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Age-Related Macular Degeneration and Incident Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—To determine whether age-related macular degeneration (AMD) is a risk indicator for coronary heart disease (CHD) and cardiovascular disease (CVD) events independent of other known risk factors in a multi-ethnic cohort.

Design—Population-based prospective cohort study.

Participants—A diverse population sample of 6233 men and women aged 45–84 without known CVD from the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods—Participants in the MESA had retinal photographs taken between 2002 and 2003. Photographs were evaluated for AMD. Incident CHD/CVD events were ascertained during clinical follow-up visits for up to 8 years after the retinal images were taken.

Main Outcome Measures—Incident CHD/CVD events.

Results—Of the 6814 persons at risk of CHD, there were 893 participants with early AMD (13.1%) and 27 (0.5%) at baseline. Over a mean follow-up period of 5.4 years, there was no statistically significant difference in incident CHD or CVD between the AMD and non-AMD

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groups (5.0%vs. 3.9%, p=0.13 for CHD and 6.6 vs. 5.5%, p=0.19 for CVD, respectively). In Cox regression models adjusting for CVD risk factors, there was no significant relationship between presence of any AMD and any CHD/CVD events (HR=0.99, 95% CI 0.74–1.33, p=0.97). No significant association was found between subgroups of early AMD or late AMD and incident CHD/CVD events.

Conclusions—In persons without a history of cardiovascular disease, AMD was not associated with an increased risk of CHD or CVD.

Introduction

Age-related macular degeneration (AMD) is a leading cause of severe loss of vision. AMD affects over 7 million individuals in the United States, and approximately 6.5% of the US population aged 40 years and older.[1] Even though the etiology of AMD remains unclear, the disease has been associated with various traditional cardiovascular disease (CVD) risk factors, such as age, [2] elevated serum cholesterol levels, [3] hypertension, [4] and cigarette smoking. [5, 6] Associations with genetic variants of the complement factor H gene [6] and with decreased survival [7] have also been reported. Whether AMD is a risk indicator for CVD beyond the effects of age and other CVD risk factors is unclear.

There are multiple similarities in the pathophysiology of both AMD and CVD. Both diseases are associated with atherosclerosis, [8] inflammation, [9, 10] complement activation [11] and a local up-regulation of vascular endothelial growth factor (VEGF). [12, 13] In the choroidal vasculature of patients with AMD, the local up-regulation of VEGF promotes the formation of new subretinal vessels, [12] which lead to late stage "wet" AMD. [14] In the coronary tree, a local up-regulation of VEGF promotes formation of new fragile vessels within the atherosclerotic plaques; neoangiogenesis of coronary atherosclerotic lesions is closely associated with plaque progression and is a likely source of intraplaque hemorrhage leading to CVD events. [15] Furthermore, the density and number of these vessels within the plaque have been recently implicated in plaque instability, plaque rupture, and the development of acute atherothrombotic events. [16, 17]

Data from population studies relating AMD to the development of atherosclerotic CVD events have been inconsistent [18–20] and whether ethnicity affects the observed differences has not been studied. [21] The purpose of the present study is to examine the association of AMD with the incidence of atherosclerotic coronary heart disease (CHD) and CVD outcomes across different racial/ethnic groups in the Multi-Ethnic Study of Atherosclerosis (MESA) and to determine if AMD is a marker for CHD/CVD events independent of traditional CVD risk factors.

Methods

Study Population and Data Collection

The MESA is a prospective observational study sponsored by the National Institutes of Health. It was initiated in July 2000 with the purpose of identifying risk factors for subclinical cardiovascular disease (CVD) and its progression to clinically manifested CVD in a diverse population sample of 6233 men and women aged 45–84. The sampled population comprised self-identified White (n=2466), African-American (n=1689), Hispanic (n=1349), and Asian (n=729) participants. The cohort was recruited from 6 field centers: Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota. Individuals with prior history of known CVD were excluded from the study: myocardial infarction (MI), angina, heart failure, stroke, or transient ischemia attack or the following procedures: coronary artery bypass graft,

angioplasty, or other vascular surgeries. This research was conducted with institutional review board approval by each of the participating MESA field centers. All participants gave informed consent for the use of their data collected in the study. [22]

The initial measurements included socio-demographic, lifestyle, clinical and laboratory data; as well as assessment of cardiovascular risk factors. [22] Our cohort consisted of adults free of known CVD who had baseline retinal photographs during the first follow-up examination (second examination) conducted from August 2002 through January 2004. Characteristics of the cohort with and without gradable retinal photographs have been previously reported. [23]

Retinal Examination and AMD Grading

Retinal photography was performed using a standardized protocol. [24] Both eyes of each participant were photographed using a 45° 6.3-megapixel digital nonmydriatic camera (Canon, Lake Success, NY). Two photographic fields were taken of each eye, the first centered on the optic disc and the second centered on the fovea. Using a standard AMD grading protocol, [25] the macula area was graded at the University of Wisconsin Ocular Epidemiology Reading Center for AMD features including drusen size, type, and area; increased retinal pigment; retinal pigment epithelial depigmentation; pure geographic atrophy; and signs of exudative macular degeneration (subretinal hemorrhage, subretinal fibrous scar, retinal pigment epithelial detachment, and/or serousdetachment of the sensory retina or laser or photodynamic treatment for neovascular AMD). Graders were masked with respect to information about the participant. Each image was graded twice (preliminary and detail grading) using a modification of the Wisconsin Age-Related Maculopathy Grading scheme. [25]

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 gray or black pigment in or beneath the retina. RPE depigmentation 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-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 vessel, or subretinal fibrous scar or laser treatment scar for AMD. When two 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. [23] Any AMD was defined if either early or late AMD was present.

Ascertainment of Cardiovascular Events

For these analyses the primary outcomes of interest were coronary heart disease (CHD) and CVD event rates. CHD events were defined as myocardial infarction, resuscitated cardiac arrest, definite angina with or without revascularization, probable angina (if followed by revascularization) and CHD death. CVD included all CHD plus stroke, stroke death, CHD death, other atherosclerotic death, and other CVD death. [22] Participants were followed up for incident events up to 8 years after the retinal images were taken. Clinical examinations were performed at 9–12 month intervals, an interviewer contacted each participant by

telephone to inquire about all interim hospital admissions or CVD outpatient diagnoses. Study personnel requested copies of all death certificates and medical records for all hospitalizations and outpatient cardiovascular diagnosis. Next-of-kin interviews for out-of-hospital CVD deaths were obtained. Two physicians from the MESA study's Events Committee independently reviewed, without knowledge of the macular degeneration status of the participants, all medical records for end point classification and assignment of incidence dates. If the reviewing physician disagreed on the event classification, they adjudicated their differences after discussion. If disagreements persisted, the full MESA Events Committee made the final classification. Criteria for events are available on the MESA website (http://www.mesa-nhlbi.org/Mesa-Internal/manuals.asp. Accessed January 22 2010). Adjudicated CHD and CVD events occurring between the date of retinal exam in 2002 and August 23, 2010 were available for analysis, providing a maximum of 8 years of follow-up for the present study.

Statistical Analysis

We used the two-sided Fisher exact test and chi square (X^2) statistic to compare the means or proportions of demographic variables, baseline cardiovascular risk factors, baseline AMD status (none, early, late) and incident CHD/CVD. We used multivariate Cox proportional hazard models to assess the risk of incident CHD/CVD events in AMD participants using age-sex adjusted models. Then we estimated multivariate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for incident CHD and CVD adding race, hypertension, diabetes, cigarette smoking, CRP, site of enrollment, level of education, BMI and serum total cholesterol and LDL-C. In our study, we had over 99% power to detect a HR of at least 1.2. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Of the 6,814 participants seen at baseline, 6,176 had retinal photographs, and 5,951 had images gradable for AMD: 219 had gradable fundus photographs for AMD in the right eye only, 205 had them for AMD in the left eye only, and 5,527 had them for AMD in both eyes. Participants with confounding lesions such as retinal vein occlusions were excluded. 893 persons (13.1%) had early AMD and 27 (0.5%) had late AMD (exudative or pure geographic atrophy). Increased pigment was present in 52 participants (0.98%). Early AMD was statistically more prevalent in Chinese Americans (21.60%) than in Hispanics (15.10%), Caucasians (14.10%), or African Americans (10.80%), P <0.0001. There also was more late AMD among Chinese Americans (1.09%) than in Caucasians (0.61%), African Americans (0.28%) or Hispanics (0.26%), P=0.05. Mean age of the cohort was 62 yr, and 52% were women. The general characteristics of our cohort are summarized on Table 1.

The overall incidence of CVD events over a mean follow-up time of 5.4 years was low: MI 1.85% (n=126), percutaneous coronary intervention 2.13% (n=145), coronary artery bypass graft surgery 1.26% (n=86) and stroke 1.54% (n=105) respectively (Table 2). There were 278 CHD events in the cohort as a whole (4.08%) of which 233 (3.94%) occurred in the no AMD group, 45 (5.03%) occurred in the participants with early AMD and 3 (11.10 %) in participants with late AMD. The total number of CVD events were 384 (5.64%), of these, 325 (5.50%) occurred in the no AMD group, 59 (6.61%) occurred in the early AMD group and only 4 (14.81%) in participants with late AMD. The all-cause mortality rate was 4.16% (n=283), of which CHD death represented 12.37% and stroke death represented 4.59 %.

Table 2 demonstrates that there was no statistically significant difference in incident CHD or CVD between the AMD and non-AMD groups (5.03% vs. 3.9%, p=0.13 for CHD and 6.6 vs. 5.5%, p=0.19 for CVD, respectively); or between early AMD and non-AMD subgroups

(5.0% vs. 3.9%, p=0.12 for CHD and 6.6 vs. 5.5%, p=0.18 for CVD, respectively). Although based on a small sample size, we found higher incidence of events in the late AMD cohort compared to the non-AMD cohort (11.10% vs. 3.94%, p=0.04 for CHD and 14.81 vs. 5.50%, p=0.01 for CVD).

The baseline presence of early and/or late AMD did not predict subsequent CHD or CVD in age-adjusted or multivariate models. (Table 3) The baseline presence of late AMD was suggestive of but did not significantly predict CHD (HR=1.65, 95% CI, 0.52–5.25, p=0.39) or CVD events (HR=1.73, 95% CI, 0.64–4.67, p=0.28) in age-sex adjusted models. Further risk adjustments in multivariate models did not affect this association.

In secondary analyses, no significant association was found between early AMD or late AMD and CHD/CVD events by ethnicity. In an exploratory secondary analysis, there was a small subgroup of Caucasian participants aged 65 years and older (n=27) where late AMD was significantly associated with increased risk for CHD in age-sex adjusted models (HR=4.12, 95% CI, 1.28–13.72, p=0.018) and CVD events (HR=4.22, 95% CI, 1.51–11.77, p=0.006). The sample size was too small to do a complete multivariate analysis. We found no other significant racial differences or gender differences in the predictive value of early or late AMD on CHD/CVD events.

Discussion

This study suggests that participants with AMD without a history of cardiovascular disease at their initial exam visit were not at an increased risk of CHD/CVD events as compared to those without AMD after a mean follow up of 5.4 years. When we performed analyses by type of AMD, early AMD did not confer a higher risk of CHD/CVD events. No ethnic or gender differences were noted in these prediction models.

There is no general agreement about the clinical importance of AMD as a marker for stroke and cardiac related events. [19, 26, 27] Our results are at variance with the results from Wong et al in the Atherosclerosis Risk In Communities (ARIC) study which demonstrated that the early form of AMD portended a higher risk of stroke over 10 years of follow-up (1.85, 95% CI, 1.19–2.87) [28] and that individuals with late AMD had three times higher risk of incident CHD events (HR= 3.05, 95% CI, 1.14–8.17) as compared to participants without late AMD. [19] Hu et al [21] in a Taiwanese population, showed that late AMD was associated with a 2-fold increased incidence of stroke. Duan et al, [18] in a Medicare claim-based data review showed that in participants aged 65 and older, AMD was significantly associated with the development of incident MI (odds ratio [OR]= 1.19, 95% CI, 1.16–1.22) at two years. This association was stronger (OR =1.26, 95% CI, 1.20 –1.33) in subjects with neovascular AMD; nonetheless there was lack of clinical validation to confirm the AMD diagnosis and no information about the confounding effect of smoking on the relationship. Lastly, Tan et al [20] in the Blue Mountains Eye Study found that participants with early AMD had a 2-time increased risk of CHD mortality when compared to age and sex matched controls (HR= 2.32, 95% CI, 1.03 to 5.19). They also found a 5-time increased risk of CHD death among participants with baseline late AMD (HR = 5.57, 95% CI, 1.35–22.99), these associations were only significant in younger individuals (<75 years). Their late AMD analyses were also based in a small number of subjects (n=9).

Our findings are consistent with the results from Knudtson et al [29] in the Beaver Dam Study where participants with AMD had similar survival to those without AMD (HR=0.97 95% CI 0.88–1.08). In a review of healthcare claims, Nguyen-Khoa et al [30] found that late AMD was a protective marker for MI (RR = 0.58, 95% CI, 0.48–0.72) and stroke (RR = 0.56, 95% CI, 0.45–0.70) over a 3 year period. Lastly, Sun et al [31] in the Community

Health Study revealed that there was an increased likelihood of CHD in participants with early AMD but contrary to the ARIC study findings, neither the presence of early nor the presence of late AMD increased the likelihood of stroke.

Our results, as well as previous work in the topic highlight the paucity of data regarding the predictive value of AMD in CHD/CVD events. It also likely reflects the heterogeneity in the study design, length of follow-up, and accuracy of the definitions of ocular and CVD outcomes used in the few studies addressing this clinical question. It is possible that these differences may explain the discordance of results across studies. The inability to find significant associations in our cohort could be related to the low incidence and frequency of the main outcome measures in the MESA population. Similarly, the assessment of differences in prevalence of AMD among ethnicities likely requires a larger number of patients for sufficient power.

The selection bias inherent to the MESA cohort design may explain the discrepancy found with results from other cohorts. MESA participants were selected on the basis of absence of cardiovascular disease, they were likely healthier than those in other studies. Overall, definitive assessment of the relationship between AMD and CHD/CVD events will require a larger number of clinical outcomes, longer term follow-up, and confirmed and validated events.

In conclusion, in persons without a history of cardiovascular disease, AMD was not found to be significantly associated with an increased risk of CHD or CVD events. Future research designed to overcome the limitations of previous studies may provide an answer to this clinical question and advance the understanding of these two major public health issues.

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Table 1

General Patient Characteristics

Characteristics	Overall Cohort (n=6,233)	No AMD (n=5,338)	Any AMD* (n=895)	Early AMD (n=893)	Late AMD (n=27)	p-value†
Age (SD)	62.0(10.2)	607(9.8)	66.7(9.8)	66.7(9.8)	74.3(7.5)	<0.0001
Female (%)	52.4	47.5	50.4	50.4	40.7	0.22
Race Black (%) (n=1689)	24.8	26.6	20.4	20.4	14.8	0.001
White Caucasian (%)(n=2466)	36.2	39.6	39.0	39.0	48.1	0.06
Chinese American (%)(n=729)	10.7	11.9	17.5	17.6	25.9	<0.0001
Hispanic (%) (n=1349)	19.8	21.8	22.9	22.8	11.1	0.01
Hypertension (%)	45.8	43.6	49.8	49.7	66.7	0.01
Smoking status (%)						
Past (%)	38.5	38.2	38.6	38.5	51.9	0.06
Current (%)	10.5	11.7	9.6	9.6	3.7	0.33
High school graduate (%)	81.7	83.8	77.5	77.4	85.2	0.0004
BMI (SD)	28.3(5.5)	28.3(5.4)	27.7(5.3)	27.7(5.3)	27.5(4.4)	<0.0001
Diabetes (%)	31.7	30.3	31.4	31.5	29.6	0.83
Cholesterol (mg/dl) (SD)	191.3(35.8)	191.7(35.6)	190.3(34.8)	190.1(34.8)	196.3(45.1)	0.34
LDL-C (mg/dl) (SD)	113.6(32.1)	113.8(32.0)	112.0(31.4)	111.9(31.4)	120.5(39.3)	0.16
CRP (mg/dl) (SD)	3.8(5.9)	3.6(5.3)	3.7(5.7)	3.7(5.7)	5.2(7.9)	0.24

AMD = age-related macular degeneration

BMI = body mass index

SD = standard deviation

LDL-C = low density lipoprotein cholesterol

CRP = C-reactive protein

† P-values are from chi square (X2) statistic tests comparing any AMD and no AMD.

* There was some overlap in the severity of AMD between the eyes of some participants. Analyses were performed using the worst eye.

Table 2

Cardiovascular outcomes in patients with and without age-related macular degeneration

Event	Overall Cohort (n=6809)	No AMD (n=5914)	AMD (n=895)	Early AMD (n=892)	Late AMD (n= 27)	p-value*
MI	126 (1.85%)	105(1.78%)	21(2.35%)	21(2.35%)	2(7.41%)	0.24
Resuscitated Cardiac Arrest	17 (0.25%)	14(0.24%)	3(0.34%)	3(0.34%)	0(0.00%)	0.58
Resuscitated Cardiac Arrest (probable)	2 (0.03%)	2(0.04%)	0(0.00%)	0(0.00%)	0(0.00%)	0.58
Resuscitated Cardiac Arrest (definite)	15 (0.22%)	12(0.20%)	3(0.34%)	3(0.34%)	0(0.00%)	0.43
Angina pectoris	199 (2.92%)	167(2.82%)	32(3.58%)	32(3.59%)	2(7.41%)	0.21
Definite angina	135 (1.98%)	109(1.84%)	26(2.91%)	26(2.92%)	1(3.70%)	0.03
Probable Angina	64 (0.94%)	58(0.98%)	6(0.67%)	6(0.67%)	1(3.70%)	0.37
PTCA or arterectomy	145 (2.13%)	128(2.16%)	17(1.90%)	17(1.91%)	1(3.70%)	0.61
CABG	86 (1.26%)	68(1.15%)	18(2.01%)	18(2.02%)	0(0.00%)	0.03
Stroke	105 (1.54%)	94(1.59%)	11(1.23%)	11(1.23%)	1(3.70)	0.42
Death	283 (4.16%)	243(4.11%)	40(4.47%)	40(4.48%)	4(14.81%)	0.62
CHD death	35 (0.51%)	31(0.52%)	4(0.45%)	4(0.45%)	0(0.00%)	0.76
Stroke death	13 (0.19%)	12(0.20%)	1(0.11%)	1(0.11%)	1(3.70%)	0.56

*P-values are from two-sided Fisher Exact tests.

AMD = age-related macular degeneration

MI=myocardial infarction

PTCA = percutaneous coronary angioplasty

CABG = coronary artery bypass graft surgery

CHD= coronary heart disease

Table 3

Cumulative Incidence and Hazard Ratios of Coronary Heart Disease and Cardiovascular Disease in Association with Age-Related Macular Degeneration

AMD status	Age-sex adjusted CHD HR (95% CI)	Multivariable CHD HR (95% CI)*
Any AMD	0.97 (0.70–1.34) p=0.85	1.01 (0.73–1.41) p=0.95
Early AMD	0.97(0.70,1.35) p=0.87	1.03(0.74,1.43)p=0.88
Late AMD	1.65(0.52,5.21)p=0.39	1.63(0.52,5.17)p=0.40
AMD Status	**Age-sex adjusted CVD HR (95% CI)**	**Multivariable CVD HR (95% CI)***
Any AMD	0.94(0.70–1.25) p=0.66	0.99(0.74,1.33)0.97
Early AMD	0.94(0.71,1.26)p=0.69	1.01(0.76,1.35)p=0.95
Late AMD	1.73(0.64,4.67)p=0.28	1.72(0.63,4.58)p=0.29

CHD = coronary heart disease

HR = hazard ratio

CI = confidence interval

AMD = age-related macular degeneration

CVD = cardiovascular disease

*Adjusted for race, hypertension, cigarette smoking, site of enrolment, C-reactive protein, level of education and diabetes, body mass index, serum total cholesterol and LDL-cholesterol