Cardiovascular Disease and Hypertension Are Strong Risk Factors for Choroidal Neovascularization

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Purpose: To investigate the association of cardiovascular risk factors and inflammatory markers with neovascular age-related macular degeneration (AMD).

Design: Cross-sectional case–control study.

Participants: Of the 410 of the ≥65-year-old community sample invited to attend, 205 participated (50% response rate). Of the 215 clinic attendees who were invited to participate, 212 agreed to take part (98% response rate). A diagnosis of neovascular AMD in at least one eye was made in 193 clinic attendees and 2 of the community sample.

Methods: Clinic and community participants underwent a detailed ophthalmic examination with fundus imaging, were interviewed for assessment of putative risk factors, and provided a blood sample. Analysis included levels of serum lipids, intercellular adhesion molecule 1 (ICAM), vascular cellular adhesion molecule (VCAM), and C-reactive protein (CRP). All participants were classified by fundus image grading on the basis of the eye with more severe AMD features.

Main Outcome Measure: Neovascular AMD.

Results: There were 195 participants with choroidal neovascularization in at least one eye, 97 nonneovascular AMD participants, and 115 controls (no drusen or pigmentary irregularities in either eye). In confounder-adjusted logistic regression, a history of cardiovascular disease was strongly associated with neovascular AMD (odds ratio [OR], 7.53; 95% confidence interval [CI], 2.78–20.41). Cigarette smoking (OR, 3.71; 95% CI, 1.25–11.06), being in the highest quartile of body mass index (OR, 3.82; 95% CI, 1.22–12.01), stage 2 hypertension (OR, 3.21; 95% CI, 1.14–8.98), and being in the highest quartile of serum cholesterol (OR, 4.66; 95% CI, 1.35–16.13) were positively associated with neovascular AMD. There was no association between AMD status and serum CRP, ICAM, or VCAM.

Conclusions: Our results suggest that cardiovascular disease plays an etiological role in the development of choroidal neovascularization in a proportion of older adults and highlight the importance of control of blood pressure and cholesterol, avoidance of smoking, and maintenance of a normal body weight. *Ophthalmology 2008;115:1046–1052 © 2008 by the American Academy of Ophthalmology.*

Choroidal neovascularization is a serious late manifestation of the condition age-related macular degeneration (AMD). The neovascular process ultimately evolves into a scar that destroys the architectural integrity of the macular retina and other associated tissue layers, with devastating consequences for vision when the condition is bilateral.[1] The macular retina of older adults also commonly exhibits drusen, hypopigmentation, and hyperpigmentation, which are considered signs of aging, and these manifestations are not associated with overt vision loss.[2] As these features often precede the development of choroidal neovascularization, they are considered to represent earlier stages. The spectrum of drusen and pigmentary irregularities is widely referred to as early or nonneovascular AMD, whereas cho-

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roidal neovascularization, which can cause marked visual impairment, is referred to as neovascular AMD.[3] Recently, polymorphisms in complement factor H and related genes were shown to confer a high risk for choroidal neovascularization, and this has resulted in a resurgence of interest in the hypothesis that inflammation and immune activation play a role in its development.[4,5] Although genetic factors account for some 50% of the attributable risk of neovascularization, other important risk factors are also operational in the remainder of the population with neovascular AMD.

Cigarette smoking, obesity, high blood pressure (BP), duration of hypertension, adverse lipid profiles, and the markers of endothelial dysfunction intercellular adhesion molecule 1 (ICAM) and vascular cellular adhesion molecule (VCAM), which are important risk factors for cardiovascular disease, are also associated with nonneovascular and neovascular AMD.[6–9] Notably, ICAM and VCAM have been found to be overexpressed in eyes harboring choroidal neovascularization when compared with normal eyes.[10] Also, higher levels of C-reactive protein (CRP), an acute-phase inflammatory marker for cardiovascular disease, have been shown to be associated independently with progression from early AMD to choroidal neovascularization.[11] Therefore, there is a body of evidence linking early and late AMD with cardiovascular disease, suggesting that a disordered circulation may be the common denominator for both conditions. In Northern Ireland, the prevalence of cardiovascular disease is high.[12] Therefore, we undertook a case–control study to examine comprehensively the risk factor profile in older adults without early or late AMD in either eye, comparing them with patients with choroidal neovascularization in at least one eye.

Materials and Methods

The study adhered to the tenets of the Declaration of Helsinki on research into human volunteers, and the design was approved by the Research Ethics Committee of Queen's University of Belfast.

Sample Size

To detect an odds ratio (OR) of 2 at 80% power and 5% α, we required 200 cases and 200 controls. We expected fewer than 5% of advanced AMD cases to come from the community-based sample, with the vast majority of the case group being recruited from the clinic population. We also expected the response rate to be high in the clinic but lower in the general population. For this reason, we invited in excess of 400 persons from the general population to participate in this study.

Community-Based Sampling. This consisted of adults who were randomly identified from 2 general practice registers. Men and women 65 years or older and without severe physical disability, dementia, or other debilitating disease that would preclude a visit to the study clinic were eligible to participate. These exclusions were applied by the study participants' general practitioner. Of the 410 persons invited, 205 (50%) attended the study clinics (Fig 1 [available at http://aaojournal.org]).

Clinic-Based Sampling. Attendees at a macular clinic who were 50 years and older were approached if a diagnosis of AMD was made on clinical examination. In the case of nonneovascular AMD, large drusen (>5 in number and with a diameter of 125 μm, equivalent to that of a large retinal vessel at the optic disc margin) had to be present in at least one eye of an individual. Of the 215 who were identified with either early or late AMD, 212 agreed to take part (98% response rate). The recruitment from the clinic occurred concurrently with the community-based study.

Clinical Examination

Study procedures were identical in case and control participants for best-corrected visual acuity measurements in both eyes, anterior and posterior segment clinical examination with pupillary dilation, and digital stereoscopic fundus photography. Structured questionnaires were used to obtain information on medical histories, including history of and treatment for hypertension and use of statins. History of cardiovascular disease was considered to be present when there was a positive history of angina, transient ischemic attacks, intermittent claudication, overt myocardial infarction, or stroke. Information on lifestyle was collected, with a particular emphasis on cigarette smoking habit, and included number of cigarettes smoked per day, years smoked, and any major intervals of stopped smoking or restarted smoking. Height, weight, and 2 BP measurements made while comfortably seated were recorded. A nonfasting blood sample, either clotted or anticoagulated with ethylenediaminetetra-acetic acid was taken for serum biochemistry, separated within 3 hours of collection and stored at −80° C until analysis. In clinic participants, additional retinal imaging procedures consisting of angiography and optical coherence tomography were also available and used to confirm the presence or absence of neovascular AMD.

Fundus Image Grading

Fundus photographs of the community sample were graded in the photographic reading center at Queen's University of Belfast by trained graders using the definitions of the Wisconsin Age-Related Maculopathy Grading System.[13] In brief, the presence and type of drusen and pigmentary irregularities were evaluated within segments of the 3000-μm-radius grid, which was placed with its center on the fovea. A graded categorical approach was used to obtain an estimate of the number of drusen within the grid. Geographic atrophy (GA) was defined as areas of atrophy in excess of 175 μm with well-delineated margins within which choroidal vessels could be observed. Choroidal neovascularization was said to be present if stereoscopic examination showed subretinal fluid, exudate, hemorrhage, and/or scar tissue in the macular region of the fundus. When both GA and choroidal neovascularization were present in the same eye, the person was classified as having neovascular AMD. In patients recruited from hospital clinics, the clinical diagnosis of choroidal neovascularization due to AMD was also confirmed by other imaging modalities, including stereoscopic color photography with fluorescein, indocyanine green angiography, and optical coherence tomography.

Biochemical Analysis

Analysis of ICAM and VCAM 1 was carried out by enzyme-linked immunosorbent assay (Immunodiagnostics, Boldon, United Kingdom).

C-reactive protein (CRP) was assessed by a high-sensitivity latex-enhanced turbidometric immunoassay (Wako Chemicals GmbH, Neuss, Germany) using a Cobas Fara analyzer (Roche Diagnostics, Burgess Hill, United Kingdom).

Enzymatic methods were employed to measure total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol using a commercial kit (Randox Pharmaceuticals, United Kingdom) on a Cobas Fara analyzer.

Table 2. Clinical Parameters and Serum Biochemistry by Age-Related Macular Degeneration (AMD) Grade and History of Cardiovascular Disease (CVD)

	AMD Grade 0 (n = 112)	AMD Grade 1 (n = 97)	AMD Grade 2 (n = 195)	*P* Value*	History of CVD (n = 107)	No History of CVD (n = 282)	*P* Value*	Missing
BMI	24.5	24.5	27.3	<0.001	26.4	25.7	0.299	59
Hypertension category				0.001			0.199	17
Stage 0 (0 + prehypertension) (%)	36	37	21		29	27		
Stage 1 (%)	39	35	34		31	39		
Stage 2 (%)	25	28	45		40	34		
AMD status							<0.001	10
Grade 0 (%)	—	—	—	—	15	33		
Grade 1 (%)	—	—	—	—	12	24		
Grade 2 (%)	—	—	—	—	73	43		
Cholesterol (mmol/l)	4.87	5.23	5.41	0.001	4.80	5.37	<0.001	40
HDL (mmol/l)	1.15	1.23	5.41	0.329	1.07	1.22	0.001	40
Triglycerides (mmol/l)	1.61	1.40	1.50	0.132	0.27	0.28	0.801	40
CRP (mmol/l)	168.96	216.23	223.85	0.142	5.11	4.90	0.044	40
ICAM (ng/ml)	401.29	369.05	393.20	0.436	386.68	377.25	0.666	42
VCAM 1 (ng/ml)	774.04	800.04	863.80	0.174	790.15	831.40	0.090	42

BMI = body mass index; CRP = C-reactive protein; HDL = high-density lipoprotein; ICAM = intercellular adhesion molecule 1; n = maximum in each group; VCAM 1 = vascular cellular adhesion molecule 1.
Grade 0, absence of drusen ≥ 63 μm or pigmentary irregularities in either eye; grade 1, nonneovascular AMD; grade 2, evidence of neovascular AMD in one or both eyes.
*Chi-square test for categories or Kruskal–Wallis test for continuous data.

Data Management

Hypertension. Participants were categorized into 4 stages of hypertension according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.[14] These were normal (systolic BP < 120 mmHg and diastolic BP < 80 mmHg), prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg), stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg), and stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg). Of the 417 participants, only 25 met the criteria for classification as normotensive. For the purposes of analysis, data from the normal and prehypertension groups were combined to form the reference group.

Cardiovascular Disease. Participants were dichotomized on the basis of a history of cardiovascular disease into cardiovascular disease present or absent.

Cigarette Smoking. Participants were categorized as nonsmokers, ex-smokers, or current smokers.

Body Mass Index. Body mass index (BMI) was calculated as weight in kilograms per height in meters squared.

Age-Related Macular Degeneration Grade. Participants were categorized based on the features observed in the more severely affected eye. In the absence of drusen ≥ 63 μm or pigmentary irregularities in either eye, participants were placed in grade 0. Participants with drusen ≥ 63 μm or pigmentary irregularities in at least one eye were classified as nonneovascular AMD or grade 1. As there were only 3 participants with GA, they were included within grade 1 (i.e., nonneovascular). Participants with evidence of neovascular AMD were designated as AMD grade 2. In all analyses, the reference group was grade 0.

Statistical Analysis

All analyses were carried out using Stata statistical software (StataCorp, College Station, TX) and followed several steps:

1. The distribution of continuous variables (BMI, cholesterol, HDL, triglycerides, CRP, ICAM, VCAM) was assessed for normality and categorized into tertiles or quartiles.
2. Linear regression adjusted for age, gender, and AMD grade was used for log CRP, log ICAM, and log VCAM to investigate the relationship between these biomarkers of endothelial inflammation and various covariates (history of cardiovascular disease, hypercholesterolemia, diabetes, and smoking; BMI; and hypertension category).
3. Univariate analysis (chi-square test for categorical variables or Kruskal–Wallis test for continuous variables) was used to examine differences in demographic information (Table 1 [available at http://aaojournal.org]) and differences in means for the biochemical markers (Table 2) by the 3 AMD grades and by history of cardiovascular disease.
4. Univariate logistic regression with adjustment for age (using an age-squared term) and gender was then used to examine for differences between participants in AMD grade 0 (those without any AMD features) and those in grade 2 (neovascular AMD) in demographic, clinical, and biochemical risk factors.
5. Multivariable logistic regression adjusted for age and gender was performed, and likelihood ratio tests were used to determine the contributions of terms to the model, which were removed if nonsignificant (for exclusion, the limit was set at $P>02$). Odds ratios and 95% confidence intervals (CIs) were calculated for AMD grade 2 relative to the control group.

Results

Of the overall study sample (n = 417), 45.1% were male and 54.9% were female, mean age was 74.97 years (±6.76 [standard deviation]; range, 49–95). Of the community-based sample, those

Table 4. Multiple Regressions of Log C-Reactive Protein (CRP), Intercellular Adhesion Molecule (ICAM), and Vascular Cellular Adhesion Molecule (VCAM) on Age-Related Macular Degeneration (AMD) Risk Factors and Other Covariates

	Log CRP (n = 278)		Log ICAM 1 (n = 281)		Log VCAM 1 (n = 281)	
	β Coefficient ± SE	P *Value*	*β Coefficient ± SE*	P *Value*	*β Coefficient ± SE*	P *Value*
History of CVD (%)	0.133±0.128	0.301	−0.003±0.039	0.931	0.048±0.050	0.337
History of hypercholesterolemia	0.014±0.117	0.903	0.048±0.036	0.182	−0.007±0.046	0.886
History of diabetes	−0.003±0.185	0.987	0.066±0.056	0.234	−0.038±0.071	0.595
Smoking status	0.148±0.075	0.049	0.058±0.023	0.011	−0.002±0.029	0.941
Hypertension category	0.073±0.068	0.284	0.046±0.021	0.029	0.019±0.027	0.477

CVD = cardiovascular disease; n = maximum in each group; SE = standard error.

who refused participation (n = 205) were significantly older (74.8 vs 71.9, $P = 0.001$) than those who attended (n = 205). There was no significant difference in gender distribution (37% male vs. 42% female, $P = 0.418$).

In 10 of the 205 in the community-based sample, fundus images were either unavailable (n = 5) or ungradable due to poor quality (n = 5). The remaining images from the community-based sample (195) and all of the 212 from the clinic-based sample were gradable and classified on the basis of fundus appearance (Fig 1 [available at http://aaojournal.org]).

In the community-based sample, 115 participants were assigned to the control or reference grade 0 (Fig 1). There were 78 participants (grade 1) in whom the fundus image from at least one eye was classified as nonneovascular AMD (75 with drusen and pigmentary irregularities and 3 with GA). There were 2 participants with choroidal neovascularization in the community-based sample. In the clinic-based sample, there were 19 participants assigned to grade 1 (features of nonneovascular AMD) and 193 with neovascular AMD (grade 2). There were no participants in the clinic sample who were assigned to grade 0 (Fig 1).

Tables 1 and 2 (the former available at http://aaojournal.org) show the completeness of the demographic and biochemical data by AMD grade and by history of cardiovascular disease. When there was categorization by AMD grade, there were statistically significant differences in mean age ($P<0.001$), history of cardiovascular disease ($P<0.001$), mean BMI ($P<0.001$), hypertension stage ($P<0.001$), and mean serum cholesterol ($P = 0.001$). When there was categorization by history of cardiovascular disease, statistically significant differences were noted for age ($P = 0.002$), history of hypercholesterolemia ($P = 0.001$), history of diabetes ($P = 0.035$), statin intake ($P<0.001$), AMD grade, mean cholesterol, mean HDL, and mean serum CRP.

Age- and gender-adjusted logistic regression showed that when compared with participants from AMD grade 0 those in grade 2 were more likely to be placed in the highest quartile of BMI (OR, 4.85; 95% CI, 2.14–11.01) and highest quartile of serum cholesterol (OR, 3.54; 95% CI, 1.59–7.88) and have a positive history of cardiovascular disease (OR, 3.47; 95% CI, 1.84–6.53). Statistically significant adverse associations were also seen for stage 2 hypertension, past or current smoking, quartiles 2 and 3 of triglycerides, and increased CRP (Table 3 [available at http://aaojournal.org]). Hypertension, BMI, cholesterol, CRP, and smoking status showed a clear trend of increasing ORs across the categories.

In confounder-adjusted analyses (Table 3), participants with stage 2 hypertension had significantly higher ORs of neovascular AMD (OR, 3.21), with evidence of increasing trend across categories. Body mass index also showed a significant trend of increasing ORs across the quartiles, with those in the highest quartile having a near 4-fold OR. Serum cholesterol was also associated with neovascular AMD (quartile 4 vs. quartile 1; OR, 4.66). The other biochemical variables did not show significant associations, with the exception of quartile 2 of serum HDL and quartile 3 of VCAM (Table 3), but a steady trend across the categories was not observed.

Table 4 illustrates the relationship between the biomarkers of inflammation and risk factors for AMD. After controlling for age, gender, and AMD grade, both CRP and ICAM were positively associated with smoking status ($\beta = 0.148\pm0.075$, $P = 0.049$, and $\beta = 0.058\pm0.023$, $P = 0.049$, respectively), and ICAM was positively associated with hypertension category ($\beta = 0.046\pm0.021$, $P = 0.029$).

No statistically significant associations were seen between the risk factors measured in this study and nonneovascular (grade1) AMD (data not shown).

Discussion

This study was motivated by the fact that there is still no agreement on whether preexisting vascular disease plays an important pathogenetic role in the initiation and development of neovascular AMD.[15–17] A meta-analysis of risk factors of the 3 largest epidemiological studies (Beaver Dam, Rotterdam, and Blue Mountains eye studies) found no evidence of an association between cardiovascular disease and incident late AMD.[18] In Northern Ireland, the prevalence and incidence of cardiovascular disease are among the highest in the world,[12] and exudative AMD is also a common condition in this geographical location.[19] The present study was therefore undertaken and represents a comprehensive analysis of a wide spectrum of shared risk factors for neovascular AMD and cardiovascular disease. Cases and controls were derived from a common geographical location and thus likely to have shared genetic antecedents, and there was no difference in gender distribution. Because cases were, on average, 4 years older than controls, we adjusted for age in all analyses. However, there may be residual confounding from unmeasured factors.

In the past couple of years, attention has been refocused on the role of inflammation in the pathogenesis of AMD. C-reactive protein is an established inflammatory biomarker that displays strong relationships with cardiovascular diseases.[20] Elevated CRP has been reported to be independently associated with AMD.[21] More recently, in a prospective cohort study of 251 participants with early AMD Seddon et al found a multivariate adjusted relative risk of 2.1 (95% CI, 1.06–4.18) in persons with higher levels of the systemic inflammatory markers CRP and interleukin 6.[11] In the present study, we also noted a similar statistically sig-

nificant increase in odds of neovascular AMD with higher levels of CRP (tertile 3 vs. 1; OR, 2.13, and 95% CI, 1.07–4.24, in the age- and gender-adjusted logistic regression model). However, statistical significance was lost in the fully adjusted model, indicating that elevated CRP within our population may be attributed to concurrent cardiovascular disease, a finding that is in broad agreement with those of Dasch et al.[22]

We did not find a relationship between the risk of neovascular AMD and the 2 biomarkers ICAM and VCAM; however, participants who had VCAM levels in the third quartile appeared to have an increase in odds that just reached statistical significance. In this context, it is notable that Seddon et al likewise found a weak nonsignificant positive association between VCAM and progression to neovascular AMD.[11]

A key finding from the present study is the strong and significant trend of increasing odds of neovascular AMD with increasing severity of hypertension. After correction for age and gender, the odds for neovascular AMD more than doubled for participants in the most severe stage of hypertension. Our findings are in strong agreement with the Age-Related Macular Degeneration Risk Factor Study, which found that neovascular AMD was positively associated with diastolic BP >95 mmHg, history of use of hypertensive medication, or taking of hypertensive medication.[8] The Age-Related Eye Diseases Study also found a significant association between measured BP or a history of hypertension and neovascular AMD at baseline (Age-Related Eye Diseases Study report 3),[23] but no association with incident choroidal neovascularization was detected at follow up (Age-Related Eye Diseases Study report 19).[24] The present study, however, did not find a statistically significant association between history of hypertension or use of antihypertensive medications and neovascular AMD. The large population-based epidemiological studies have generally been unable to demonstrate a clear positive association with BP, but this is unsurprising, as the small numbers of late AMD cases would have limited their ability to identify such relationships.[15,17,25] A strength of the present study is its use of a robust internationally accepted classification system to categorize participants into different clinical stages of BP.[14]

In the present study, we observed a marked elevation in odds of neovascular AMD with a positive history of cardiovascular disease. Although a number of case–control studies[26,27] and population-based studies[15,28] have demonstrated statistically significant adverse relationships between cardiovascular disease and neovascular AMD, none, apart from the Beaver Dam Eye Study, has accounted for the wide range of confounding variables.[28]

The relation between serum cholesterol concentrations and incidence of coronary heart disease is widely recognized as continuous and curvilinear and, hence, provides a robust surrogate biomarker of cardiovascular disease risk. It is noteworthy, therefore, that the present study found a significant trend of increasing odds for neovascular AMD across the quartiles of cholesterol after controlling for all other factors. Although this is in accord with the Eye Disease Case–Control Study,[29] it was not confirmed in the Rotterdam,[30] Blue Mountains,[17] or Beaver Dam[16] studies or in the subsequent meta-analyses.[6,18] Statin usage was associated with a history of cardiovascular disease, but we did not find a statistically significant association between neovascular AMD and statin use.

As in the overwhelming majority of previous studies,[6,18] we also found a nearly 4-fold increased association of neovascular AMD in current smokers and a 2-fold one for ex-smokers. Body mass index is another modifiable risk factor that has been linked to an increased risk of AMD in several observational studies.[7,17,31] However, most data, including the 3-continent meta-analysis, have not supported an association.[6,29,32] The present study found a clear trend of increasing odds from the lowest to the highest quartile of BMI, with a quadrupling of the odds for neovascular AMD in the most obese (OR, 3.82). As genetic susceptibility associated with the (Y402H) variant of the complement factor H gene is modified by both smoking habit and BMI,[33] there is a need to account for gene–environment interactions to prevent confounding when planning future studies.

It is recognized that cross-sectional case–control studies by nature of their design are subject to several inherent limitations, and ours is no exception. First, our cases and controls were not individually matched, although we adjusted all analyses for age and gender. Second, the vast majority of our AMD cases were recruited from hospital clinics with the potential for introducing bias. However, we minimized the bias associated with selection of controls through community-based sampling while ensuring similarity with our case group by drawing our control sample from a similar geographical and socioeconomic area. As only half of the control sample who was invited attended, it is possible that participant characteristics may have differed from nonparticipants or from the general population. This phenomenon, commonly referred to as the healthy participant effect, can lead to overestimation of differences, as controls are known to come from groups of highly motivated healthy volunteers.[34] We therefore compared the physical and comorbid disease characteristics of our control participants with that of an existing Northern Ireland database of ≥55 years olds.[35] Although methods of data collection differed and not all of the variables evaluated in the current study were available for comparison, those that were included—namely, BMI and serum cholesterol levels—were similar in the overall Northern Ireland population and our controls. Likewise, prevalences of ischemic heart disease, diabetes, and hypertension were also similar in the 2 groups, thus minimizing the possibility of significant confounding. Third, all measurements were made at a single point in time and suffer from the limitations of the cross-sectional approach. Fourth, the serum samples were obtained from participants in a nonfasting state, raising the possibility that dietary and diurnal variation in serum concentrations of triglycerides could have introduced noise to the measurements. However, several studies have shown that total and HDL cholesterol levels are not significantly affected by fasting.[36,37] Despite these caveats and the nature of the cross-sectional design, which does not allow us to attribute causality, we believe that the present study has provided evidence for a strong association between cardiovascular

disease and neovascular AMD. The strengths of this study include a well-characterized population, the use of standardized data collection instruments, ophthalmic examination, and fundus photography employing previously validated methods.[38] Information bias is unlikely, as AMD grade was assigned without prior knowledge of biomarker or demographic information and confounding was controlled by using multivariate analysis.

We believe that our findings demonstrate that cardiovascular disease is associated with the development of choroidal neovascularization and that they have similar pathogenic pathways. The improvements in survival experienced in recent years through advances in clinical management of cardiovascular disease may contribute to an increase in the prevalence of AMD as more people live to experience the result of atherosclerotic changes in the choroidal circulation. Particularly pertinent is the question of whether statin therapy and aggressive control of BP may prevent or delay the onset of neovascular AMD.

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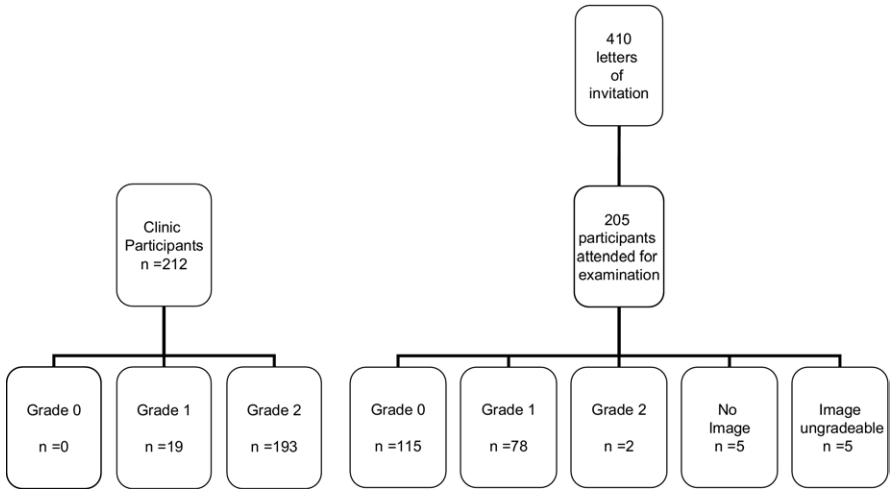

Figure 1. Flow diagram of participant sampling and response. Grade 0, absence of both drusen ≥ 63 μm and pigmentary irregularities in either eye; grade 1, drusen ≥ 63 μm or pigmentary irregularities in at least one eye, grade 2, neovascular AMD.

Table 1. Demographic and Medical History by Age-Related Macular Degeneration (AMD) Grade and History of Cardiovascular Disease

	AMD Grade 0 (n = 115)	AMD Grade 1 (n = 97)	AMD Grade 2 (n = 195)	*P* Value*	History of Cardiovascular Disease (n = 107)	No History of Cardiovascular Disease (n = 282)	*P* Value*	Missing
Age (yrs) (mean ± SD)	72.6±5.0	73.9±7.2	76.9±6.8	<0.001	76.76	74.44	0.002	0
Gender (% male)	46	45	45	0.968	56	43	0.058	0
History of cardiovascular disease (%)	15	17	40	<0.001	—	—	—	28
History of hypertension (%)	50	50	46	0.783	53	46	0.225	23
History of antihypertensive medication (%)	42	45	43	0.926	45	38	0.073	52
History of hypercholesterolemia	40	31	27	0.081	50	25	<0.001	45
History of statins (%)	35	24	20	0.019	39	18	<0.001	53
History of diabetes	9	10	1	0.987	14	7	0.035	53
Smoking status (%)								
Nonsmoker	47	49	35		37	44		
Ex-smoker	35	38	44		47	37		
Current smoker	18	13	21	0.111	16	19	0.199	29

n = maximum in each group; SD = standard deviation.
Grade 0, absence of drusen ≥ 63 μm or pigmentary irregularities in either eye; grade 1, nonneovascular; grade 2, evidence of neovascular AMD in one or both eyes.
*Chi-square test for categories or Kruskal–Wallis test for continuous data.

Table 3. Age- and Gender-Adjusted Associations Showing Odds Ratios (ORs) and 95% Confidence Intervals (CIs) of Clinical and Biochemical Factors Associated with Neovascular Age-Related Macular Degeneration (AMD) (Grade 0 vs. Grade 2*)

	Age- and Gender-Adjusted Logistic Regression				Multivariate-Adjusted Logistic Regression (Final Model)			
	Adjusted OR	*95% CI*	*P Value*	*P Value for Trend*	*Adjusted OR*	*95% CI*	*P Value*	*P Value for Trend*
History of cardiovascular disease (%)	3.47	1.84–6.53	<0.001		7.53	2.78–20.41	<0.001	
History of diabetes† (%)	0.90	0.35–2.30	0.819					
Smoking status				0.001				0.003
Nonsmoker					1			
Ex-smoker	2.16	1.15–4.04	0.016		2.00	0.81–4.98	0.137	
Current smoker	2.51	1.22–5.15	0.012		3.71	1.25–11.06	0.019	
BMI (quartiles)				<0.001				0.004
1 (18.73–22.73)					1			
2 (22.74–24.92)	1.80	0.82–3.96	0.146		1.98	0.63–6.25	0.246	
3 (24.93–27.42)	1.82	0.82–4.01	0.140		2.72	0.81–9.20	0.107	
4 (27.43–39.62)	4.85	2.14–11.01	<0.001		3.82	1.22–12.01	0.022	
Hypertension category (%)				0.011				0.032
Stage 0 (0 + prehypertension)	1				1		0.829	
Stage 1	1.42	0.77–2.64	0.266		0.90	0.34–2.35	0.027	
Stage 2	2.44	1.27–4.72	0.008		3.21	1.14–8.98		
Cholesterol (quartiles)				<0.001				0.001
1 (2.01–4.30)					1			
2 (4.31–5.22)	1.20	0.56–2.55	0.637		0.89	0.27–2.89	0.845	
3 (5.23–6.13)	2.75	1.22–6.17	0.014		3.37	0.95–11.91	0.060	
4 (6.14–8.10)	3.54	1.59–7.88	0.002		4.66	1.35–16.13	0.015	
HDL (quartiles)				0.902				0.405
1 (0.53–0.91)					1			
2 (0.92–1.15)	1.65	0.78–3.50	0.191		3.99	1.28–12.44	0.017	
3 (1.16–1.41)	1.11	0.52–2.36	0.792		2.53	0.75–8.60	0.136	
4 (1.42–2.58)	1.19	0.54–2.61	0.666		3.35	0.92–12.26	0.067	
Triglycerides (quartiles)				0.483				0.189
1 (0.44–0.96)					1			
2 (0.97–1.34)	2.22	1.00–4.90	0.05		1.69	0.51–5.64	0.394	
3 (1.35–1.87)	2.24	1.05–4.81	0.038		1.68	0.50–5.71	0.405	
4 (1.88–4.20)	1.35	0.63–2.90	0.446		0.90	0.25–3.23	0.873	
CRP (tertiles)				0.032				0.182
1 (5.34–91.67)					1			
2 (91.68–206.17)	1.31	0.68–2.50	0.419		0.922	0.35–2.43	0.870	
3 (206.18–1569.52)	2.13	1.07–4.24	0.031		2.31	0.82–6.52	0.115	
ICAM 1† (quartiles)				0.732				
1 (0.343–0.622)								
2 (0.622–0.732)	0.92	0.43–1.97	0.838					
3 (0.732–0.900)	1.44	0.64–3.25	0.377					
4 (0.900–2.013)	0.77	0.36–1.65	0.507					
VCAM 1 (quartiles)				0.444				0.532
1 (2.66–5.80)					1			
2 (5.80–7.16)	1.61	0.76–3.39	0.210		1.54	0.52–4.60	0.435	
3 (7.16–8.38)	2.81	1.03–4.63	0.042		3.39	1.13–10.17	0.030	
4 (1677.0–3936.0)	1.12	0.49–2.53	0.788		1.15	0.36–3.66	0.810	

BMI = body mass index; CRP = C-reactive protein; CVD = cardiovascular disease; HDL = high-density lipoprotein; ICAM = intercellular adhesion molecule; n = maximum in each group; VCAM = vascular cellular adhesion molecule.

*Grade 0, absence of drusen ≥ 63 μm, or pigmentary irregularities in either eye; grade 1, nonneovascular AMD; grade 2, evidence of neovascular AMD in one or both eyes.

†Diabetes, statin medication, hypertensive medication, and ICAM 1 were not entered into the multivariate model, as they were not statistically significant on univariate analyses.