, 1–3 vs. none		0.67 (0.19, 2.37)	0.53		0.51 (0.13, 2.05)	0.35		1.28 (0.40, 4.02)	0.68
Plaque sites, 4–6 vs. none		2.14 (0.59, 7.72)	0.24		2.72 (0.63, 11.70)	0.18			
History of MI present		0.34 (0.04, 2.63)	0.34		0.61 (0.07, 5.34)	0.61			
History of stroke present		‡			‡				
History of CVD present		0.63 (0.18, 2.22)	0.47		1.31 (0.32, 5.27)	0.71			
History of angina present		0.62 (0.14, 2.73)	0.53		1.53 (0.30, 7.85)	0.61			

AMD Outcome	Model 1*			Model 2*			Model 3*		
	N at risk [†] (N events)	OR (95% CI)	P value	N at risk [†] (N events)	OR (95% CI)	P value	N at risk [†] (N events)	OR (95% CI)	P value
Exudative AMD	1700 (44)			1419 (38)			2739 (43)		
Mean IMT, per 0.1 mm		1.14 (1.00, 1.30)	0.05		1.14 (0.97, 1.34)	0.11		1.11 (0.98, 1.25)	0.09
Maximum IMT, per 0.1 mm		1.04 (1.00, 1.08)	0.04		1.05 (1.00, 1.10)	0.03		1.04 (0.99, 1.09)	0.09
Plaque sites, 1–3 vs. none		1.85 (0.74, 4.68)	0.19		1.82 (0.69, 4.82)	0.23		1.76 (0.76, 4.07)	0.19
Plaque sites, 4–6 vs. none		2.92 (1.03, 8.26)	0.04		2.59 (0.78, 8.66)	0.12			
History of MI present		1.46 (0.58, 3.67)	0.42		1.56 (0.48, 5.08)	0.46			
History of stroke present		[‡]	[‡]		[‡]	[‡]			
History of CVD present		1.59 (0.77, 3.31)	0.21		1.66 (0.65, 4.26)	0.29			
History of angina present		1.08 (0.44, 2.67)	0.88		0.92 (0.27, 3.13)	0.89			

AMD, age-related macular degeneration; CI, confidence interval; CVD, cardiovascular disease; IMT, intima-media thickness; MI, myocardial infarction; OR, odds ratio.

* Model 1 adjusted for age and sex. Model 2 adjusted for all factors in Model 1 as well as BMI, smoking status, history of multivitamin use, serum high-density lipoprotein cholesterol and C-reactive protein levels, hypertension status, diabetes status, history of statin use, white blood cell count, and *CFH* and *ARMS2* genotypes. Model 3 adjusted for all factors in Model 2 while examining carotid IMT and plaque by specific side and limiting the AMD outcome to the same side accounting for correlation between the eyes using a generalized estimating equation sandwich variance estimator.

[†] N at risk and N events are the number of individuals at risk and the number of individuals with the outcome over the 10-year follow-up period for Models 1 and 2 and are the number of eyes at risk and the number of eyes with the outcome over the 10-year follow-up period in Model 3.

[‡] Cannot estimate (no individuals with a history of stroke developed late AMD over the 10-year follow-up period).