

SUPPLEMENTAL MATERIAL

Bivariate Analysis of Age-Related Macular Degeneration Progression Using Genetic Risk Scores

Ying Ding,[†] Yi Liu,^{†,§} Qi Yan,[§] Lars G. Fritsche,[‡] Richard J. Cook,^{††} Traci Clemons,^{§§} Rinki Ratnapriya,^{‡‡} Michael L. Klein,⁺ Gonçalo R. Abecasis,[‡] Anand Swaroop,^{‡‡} Emily Y. Chew,⁺⁺ Daniel E. Weeks,^{*,†} Wei Chen,^{†,§,*}

[†]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA;

[§]Division of Pulmonary Medicine, Allergy and Immunology, Department of Pediatrics, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA;

[‡]Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, MI;

^{††}Department of Statistics and Actuarial Science, University of Waterloo, Canada;

^{§§}The EMMES Corporation, Rockville, MD;

^{‡‡}Neurobiology Neurodegeneration and Repair Laboratory, National Eye Institute, National Institutes of Health, Bethesda, MD;

⁺Casey Eye Institute, Oregon Health & Science University, Portland, Oregon;

⁺⁺Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, MD;

^{*}Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, PA

Table S1: Multivariable robust Cox model¹ results for the 34 top AMD risk variants on progression to choroidal neovascularization (CNV).

Variant	Chr	Major/ minor allele	Locus name ²	Effect on Progression (AREDS)		Effect on Progression (AREDS2)	
				HR	<i>p</i>	HR	<i>p</i>
rs10922109	1	C/A	<i>CFH</i>	0.60	1.40x10 ⁻⁸	1.18	6.1x10 ⁻²
rs11884770	2	C/T	<i>COL4A3</i>	1.09	0.33	0.80	7.1x10 ⁻³
rs62247658	3	T/C	<i>ADAMTS9-AS2</i>	1.00	0.95	0.90	0.14
rs140647181	3	T/C	<i>COL8A1</i>	2.29	4.5x10 ⁻³	0.88	0.73
rs10033900	4	C/T	<i>CFI</i>	1.00	0.96	0.88	6.3x10 ⁻²
rs62358361	5	G/T	<i>C9</i>	0.86	0.66	0.40	4.5x10 ⁻³
rs114092250	5	G/A	<i>PRLR/SPEF2</i>	0.44	0.02	0.92	0.79
rs116503776	6	G/A	<i>C2/CFB/SKIV2L</i>	0.72	1.4x10 ⁻²	1.03	0.82
rs943080	6	T/C	<i>VEGFA</i>	0.95	0.45	0.94	0.39
rs7803454	7	C/T	<i>PILRB/PILRA</i>	1.01	0.95	1.09	0.33
rs1142	7	C/T	<i>KMT2E/SRPK2</i>	1.03	0.68	1.07	0.35
rs79037040	8	T/G	<i>TNFRSF10A</i>	0.94	0.43	0.96	0.56
rs71507014	9	GC/G	<i>TRPM3</i>	0.99	0.87	0.93	0.33
rs10781182	9	G/T	<i>MIR6130/RORB</i>	0.85	3.6x10 ⁻²	0.94	0.42
rs1626340	9	G/A	<i>TGFBR1</i>	0.85	0.11	0.89	0.22
rs2740488	9	A/C	<i>ABCA1</i>	0.96	0.60	1.00	1.0
rs12357257	10	G/A	<i>ARHGAP21</i>	1.05	0.57	1.03	0.68
rs3750846	10	T/C	<i>ARMS2/HTRA1</i>	1.57	3.2x10 ⁻⁹	1.37	2.1x10 ⁻⁶
rs3138141	12	C/A	<i>RDH5/CD63</i>	1.25	5.3x10 ⁻²	0.98	0.87
rs61941274	12	G/A	<i>ACAD10</i>	0.97	0.91	1.20	0.54
rs9564692	13	C/T	<i>B3GALTL</i>	0.76	2.3x10 ⁻³	0.94	0.46
rs61985136	14	T/C	<i>RAD51B</i>	1.17	4.2x10 ⁻²	1.00	1.0
rs2043085	15	T/C	<i>LIPC</i>	1.15	7.4x10 ⁻²	0.99	0.91
rs5817082	16	C/CA	<i>CETP</i>	0.87	9.7x10 ⁻²	1.00	0.98
rs72802342	16	C/A	<i>CTRB2/CTRB1</i>	0.81	0.21	0.93	0.66
rs11080055	17	C/A	<i>TMEM97/VTN</i>	1.16	4.9x10 ⁻²	1.16	0.04
rs6565597	17	C/T	<i>NPLOC4/TSPAN10</i>	1.14	9.5x10 ⁻²	1.08	0.31
rs67538026	19	C/T	<i>CNN2</i>	0.89	0.14	0.91	0.29
rs2230199	19	C/G	<i>C3</i>	0.82	2.6x10 ⁻²	1.06	0.48
rs429358	19	T/C	<i>APOE</i>	0.96	0.70	0.93	0.57
rs142450006	20	TTTTTC/T	<i>MMP9</i>	0.65	6.3x10 ⁻⁴	0.71	3.8x10 ⁻³
rs201459901	20	T/TA	<i>C20orf85</i>	0.95	0.74	0.87	0.41
rs5754227	22	T/C	<i>SYN3/TIMP3</i>	0.88	0.27	0.63	1.8x10 ⁻⁴
rs8135665	22	C/T	<i>SLC16A8</i>	0.92	0.35	0.98	0.83

¹: Model was adjusted for baseline age, education, smoking status and study eye's baseline AMD severity score.

²: The locus name identifies the nearest gene(s), but does not necessarily identify the responsible gene

Table S2: Multivariable robust Cox model results for the 34 top AMD risk variants on progression to geographic atrophy (GA).

Variant	Chr	Major/ minor allele	Locus name	Effect on Progression (AREDS)		Effect on Progression (AREDS2)	
				HR	<i>p</i>	HR	<i>p</i>
rs10922109	1	C/A	<i>CFH</i>	0.70	1.9x10 ⁻⁵	1.01	0.96
rs11884770	2	C/T	<i>COL4A3</i>	0.95	0.52	0.88	0.11
rs62247658	3	T/C	<i>ADAMTS9-AS2</i>	1.16	3.7x10 ⁻²	0.85	2.2x10 ⁻²
rs140647181	3	T/C	<i>COL8A1</i>	1.19	0.70	1.02	0.94
rs10033900	4	C/T	<i>CFI</i>	0.96	0.56	0.94	0.39
rs62358361	5	G/T	<i>C9</i>	1.10	0.77	0.82	0.41
rs114092250	5	G/A	<i>PRLR/SPEF2</i>	0.67	7.2x10 ⁻²	0.97	0.91
rs116503776	6	G/A	<i>C2/CFB/SKIV2L</i>	0.69	2.3x10 ⁻⁴	0.84	0.19
rs943080	6	T/C	<i>VEGFA</i>	0.95	0.40	0.99	0.87
rs7803454	7	C/T	<i>PILRB/PILRA</i>	0.97	0.68	1.37	4.1x10 ⁻⁴
rs1142	7	C/T	<i>KMT2E/SRPK2</i>	0.97	0.72	1.03	0.69
rs79037040	8	T/G	<i>TNFRSF10A</i>	0.91	0.15	0.94	0.41
rs71507014	9	GC/G	<i>TRPM3</i>	1.00	0.96	0.84	8.6x10 ⁻³
rs10781182	9	G/T	<i>MIR6130/RORB</i>	0.87	6.1x10 ⁻²	0.84	0.015
rs1626340	9	G/A	<i>TGFBR1</i>	0.97	0.73	0.97	0.69
rs2740488	9	A/C	<i>ABCA1</i>	0.99	0.93	1.07	0.41
rs12357257	10	G/A	<i>ARHGAP21</i>	1.07	0.38	1.17	0.05
rs3750846	10	T/C	<i>ARMS2/HTRA1</i>	1.49	2.1x10 ⁻⁸	1.19	1.4x10 ⁻²
rs3138141	12	C/A	<i>RDH5/CD63</i>	1.24	0.04	0.89	0.33
rs61941274	12	G/A	<i>ACAD10</i>	1.17	0.57	0.95	0.87
rs9564692	13	C/T	<i>B3GALTL</i>	0.83	1.9x10 ⁻²	0.92	0.29
rs61985136	14	T/C	<i>RAD51B</i>	1.18	3.4x10 ⁻²	0.95	0.53
rs2043085	15	T/C	<i>LIPC</i>	1.20	1.1x10 ⁻²	1.00	0.95
rs5817082	16	C/CA	<i>CETP</i>	0.91	0.24	1.14	0.12
rs72802342	16	C/A	<i>CTRB2/CTRB1</i>	0.69	3.5x10 ⁻²	0.78	0.11
rs11080055	17	C/A	<i>TMEM97/VTN</i>	1.11	0.11	1.03	0.70
rs6565597	17	C/T	<i>NPLOC4/TSPAN10</i>	1.00	0.97	0.96	0.57
rs67538026	19	C/T	<i>CNN2</i>	0.86	4.4x10 ⁻²	0.83	2.9x10 ⁻²
rs2230199	19	C/G	<i>C3</i>	0.87	8.7x10 ⁻²	0.91	0.20
rs429358	19	T/C	<i>APOE</i>	0.89	0.35	1.11	0.37
rs142450006	20	TTTTTC/T	<i>MMP9</i>	0.82	8.3x10 ⁻²	0.76	1.3x10 ⁻²
rs201459901	20	T/TA	<i>C20orf85</i>	1.16	0.24	0.88	0.45
rs5754227	22	T/C	<i>SYN3/TIMP3</i>	0.95	0.59	0.81	4.7x10 ⁻²
rs8135665	22	C/T	<i>SLC16A8</i>	1.01	0.86	1.05	0.57

Table S3: AUC¹ values (with 5-fold cross validation SD in parenthesis for AREDS data) for different prediction models evaluated in all (evaluable) eyes.

Model ²	AREDS			AREDS2		
	4 yr (n=5000)	10 yr (n=4126)	iAUC ² (up to 4yr)	iAUC (up to 10yr)	4 yr (n=2633)	iAUC (up to 4yr)
A	0.678 (0.025)	0.669 (0.034)	0.676 (0.054)	0.672 (0.042)	0.635	0.617
B	0.739 (0.041)	0.774 (0.043)	0.767 (0.046)	0.769 (0.043)	0.632	0.618
C	0.906 (0.010)	0.915 (0.013)	0.905 (0.020)	0.909 (0.013)	0.756	0.744
D	0.913 (0.009)	0.920 (0.013)	0.908 (0.018)	0.914 (0.013)	0.773	0.755
E	0.908 (0.010)	0.922 (0.015)	0.905 (0.021)	0.912 (0.014)	0.762	0.742

Table S4: AUC values (with 5-fold cross validation SD in parenthesis for AREDS data) for different prediction models evaluated in (evaluable) eyes with baseline severity score greater than 3.

Model	AREDS			AREDS2		
	4 yr (n=1888)	10 yr (n=1657)	iAUC (up to 4yr)	iAUC (up to 10yr)	4 yr (n=2520)	iAUC (up to 4yr)
A	0.626 (0.016)	0.601 (0.034)	0.619 (0.063)	0.619 (0.061)	0.631	0.612
B	0.638 (0.030)	0.669 (0.038)	0.681 (0.051)	0.670 (0.058)	0.625	0.611
C	0.787 (0.034)	0.785 (0.017)	0.806 (0.037)	0.786 (0.035)	0.749	0.738
D	0.802 (0.033)	0.795 (0.016)	0.816 (0.037)	0.797 (0.034)	0.766	0.748
E	0.788 (0.041)	0.803 (0.019)	0.817 (0.034)	0.797 (0.035)	0.757	0.738

¹: these prediction models were established using AREDS data and evaluated on both AREDS (5-fold cross validation) and AREDS2.

²: predictors for each model are listed in Table 6.

³: iAUC: integrated AUC

Figure S1: Distribution plot on baseline age in AREDS and AREDS2.

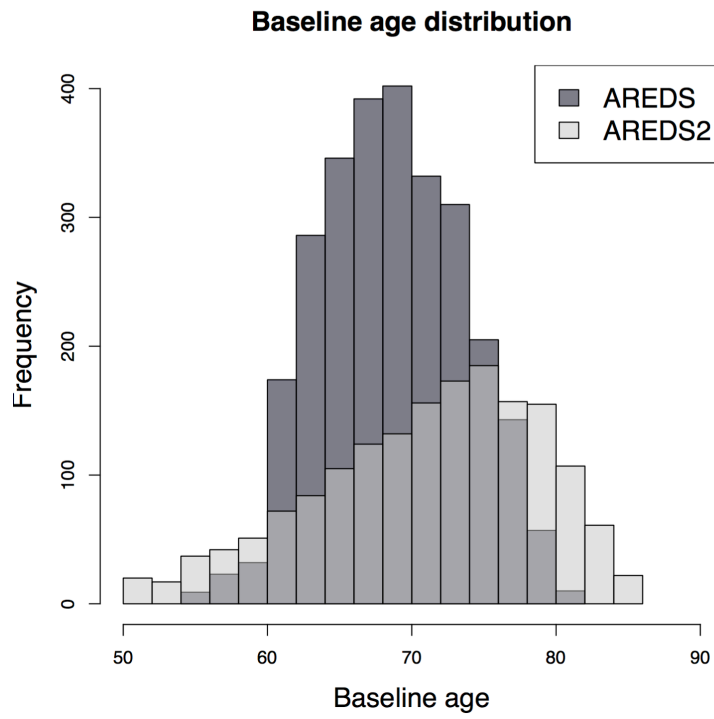


Figure S2: Distribution of the genetic risk score in AREDS and AREDS2.

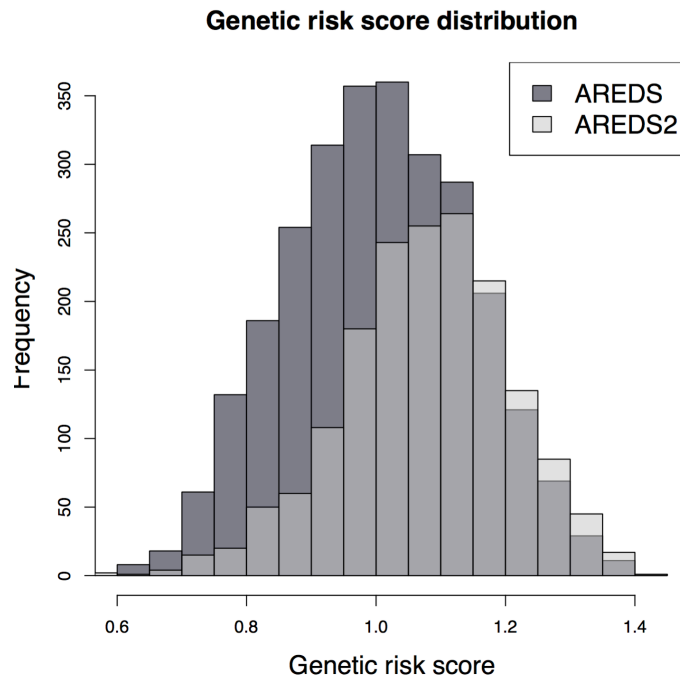


Figure S3: The corresponding forest plots for Table 4.

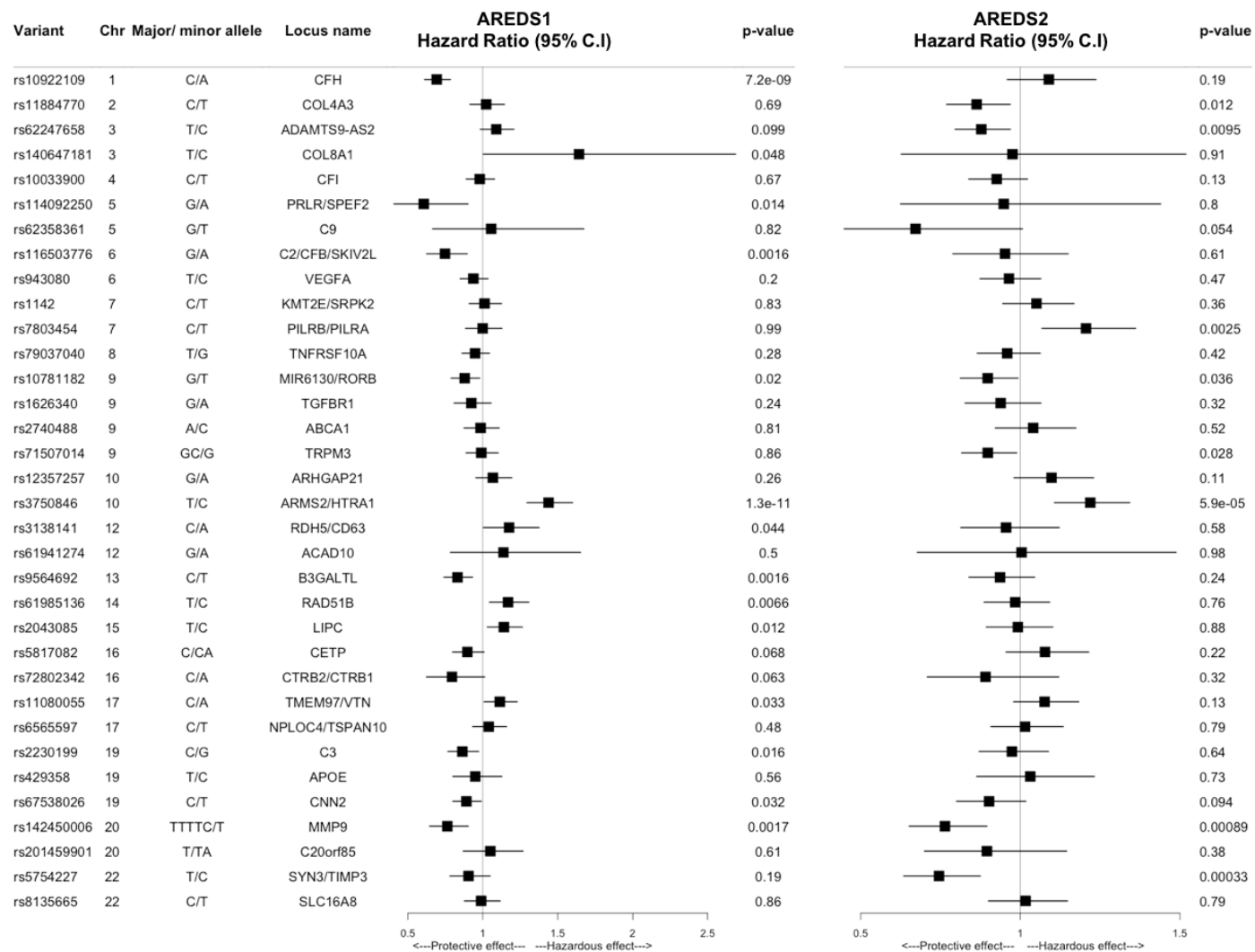


Figure S4: The corresponding forest plots for Table S1.

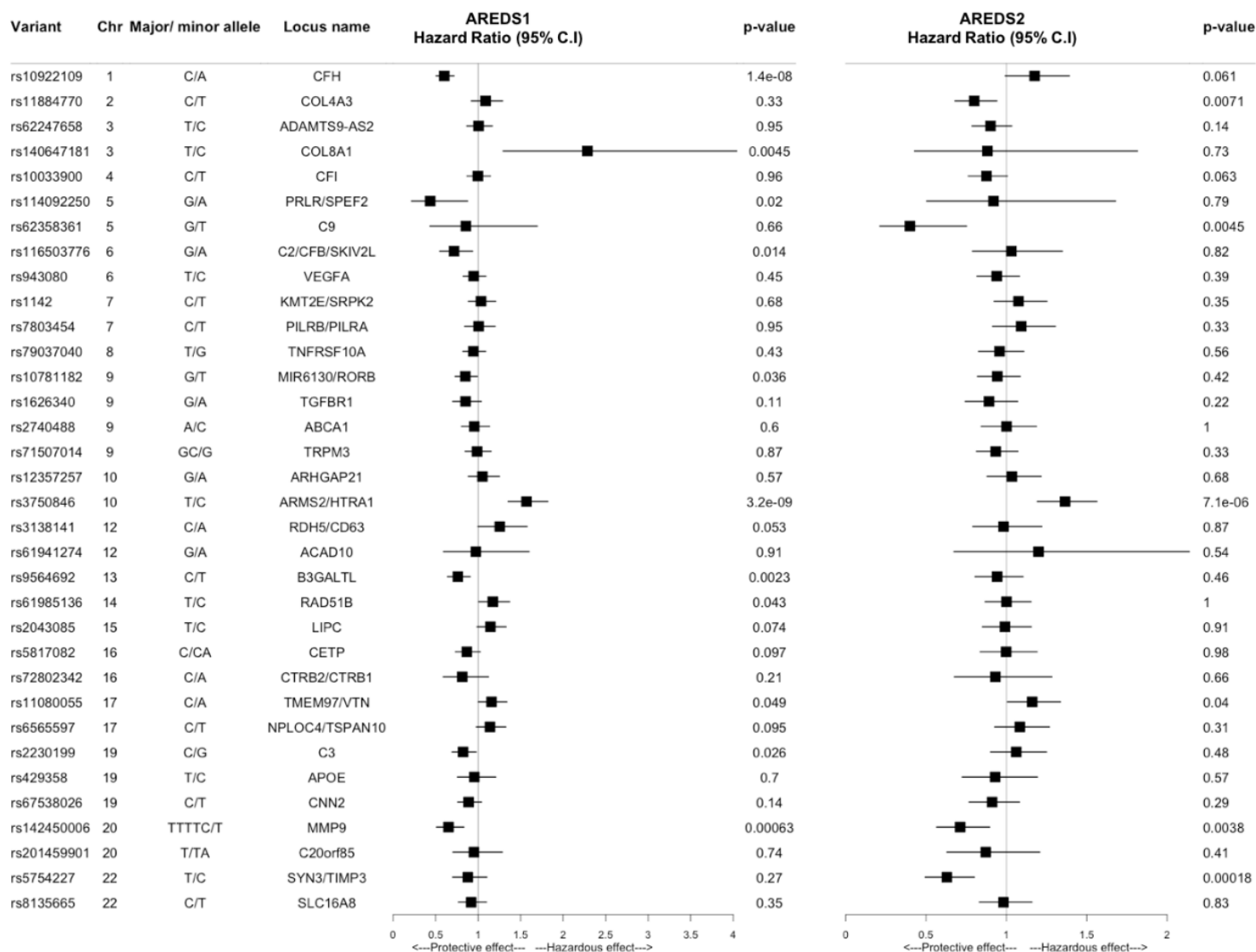


Figure S5: The corresponding forest plots for Table S2.

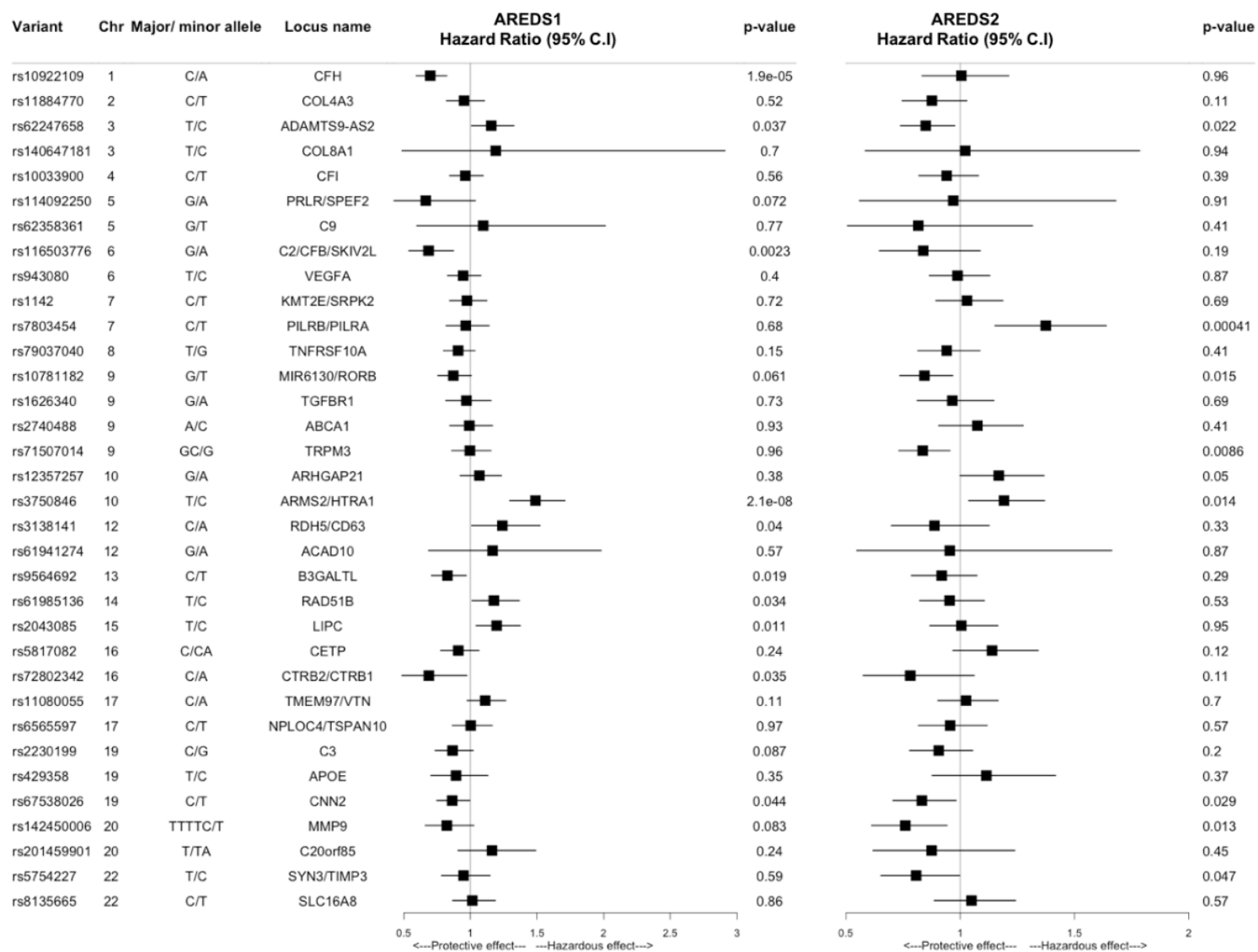


Figure S6: A: ROC curves for Model D in AREDS data; B: ROC curves for Model E in AREDS data.

