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## Association between dietary xanthophyll (lutein and zeaxanthin) intake and early age-related macular degeneration: the Atherosclerosis Risk in Communities Study

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### Abstract

**Purpose**—To examine the association between xanthophyll intake and prevalent early age-related macular degeneration (AMD) using data from the Atherosclerosis Risk in Communities Study (n=10,295). Potential effect modification by genetic polymorphisms and biomarkers of high-density lipoprotein (HDL) metabolism was explored.

**Methods**—Xanthophyll intake was assessed at visit 1 (1987-89) using food frequency questionnaires. Prevalent early AMD was assessed at visit 3 (1993-95) via retinal photographs. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for AMD by quintiles of xanthophyll intake, adjusted for age, sex, race, field center, and pack-years of smoking. To evaluate effect modification, the association between tertiles (T) of xanthophyll intake and AMD was stratified by complement factor H (*CFH*) rs1061170 and age-related maculopathy susceptibility 2 (*ARMS2*) rs10490924 genotypes, as well as by median cutpoints of HDL biomarkers.

**Results**—Xanthophyll intake was not associated with AMD in the overall sample, Caucasians (n=8,257), or African-Americans (n=2,038). Exploratory analyses observed that the association between xanthophyll intake and AMD varied statistically significantly by *CFH* rs1061170 genotype (p for interaction = 0.045) among Caucasians but not African Americans. No interactions were observed between xanthophyll intake and *ARMS2* rs10490924. Moreover, higher xanthophyll intake observed a decreased odds of AMD among participants with lower HDL (OR=0.79, 95% CI 0.57-1.09) but not higher HDL (p for interaction=0.048).

**Conclusion**—Xanthophyll intake was not associated with early AMD. Further studies to investigate this association by genetic susceptibility or variations in HDL metabolism are needed.

## Keywords

Age-related macular degeneration; xanthophyll; lutein and zeaxanthin; HDL; CFH; ARMS2

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## INTRODUCTION

Age-related macular degeneration (AMD) is the third leading cause of blindness worldwide, accounting for 5% of total blindness in 2010.(1) A recent meta-analysis estimated the global prevalence of AMD among individuals 45-85 years of age to be 8.7%, and projected that the burden of disease will rise exponentially over the next few decades given the current trends of population aging.(2) While available therapies slow progression from early AMD to advanced AMD,(3, 4) they do not reverse existing damage to the retina. Taken together, these findings highlight the importance of AMD prevention.

Oxidative stress that incites inflammatory responses and disrupts lipid metabolism within the retina has been implicated in AMD pathogenesis.(5, 6) Supplementation or increased dietary intake of the xanthophyll pigments – lutein and zeaxanthin – may play an essential role in limiting intraretinal oxidative stress.(7, 8) However, while xanthophyll supplementation may decrease progression from early AMD to advanced AMD,(9) no clinical trial has investigated whether it decreases development of early AMD. Inconsistent results between xanthophyll intake and early AMD in observational studies (10-14) could reflect the presence of unmeasured effect modifiers. In particular, two single-nucleotide polymorphisms strongly associated with AMD – complement factor H (*CFH*) rs1061170 (Y402H) and age-related maculopathy susceptibility 2 (*ARMS2*) rs10490924 (A69S) – may increase early AMD risk by 1.5-fold.(15) Pooled analysis of two population-based cohorts found that greater xanthophyll intake reduced early AMD incidence only among participants carrying 2 risk alleles from either locus (*CFH* rs1061170 C or *ARMS2* rs10490924 T).(16) Moreover, xanthophyll transport to and within the retina is facilitated by processes dependent upon high-density lipoprotein cholesterol (HDL).(17, 18) HDL is also involved in numerous pathways that reduce oxidative stress,(19) and HDL dysfunction has been observed in animal models and chronic systemic diseases that increase AMD risk.(20, 21) Collectively, these findings suggest that differential genetic susceptibility and variations in HDL metabolism may influence the relationship between xanthophyll intake and early AMD.

More work is needed to better understand the association between xanthophyll intake and early AMD. The potential interaction between high risk polymorphisms and xanthophyll intake on early AMD has not been extensively explored. In addition, to the authors' best knowledge, previous studies have not examined the association between xanthophyll intake and early AMD by circulating biomarkers of HDL metabolism. Thus, the current study used data from the Atherosclerosis Risk in Communities Study (ARIC) to evaluate the association between xanthophyll intake (assessed at visit 1, 1987-1989) and prevalent early AMD (subsequently assessed at visit 3, 1993-1995). *CFH* rs1061170 and *ARMS2* rs10490924 genotype, as well as plasma concentrations of total HDL, HDL2, HDL3 and apolipoprotein

A1 (apoA1) assessed at visit 1, were tested as potential effect modifiers in exploratory analyses.

## METHODS

### Study Sample

The ARIC Study is a population-based prospective cohort designed to investigate the etiology of atherosclerosis and its relationship to cardiovascular disease endpoints, as well as the potential modifying effects of race, sex and differential access to medical care. At visit 1 (1987-1989), a total of 15,792 participants between the ages of 45-64 were recruited via probability sampling of four geographic regions in the United States: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland. At visit 1, visit 2 (1990-1992), and visit 3 (1993-1995), participants underwent physical examination and completed surveys inquiring about sociodemographic factors, lifestyle choices, and medical history. A total of 12,887 participants attended visit 3, when fundus photographs were taken.(22) Participants who were neither Caucasian nor African American (n=34); had missing or ungradable fundus photographs (n=1,250); declined to provide consent for research unrelated to cardiovascular disease outcomes (n=796); had advanced AMD (n=14); or had missing data on visit 1 xanthophyll intake (n=224), pack-years of smoking (n=155), HDL (n=118) or HDL2 data (n=1) were excluded from analysis. Supplemental Figure 1 depicts study sample selection (n=10,295).

### Disease endpoints

Prevalent AMD status was ascertained via fundus photographs taken at visit 3 (1993-1995), using a non-mydratiac automatically focusing camera (Canon CR-45UAF) and without pharmacologic dilation. Patients were asked to sit in a darkened room for 5 minutes, after which the camera was centered on the region between the optic disc and the fovea of a randomly chosen eye. Nonstereoscopic 45-degree color film retinal images thus obtained were then evaluated by a masked grader at the University of Wisconsin Fundus Photograph Reading Center.(23) Given the low prevalence of advanced AMD (presence of geographic atrophy or choroidal neovascularization, n=14), the primary endpoint variable used in the present analyses was prevalent early AMD (presence of soft drusen with diameter  $\geq 63 \mu\text{m}$  or retinal pigment epithelium depigmentation, in the absence of advanced AMD).

### Assessment of dietary xanthophyll intake

A 66-item food frequency questionnaire (FFQ) completed at visit 1, six years prior to fundus photography at visit 3, was used to estimate daily dietary intake of lutein and zeaxanthin (micrograms). This instrument was modified from a version developed by Willet *et al*, and its validity and reliability has been previously demonstrated.(24, 25) Dietary xanthophyll intake was adjusted for estimated daily caloric intake using the multivariate nutrient density model.(26) Participants with implausible caloric intake (women:  $<500$  or  $>3600$  kcal; men:  $<600$  or  $>4200$  kcal) or with  $>10$  missing values on the visit 1 FFQ were excluded.(27) Dietary supplements of xanthophylls were not available during the time of the study. An FFQ was also completed at visit 3, and these data were used to explore the potential effects of interval changes in dietary xanthophyll intake on odds of AMD.

### Assessment of CFH rs1061170 and ARMS2 rs10490924 genotype

Genotyping of single nucleotide polymorphisms (SNPs) in ARIC was completed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix, Inc., Santa Clara, CA).(28) The ARMS2 rs10490924 (A69S) was genotyped directly as part of the Affymetrix chip. Subsequent imputation, using both HapMap and the 1000 Genomes reference panels as appropriate for Caucasians and African Americans, yielded data on CFH rs1061170 (Y402H). Minor allele frequency and Hardy-Weinberg equilibrium for the genotyped *ARMS2 rs10490924* was met. The imputation quality for CFH rs1061170 was high in both the Caucasian and African-American datasets (scores >0.8).

### Assessment of plasma biomarkers of high-density lipoprotein metabolism

Participants were asked to fast for 12 hours prior to the clinical examination. Blood was drawn from the antecubital vein into tubes containing EDTA, which were then fractionated via centrifugation at 3000g and 4°C for 10 minutes. Plasma samples were stored at -70°C until analysis at the ARIC Central Lipid Laboratory (Baylor College of Medicine, Houston, TX).(29) Total cholesterol and triglycerides concentrations were assayed using the cholesterol oxidase-4-aminophenazone reaction scheme. HDL was then separated into subfractions and quantified using the Warnick dual-precipitation method. ApoA1 was measured via radioimmunoassay.(30, 31) Visit 1 plasma concentrations of total HDL cholesterol (HDL), HDL2 cholesterol (HDL2), HDL3 cholesterol (HDL3), and apolipoprotein A1 (apoA1) were used in these analyses.

### Statistical Analyses

The distribution of participant characteristics and other risk factors according to xanthophyll intake (quintiles), prevalent early AMD status (no vs. yes), and the presence of stigmata of early AMD (i.e., soft drusen, retinal pigment epithelium depigmentation) were examined using chi-square tests, t-tests and analyses of variance.

Multivariable logistic regression was used to evaluate the association between visit 1 xanthophyll intake and AMD. Odds ratios (ORs) and 95% Confidence Intervals (95% CIs) for AMD status by quintiles of xanthophyll intake were estimated with quintile 1 (low intake) as the reference group. Linear trend were estimated using quintile medians as a continuous variable, and were considered statistically at  $p < 0.05$ . Age, sex, race, and pack-years of smoking were determined to be included in the multivariable model *a priori*. In addition, a factor was included as a confounder if it were associated with both xanthophyll intake and prevalent AMD at  $p < 0.20$ , and changed the OR >10% after adjustment. Daily caloric intake was included as a covariate per the multivariate nutrient density method,(26) while field center was adjusted for to partially account for possible center bias.(32) To explore whether changes in diet influenced the pattern of results, the same set of analyses were also conducted using xanthophyll intake assessed at visit 3, the average of xanthophyll intakes assessed at visit 1 and 3, and after restricting the sample to only participants who exhibited dietary stability ( $\pm 1$  quintile change in xanthophyll intake from visit 1 to 3).

To assess for effect modification by CFH rs1061170 and ARMS2 rs10490924, analyses of the associations between visit 1 xanthophyll intake (tertiles) and AMD were stratified by

CFH rs1061170 genotype (CC/CT/TT), ARMS2 rs10490924 genotype (GT/TT/GG), and combined genetic risk ( 2 alleles of rs1061170 C or rs10490924 T). Both xanthophyll intake and genotypes were treated as categorical variables. Since the allelic frequency and associations of CFH and ARMS2 polymorphisms with AMD may vary across populations, genetic analyses were further stratified by race.(33) Similarly, to assess for effect modification by HDL, HDL2, HDL3, and apoA1, analyses of the associations between visit 1 xanthophyll intake (tertiles) and AMD status were stratified by the sample medians of these lipid biomarkers. P-values <0.10 were considered statistically significant when testing for multiplicative interaction. Linear trends were assessed by examining the association between xanthophyll intake (treated as a continuous variable,  $\mu\text{g}/1000$  kcal) and AMD by each category of the potential effect modifiers. Analyses were conducted using SAS software, Version 9 for Windows (SAS Institute Inc., Cary, NC).

## RESULTS

### Participant characteristics by prevalent early AMD status and xanthophyll intake

Compared to participants without AMD, participants with prevalent early AMD were more likely to be older, men, Caucasian, from lower-income households, from Forsyth or Washington County field centers, to have greater cumulative tobacco exposure, prevalent hypertension, and to have higher low-density lipoprotein cholesterol (LDL) concentrations ( 3.49 mmol/L) (Supplemental Table 1). Among Caucasian participants with AMD, there were more carriers of the high-risk *CFH* rs1061170 CC and *ARMS2* rs10490924 genotypes. Intake of macronutrients, unsaturated fats, carotenoids and other antioxidant micronutrients (vitamin C, vitamin E, and zinc) did not differ by AMD status.

Compared to participants reporting lower xanthophyll intake, participants reporting higher xanthophyll intake were more likely to be older, women, African American, less educated, from lower-income households, to not have health insurance, and to have been recruited from Forsyth County and Jackson. They were more likely to have lower cumulative tobacco exposure, prevalent hypertension, prevalent diabetes, prevalent congestive heart failure, to be obese, and to have higher HDL, HDL2, HDL3, and apoA1 concentrations, and lower LDL and triglyceride concentrations (Table 1). Dietary factors associated with higher xanthophyll intake were lower ethanol, caloric, total fat, monounsaturated fat, and polyunsaturated fat intake and higher carbohydrate, protein, omega-3 fatty acid, zinc, copper, vitamin C, vitamin E, and carotenoid intake.

Age, sex, race, adjusted household income, field center, pack-years of smoking, prevalent hypertension, HDL2, and LDL concentrations were associated with both AMD and quintiles of xanthophyll intake ( $p < 0.20$ ). However, only age and race changed the estimated ORs of the association between AMD and quintiles of xanthophyll intake by 10%. No other potential covariates were identified after further adjusting for sex, pack-years of smoking, field center, and daily caloric intake. The final multivariable model thus adjusted for age, sex, race, pack-years of smoking, field center, and daily caloric intake. As sex and pack-years of smoking could potentially influence HDL metabolism, data from a multivariable model adjusting for just age, race, field center, and daily caloric intake were also shown.

### Associations of xanthophyll intake with prevalent early AMD

Crude, age-adjusted and multivariable-adjusted ORs and 95% CIs for the associations of xanthophyll intake (quintiles) with AMD, soft drusen, and retinal pigment epithelium (RPE) depigmentation are shown in Table 2. Xanthophyll intake was not associated with AMD, soft drusen or RPE depigmentation in the overall sample. Furthermore, when the overall sample was stratified by race, xanthophyll intake was not statistically significantly associated with AMD, soft drusen or RPE depigmentation in either Caucasian or African American participants.

Repeating these analyses using visit 3 xanthophyll intake (Supplemental Table 2), average xanthophyll intake (arithmetic mean of visit 1 and 3 intake, Supplemental Table 3), or visit 1 intake among only participants exhibiting dietary stability ( $\pm 1$  quintile change from visit 1 to 3, Supplemental Table 4) yielded a similar pattern of results.

### Effect modification by genetic risk

Having  $< 2$  high-risk alleles of *CFH* rs1061170 was associated with a decreased odds of AMD among Caucasians, but not among African Americans (Supplemental Table 5). Similarly, having  $< 2$  high-risk alleles of *ARMS2* rs10490924 or having  $< 2$  high-risk alleles for the combined genetic risk score was associated with a decreased odds of AMD among Caucasian, but not among African Americans.

Among Caucasians, greater xanthophyll intake was associated with decreased odds of AMD in carriers of the moderate-risk CT genotype (T3 vs. T1, OR=0.63, 95% CI 0.41-0.91, p for trend=0.28), but not the low-risk TT (OR=1.20, 95% CI 0.73-1.97, p for trend=0.36) or high-risk CC (OR=1.76, 95% CI 0.94-3.29, p for trend=0.02) genotypes of *CFH* rs1061170 (p for interaction=0.045). *ARMS2* 10490924 genotype and combined genetic risk did not interact with xanthophyll intake to influence the odds of AMD among either race (Table 4).

### Effect modification by HDL, HDL2, HDL3, and apoA1

In the overall sample, HDL ( 1.27 vs.  $< 1.27$  mmol/L; OR=1.08, 95% CI 0.89-1.30, p=0.45), HDL2 ( 0.33 vs.  $< 0.33$  mmol/L; OR=0.93, 95% CI 0.77-1.13, p=0.47), HDL3 ( 0.95 vs.  $< 0.95$  mmol/L; OR=0.97, 95% CI 0.81-1.17, p=0.77), and ApoA1 ( 46.26 vs.  $< 46.26$   $\mu$ mol/L; OR=0.98, 95% CI 0.81-1.17, p=0.79) were not associated with AMD.

Multivariable-adjusted associations between xanthophyll intake (tertiles) and AMD, stratified by median cutpoints of HDL, HDL2, HDL3 or ApoA1 are shown in Table 4. While there were statistically significant multiplicative interactions of xanthophyll intake with HDL, HDL2 and ApoA1, there were no relationships between xanthophyll intake and AMD within any of the lipid biomarker subgroups.

## DISCUSSION

In this cohort of Caucasians and African Americans, xanthophyll intake was not associated with prevalence of early AMD in the overall sample, or when analyses were stratified by race. These findings are in agreement with previously published literature. With the exception of the Blue Mountains Eye Study (BMES),(14) xanthophyll intake was not



associated with the incidence of early AMD in four other prospective cohorts (i.e. Rotterdam Study, Beaver Dam Eye Study, Nurses' Health Study, and Health Professionals Study). (11-14) The Carotenoids in Age-Related Eye Disease Study also found no overall association between xanthophyll intake and prevalence of early AMD in postmenopausal women; however a significant inverse association emerged after analyses were restricted to younger participants with stable dietary intake and without a history of chronic diseases that frequently lead to dietary changes.(10) In the current study, exploratory analyses excluding participants exhibiting possible dietary instability did not influence the null association between xanthophyll intake and early AMD. To date, no previously conducted clinical trials have investigated whether xanthophyll supplementation decreases risk of early AMD.

Difference between findings among ARIC and BMES participants may be explained by age; ARIC participants were younger than the BMES participants (mean age, 53.9 years vs 64.0 years).(14) Moreover, ARIC defined early AMD as presence of either soft drusen  $\geq 63 \mu\text{m}$  in diameter or RPE depigmentation, whereas BMES defined early AMD as presence of soft drusen  $\geq 125 \mu\text{m}$  in diameter involving the macula or with concurrent retinal pigmentary abnormalities.(14) Unfortunately, ARIC graders did not specify the sizes of soft drusen observed in fundus photographs taken at visit 3, other than to indicate whether they exceeded  $63 \mu\text{m}$  in diameter. Taken together with the cross-sectional nature of the ARIC data, these differences may partially explain the disparate study findings.

Analyses in ARIC found that *CFH* rs1061170 genotype appeared to statistically significantly modify the association between xanthophyll intake and early AMD among Caucasian participants, such that greater xanthophyll intake was related to lower odds of AMD among individuals carrying the moderate-risk CT genotype, greater odds among those carrying the high-risk CC genotype, and no statistically significant association among those with the low-risk TT genotypes. No effect modification by genetics was observed among African American participants, though there was likely insufficient statistical power due to the relatively small number of AMD cases.

*CFH* rs1061170 has been associated with higher oxidative stress in the retina due to impaired clearance reactive species, disinhibition of the complement cascade, heightened systemic inflammation, as well as elevated intravitreal GM-CSF levels and increased abundance of choroidal macrophages.(34, 35) Pooled analysis of the BMES and Rotterdam Study demonstrated that increased xanthophyll intake marginally reduced incidence of early AMD, but only among individuals at high genetic risk, as defined by  $\geq 2$  alleles of either *CFH* rs1061170 C or *ARMS2* rs10490924.(16) Interestingly, increased xanthophyll intake was associated with greater incidence of early AMD among participants carrying 0 risk alleles.(16) In contrast, data from the AREDS study suggest that the protective effect of high-dose antioxidant supplementation on AMD progression may be more pronounced among carriers of *CFH* rs1061170 low-risk TT genotype.(36) Our findings are not in agreement with either of these previous studies. Whether and how genetic variation at this locus modifies the association between xanthophyll intake and AMD remains an open question.

Analyses in ARIC observed that greater xanthophyll intake trended towards decreased odds of early AMD among participants with lower HDL, HDL2, and apoA1, but not among participants with higher HDL, HDL2 or ApoA1. HDL concentration and function both tend to decline with age.(37) Research suggests that HDL is involved in both peripheral and intraretinal transport of xanthophylls,(17, 18) as well as in numerous processes that decrease oxidative stress and inflammation, including inhibition of lipid peroxidation, clearance of cholesterol waste products, neutralization of reactive oxygen species, regulation of the complement cascade, and suppression of monocyte-macrophage recruitment.(19) Therefore, variations in HDL metabolism could influence xanthophyll uptake into as well as its antioxidant effects within the retina. The current observations suggest that greater xanthophyll intake may be protective against development of early AMD among individuals experiencing perturbations in HDL metabolism. Yet, while some studies have found inverse associations between HDL and AMD, others have reported positive or null associations.(38) In addition, though HDL has been positively associated with plasma xanthophyll levels, most studies have found HDL to be unrelated to macular pigment optical density (MPOD). (39) At the same time, some genetic polymorphisms in the HDL pathway may influence MPOD independently of dietary xanthophyll intake,(40) and decrease AMD risk or increase plasma xanthophyll levels without influencing HDL.(41) More research is needed to expound the potential interactive effects of HDL and xanthophyll intake on risk of early AMD. Whether systemic and intraretinal xanthophyll transport by HDL are related but distinct processes, whether HDL may influence AMD risk via non-lipid factors, and the possible role of HDL dysfunction in AMD pathogenesis should also be explored.

The present study had several limitations. The availability of prevalent rather than incident cases of early AMD as an outcome precludes inference of causality. However, since the five-year incidence of early AMD is relatively low in adults <75 years of age,(42) disease odds may reasonably approximate disease risk in ARIC. Although, there was only a 6-year interval between exposure and outcome assessment, *posthoc* analyses of the AREDS2 randomized trial showed significant effects of xanthophyll supplementation after a median follow-up of 4.9 years.(9) Thus, the timespan between visit 1 and visit 3 could have been sufficient for evaluating the association between xanthophyll intake and early AMD. We were also unable to examine associations with late-staged disease.

As dietary xanthophyll intake was estimated using a self-report FFQ, reported dietary patterns may reflect neither long-term xanthophyll intake nor xanthophyll intake during the critical window of exposure for development of early AMD. Previous research using a subset of the ARIC cohort suggests that responses on the FFQ were reliable across the 3-year interval of interest.(25) Furthermore, analyses of the associations of xanthophyll intake with prevalent early AMD, soft drusen, and RPE depigmentation did not change significantly when replicated using visit 3 xanthophyll intake, average xanthophyll intake, or visit 1 xanthophyll intake after excluding participants exhibiting dietary instability. Future research should utilize objective measures of xanthophyll bioavailability such as serum concentrations and MPOD, but the current FFQ data – collected during an era when commercial lutein and zeaxanthin supplements were unavailable – may still offer some useful insights into the association between xanthophyll intake and early AMD.



Lastly, only 12,887 of the 15,792 participants recruited at visit 1 returned for visit 3. Of these individuals, 1,317 had ungradable fundus photographs, and may have been at greater risk of AMD (i.e. older, more likely to have diabetes mellitus, and more likely to have evidence of CVD on magnetic resonance imaging).(23) We also acknowledge that multiple testing with respect to exploratory analyses of effect modification by genetic and biomarkers of HDL metabolism may have led to spurious findings. Conclusions drawn from this study should therefore be interpreted with caution.

In summary, findings from the ARIC study suggest that xanthophyll intake was not associated with prevalence of soft drusen, RPE depigmentation, or early AMD in middle-aged Caucasians or African Americans. The observed effect modification of the xanthophyll and AMD association by *CFH* rs1061170 genotype and HDL concentrations highlight the need to for additional research to elucidate these associations by genetic susceptibility and HDL metabolism.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**SUMMARY STATEMENT**

Dietary xanthophyll (lutein and zeaxanthin) intake was not associated with prevalent early AMD in a biracial cohort of middle-aged adults (n=10,295). Additional research is needed to elucidate this relationship, especially among African-Americans, as well as to clarify potential interactions with genetic susceptibility and HDL metabolism.

**Table 1**

Participant characteristics by quintiles of energy-adjusted xanthophyll intake, visit 1 (n=10,295).\*

	<i>Total</i>	<i>Q1</i>	<i>Q2</i>	<i>Q3</i>	<i>Q4</i>	<i>Q5</i>	<i>p-value</i>	<i>correlation</i>
	<i>n (%)<sup>†</sup></i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>		<i>r; p-value</i>
<b>DEMOGRAPHICS</b>								
<b>Age (mean±SEM)</b>	53.9±0.1	53.5±0.1	53.7±0.1	53.8±0.1	53.9±0.1	54.4±0.1	<0.001	0.04; <0.001
<b>Sex</b>								<0.001
Men	4,662 (45)	1,164 (57)	1,014 (49)	923 (45)	783 (38)	778 (38)		
Women	5,633 (55)	895 (43)	1,045 (51)	1,136 (55)	1,276 (62)	1,281 (62)		
<b>Race</b>								<0.001
African-American	2,038 (20)	76 (4)	197 (10)	373 (18)	597 (29)	795 (39)		
Caucasian	8,257 (80)	1,983 (96)	1,862 (90)	1,686 (82)	1,462 (71)	1,264 (61)		
<b>Education</b>								<0.001
Missing Data (n)	10	1	4	1	1	3		
Basic (<11 years)	1,972 (19)	345 (17)	338 (17)	392 (19)	390 (19)	507 (25)		
Intermediate (12-16 years)	4,368 (43)	1,011 (49)	969 (47)	862 (42)	785 (38)	741 (36)		
Advanced (17-21 years)	3,945 (38)	702 (34)	748 (36)	804 (39)	883 (43)	808 (39)		
<b>Household Income, Adjusted for Family Size<sup>‡</sup></b>								<0.001
Missing Data (n)	337	43	62	49	87	96		
Tertile 1 ( < \$17,350)	3,453 (35)	589 (29)	611 (30)	674 (34)	721 (37)	858 (44)		
Tertile 2 (>=\$17,350-\$31,249)	3,322 (33)	735 (37)	715 (36)	686 (34)	622 (31)	564 (29)		
Tertile 3 ( > \$31,250)	3,183 (32)	692 (34)	671 (34)	650 (32)	629 (32)	541 (27)		
<b>Health Insurance</b>								<0.001
Missing Data (n)	11	2	3	4	1	1		
No	758 (7)	95 (5)	127 (6)	156 (8)	156 (8)	224 (11)		
Yes	9,526 (93)	1,962 (95)	1,929 (94)	1,899 (92)	1,902 (92)	1,834 (89)		
<b>ARIC Field Center</b>								<0.001
Forsyth County, NC	2787 (27)	380 (18)	517 (25)	577 (28)	646 (31)	667 (32)		
Jackson, MS	1759 (17)	66 (3)	162 (8)	321 (16)	515 (25)	695 (34)		
Minneapolis, MN	3000 (29)	1,003 (49)	763 (37)	581 (28)	406 (20)	247 (12)		



	Total n (%) <sup>†</sup>	Q1 n (%)	Q2 n (%)	Q3 n (%)	Q4 n (%)	Q5 n (%)	p-value	correlation r, p-value
<b>HEALTH BEHAVIORS</b>								
<b>Cigarette Smoking Status</b>								
Washington County, MD	2749 (27)	610 (30)	617 (30.0)	580 (28)	492 (24)	450 (22)		
Never	4,534 (44)	810 (39)	871 (42)	897 (43)	971 (47)	985 (48)	<0.001	
Former	3,419 (33)	730 (36)	706 (34)	715 (35)	654 (32)	614 (30)		
Current	2,342 (23)	519 (25)	482 (24)	447 (22)	434 (21)	460 (22)		
<b>Pack-years (mean±SEM)</b>	14.9±0.2	18.2±0.5	16.0±0.5	14.8±0.5	12.7±0.5	13.1±0.5	<0.001	-0.07; <0.001
<b>Ethanol Intake (mean±SEM)</b>	43.2±0.9	56.3±2.1	50.8±2.1	41.9±2.1	33.3±2.1	33.5±2.1	<0.001	-0.09; <0.001
Missing Data (n)	36	4	6	8	6	12		
<b>PHYSICAL EXAMINATION, FAST MEDICAL HISTORY, AND ANTHROPOMETRICS</b>								
<b>Hypertension ( 140/90 mmHg or use of antihypertensive medications)</b>								
Missing Data (n)	41	7	5	9	8	12	<0.001	
No	7,050 (69)	1,520 (74)	1,477 (72)	1,432 (70)	1,373 (67)	1,248 (61)		
Yes	3,204 (31)	532 (26)	577 (28)	618 (30)	678 (33)	799 (39)		
<b>BMI Category</b>								
Missing Data (n)	6	2	0	1	2	1	<0.001	
Not overweight or obese (<25)	3,463 (34)	683 (33)	736 (36)	717 (35)	702 (34)	625 (30)		
Overweight ( 25 and <30)	4,147 (40)	868 (42)	842 (41)	808 (39)	809 (39)	820 (40)		
Obese ( 30)	2,679 (26)	506 (25)	481 (23)	533 (26)	546 (27)	613 (30)		
<b>Prevalent Diabetes (fasting glucose 126; random glucose 200; use of diabetes medications)</b>								
Missing Data (n)	18	4	3	4	4	3	<0.001	
No	9,294 (90)	1,894 (92)	1,880 (91)	1,878 (91)	1,865 (91)	1,777 (86)		
Yes	983 (10)	161 (8)	176 (9)	177 (9)	190 (9)	279 (14)		
<b>Prevalent Congestive Heart Failure</b>								
Missing Data (n)	177	33	31	32	47	34	<0.001	
No	9,708 (96)	1,978 (98)	1,955 (96)	1,954 (96)	1,918 (95)	1,903 (94)		
Yes	410 (4)	48 (2)	73 (4)	73 (4)	94 (5)	122 (6)		
<b>Prevalent Myocardial Infarction</b>								
Missing Data (n)	132	23	21	24	34	30	0.84	

	Total n (%) <sup>†</sup>	Q1 n (%)	Q2 n (%)	Q3 n (%)	Q4 n (%)	Q5 n (%)	p-value	correlation r, p-value
No	9,815 (97)	1,973 (97)	1,966 (96)	1,963 (96)	1,959 (97)	1,954 (96)		
Yes	348 (3)	63 (3)	72 (4)	72 (4)	66 (3)	75 (4)	0.10	
<b>Prevalent Stroke</b>								
Missing Data (n)	23	6	2	4	7	4		
No	10,152 (99)	2,036 (99)	2,040 (99)	2,027 (99)	2,026 (99)	2,023 (98)		
Yes	120 (1)	17 (1)	17 (1)	28 (1)	26 (1)	32 (2)		
<b>LIPID METABOLISM</b>								
<b>HDL (mean±SEM, mmol/L)</b>	1.34±0.004	1.26±0.01	1.31±0.01	1.33±0.01	1.38±0.01	1.39±0.01	<0.001	0.09; <0.001
<b>HDL Category, Median Split (mmol/L)</b>								
Low (<1.27 mmol/L)	5,122 (50)	1,176 (57)	1,070 (52)	1,016 (49)	933 (45)	927 (45)		
High (≥ 1.27 mmol/L)	5,173 (50)	883 (43)	989 (48)	1,043 (51)	1,126 (55)	1,132 (55)		
<b>HDL2 (mean±SEM, mmol/L)</b>	0.37±0.002	0.33±0.005	0.36±0.005	0.36±0.005	0.39±0.005	0.40±0.005	<0.001	0.09; <0.001
<b>HDL2 Category, Median Split (mmol/L)</b>								
Low (<0.33 mmol/L)	5,039 (49)	1,165 (57)	1,053 (51)	1,025 (50)	892 (43)	904 (44)		
High (≥ 0.33 mmol/L)	5,256 (51)	894 (43)	1,006 (49)	1,034 (50)	1,167 (57)	1,155 (56)		
<b>HDL3 (mean±SEM, mmol/L)</b>	0.97±0.003	0.95±0.006	0.95±0.006	0.97±0.006	0.99±0.006	1.00±0.006	<0.001	0.07; <0.001
<b>HDL3 Category, Median Split (mmol/L)</b>								
Low (<0.95 mmol/L)	5,198 (50)	1,174 (57)	1,072 (52)	1,016 (49)	980 (48)	956 (46)		
High (≥ 0.95 mmol/L)	5,097 (50)	885 (43)	987 (48)	1,043 (51)	1,079 (52)	1,103 (54)		
<b>Apolipoprotein A1 (mean±SEM, μmol/L)</b>	47.3±0.1	45.2±0.2	46.9±0.2	47.2±0.2	48.4±0.2	49.0±0.2	<0.001	0.10; <0.001
<b>Apolipoprotein A1 Category, Median Split (μmol/L)</b>								
Low (<46.26 μmol/L)	5,103 (50)	1,192 (58)	1,039 (50)	1,047 (51)	933 (45)	892 (43)		
High (≥ 46.26 μmol/L)	5,192 (50)	867 (42)	1,020 (50)	1,012 (49)	1,126 (55)	1,167 (57)		
<b>Apolipoprotein B (mean±SEM, μmol/L)</b>	1.69±0.01	1.70±0.01	1.68±0.01	1.72±0.01	1.68±0.01	1.69±0.01	0.086	-0.02; 0.09
<b>Apolipoprotein B Category, Median Split (μmol/L)</b>								
Missing Data (n)	2	0	1	0	0	1	0.25	
Low (<1.62 μmol/L)	5,121 (50)	1,003 (49)	1,037 (50)	998 (48)	1,062 (52)	1,021 (50)		
High (≥ 1.62 μmol/L)	5,172 (50)	1,056 (51)	1,021 (50)	1,061 (52)	997 (48)	1,037 (50)		
<b>LDL (mean±SEM, mmol/L)</b>	3.55±0.01	3.57±0.02	3.51±0.02	3.60±0.02	3.55±0.02	3.52±0.02	0.036	-0.01; 0.26
<b>LDL Category, Median Split (mmol/L)</b>							0.032	

	Total n (%) <sup>†</sup>	Q1 n (%)	Q2 n (%)	Q3 n (%)	Q4 n (%)	Q5 n (%)	p-value	correlation r; p-value
Missing Data (n)	144	33	26	28	29	28		
Low (<3.49 mmol/L)	5,074 (50)	994 (49)	1,044 (51)	963 (47)	1,019 (50)	1,054 (52)		
High ( 3.49 mmol/L)	5,077 (50)	1,032 (51)	989 (49)	1,068 (53)	1,011 (50)	977 (48)		
Triglycerides (mean±SEM, mmol/L)	1.48±0.01	1.52±0.02	1.51±0.02	1.48±0.02	1.45±0.02	1.44±0.02	0.028	-0.02; <0.02
Triglycerides Category, Median Split (mmol/L)							0.021	
Low (<1.24 mmol/L)	5,117 (50)	968 (47)	1,012 (49)	1,022 (50)	1,072 (52)	1,043 (51)		
High ( 1.24 mmol/L)	5,178 (50)	1,091 (53)	1,047 (51)	1,037 (50)	987 (48)	1,016 (49)		
<b>NUTRITIONAL AND DIETARY FACTORS</b>								
Daily caloric intake (kcal)	1631±6	1739±13	1786±13	1618±13	1469±13	1544±13	<0.001	-0.15; <0.001
Daily carbohydrate intake (%kcal)	48.7±0.1	47.0±0.2	48.5±0.2	48.5±0.2	49.4±0.2	50.3±0.2	<0.001	0.10; <0.001
Daily protein intake (%kcal)	17.9±0.04	16.5±0.1	17.2±0.1	17.8±0.1	18.8±0.1	19.4±0.1	<0.001	0.24; <0.001
Daily total fat intake (%kcal)	33.0±0.1	35.1±0.1	33.7±0.1	33.3±0.1	31.9±0.1	30.9±0.1	<0.001	-0.19; <0.001
Daily monounsaturated fat intake (%kcal)	12.7±0.03	13.6±0.06	13.0±0.06	12.8±0.06	12.2±0.06	11.8±0.06	<0.001	-0.19; <0.001
Daily polyunsaturated fat intake (%kcal)	5.1±0.01	5.2±0.03	5.1±0.03	5.1±0.03	5.0±0.03	4.9±0.03	<0.001	-0.05; <0.001
Daily omega-3 fatty acid intake (% kcal)	0.14±0.001	0.09±0.003	0.11±0.003	0.14±0.003	0.17±0.003	0.20±0.003	<0.001	0.25; <0.001
Daily zinc intake (mg/1000 kcal)	6.8±0.02	6.7±0.04	6.7±0.04	6.8±0.04	6.9±0.04	7.0±0.04	<0.001	0.07; <0.001
Daily copper intake (mg/1000 kcal)	0.85±0.002	0.78±0.004	0.81±0.004	0.84±0.004	0.88±0.004	0.95±0.004	<0.001	0.29; <0.001
Daily vitamin C intake (mg/1000 kcal)	77.1±0.4	53.5±0.9	69.2±0.9	77.1±0.9	89.5±0.9	96.2±0.9	<0.001	0.30; <0.001
Daily vitamin E intake (mg/1000 kcal)	3.1±0.02	2.6±0.04	2.8±0.04	3.1±0.04	3.3±0.04	3.5±0.04	<0.001	0.17; <0.001
Daily lycopene intake (µg/1000 kcal)	2119±26	1423±57	1791±57	2046±57	2527±57	2807±57	<0.001	0.18; <0.001
Daily α-carotene intake (µg/1000 kcal)	342±5	191±11	286±11	324±11	418±11	491±11	<0.001	0.20; <0.001
Daily β-carotene intake (µg/1000 kcal)	1699±16	698±31	1140±31	1438±31	1970±31	3249±31	<0.001	0.61; <0.001
Daily β-cryptoxanthin intake (µg/1000 kcal)	52.3±0.5	36.8±1.1	48.2±1.1	51.5±1.1	61.8±1.1	63.1±1.1	<0.001	0.16; <0.001
Visit 1 Diet Status								
Missing Data (n)	5	0	3	0	0	2		<0.001
No	8,529 (83)	1,811 (88)	1,759 (86)	1,725 (84)	1,675 (81)	1,559 (76)		
Yes	1,761 (17)	248 (12)	297 (14)	334 (16)	384 (19)	498 (24)		
<b>GENETICS</b>								

	Total n (%) <sup>†</sup>	Q1 n (%)	Q2 n (%)	Q3 n (%)	Q4 n (%)	Q5 n (%)	p-value	correlation r, p-value
<b>CFH rs1061170 genotype</b>								
<b>African-American</b>								
Missing Data (n)	168	6	21	23	57	61	0.88	
TT	552 (37)	18 (33)	53 (35)	105 (38)	153 (36)	223 (38)		
CT	772 (51)	28 (52)	79 (52)	140 (50)	218 (51)	307 (52)		
CC	179 (12)	8 (15)	19 (13)	34 (12)	58 (13)	60 (10)	0.24	
<b>Caucasian</b>								
TT	2906 (42)	727 (44)	652 (41)	566 (40)	516 (42)	445 (42)		
CT	3131 (45)	701 (42)	729 (46)	666 (47)	566 (46)	469 (45)		
CC	904 (13)	231 (14)	204 (13)	191 (13)	146 (12)	132 (13)		
<b>ARMS2, rs10490924 genotype</b>								
<b>African-American</b>								
Missing Data (n)	6	1	0	0	0	5	0.75	
GG	983 (59)	38 (65)	107 (62)	176 (58)	293 (60)	369 (57)		
GT	583 (35)	19 (32)	55 (32)	104 (35)	163 (34)	242 (38)		
TT	99 (6)	2 (3)	10 (6)	22 (7)	30 (6)	35 (5)	0.44	
<b>Caucasian</b>								
GG	4272 (61)	997 (60)	963 (61)	902 (63)	771 (63)	639 (61)		
GT	2352 (34)	580 (35)	559 (35)	453 (32)	405 (33)	355 (34)		
TT	317 (5)	82 (5)	63 (4)	68 (5)	52 (4)	52 (5)		
<b>Genetic Risk (CFH rs1061170 C + ARMS2 rs10490924 T)</b>								
<b>African-American</b>								
Missing Data (n)	174	7	21	23	57	66	0.98	
0 alleles	322 (22)	11 (21)	33 (22)	64 (23)	91 (21)	123 (21)		
1 alleles	650 (43)	25 (47)	66 (44)	122 (44)	178 (42)	259 (44)		
2 alleles	525 (35)	17 (32)	52 (34)	93 (33)	160 (37)	203 (35)	0.61	
<b>Caucasian</b>								
0 alleles	1754 (25)	420 (25)	395 (25)	338 (24)	325 (26)	276 (26)		
1 alleles	2947 (42)	691 (42)	669 (42)	639 (45)	516 (42)	432 (41)		
2 alleles	2240 (32)	548 (33)	521 (33)	446 (31)	387 (32)	338 (32)		

\* Data are presented as number (percentage) unless otherwise noted; n=10,295 for dietary analyses; n=8,612 for genetic analyses

<sup>†</sup> Column percentages may not sum to 100% due to rounding

<sup>‡</sup> Adjusted household income = Household income / (Household size)<sup>0.5</sup>

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**Table 2**

Prevalence of early AMD, soft drusen, and RPE depigmentation by quintiles of energy-adjusted xanthophyll intake, visit 1 (n=10,295).

Association	Outcome n/Total n †	Model I (Unadjusted)		Model II (Age-adjusted)		Model III (Multivariable-adjusted)*		Model IV (Multivariable-adjusted)	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
<b>Early AMD</b>									
<i>Overall</i>									
Q1 (251-456) ‡	102/2059	1.00	referent	1.00	referent	1.00	referent	1.00	referent
Q2 (660-867)	110/2059	1.08	0.82-1.43	1.07	0.81-1.41	1.05	0.80-1.39	1.07	0.81-1.42
Q3 (1082-1305)	109/2059	1.07	0.81-1.42	1.05	0.79-1.38	1.04	0.79-1.39	1.07	0.80-1.42
Q4 (1592-2027)	109/2059	1.07	0.81-1.42	1.04	0.79-1.38	1.05	0.79-1.41	1.09	0.81-1.46
Q5 (2910-4936)	105/2059	1.03	0.78-1.36	0.97	0.73-1.28	0.99	0.73-1.33	1.02	0.76-1.38
	<i>p</i> for trend ‡	0.97		0.61		0.78		0.91	
<i>African-American</i>									
Q1 (256-492) ‡	3/76	1.00	referent	1.00	referent	1.00	referent	1.00	referent
Q2 (682-892)	10/197	1.30	0.35-4.86	1.32	0.35-4.95	1.32	0.35-4.95	1.31	0.35-4.92
Q3 (1116-1316)	13/373	0.88	0.24-3.16	0.88	0.24-3.16	0.88	0.24-3.20	0.88	0.24-3.19
Q4 (1621-2057)	21/597	0.88	0.26-3.05	0.87	0.25-3.01	0.91	0.26-3.16	0.90	0.26-3.15
Q5 (2950-5005)	35/795	1.12	0.34-3.73	1.06	0.32-3.55	1.09	0.33-3.68	1.10	0.33-3.69
	<i>p</i> for trend	0.65		0.81		0.74		0.72	
<i>Caucasian</i>									
Q1 (251-455) ‡	99/1983	1.00	referent	1.00	referent	1.00	referent	1.00	referent
Q2 (659-865)	100/1862	1.08	0.81-1.44	1.05	0.79-1.40	1.03	0.77-1.37	1.05	0.79-1.40
Q3 (1077-1303)	96/1686	1.15	0.86-1.53	1.10	0.82-1.47	1.06	0.79-1.42	1.09	0.81-1.46
Q4 (1578-2012)	88/1462	1.22	0.91-1.64	1.15	0.85-1.55	1.09	0.80-1.48	1.13	0.83-1.54
Q5 (2875-4871)	70/1264	1.12	0.82-1.53	1.01	0.73-1.38	0.94	0.68-1.30	0.97	0.70-1.35
	<i>p</i> for trend	0.50		0.99		0.64		0.79	
<b>Soft Drusen</b>									
<i>Overall</i>									
Q1	81/2059	1.00	referent	1.00	referent	1.00	referent	1.00	referent



Association	Outcome n/Total n	Model I (Unadjusted)		Model II (Age-adjusted)		Model III (Multivariable-adjusted)*		Model IV (Multivariable-adjusted)	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Q2	94/2059	1.17	0.86-1.58	1.15	0.85-1.56	1.13	0.83-1.53	1.15	0.84-1.56
Q3	93/2059	1.16	0.85-1.57	1.13	0.83-1.53	1.11	0.81-1.51	1.13	0.83-1.54
Q4	91/2059	1.13	0.83-1.53	1.10	0.81-1.49	1.08	0.79-1.49	1.11	0.81-1.53
Q5	96/2059	1.19	0.88-1.62	1.12	0.83-1.52	1.11	0.80-1.53	1.14	0.82-1.57
<i>p</i> for trend		0.42		0.70		0.77		0.67	
<i>African-American</i>									
Q1	3/76	1.00	referent	1.00	referent	1.00	referent	1.00	referent
Q2	9/197	1.17	0.31-4.42	1.18	0.31-4.50	1.19	0.31-4.51	1.17	0.31-4.47
Q3	13/373	0.88	0.24-3.16	0.88	0.24-3.16	0.87	0.24-3.14	0.86	0.24-3.10
Q4	18/597	0.76	0.22-2.63	0.75	0.21-2.59	0.75	0.21-2.64	0.74	0.21-2.60
Q5	33/795	1.05	0.32-3.52	1.00	0.30-3.35	1.00	0.30-3.37	0.99	0.29-3.33
<i>p</i> for trend		0.63		0.78		0.76		0.76	
<i>Caucasian</i>									
Q1	78/1983	1.00	referent	1.00	referent	1.00	referent	1.00	referent
Q2	85/1862	1.17	0.85-1.60	1.14	0.83-1.56	1.11	0.81-1.52	1.13	0.82-1.55
Q3	80/1686	1.22	0.88-1.67	1.17	0.85-1.60	1.12	0.81-1.55	1.15	0.83-1.59
Q4	73/1462	1.28	0.93-1.78	1.21	0.87-1.68	1.14	0.82-1.60	1.19	0.85-1.66
Q5	63/1264	1.28	0.91-1.80	1.16	0.82-1.63	1.07	0.75-1.52	1.11	0.78-1.58
<i>p</i> for trend		0.19		0.50		0.86		0.73	

**RPE Depigmentation**

Association	Outcome n/Total n	Model I (Unadjusted)		Model II (Age-adjusted)		Model III (Multivariable-adjusted)*		Model IV (Multivariable-adjusted)	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
<i>Overall</i>									
Q1	27/2059	1.00	referent	1.00	referent	1.00	referent	1.00	referent
Q2	29/2059	1.08	0.63-1.82	1.06	0.62-1.79	1.10	0.65-1.87	1.13	0.67-1.93
Q3	21/2059	0.78	0.44-1.38	0.75	0.43-1.34	0.85	0.48-1.52	0.88	0.49-1.58
Q4	22/2059	0.81	0.46-1.43	0.79	0.45-1.39	0.99	0.55-1.78	1.05	0.58-1.89
Q5	16/2059	0.59	0.32-1.10	0.55	0.30-1.02	0.75	0.39-1.44	0.80	0.41-1.53
<i>p</i> for trend		0.055		0.033		0.32		0.41	
<i>African-American</i>									
Q1	0/76	1.00	referent	1.00	referent	1.00	referent	1.00	referent

Association	Outcome n/Total n <sup>†</sup>	Model I (Unadjusted)		Model II (Age-adjusted)		Model III (Multivariable-adjusted)*		Model IV (Multivariable-adjusted)	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Q2	1/197	-	-	-	-	-	-	-	-
Q3	1/373	-	-	-	-	-	-	-	-
Q4	3/597	-	-	-	-	-	-	-	-
Q5	2/795	-	-	-	-	-	-	-	-
<b>p for trend</b>		-	-	-	-	-	-	-	-
<b>Caucasian</b>									
Q1	27/1983	1.00	referent	1.00	referent	1.00	referent	1.00	referent
Q2	28/1862	1.11	0.65-1.88	1.08	0.63-1.84	1.08	0.64-1.85	1.11	0.65-1.90
Q3	20/1686	0.87	0.49-1.56	0.83	0.46-1.49	0.84	0.47-1.51	0.87	0.48-1.56
Q4	19/1462	0.95	0.53-1.72	0.90	0.50-1.62	0.92	0.50-1.68	0.96	0.52-1.77
Q5	14/1264	0.81	0.42-1.55	0.73	0.38-1.40	0.75	0.38-1.46	0.79	0.40-1.55
<b>p for trend</b>		0.43		0.27		0.32		0.40	

\* Model III: adjusted for age, race, field center, and visit 1 daily caloric intake  
 Model IV: adjusted for age, sex, race, pack-years of smoking, field center, and visit 1 daily caloric intake  
<sup>†</sup> Quintiles and interquartile range (µg/1000 kcal) of energy-adjusted daily xanthophyll intake at visit 1  
<sup>‡</sup> Reflects distribution of unadjusted model; data was missing for pack-years of smoking in multivariable-adjusted model  
<sup>§</sup> p-value for linear trend was calculated using quintile medians

Prevalent early AMD by race and tertiles of energy-adjusted xanthophyll intake (visit 1), stratified by *CFH* rs1061170 and *ARMS2* rs10490924 genotype.

**Table 3**

Outcome n/ Total n	Multivariable-adjusted OR (95% CI)*	p-value for trend†	p-value for multiplicative interaction
<b><i>CFH</i> rs1061170</b>			
<b>African-Americans</b>			
CC (2 risk alleles) 12/179	referent	0.95 (0.09-10.59)	1.39 (0.15-13.03) 0.42
CT (1 risk allele) 28/772	referent	0.42 (0.12-1.50)	0.50 (0.16-1.59) 0.53
TT (0 risk alleles) 23/552	referent	1.28 (0.26-6.44)	1.13 (0.23-5.47) 0.99
<b>Caucasians</b>			
CC (2 risk alleles) 82/904	referent	1.70 (0.96-3.02)	1.76 (0.94-3.29) 0.02
CT (1 risk allele) 170/3131	referent	0.86 (0.60-1.23)	0.63 (0.41-0.96) 0.28
TT (0 risk alleles) 113/2906	referent	1.24 (0.78-1.98)	1.20 (0.73-1.97) 0.36
<b><i>ARMS2</i> rs10490924</b>			
<b>African-Americans</b>			
TT (2 risk alleles) 7/99	referent	-	- 0.47
GT (1 risk allele) 20/583	referent	0.84 (0.16-4.45)	0.75 (0.15-3.69) 0.94
GG (0 risk alleles) 41/983	referent	0.50 (0.18-1.35)	0.56 (0.22-1.40) 0.73
<b>Caucasians</b>			
TT (2 risk alleles) 38/317	referent	0.74 (0.30-1.82)	0.90 (0.37-2.23) 0.88
GT (1 risk allele) 117/2352	referent	1.29 (0.84-1.98)	0.84 (0.50-1.41) 0.52
GG (0 risk alleles) 210/4272	referent	1.08 (0.77-1.51)	1.04 (0.72-1.50) 0.87
<b>Combined genetic risk (<i>CFH</i> rs1061170 C and <i>ARMS2</i> rs10490924 T)</b>			
<b>African-Americans</b>			
2 risk alleles 26/525	referent	0.62 (0.15-2.53)	0.52 (0.13-1.98) 0.85
1 risk alleles 26/650	referent	0.90 (0.17-4.70)	1.52 (0.33-7.08) 0.48
0 risk alleles 11/322	referent	0.55 (0.08-3.60)	0.45 (0.07-2.78) 0.85
<b>Caucasians</b>			
2 risk alleles 159/2240	referent	1.18 (0.80-1.73)	0.97 (0.63-1.50) 0.45
1 risk alleles 141/2947	referent	1.04 (0.70-1.55)	0.95 (0.60-1.50) 0.71

Outcome	n/Total n	Multivariable-adjusted OR (95% CI)*	p-value for trend†	p-value for multiplicative interaction	
0 risk alleles	65/1754	referent	1.18 (0.64-2.18)	1.05 (0.54-2.03)	0.33
		Tertile 1‡ (322-799)	Tertile 2 (1014-1383)	Tertile 3 (2027-3996)	

\* Adjusted for age, race, pack-years of smoking, field center, visit 1 daily caloric intake

‡ Tertiles and interquartile range (µg/1000 kcal) of energy-adjusted daily xanthophyll intake at visit 1

† P-value of the association between xanthophyll intake (continuous, µg/1000 kcal) and odds of prevalent early AMD by genotype

Prevalent early AMD by tertiles of dietary xanthophyll intake (visit 1), stratified by plasma biomarkers of HDL cholesterol metabolism (n=10,295).

**Table 4**

Outcome n/ Total n	Multivariable-adjusted OR (95% CI)*	p-value for trend <sup>‡</sup>	p-value for multiplicative interaction
	Tertile 1 <sup>†</sup> (322-799)	Tertile 2 (1014-1383)	Tertile 3 (2027-3996)
<b>HDL (mmol/L)<sup>‡</sup></b>			
<1.27	referent	1.15 (0.87-1.54)	0.79 (0.57-1.09)
1.27	referent	0.98 (0.71-1.36)	1.14 (0.83-1.58)
		0.86	0.88
<b>HDL2 (mmol/L)</b>			
<0.33	referent	1.17 (0.88-1.55)	0.82 (0.59-1.13)
0.33	referent	0.96 (0.69-1.33)	1.11 (0.80-1.54)
		0.69	0.67
<b>HDL3 (mmol/L)</b>			
<0.95	referent	1.19 (0.89-1.59)	0.96 (0.70-1.31)
0.95	referent	0.94 (0.68-1.29)	0.95 (0.69-1.33)
		0.92	0.89
<b>ApoA1 (µmol/L)</b>			
<46.26	referent	1.22 (0.92-1.63)	0.86 (0.62-1.19)
46.26	referent	0.90 (0.65-1.25)	1.05 (0.76-1.44)
		0.73	0.70

\* Adjusted for age, sex, race, pack-years of smoking, field center, visit 1 daily caloric intake,

<sup>†</sup> HDL, HDL2, HDL3 and ApoA1 were categorized by median split

<sup>‡</sup> Tertiles and interquartile range (µg/1000 kcal) of energy-adjusted daily xanthophyll intake at visit 1

<sup>‡</sup> P-value of the association between xanthophyll intake (continuous, µg/1000 kcal) and odds of prevalent early AMD within lipid biomarker category