Title

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Apolipoprotein E Gene and Age-Related Maculopathy in Older Individuals

The Cardiovascular Health Study

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Objective: To examine the association between the apolipoprotein E (*APOE*) gene and age-related maculopathy (ARM) in an older population.

Methods: Two thousand one hundred seventy persons 65 years and older sampled from 4 US communities had ARM signs assessed from retinal photographs using a modified Wisconsin Age-Related Maculopathy Grading System. DNA extracted from blood samples was analyzed for common *APOE* alleles.

Results: After controlling for age, sex, cigarette smoking, and other factors, white participants carrying the ε2 allele had an increased risk of late ARM (odds ratio, 2.53 [95% confidence interval, 1.08-5.90]) while carriers of the ε4 allele had a lower risk of late ARM (odds ratio, 0.69 [95% confidence interval, 0.19-2.50]). There were too few late ARM cases in African American individuals for analysis.

Conclusion: *APOE* polymorphism is associated with late ARM in older white persons 65 years and older. Consistent with previous studies, the *APOE* ε2 allele is associated with a significant increased risk of late ARM development, whereas the ε4 allele may confer some protection.

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AGE-RELATED MACULOPATHY (ARM) is a leading cause of visual impairment in the elderly population.[1] Genetic predisposition to ARM has been hypothesized,[2] and specific genes (eg, complement factor H) have recently been identified.[3-5]

The apolipoprotein E (*APOE*) gene, a major apolipoprotein of the central nervous system and a key regulator of lipid transport,[6] has been linked with a variety of neurodegenerative and cardiovascular disorders, including Alzheimer disease[7] and stroke,[8] and is another attractive candidate gene to investigate possible links with ARM. However, previous studies that have examined the association of the *APOE* gene and ARM have shown somewhat inconsistent results.[9-18] Of the 3 common alleles of *APOE* (ε2, ε3, and ε4), the ε4 carrier has been inversely associated with late ARM in some,[9-13,16] but not all,[14,15] studies, whereas the ε2 carrier may be associated with an increased ARM risk.[9,12,16,17]

The majority of these studies have been clinic based, and few population-based data are available.[9] Further, there have been suggestions that the relationship between *APOE* and ARM is modified by age and possibly race.[3,11,14,15,17] In particular, 1 study showed a significant protective association of the ε4 carrier and ARM only among participants younger than 70 years and not in older persons.[17] It was suggested that genetic factors may play a less important role in the pathogenesis of ARM in older people.

The Cardiovascular Health Study (CHS) is a population-based study of white and African American persons 65 years and older at baseline.[19] We have previously reported the prevalence of ARM in the CHS.[20] In the current study, we examine its association with *APOE*.

METHODS

STUDY POPULATION

The CHS has been previously described.[19] The original cohort recruited 5201 persons in 1989-1990 in 4 field centers: Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pa. An additional 687 eligible African American individuals were recruited from Forsyth County,

Sacramento County, and Pittsburgh in 1992-1993.[21] This report used data from the 1997-1998 examination, when retinal photography was first performed.[20] Of the 4249 participants (95.6% of survivors) who were contacted for this examination, we excluded 29 participants whose race was neither white nor African American, 491 without *APOE* data, and 1559 who were not examined in the clinic and did not have retinal photography or who had ungradeable photographs, leaving 2170 who provided data for the current analysis. Differences between persons with and without gradable retinal photographs have been previously reported.[20] In general, persons who did not have retinal photography or had ungradeable photographs were older and, while controlling for age, were more likely to be African American and female; to have diabetes mellitus and hypertension; and to be current cigarette smokers. There were no significant age-adjusted differences between those included and excluded with regard to body mass index, hypertension status, systolic blood pressure, plasma total cholesterol level, high-density lipoprotein (HDL) cholesterol level, low-density lipoprotein cholesterol level, and common carotid intima media thickness.[20]

ARM GRADING AND DEFINITIONS

The retinal photography procedure and retinal grading have been previously reported.[20,22] Briefly, a 45° nonmydriatic retinal photograph of 1 randomly selected eye of each participant was taken at the follow-up examination following 5 minutes of dark adaptation. The photograph was centered on the region of the optic disc and the macula. The photographs were sent to the University of Wisconsin Fundus Reading Center, Madison, for assessment and grading of ARM. Trained graders masked to the subject identity evaluated the photographs using a modification of the Wisconsin Age-Related Maculopathy Grading System.[23]

For grading, a grid consisting of 2 circles concentric with the center of the macula and 4 radial lines was superimposed over the photograph. The presence of soft drusen, retinal pigment epithelial depigmentation, increased retinal pigment, pure geographic atrophy, and signs of exudative macular degeneration (subretinal hemorrhage, subretinal fibrous scar, retinal pigment epithelial detachment, and/or serous detachment of the sensory retina) were determined in the macular area circumscribed by the outermost circle of the grading grid. The circle had a radius that corresponded to 3450 µm in the fundus of an average eye.

Soft drusen were defined as those having a diameter larger than 63 µm. Retinal pigment epithelial depigmentation, increased retinal pigment associated with ARM (the presence of granules or clumps of gray or black pigment in or beneath the retina), and pigmentary abnormalities were defined as present or absent/questionable. Early ARM was defined as the presence of either soft drusen alone, retinal pigment epithelial depigmentation alone, or a combination of soft drusen with increased retinal pigment and/or depigmentation in the absence of late ARM.[20,23] Late ARM was defined as the presence of signs of exudative ARM degeneration or pure geographic atrophy.[20,23]

APOE GENOTYPING

Genotyping of *APOE* in the CHS has been previously described.[24,25] Only participants who gave consent for DNA use for noncardiovascular outcomes were included in this analysis. We analyzed separately the 3 common carriers of *APOE* (ε2, ε3, and ε4) and its 6 common genotypes. The 3 major allelic forms of the *APOE* gene were determined in the Core Molecular Genetics facility at the University of Vermont College of Medicine by the method of Hixson and Vernier.[26] The 2 primers used for polymerase chain reaction amplification, done in 96-well microtiter plates, were 5′GGCACGGCTGTCCAAGGA3′ and 5′ACAGAATTCGCCCCGGCCTGGTACAC3′. Amplitaq T4 DNA polymerase was obtained from Perkin-Elmer (Wellesley, Mass); the restriction enzyme *Hha*I was obtained from New England BioLabs (Ipswich, Mass). DNA samples known to be ε4/ε2 and ε2/ε3 were analyzed with each batch as positive controls. The restriction patterns were determined with the use of agarose electrophoresis.[26]

DEFINITION OF OTHER VARIABLES

Participants underwent clinical and laboratory assessment of cardiovascular diseases and its risk factors during the course of the study.[27-29] Relevant portions are highlighted herein. Blood pressures were taken according to a standardized protocol.[27] Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or the combination of self-reported high blood pressure diagnosis and use of antihypertensive medications. Medical history, medication use, cigarette smoking, and alcohol consumption status were ascertained from questionnaires. Technicians assessed body mass index (calculated as weight in kilograms divided by height in meters squared) and the waist-hip ratio. Blood collection, processing, and definitions for fasting glucose level; total, low-density lipoprotein, and HDL cholesterol levels; and triglyceride level are described elsewhere.[19] All variables defined were based on the 1997-1998 clinic examination, concurrent with retinal photography, except data on most blood chemistry results and body measurements, which were taken from the 1992-1993 examination.

STATISTICAL ANALYSIS

We examined whether the distribution of *APOE* carriers (any ε2, ε3, and ε4) and specific genotypes by presence or absence of ARM was in Hardy-Weinberg equilibrium using the χ^2 test. Where the reliability of *P* values based on χ^2 approximations was questionable, we report *P* values for Fisher exact test. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for ARM by *APOE* genotype frequency using the ancestral ε3/ε3 as the reference group in logistic regression models. In the multivariate analysis, we adjusted for age, sex, race, cigarette smoking, hypertension, and glucose and total triglyceride levels for models of early ARM and age, sex, race, cigarette smoking, hypertension, and HDL cholesterol level for late ARM. Because genotype frequency differed by race, analyses were also performed separately in white individuals and African American individuals.

Finally, *APOE* variation was also modeled in a risk score model, because risk scores have been demonstrated to increase power in modeling genetic exposures.[30] Because previous studies suggested ε4 conferred protection while ε2 increased risk, a genotypic risk scoring system was devised to test this hypothesis, which respectively assigned +1, 0, or –1 risk units for each ε2, ε3, or ε4 carrier of an individual with genotypes (scores) of ε2/ε2 (+2), ε2/ε3 (+1), ε2/ε4 (+0), ε3/ε3 (+0), ε3/ε4 (–1), and ε4/ε4 (–2). All *P* values are 2-sided and STATA 8.2 (StataCorp, College Station, Tex) was used for all analyses.

RESULTS

Characteristics between persons with early ARM (n = 336) or late ARM (n = 28) compared with those with no ARM

Table 1. Participant Characteristics by Presence of Early and Late ARM*

	No ARM (n = 1806)	Early ARM (n = 336)	Late ARM (n = 28)
Age, y, mean	78.2	79.9†	82.2†
Men, %	39.2	41.1	42.9
African American, %	16.1	8.6†	3.6
High school graduate, %	49.6	45.5	60.7
BMI, mean	27.1	26.4	27.2
Hypertension, %	49.2	49.7	46.4
Systolic blood pressure, mm Hg, mean	131.4	131.1	133.1
Diastolic blood pressure, mm Hg, mean	66.7	66.0	65.3
Diabetes mellitus, %	17.9	16.7	17.9
Glucose level, mg/dL, mean	101.0	103.6†	96.6
Total plasma cholesterol level, mg/dL, mean	203.1	200.3	192.6
HDL cholesterol level, mg/dL, mean	53.7	53.8	57.7†
Total triglyceride level, mg/dL, mean	144.6	134.6†	124.9
Cigarette smoking, current, %	6.8	6.9	7.1
Alcohol use, units/wk	2.1	2.2	3.4

Abbreviations: ARM, age-related maculopathy; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein.

SI conversion factors: To convert glucose to micromoles per liter, multiply by 0.0555; plasma total cholesterol and HDL cholesterol to micromoles per liter, multiply by 0.0259; triglycerides to micromoles per liter, multiply by 0.0113.

*Adjusted for age, sex, and race (except for rows "Age," "Men," and "African American," which are not adjusted for age, sex, and race, respectively).

†*P* value <.05, comparing difference in adjusted means or proportions between early or late ARM with no ARM.

(n=1806) are presented in **Table 1**. In general, persons with early ARM were significantly older, less likely to be African American, and had a higher plasma glucose level than persons without ARM, while persons with late ARM were significantly older and had a significantly higher plasma HDL cholesterol level compared with those with no ARM. All other characteristics were not associated with any ARM status.

Table 2 shows the prevalence of no ARM, early and late ARM, and specific early ARM signs by *APOE* allele carrier and genotype status. The *APOE* carrier and genotype distribution did not differ significantly between subjects with early ARM or early ARM signs compared with those with no ARM.

The prevalence of early and late ARM as compared with no ARM by *APOE* allele carrier and genotype status in white and African American individuals is presented in **Table 3**. Overall, ε3/ε3 was the dominant genotype and ε3, the dominant allele carrier in both white and African American individuals. White individuals with late ARM were more likely to have the ε2 allele (18.5%) and less likely to have the ε4 allele (7.4%) as compared with white individuals with no ARM (8.7% and 12.6%; $P<.05$ for both comparisons). African American individuals with early ARM were more likely to carry the ε2 allele (24.1%) as compared with those with no ARM (13.4%; $P<.05$).

Table 4 shows multivariate logistic regression models of early and late ARM, controlling for age, sex, race, cigarette smoking, and other factors. In all persons, white individuals, and African American individuals, neither ε2 carriers nor ε4 carriers were associated with early ARM. In all persons and white individuals, ε2 carriers were more likely to have late ARM (OR, 2.53 for both groups) after multivariable adjustment, while the ε4 carrier was associated with a slightly decreased but not significant risk of late ARM in all persons (OR, 0.89 [95% CI, 0.28-2.79]) and in white individuals (OR, 0.69 [95% CI, 0.19-2.50]).

The results of the logistic regression models for early and late ARM by *APOE* risk score are shown in Table 4. There was a significant association between increasing *APOE* score and late ARM in white individuals (OR, 1.87 [95% CI, 1.01-3.47]) after controlling for other factors, but no associations were found for early ARM.

Finally, Table 4 shows that in comparison with the ε3/ε3 genotype, the ε2/ε3 genotype was associated with an increased risk of having late ARM in all persons (OR, 2.74 [95% CI, 1.14-6.58]) and in white individuals (OR, 2.78 [95% CI, 1.16-6.67])

COMMENT

Mounting evidence from molecular investigations,[10,31] animal models,[32] and epidemiologic studies[9-13,16,17] indicates that *APOE* is associated with ARM development. Previous studies that have examined a possible relationship between *APOE* and ARM have suggested a lower risk of ARM[9-13,16] in carriers of the ε4 allele while, less consistently, the ε2 carrier appears to confer an increased risk of ARM.[9,12,16,17] Our results concur with these findings in that the frequency of carrying the ε4 allele was significantly lower and the frequency of carrying the ε2 allele was significantly higher in white individuals with late ARM as compared with white individuals with no ARM. After adjusting for age, sex, cigarette smoking, total triglyceride level, and hypertension, we observed a 2.5-fold increased risk in all persons and white individuals with late ARM if they were carriers of the ε2 allele and a nonsignificant 31% decrease in risk for white individuals of having late ARM if they were ε4 carriers.

Because 1 study reported a significant protective association of the ε4 carrier and ARM only among participants younger than 70 years,[17] it has been suggested that genetic factors may play a more important role in the etiology of ARM in younger people. Our current study, however, shows that *APOE* polymorphism may still have a significant role in late ARM development in older persons (mean age of 78 years in the current study).

With regard to early ARM, we did not find a consistent pattern of association with *APOE*. In particular, we found no evidence that the ε4 carrier was associated with a lower risk or that the ε2 carrier was associated with a higher risk of early ARM. It is possible that the lack of a consistent association of *APOE* and early ARM in our study reflects the more prominent role of *APOE* on the development of late ARM signs only. This was also observed by Baird and colleagues,[12] in which significant associations of *APOE* ε2 and ε4 with ARM were confined to late disease.

Table 2. Distribution of *APOE* Allele and Genotype by Specific ARM Signs

	No. (%) With *APOE* Allele Carrier and Genotype					
APOE	**No ARM**	**Early ARM**	**Soft Drusen**	**Increased RPE Pigmentation**	**RPE Depigmentation**	**Late ARM**
Carrier*						
ε2	342 (9.5)	67 (10.0)	66 (10.0)	37 (11.9)	17 (14.7)	10 (17.9)
ε3	2784 (77.1)	533 (79.3)	530 (80.1)	239 (77.1)	85 (73.3)	41 (73.2)
ε4	481 (13.3)	72 (10.7)	66 (10.0)	34 (11.0)	14 (12.1)	5 (8.9)
P value†	. . .	.18	.06	.22	.18	.08
Total	**3607**	**672**	**662**	**310**	**116**	**56**
Genotype						
ε2/ε2	12 (0.7)	2 (0.6)	1 (0.3)	2 (1.3)	1 (1.7)	0
ε2/ε3	264 (14.6)	52 (15.5)	54 (16.4)	27 (17.4)	12 (20.7)	9 (32.1)
ε2/ε4	54 (3.0)	11 (3.3)	10 (3.0)	6 (3.9)	3 (5.2)	1 (3.6)
ε3/ε3	1075 (59.5)	210 (62.5)	210 (63.4)	92 (59.4)	31 (53.4)	15 (53.6)
ε3/ε4	375 (20.8)	61 (18.2)	56 (16.9)	28 (18.1)	11 (19.0)	2 (7.1)
ε4/ε4	26 (1.4)	0	0	0	0	1 (3.6)
P value†	. . .	.27	.12	.46	.49	.09
Total	**1806**	**336**	**331**	**155**	**58**	**28**

Abbreviations: APOE, apolipoprotein E; ARM, age-related maculopathy; RPE, retinal pigment epithelial.
*Genotypes with the ε2 carrier are grouped and genotypes with the ε4 carrier are grouped; subjects with the ε2/ε4 genotype are present in both the ε2 and ε4 groups.
†Compares distribution of *APOE* carrier or genotype with subjects with no ARM (control).

Table 3. Distribution of *APOE* Allele and Genotype by Early and Late ARM in White and African American Individuals

	No. (%)				
	White			African American	
APOE	**No ARM (n = 1515)**	**Early ARM (n = 307)**	**Late ARM (n = 27)**	**No ARM (n = 291)**	**Early ARM (n = 29)**
Carrier*					
ε2	264 (8.7)	53 (8.6)	10 (18.5)†	78 (13.4)	14 (24.1)‡
ε3	2383 (78.6)	497 (80.9)	40 (74.1)	406 (69.8)	36 (62.1)
ε4	383 (12.6)	64 (10.4)	4 (7.4)§	98 (16.8)	8 (13.8)
Genotype					
ε2/ε2	9 (0.6)	1 (0.3)	0	3 (1.0)	1 (3.5)
ε2/ε3	199 (13.1)	44 (14.3)	9 (33.3)‖	65 (22.3)	8 (27.6)
ε2/ε4	47 (3.1)	7 (2.3)	1 (3.7)	7 (2.4)	4 (13.8)¶
ε3/ε3	939 (62.0)	198 (64.5)	15 (55.6)	136 (46.7)	12 (41.4)
ε3/ε4	306 (20.2)	57 (18.6)	1 (3.7)	69 (23.7)	4 (13.8)
ε4/ε4	15 (1.0)	0	1 (3.7)	11 (3.8)	0

Abbreviations: APOE, apolipoprotein E; ARM, age-related maculopathy.
*Genotypes with the ε2 allele are grouped and genotypes with the ε4 allele are grouped; subjects with the ε2/ε4 genotype are present in both the ε2 and ε4 groups.
†$P<.05$ for pairwise comparison between ε2 and ε3 allele carriers in white individuals with late ARM compared with the group with no ARM.
‡$P<.05$ for pairwise comparison between ε2 and ε3 allele carriers in African American individuals with early ARM compared with the group with no ARM.
§$P<.05$ for pairwise comparison between ε2 and ε4 carriers in white individuals with late ARM compared with the group with no ARM.
‖$P<.05$ for pairwise comparison between the ε2/ε3 and ε3/ε3 genotypes in white individuals with late ARM compared with the group with no ARM.
¶$P<.05$ for pairwise comparison between the ε2/ε4 and ε3/ε3 genotypes in African American individuals with early ARM compared with the group with no ARM.

One of the purposes of this study was to investigate possible racial variation in the association of *APOE* and ARM. In contrast to white populations, the association between *APOE* and ARM has been inconsistent in studies of other ethnic groups such as Chinese[14] and Italian[16] populations. In our study, there was a significant difference in the distribution of the *APOE* genotype in African American individuals with early ARM as compared with those with no ARM. In fact, African American subjects with the ε2/ε4 genotype had an almost 7-fold higher risk of early ARM compared with those who had the ε3/ε3 genotype (multivariate adjusted OR, 6.42 [95% CI, 1.47-28.12], data not shown). This association was not seen in white individuals, where ARM was more prevalent.

In a recent report by Schmidt et al,[33] the possible association between exudative ARM and *APOE* ε2 carriers was suggested to be stronger in cigarette smokers compared with people who had never smoked, although the finding was not significant. In our cohort, we also examined the association of *APOE* and early ARM in per-

Table 4. Association of *APOE* Carrier and Genotype With Early or Late ARM in All Persons, White Individuals, and African American Individuals*

ARM	*APOE*	Multivariate OR (95% CI) of Early or Late ARM†		
		All	White	African American
Early ARM	ε2 carrier‡	1.04 (0.76-1.44)	0.96 (0.67-1.36)	1.65 (0.67-4.07)
	ε4 carrier‡	0.99 (0.73-1.34)	0.97 (0.71-1.34)	1.27 (0.47-3.40)
	APOE risk score‖	1.08 (0.90-1.31)	1.03 (0.84-1.27)	1.39 (0.83-2.34)
Late ARM	ε2 carrier‡	2.53 (1.08-5.90)	2.53 (1.08-5.90)	§
	ε4 carrier‡	0.89 (0.28-2.79)	0.69 (0.19-2.50)	§
	APOE risk score‖	1.68 (0.93-3.07)	1.87 (1.01-3.47)	§
	ε2/ε2	NA	NA	§
	ε2/ε3	2.74 (1.14-6.58)	2.78 (1.16-6.67)	§
	ε2/ε4	2.18 (0.27-17.40)	2.15 (0.27-17.27)	§
	ε3/ε3	1	1	§
	ε3/ε4	0.51 (0.11-2.28)	0.26 (0.03-2.02)	§
	ε4/ε4	3.50 (0.41-30.16)	3.79 (0.43-33.32)	§

Abbreviations: APOE, apolipoprotein E; ARM, age-related maculopathy; CI, confidence interval; HDL, high-density lipoprotein; NA, not applicable; OR, odds ratio.

*There were no early ARM cases in persons with the ε4/ε4 genotype and no late ARM cases in persons with the ε2/ε2 genotype.

†Odds ratio (95% CIs) of early or late ARM in association with *APOE* allele, *APOE* risk score, or *APOE* genotype, adjusted for age; sex; cigarette smoking; glucose and total triglyceride levels; and hypertension (and race for all persons) for early ARM and adjusted for age, sex, cigarette smoking, HDL cholesterol level, and hypertension (and race for all persons) for late ARM.

‡Odds ratio (95% CIs) of early or late ARM comparing ε2 or ε4 *APOE* allele carrier vs ε3/ε3 *APOE* genotype as reference.

§There were too few late ARM cases in African American individuals for analysis.

‖Odds ratio (95% CIs) of early or late ARM per unit increase in *APOE* risk score assigned as +1, 0, or –1 risk units for each ε2, ε3, or ε4 carrier of an individual with genotypes (scores) of ε2/ε2 (+2), ε2/ε3 (+1), ε2/ε4 (+0), ε3/ε3 (+0), ε3/ε4 (–1), or ε4/ε4 (–2).

sons who were current or previous cigarette smokers compared with those who were never smokers. The multivariate adjusted odds of having early ARM among participants who were ε2 carriers was increased but not significantly so among participants who had a history of smoking (OR, 1.40 [95% CI, 0.89-2.20]). In contrast, participants who were ε2 carriers and had never smoked were at a reduced risk of having early ARM (OR, 0.80 [95% CI, 0.50-1.27]). Larger epidemiologic studies are required to provide further evidence to support these findings.

The current study has a number of strengths. These include a population drawn from the community, a large sample size, standardized ARM evaluation from photographs, and detailed information on a variety of potential risk factors. Several important limitations should also be mentioned. First, the CHS used a 45° nonstereoscopic fundus photograph taken through nonpharmacologically dilated pupils to determine the presence of ARM. Thus, the sensitivity related to the detection of ARM (in particular, early ARM signs) is more likely to be lower compared with the prevalence of ARM assessed from photographs taken with pharmacologically dilated pupils. Similarly, the grading of ARM is more variable when assessed through nonpharmacologically dilated pupils compared with the grading of 30° stereoscopic fundus photographs taken through dilated pupils.[34] In addition, because the CHS was primarily interested in examining the value of retinal vascular signs in the prediction of cardiovascular disease, only 1 randomly selected eye was photographed. This may lead to an increased variability of ARM detection, which in turn increases the likelihood of measurement error and misclassification. However, misclassification of the small number of "false-negative" cases (ie, true ARM cases misclassified as noncases) is unlikely to substantially bias the results except toward the null.

Second, selection bias may have obscured associations because the study population was derived from the cohort examined 10 years from the baseline. If persons with ARM and the ε2 or ε4 carrier were less likely to participate in this examination because of higher mortality, Alzheimer disease, or other reasons, the potential ARM-*APOE* association could be falsely distorted.

Finally, as noted earlier, we did not have sufficient cases of late ARM in African American individuals to analyze potential associations with *APOE*. In fact, the CHS population had a lower prevalence of late ARM cases in both racial groups analyzed (1.3%) compared with other population-based studies, such as the Beaver Dam Eye Study (1.6%)[35] and the Blue Mountains Eye Study (1.9%).[36] The lower prevalence may be attributed to the use of a nonmydriatic camera, which resulted in less ARM being detected, or the fact that retinal photographs were only taken at the 10-year follow-up examination when many of the participants who may have had late ARM (and thus were more likely to be older) were either unable to attend the examination because of poor health or may have died in the interim or, alternatively, the CHS population may have a lower prevalence of late ARM cases.

In conclusion, in this older, population-based cohort, we showed that the ε2 carrier may be associated with an increased risk of developing late ARM. While the ε4 carrier appears to confer some protection, the association was not statistically significant. These findings were largely confined to white persons.

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