

**Supplementary Table 1. Multivariate associations between demographic, environmental, and ocular risk factors and progression to overall advanced age-related macular degeneration, geographic atrophy, and neovascular disease**

Risk Factors	Overall Advanced AMD				Geographic Atrophy				Neovascular Disease			
	No genes <sup>a</sup>		With genes <sup>b</sup>		No genes		With genes		No genes		With genes	
	N=995/4543		N=882/4124		N=545/4543		N=485/4124		N=450/4543		N=397/4124	
	HR (95% CI) <sup>c</sup>	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Age</b>												
75+	1.00		1.00		1.00		1.00		1.00		1.00	
65-74	0.67 (0.57 - 0.79)	<0.0001	0.69 (0.58 - 0.83)	<0.0001	0.66 (0.53 - 0.82)	<0.0001	0.67 (0.53 - 0.86)	0.001	0.68 (0.54 - 0.86)	0.001	0.71 (0.55 - 0.92)	0.009
55-64	0.49 (0.38 - 0.63)	<0.0001	0.51 (0.39 - 0.65)	<0.0001	0.50 (0.36 - 0.69)	<0.0001	0.52 (0.38 - 0.73)	<0.0001	0.48 (0.34 - 0.68)	<0.0001	0.49 (0.34 - 0.70)	<0.0001
<b>Sex</b>												
Female	1.00		1.00		1.00		1.00		1.00		1.00	
Male	0.96 (0.83 - 1.11)	0.580	1.01 (0.86 - 1.18)	0.937	1.12 (0.91 - 1.38)	0.274	1.19 (0.96 - 1.48)	0.110	0.80 (0.64 - 0.99)	0.036	0.82 (0.65 - 1.03)	0.091
<b>Education</b>												
≤ High School	1.00		1.00		1.00		1.00		1.00		1.00	
> High School	0.75 (0.65 - 0.86)	<0.0001	0.75 (0.64 - 0.87)	<0.0001	0.71 (0.58 - 0.86)	0.001	0.71 (0.57 - 0.87)	<0.0001	0.80 (0.65 - 0.98)	0.028	0.80 (0.65 - 1.00)	0.046
<b>Smoking</b>												
Never	1.00		1.00		1.00		1.00		1.00		1.00	
Past	1.12 (0.96 - 1.31)	0.138	1.09 (0.93 - 1.28)	0.297	0.98 (0.79 - 1.20)	0.831	0.92 (0.74 - 1.15)	0.464	1.32 (1.06 - 1.64)	0.014	1.34 (1.06 - 1.70)	0.015
Current	2.36 (1.85 - 3.01)	<0.0001	2.28 (1.75 - 2.96)	<0.0001	2.01 (1.43 - 2.84)	<0.0001	1.76 (1.20 - 2.57)	0.004	2.83 (2.03 - 3.94)	<0.0001	3.06 (2.15 - 4.36)	<0.0001
<b>BMI</b>												
<25	1.00		1.00		1.00		1.00		1.00		1.00	
25-29.9	1.28 (1.08 - 1.52)	0.005	1.29 (1.07 - 1.55)	0.008	1.41 (1.10 - 1.80)	0.007	1.35 (1.04 - 1.75)	0.026	1.15 (0.91 - 1.45)	0.249	1.22 (0.95 - 1.57)	0.127
30+	1.38 (1.14 - 1.66)	0.001	1.39 (1.14 - 1.71)	0.001	1.55 (1.19 - 2.01)	0.001	1.49 (1.13 - 1.96)	0.005	1.20 (0.92 - 1.56)	0.171	1.29 (0.97 - 1.71)	0.077
<b>Baseline grade<sup>d</sup></b>												

1	1.00		1.00		1.00		1.00		1.00		1.00	
2	8.30 (3.37 - 20.44)	<0.0001	7.80 (3.16 - 19.28)	<0.0001	14.41 (3.24-64.00)	0.001	13.27 (3.96-59.62)	0.001	5.19 (1.63-16.54)	0.005	5.04 (1.58-16.02)	0.006
3	42.25 (15.69-113.77)	<0.0001	33.47 (12.17-92.09)	<0.0001	148.3 (28.2-780.3)	<0.0001	122.7 (22.1-679.6)	<0.0001	14.24 (4.07-49.82)	<0.0001	10.89 (3.06-38.78)	<0.0001
<b>Baseline drusen size (µm)</b>												
<63	1.00		1.00		1.00		1.00		1.00		1.00	
63-124	0.86 (0.53 - 1.40)	0.544	0.77 (0.46 - 1.27)	0.303	0.46 (0.21 - 1.02)	0.056	0.41 (0.17 - 0.98)	0.046	1.41 (0.72 - 2.76)	0.310	1.22 (0.62 - 2.38)	0.567
125-249	0.79 (0.44 - 1.42)	0.431	0.75 (0.40 - 1.40)	0.366	0.34 (0.14 - 0.87)	0.024	0.32 (0.12 - 0.90)	0.030	1.73 (0.78 - 3.82)	0.176	1.63 (0.72 - 3.68)	0.240
≥250	1.80 (1.00 - 3.24)	0.050	1.60 (0.86 - 2.99)	0.139	0.94 (0.37 - 2.37)	0.899	0.84 (0.31 - 2.33)	0.742	3.12 (1.42 - 6.87)	0.005	2.69 (1.19 - 6.08)	0.017

<sup>a</sup>Sample includes individual eyes from all subjects.

<sup>b</sup>Sample includes individual eyes from the subgroup with an available genetic specimen.

<sup>c</sup>Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by multivariate Cox proportional hazards models using the individual eye as the unit of analysis. In the analyses including all subjects, models are adjusted for all demographic, environmental, and ocular variables in the table. In the analyses including all subjects with an available genetic specimen, models are adjusted for all demographic, environmental, and ocular variables in the table as well as the genetic variables: *CFH* Y402H rs1061170 and *ARMS2* A69S rs10490924.

<sup>d</sup>Grade at baseline[16]: 1 (no AMD); 2 (early AMD); 3 (intermediate AMD).

Supplementary Table 2. Multivariate associations between antioxidant and zinc supplements and progression to advanced AMD, geographic atrophy, and neovascular disease stratified by genotype for *CFH* Y402H rs1061170 and *ARMS2* A69S rs10490924

		Overall Advanced AMD			Geographic Atrophy			Neovascular Disease		
		N=882/4124			N=485/4124			N=397/4124		
Treatment Group	Genotype	HR (95% CI) <sup>a</sup>	P-value <sup>b</sup>	P-interaction <sup>c</sup>	HR (95% CI)	P-value	P-interaction	HR (95% CI)	P-value	P-interaction
<b>Antioxidant</b>										
<i>CFH</i> Y402H rs1061170	TT	0.76 (0.46 - 1.26)	0.282		1.26 (0.58 - 2.72)	0.561		0.45 (0.22 - 0.93)	0.031	
	CT	0.77 (0.56 - 1.06)	0.114	0.949	0.66 (0.41 - 1.05)	0.079	0.162	0.88 (0.57 - 1.35)	0.553	0.121
	CC	0.92 (0.65 - 1.30)	0.636	0.531	0.89 (0.55 - 1.44)	0.629	0.453	0.96 (0.60 - 1.55)	0.870	0.087
<b>ARMS2 A69S rs10490924</b>										
<i>ARMS2</i> A69S rs10490924	GG	0.86 (0.57 - 1.28)	0.447		0.82 (0.47 - 1.43)	0.486		0.91 (0.49 - 1.70)	0.758	
	GT	0.82 (0.61 - 1.11)	0.205	0.882	0.92 (0.59 - 1.44)	0.720	0.751	0.74 (0.50 - 1.11)	0.145	0.598
	TT	0.66 (0.42 - 1.03)	0.066	0.392	0.56 (0.30 - 1.05)	0.070	0.376	0.74 (0.42 - 1.31)	0.304	0.642
<b>Zinc</b>										
<i>CFH</i> Y402H rs1061170	TT	0.79 (0.47 - 1.32)	0.369		1.19 (0.53 - 2.65)	0.680		0.54 (0.28 - 1.05)	0.067	
	CT	0.88 (0.64 - 1.21)	0.429	0.724	1.16 (0.76 - 1.76)	0.491	0.960	0.60 (0.39 - 0.93)	0.023	0.801
	CC	1.15 (0.81 - 1.63)	0.426	0.234	1.41 (0.88 - 2.27)	0.155	0.715	0.87 (0.52 - 1.44)	0.578	0.265
<i>ARMS2</i> A69S rs10490924	GG	1.08 (0.73 - 1.62)	0.691		1.24 (0.74 - 2.09)	0.419		0.90 (0.49 - 1.63)	0.715	
	GT	0.88 (0.65 - 1.20)	0.438	0.429	1.18 (0.75 - 1.85)	0.471	0.890	0.62 (0.41 - 0.94)	0.024	0.324
	TT	0.76 (0.50 - 1.16)	0.200	0.228	1.15 (0.66 - 1.99)	0.617	0.848	0.46 (0.26 - 0.84)	0.011	0.123

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<sup>a</sup>Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated by multivariate Cox proportional hazards models using the individual eye as the unit of analysis. All models are adjusted for age, sex, education, smoking status, body mass index, baseline AMD grade, and baseline drusen size.

<sup>b</sup>P value reports the difference in the effectiveness of the antioxidant or zinc treatment compared to placebo for each genotype.

<sup>c</sup> P interaction reports the difference in the effectiveness of the antioxidant or zinc treatment compared to placebo for the CC versus TT genotype and the CT versus TT genotype (for *CFH* Y402H) and for the TT versus GG genotype and the GT versus GG genotype (for *ARMS2* A69S).

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