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No Clinically Significant Association Between *CFH* and *ARMS2* Genotypes and Response to Nutritional Supplements:

AREDS Report Number 38

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Abstract

Objective—To determine whether genotypes at two major loci associated with late age-related macular degeneration (AMD), *complement factor H (CFH)* and *Age-Related Maculopathy Susceptibility 2 (ARMS2)*, influenced the relative benefits of Age-Related Eye Disease Study (AREDS) supplements.

Design—Unplanned retrospective evaluation of a prospective, randomized, placebo-controlled clinical trial of vitamins and minerals for the treatment of AMD.

Subjects—AREDS participants (mean age of 69 years) who were at risk for developing late AMD and who were randomized to the 4 arms of the AREDS supplements.

Methods—Analyses were performed using the Cox proportional hazards model to predict progression to late AMD (neovascular or central geographic atrophy). Statistical models, adjusted for age, gender, smoking status and baseline AMD severity, were used to examine the influence of

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Conflicts of Interest: None of the other authors have financial disclosure.

AREDS was a clinical trial that was conducted prior to the required clinical trials registration.

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genotypes on the response to therapy with 4 randomly assigned arms of AREDS supplement components: placebo, antioxidants (vitamins C, E, beta-carotene), zinc with copper, or the combination.

Main Outcome Measures—The influence of the genotype on the relative treatment response to the randomized components of the AREDS supplement, measured as progression to late AMD.

Results—Of the 1237 genotyped AREDS participants of Caucasian ethnicity, 385 (31.1%) developed late AMD during the mean follow-up period of 6.6 years. As previously demonstrated, both *CFH* genotype ($p=0.005$), *ARMS2* (<0.0001) and supplement were each individually associated with progression to late AMD. An interaction analysis found no evidence that the relative benefits of AREDS supplementation varied by genotype. Analysis of (1) *CFH* *rs1061170* and *rs1410996* combined with *ARMS2* *rs10490924*, with the 4 randomly assigned arms of AREDS supplement and (2) analysis of the combination of *CFH* *rs412852* and *rs3766405* with *ARMS2* *c.372_815del443ins54* with the AREDS components resulted in no interaction ($p=0.06$ and $p=0.45$, respectively, before multiplicity adjustment).

Conclusions—AREDS supplements reduced the rate of AMD progression across all genotype groups. Furthermore, the genotypes at the *CFH* and *ARMS2* loci did not statistically significantly alter the benefits of AREDS supplements. Genetic testing remains a valuable research tool, but analysis of AREDS study data suggests it provides no benefits in managing nutritional supplementation for patients at risk of late AMD.

Age-related macular degeneration (AMD) is the leading cause of blindness in the United States with nearly 2 million late AMD cases and 8 million intermediate AMD cases estimated in 2004.¹ With increased population longevity, the numbers of individuals affected with AMD are projected to double by 2024.¹ The Age-Related Eye Disease Study (AREDS) followed persons with intermediate AMD (large drusen or extensive medium sized drusen) or late AMD in only one eye at enrollment and demonstrated that, over 5 years, the AREDS supplement, consisting of antioxidants (vitamins E, C, beta-carotene) and zinc (plus copper), reduced the risk of development of late AMD, especially neovascular AMD, by 25% (Figure 1A).²

AMD is a complex disease with both heritable and environmental risks. Epidemiological studies have revealed the exponential increase in prevalence of AMD with age, an increase in risk conferred by smoking, a protective effect of fatty fish and green leafy vegetable consumption, and a less consistent association with body mass index and hypertension.^{3,4,5,6,7,8,9} Genetic studies have identified 19 susceptibility loci that appear to explain over 50% of the risk of developing AMD.¹⁰ These studies point to biological pathways that may contribute to AMD pathogenesis; these include alternative complement activation, high density lipoprotein cholesterol transport and metabolism, extracellular matrix integrity and cell adhesion, and angiogenesis.³

An important question is whether knowledge of individual risk genotypes could inform the choice of therapeutic strategy among at risk individuals – as happens now in some areas of medicine. For example, in oncology, information on genetic variants that predict successful responses to therapy (or adverse events) has led to genetically-informed treatment strategies.^{11,12} Numerous studies have evaluated the association of genetic testing and

treatment with anti-vascular endothelial growth factor drugs for neovascular AMD with retrospective analyses.^{13,14,15,16,17,18} These have been several studies with varying outcome variables and duration, resulting in no clear consensus about this association. Genetic information has not added to clinical factors such as visual acuity at baseline, lesion size, age and interval between symptoms and treatment that appear to be important in determining the visual outcomes following treatment.¹⁹

Five years ago, Klein et al evaluated possible genetic predictors of response to treatment with the AREDS supplement.²⁰ Included in the analyses were all 867 AREDS participants with intermediate AMD (large drusen or extensive medium drusen in one or both eyes) or late AMD in one eye, and for whom DNA was available. The baseline AMD severity levels in these 867 individuals matched guidelines for therapy with AREDS supplement. Single nucleotide polymorphisms (SNPs) in the *CFH* (p.Y402H, *rs1061170*) and *ARMS2*, (p.A69S, *rs10490924*) genes were genotyped. Evidence for a possible interaction between the *CFH* genotype and the benefit of treatment with antioxidants plus zinc was detected. Individuals with the homozygous non-risk genotype for *CFH* (TT) had a greater reduction in progression to late AMD than those with the homozygous risk genotype (CC), 68% vs. 11%, ($p=0.03$). There was no significant interaction between *ARMS2* p.A69S genotype and treatment with any AREDS supplement regimen. Results of their study led Klein et al²⁰ to conclude that AREDS supplements were associated with a reduction in progression to late AMD in all genotypic groups, and that neither antioxidant alone nor zinc alone was superior to the combination of antioxidants and zinc in reducing progression to AMD in any genetic group. Although evidence for differences in treatment response to AREDS supplements for individuals with different genotypes was observed, the results for all groups were in the direction of a treatment benefit. These findings, together with the need for replication data and corroborative functional studies, and the lack of available alternative interventions, led the authors to conclude that routine genetic testing was not indicated prior to prescribing AREDS supplements.

A more recent study by Awh et al suggested that the administration of AREDS supplements should be modified in certain subgroups of patients based upon their *CFH* and *ARMS2* genotypes.²¹ This study examined a subset of the AREDS participants ($n=995$) for whom DNA has been collected. Here, we re-evaluate this suggestion with an unplanned retrospective analysis of a larger cohort of AREDS participants (from 1237 to 1413, depending on the SNPs) with available DNA and who were at high risk of developing late AMD.

Methods

Study Population

The AREDS design was reported previously.²² We will summarize the study details that are relevant to this report. Participants of varying severity of AMD were enrolled in 11 retinal specialty clinics. Each clinical center obtained Institutional Review Board (IRB) approval for the study protocol and all participants signed the study's informed consent form. The study was adherent to the tenets of the Declaration of Helsinki and was HIPAA compliant. Included in these analyses were 1237 participants who had available DNA and were

considered at high risk of progression to late AMD. We confined our analyses to those participants with intermediate AMD in one or both eyes (n=832) (AREDS AMD category 3) or late AMD in one eye (n=405) (AREDS AMD category 4). It is for these groups that therapy with AREDS supplement is currently recommended. The participants had been randomly assigned to one of four treatment groups: antioxidants plus zinc, antioxidants, zinc, or placebo. The antioxidants consisted of vitamins C (500 mg), E (400 IU), and beta-carotene (15 mg). Zinc was given as zinc oxide (80 mg) along with copper as cupric oxide (2 mg).

Baseline data were collected, including age, race, gender, education, smoking history, body mass index, and medical history. Stereoscopic fundus photographs of the macula, taken at baseline and annually beginning two years after enrollment, were graded centrally using standardized grading procedures. The participants were followed for the clinical trial from 1992 until 2001. Additional follow-up through 2005 was conducted as an observational study. Our analyses were confined only to the period of the randomized controlled clinical trial until 2001. Additional analyses including events after the conclusion of the trial did not alter our conclusions.

Outcomes

The primary outcome for this report is the interaction between the genotypes and treatment responses to the antioxidants and zinc, evaluated by the progression to late AMD. Disease progression was determined from (i) the grading of the stereoscopic fundus photographs for the presence of central geographic atrophy or retinal features of choroidal neovascularization or (ii) history of treatment for late AMD after study enrollment.

Genotyping

The 1237 AREDS participants were genotyped for common single nucleotide polymorphisms (SNPs) at the *CFH* locus (*rs1061170* and *rs1410996*) and *ARMS2* (*rs10490924*) using the TaqMan assay (Applied Biosystems, Foster City, CA) methodology. To reduce the multiple testing burden, genotypes of the two *CFH* SNPs, *rs1061170* and *rs1410996*, were grouped into three risk categories “low risk”, “medium risk”, and “high risk,” according to their combined risk effect. This was based on a separate analysis of 1,717 AMD non-overlapping cases and 1,150 controls from a published GWAS study (supplementary Table 1, [available at <http://aaojournal.org>]).²³ We repeated analyses using 2 other *CFH* SNPs, *rs412852* and *rs3766405* (n=1,413), to mimic the recently reported analyses¹⁴ (supplementary Table 2 [available at <http://aaojournal.org>]). There is high correlation between the two sets of risk alleles: *rs1061170* and *rs412852* have similar genotypes ($r^2 = 0.86$) as do *rs1410996* and *rs3766405* ($r^2 = 1$) (The 1000 Genomes Project Consortium 2012 [Phase I v3]).²⁴ Genotypes were checked for quality by examining call rates per marker and by calculating an exact Hardy–Weinberg test statistic.

Statistical Plan

Analyses were performed using the Cox proportional hazards model to predict progression to late AMD (neovascular or central geographic atrophy). The models included age (1

degree of freedom [df]), gender (1 df), smoking status (2 df), baseline AMD severity (1 df), AREDS treatment (3 df) and either *CFH* (2 df) or *ARMS2* (2 df) or the combination of *CFH* and *ARMS2* (8 df). Supplementary Table 3 (available at <http://aaojournal.org>) displays the degrees of freedom used in each of the models presented in this current study. The treatment by genotype interaction was included in each model. We particularly focused on evaluating evidence that interaction between treatment with AREDS supplement in the 4 randomly assigned arms (placebo, antioxidants, zinc, antioxidants and zinc) and the genetic risk alleles (at *CFH* and *ARMS2*) might affect the progression to late AMD. Two separate sets of analyses were conducted for interaction of AREDS treatments with *CFH* and *ARMS2* variants. The first set of analyses included the most commonly known and studied risk alleles: a two SNP *CFH* haplotype comprised of *rs1061170* and *rs1410996* and the *rs10490924* SNP in the *ARMS2*. A second set of analyses evaluated the variants used in the study by Awh et al:¹⁴ an alternate two SNP *CFH* haplotype (*rs412852* and *rs3766405*) and the *ARMS2* deletion *c.372_815del443ins54*.

Since the study design was a 2×2 factorial, main effects analyses were also conducted by comparing antioxidants vs. no antioxidants and zinc vs. no zinc with each genotype group (results are found in the supplementary materials because these results are not particularly informative in deciding whether to use antioxidants or zinc alone compared with the combination). To facilitate comparison with Awh et al, pairwise comparisons were conducted to evaluate evidence for benefit of each supplementation regimen as a function of each genotype. For example, for each of the three levels of the *CFH* haplotype (low risk, medium risk, high risk) we evaluated three supplementation regimens (antioxidants vs. placebo, zinc vs. placebo and combination of antioxidant and zinc vs. placebo), resulting in 9 different pairwise comparisons. These were expressed as hazard ratios with 99.9% confidence intervals, using a Bonferroni corrected p-value ($p < 0.001$) for the determination of statistical significance because a total of 45 comparisons was conducted. Nine tests for each combination of the 3 *CFH* levels for each of the 3 AREDS treatments, and similarly, 9 tests for the *ARMS2* loci. For the combination of *CFH* and *ARMS2* and the 3 AREDS treatments, there were 27 tests. This resulted in a total of 45 tests.

Results

Characteristics of the 1237 AREDS participants are summarized on Table 4. The mean age was 69 years; of these, 59% were female, and 55% were former or current smokers. Baseline characteristics and the distribution of the genotypes at *CFH* (*rs1061170* and *rs1410996*) and *ARMS2* (*rs10490924*) loci were both similar across the four AREDS supplement treatment allocations, $p=0.87$ and 0.79 chi-square, respectively (Table 4). The combined genotypes of *CFH* (*rs412852* and *rs3766405*) and *ARMS2* (*c.372_815del443ins54*) ($n=1413$) were also distributed similarly across the AREDS treatment groups, $p=0.93$ and 0.98 , respectively, chi-square, (Table 4). The call rate for each SNP analyzed here was greater than 98%. The rates of progression to late AMD by the genetic risk, ranging from low (no risk alleles) to high (homozygous) risk genotypes, demonstrated an increasing rate with higher risk alleles (*CFH* (*rs1061170* and *rs1410996*) 17.9%, 25.7%, 38.6%, *ARMS2* 18.5%, 35.9%, 48.3% for low, medium and high risk respectively).

We also compared the rates of progression to late AMD among the AREDS participants with (n=1237) or without DNA (n=1340) (supplementary Table 5 [available at <http://aaojournal.org>]) and found no statistically significant differences (P= 0.96 Cochran-Mantel-Haenszel test). The supplementary Tables 6A and B (available at <http://aaojournal.org>) show the highest rates of progression to late AMD were seen in those groups with the heterozygous and homozygous risk genotypes.

Main Analyses of Influence of Combination *CFH* and *ARMS2* Genotypes on AREDS Supplement Treatment Effect

The Cox proportional hazards model evaluating the interaction of genotype of the combination of *CFH* (*rs1061170* and *rs1410996*) and *ARMS2* (*rs10490924*) and treatment with the four different randomized arms of AREDS trial: placebo, antioxidant, zinc, and antioxidant plus zinc, resulted in no statistically significant interaction (p=0.06). In order to be statistically significant with the Bonferroni correction, the p-value needs to be less than 0.01. Given this lack of statistical significance in the overall analyses, we would usually terminate our investigation at this point. However, as stated a priori and because of recent interest, we also carried out subgroup analyses. Figure 1B demonstrates the results of the pairwise comparison of the components of the AREDS supplement, antioxidant and zinc, antioxidant alone and zinc alone with placebo for *CFH* (*rs1061170* and *rs1410996*) combined with *ARMS2* (*rs10490924*). Again, none of these results reached statistical significance and all were consistent with treatment benefit. As noted in the methods, our analysis involves a total of 45 comparisons and a corresponding Bonferroni threshold p-value <0.001.

Similar analyses using alternate genetic variants for *CFH* (*rs412852* and *rs3766405*) and *ARMS2* (*indel: c.372_815del443ins54*), an analysis designed to mimic the study conducted by Awh et al,²¹ also demonstrate no statistically significant interaction between treatment effect and genotype (p=0.45) (Figure 1C). Similar pairwise comparisons using these genotypes were also not statistically significant (Figure 1C).

Analyses of Influence of *CFH* and *ARMS2* Genotypes Individually on AREDS Supplement

The Cox proportional hazards models evaluating the interaction of *CFH* (*rs1061170* and *rs1410996*), *ARMS2* (*rs10490924*), *CFH* (*rs412852* and *rs3766405*) and *ARMS2* (*indel: c.372_815del443ins54*), each individually with treatment with the four different randomized arms of AREDS trial resulted in no statistically significant interaction (Supplementary Figures 2A to D [available at <http://aaojournal.org>]). These figures, Supplementary 2A to 2D (available at <http://aaojournal.org>), also showed no statistically significant pairwise comparisons in these subgroups.

Analyses of Influence of *CFH* and *ARMS2* on the Main Effects of Antioxidants and Zinc

The Cox proportional hazard models evaluating the influence of *CFH* (*rs1061170* and *rs1410996*), *ARMS2* (*rs10490924*), *CFH* (*rs412852* and *rs3766405*) and *ARMS2* (*indel: c.372_815del443ins54*), individually on the treatment effects of the main effects of antioxidants (antioxidants vs. no antioxidants), demonstrated no statistically significant interactions (Supplementary Figures 3A to 3D [available at <http://aaojournal.org>]). Similar

analyses were conducted for the main effects of zinc (zinc vs. no zinc) and resulted in no consistent statistically significant interactions (Supplementary Figures 4A to 4D [available at <http://aaajournal.org>]). When the analyses were conducted by combining *CFH* (*rs1061170* and *rs1410996*) with *ARMS2* (*rs10490924*), to determine the influence of the genotypes on the main effects of antioxidants (Supplementary Figures 5A [available at <http://aaajournal.org>]) and main effects zinc (Supplementary Figures 5C [available at <http://aaajournal.org>]). These analyses were repeated by combining *CFH* (*rs412852* and *rs3766405*) with *ARMS2* (*indel: c.372_815del443ins54*) (Supplementary Figures 5B and D [available at <http://aaajournal.org>]). Again, all these analyses did not result in consistent statistically significant interactions.

Discussion

We found no statistically significant interaction between *CFH/ARMS2* genotype and treatment with AREDS supplement, as determined by progression to late AMD in these retrospective analyses of the randomized controlled clinical trial. These findings presented here do not support the conclusions of Awh et al¹ that recommended altering the composition of AREDS supplements based upon an individual's *CFH* and *ARMS2* genotypes, and are instead similar to the recommendations of Klein et al against routine genotyping prior to prescribing AREDS supplements. What can account for the differences between these current results and the Awh²¹ report? Differences in subgroup analyses are not uncommon as such analyses are fraught with the difficulties including insufficient power, multiple comparisons and possible confounders. The increase in sample size with an accompanying increase in event rates in the current study, probably accounts for some of the differences.

A repeat analysis using exactly the same *CFH* and *ARMS2* SNPs as Awh et al²¹ also did not alter our conclusions. We did not expect the use of the different SNPs at *CFH* to alter the conclusions greatly since these SNPs are highly correlated due to strong linkage disequilibrium. The statistical methods were somewhat different in the two studies as we analyzed the randomized arms for an overall interaction term whereas previous study provided the results from subgroup analyses by treatment versus placebo and main effects, and because we used a more stringent Bonferroni adjustment to appropriately account for multiple comparisons before declaring significance. We have repeated the analyses with several SNPs in *CFH* (*rs412852*, *rs3766405*, *rs10737680*, *rs1061170*, and *rs1410996*) and used two variants in *ARMS2* (*rs10490924*, *372_815del443ins54*); none of the results was however statistically significant.

We also confined our data to the randomized portion to the study up to 2001 as the participants assigned to the placebo group were recommended to take the AREDS supplements in the follow-up portion of the study from 2001 to 2005. They were no longer in a randomized comparison. Awh et al,²¹ however, using a small sample size also conducted the analyses throughout the entire follow-up period, both the complete clinical trial and the observation follow-up. Supplementary table 7 shows the imbalance in event rates to late AMD the two groups of AREDS participants with and without DNA when the

analyses are extended throughout the study, 1992-2005. This may also account for their findings which were different from the current study results.

An important limitation of the current study and the two previous reports is the lack of power to find an interaction. The number of individuals examined in each of the studies evaluating genetic interaction ranged from 895 to 1413 participants and the projected sample size in the original AREDS was nearly 4000 to evaluate the modest treatment effect of the AREDS formulation in persons at risk, assuming no interaction between the components of therapy or with other variables.²² Given this is a randomized trial that will not be repeated and the additional collection of DNA samples from the AREDS cohort will not be feasible, we will not likely increase the power of such analyses. The Age-Related Eye Disease Study 2 (AREDS2) which addresses a different clinical question regarding adding nutritional supplements of lutein/zeaxanthin and/or omega-3 fatty acids will not provide information on this subject.

As in the case of the initial genetic associations reported with response to treatment with intravitreal bevacizumab and ranibizumab,^{6,7} further analyses have failed to replicate initial findings. Genetic association analyses are vulnerable to all the problems associated with subgroup analyses, and they especially require replication before widespread clinical recommendations are implemented. Because these data are retrospective, one should also be cautious about making clinical recommendations even if the findings had been statistically significant. Such analyses are generally thought of as hypothesis generating, requiring independent verification prior to implementation, because they are often chance observations that cannot be replicated.

It is exciting to think that we are rapidly moving towards personalized medicine for AMD, as in other diseases such as breast cancer or leukemia; however, much work remains to be done before genetic knowledge can be applied for disease management.²⁵ The treatment with AREDS supplement is demonstrated to be effective when using both antioxidants and zinc together across all genetic groups defined on the basis of *CFH* and *ARMS2* genotype. We therefore continue to recommend the use of AREDS supplements for patients at risk for developing late AMD. At this stage, genetic testing does not appear helpful in improving treatment with AREDS supplements. Further investigations using larger set of genetic risk variants and with larger cohorts (case-control or family-based) may eventually allow us to make more definitive recommendations for genetic diagnosis and management of AMD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1A. Overall Results of the Age-Related Eye Disease Study (AREDS), a Randomized Controlled Clinical Trial of Antioxidants, Zinc, and the Combination of Antioxidants and Zinc¹
Foot Note: ¹From Reference 2.

Figure 1B. Combined Influence of *CFH*¹ *rs1061170* and *rs1410996* and *ARMS2*² *rs10490924* (n=1237) Genotypes on Treatment with AREDS Supplement Components^{3,4}

Foot notes:

¹ *CFH*: 0=low risk, 1=medium risk, 2=high risk

² *ARMS2*: 0=low risk (GG), 1=medium risk (GT), 2=high risk (TT)

³ *CFH/ARMS2*=*xy*, where *x*=*CFH* risk group, and *y*=*ARMS2* risk alleles

⁴ Model includes: age, gender, smoking, baseline AMD category, AREDS treatment, *CFH/ARMS2*, and the interaction term of AREDS treatment and *CFH/ARMS2*. Because of multiple comparisons, Bonferroni correction requires a p-value <0.001 to reach statistical significance.

Figure 1C. Combined Influence of Complement Factor H^1 (CFH) rs412852 and rs3766405 and ARMS2²: (*c.372_815del443ins54*) (n=1413) Genotypes on Treatment with AREDS Supplement Components (Antioxidants, Zinc or Combination of Antioxidant and Zinc)^{3,4}

Foot notes:

¹ CFH: 0=low risk, 1=medium risk, 2=high risk

² ARMS2 (*815del443ins54*): 0=low risk, 1=medium risk, 2=high risk

³ CFH/ARMS2=xy, where x=CFH risk group, and y=ARMS2 risk alleles

⁴ Model includes: age, gender, smoking, baseline AMD category, AREDS treatment, CFH/ARMS2, and the interaction term of AREDS treatment and CFH/ARMS2. Because of multiple comparisons, Bonferroni correction requires a p-value <0.001 to reach statistical significance.

Table 4

Baseline characteristics of AREDS Participants with DNA

	Total		Placebo		Antioxidants		Zinc		Antioxidants +Zinc	
	N	%	N	%	N	%	N	%	N	%
Total	1237	100.0	278	100.0	324	100.0	312	100.0	323	100.0
Age mean (standard deviation)	69	(5)	69	(5)	69	(6)	70	(5)	69	(5)
Gender										
Female	726	58.7	160	57.6	189	58.3	193	61.9	184	57.0
Male	511	41.3	118	42.4	135	41.7	119	38.1	139	43.0
Smoking										
Current	89	7.2	18	6.5	32	9.9	22	7.1	17	5.3
Former	592	47.9	127	45.7	159	49.1	146	46.8	160	49.5
Never	556	44.9	133	47.8	133	41.0	144	46.2	146	45.2
Baseline AMD category										
Intermediate AMD	832	67.3	186	66.9	216	66.7	204	65.6	226	70.0
Advanced AMD in one eye	405	32.7	92	33.1	108	33.3	108	34.6	97	30.0
CFH risk group (rs1061170 & rs1410996)										
0=low	235	19.0	53	19.1	61	18.8	62	19.9	59	18.3
1=medium	338	27.3	79	28.4	83	25.6	79	25.3	97	30.0
2=high	664	53.7	146	52.5	180	55.6	171	55.0	167	51.7
ARMS2 risk alleles (rs10490924)										
0=low (GG)	487	39.4	119	42.8	130	40.1	113	36.2	125	38.7
1=medium (GT)	543	43.9	113	40.6	143	44.1	145	46.6	142	44.0
2=high (TT)	207	16.7	46	16.5	51	15.7	54	17.4	56	17.3
Additional SNPs Evaluated										
	N	%	N	%	N	%	N	%	N	%
Total	1413	100	334	23.6	357	25.3	356	25.2	366	25.9
CFH risk group (rs412852 and rs3766405)										

	Total		Placebo		Antioxidants		Zinc		Antioxidants +Zinc	
	N	%	N	%	N	%	N	%	N	%
0=low	224	15.9	50	15.0	58	16.2	58	16.3	58	15.8
1=medium	410	29.0	96	28.7	100	28.0	99	27.8	115	31.4
2=high	779	55.1	188	56.3	199	55.7	199	55.9	193	52.7
ARMS2 risk alleles (c.372_815del/443ins54)										
0=low (GG)	565	40.0	137	41.0	142	39.8	138	38.8	148	40.4
1=medium (GT)	619	43.8	142	42.5	162	45.4	157	44.1	158	43.2
2=high (TT)	229	16.2	55	16.5	53	14.8	61	17.1	60	16.4