Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

Supplemental Materials

***** Spreadsheet available for direct download at:
http://alois.med.upenn.edu/~adamnaj/NEU13-1890_NajEtAl2014-ADGC_AAO_eTables_6_and_7.xlsx

eTable 1. Descriptive Statistics. Sample size and descriptive statistics by dataset used in age-at-onset (AAO) analyses in the ADGC.

Cohort	Cases (N)	Case Sample Characteristics By Dataset				Cases Missing AAO Data		Cases Missing AAO & AAE Data	
		# Cases with AAO Data (N (%))	Age at onset (Mean ± SD)	Female (N (%))	*APOE* ε2/ε3/ε4 (Allele Proportions)	# Cases with / # Cases without AAE Data	Mean (SD)	# Cases with / # Cases without AAD Data	Mean (SD)
ACT	566	350 (62%)	83.9 (4.76)	231 (66%)	0.06/0.74/0.20	216 / 0	83.6 (5.61)	-- / --	--
ADC1	1,566	1,411 (90%)	72.5 (7.07)	760 (54%)	0.03/0.55/0.42	0 / 155	--	155 / 0	81.1 (8.33)
ADC2	738	631 (86%)	73.2 (7.10)	316 (50%)	0.03/0.57/0.40	107 / 0	79.6 (6.84)	-- / --	--
ADC3	897	604 (67%)	74.4 (7.97)	324 (54%)	0.04/0.58/0.38	98 / 195	79.4 (10.9)	187 / 8	75.7 (9.20)
ADNI	268	138 (51%)	73.0 (7.22)	64 (46%)	0.03/0.57/0.41	130 / 0	77.7 (6.25)	-- / --	--
GenADA	669	655 (98%)	74.6 (6.18)	372 (57%)	0.04/0.57/0.39	14 / 0	84.9 (6.52)	-- / --	--
NIA-LOAD	1,811	1,800 (99%)	73.6 (6.67)	1,168 (65%)	0.02/0.51/0.46	11 / 0	84.7 (9.00)	-- / --	--
MAYO	728	0 (0%)	ND	ND	ND	728 / 0	73.9 (4.88)	-- / --	--
MIRAGE	509	502 (99%)	71.2 (6.50)	320 (64%)	0.04/0.60/0.36	7 / 0	74.7 (5.50)	-- / --	--
OHSU	132	127 (96%)	86.1 (5.53)	80 (63%)	0.07/0.70/0.23	5 / 0	90.4 (8.76)	-- / --	--
ROSMAP	296	291 (98%)	85.6 (6.26)	205 (70%)	0.05/0.75/0.20	0 / 5	--	5 / 0	91.0 (4.18)
TGEN2	864	129 (15%)	74.9 (7.23)	60 (47%)	0.05/0.56/0.39	-- / --	--	-- / --	--
UM/VU/ MSSM	1,186	1,031 (87%)	73.9 (7.75)	661 (64%)	0.03/0.59/0.38	39 / 116	78.41 (9.05)	116 / 0	85.4 (8.87)
UP	1,271	1,175 (92%)	72.9 (6.39)	742 (63%)	0.04/0.63/0.34	96 / 0	78.25 (7.77)	-- / --	--
WU	339	318 (94%)	74.2 (8.00)	177 (56%)	0.06/0.62/0.32	0 / 21	--	0 / 21	--
TOTAL	**11,840**	**9,162 (77%)**	**74.3 (7.64)**	**5,480 (60%)**	**0.03/0.58/0.38**	**1,451 / 1,227**	**77.13 (7.27)**	**1,196 / 31**	**81.15 (8.59)**

eTable 2. Replication of age-at-onset (AAO) associations of SNPs most significantly associated with LOAD in nine genomic regions and *APOE*. SNPs presented demonstrated strongest associations within each of ten genomic regions with associations of genome-wide statistical significance ($P \leq 5.0\times10^{-8}$) with LOAD risk. *P*-values for AAO associations exceeding the multiple hypothesis testing threshold ($P<0.005$) are shown in bold.

SNP	CH:MB	Nearest Gene	MA	MAF	AAO Discovery (Minimal Adjustment)			MA	MAF	AAO Replication (Minimal Adjustment)		
					β (95% CI)	*P*	Het *P*			*β* (95% CI)	*P*	Het *P*
rs6701713	1:207.8	*CR1*	A	0.24	-0.41 (-0.65, -0.17)	**7.17×10^{-4}**	0.24	A	0.22	-0.045 (-0.19, 0.10)	0.545	0.638
rs7561528	2:127.9	*BIN1*	A	0.37	-0.31 (-0.52, -0.09)	**4.78×10^{-4}**	0.37	A	0.37	-0.067 (-0.19, 0.059)	0.297	0.874
rs9349407	6:47.5	*CD2AP*	C	0.32	-0.03 (-0.25, 0.19)	0.765	0.32	C	0.28	-0.0039 (-0.14, 0.13)	0.955	0.094
rs11767557	7:143.1	*EPHA1*	C	0.18	0.03 (-0.26, 0.32)	0.830	0.18	C	0.18	0.046 (-0.11, 0.20)	0.567	0.750
rs1532278	8:27.5	*CLU*	T	0.37	0.05 (-0.18, 0.28)	0.661	0.37	T	0.37	0.017 (-0.11, 0.14)	0.790	0.108
rs4938933	11:60.0	*MS4A4A*	C	0.36	0.09 (-0.14, 0.31)	0.448	0.36	C	0.37	0.021 (-0.11, 0.15)	0.750	0.684
rs561655	11:85.8	*PICALM*	G	0.38	0.33 (-0.12, 0.55)	**2.23×10^{-3}**	0.38	G	0.32	0.10 (-0.027, 0.23)	0.123	0.953
rs3752246	19:1.1	*ABCA7*	G	0.34	-0.27 (-0.55, 0.02)	0.0640	0.34	G	0.18	-0.00030 (-0.16, 0.16)	0.998	0.125
Haplotype (rs7412/ rs429358)	19:45.4	*APOE*	ε4	0.35	-2.45 (-2.68, -2.21)	**3.30×10^{-96}**	0.35	ε4	0.34	-0.39 (-0.52, -0.26)	5.36×10^{-9}	0.917
rs3865444	19:51.7	*CD33*	A	0.20	0.10 (-0.13, 0.33)	0.377	0.20	A	0.31	0.0050 (-0.13, 0.14)	0.942	0.827

CH:MB, chromosome:position (in mega base pairs, build 19); MA, minor allele; MAF, minor allele frequency; *β*, Beta coefficient for AAO from meta-analysis (# years difference in AAO per copy of the minor allele); OR, odds ratio; 95% CI, 95% Confidence Interval; P, P-value; Het *P*, *P*-value for heterogeneity across studies.

eTable 3. Risk-weighted burden analysis results for *APOE* and 9 LOAD candidate genes excluding three datasets with later onset age (ACT, OHSU, ROSMAP). Beta coefficients (β), 95% Confidence Intervals, and *P*-values are from four linear regression models of AAO examining weighted scores for the peak SNP LOAD risk associations in *APOE* and 9 LOAD candidate genes. Scores are the product of the odds ratio for LOAD risk for each SNP multiplied by minor allele dosage from imputed genotype probabilities.

	Model 1: Adjustment for PCs & Site		**Model 2: Adjustment for Model 1 + *APOE***		**Model 3: Adjustment for Model 1 + 9 LOAD Genes**		**Model 4: Adjustment for Model 1 + *APOE* + 9 LOAD Genes**	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
(Intercept)	74.65 (73.75, 75.55)	$<10^{-320}$	76.2 (75.3, 77.1)	$<10^{-320}$	75.7 (74.5, 77.0)	$<10^{-320}$	77.4 (76.1, 78.6)	$<10^{-320}$
CR1 Score	--	--	--	--	-0.22 (-0.46, 0.03)	0.0798	-0.21 (-0.45, 0.02)	0.0795
BIN1 Score	--	--	--	--	-0.30 (-0.51, -0.09)	0.00464	-0.32 (-0.52, -0.11)	0.00221
CD2AP Score	--	--	--	--	-0.06 (-0.29, 0.17)	0.636	-0.10 (-0.32, 0.13)	0.402
EPHA1 Score	--	--	--	--	0.05 (-0.23, 0.32)	0.737	0.05 (-0.21, 0.32)	0.696
CLU Score	--	--	--	--	-0.10 (-0.33, 0.13)	0.391	-0.10 (-0.33, 0.12)	0.353
MS4A4A Score	--	--	--	--	-0.12 (-0.34, 0.09)	0.259	-0.13 (-0.34, 0.08)	0.220
PICALM Score	--	--	--	--	-0.27 (-0.49, -0.06)	0.0138	-0.24 (-0.46, -0.03)	0.0260
ABCA7 Score	--	--	--	--	-0.16 (-0.43, 0.12)	0.274	-0.15 (-0.42, 0.12)	0.282
CD33 Score	--	--	--	--	0.03 (-0.20, 0.26)	0.794	-0.04 (-0.26, 0.19)	0.739
APOE Score	--	--	-0.77 (-0.86, -0.69)	7.44×10^{-69}	--	--	-0.77 (-0.86, -0.69)	1.47×10^{-68}
ADC1	-2.37 (-3.35, -1.39)	2.03×10^{-6}	-2.52 (-3.47, -1.56)	2.41×10^{-7}	-2.34 (-3.32, -1.36)	2.84×10^{-6}	-2.48 (-3.44, -1.52)	3.80×10^{-7}
ADC2	-1.48 (-2.58, -0.39)	0.00794	-1.19 (-2.26, -0.12)	0.0295	-1.47 (-2.56, -0.37)	0.00876	-1.17 (-2.24, -0.10)	0.0321
ADC3	-0.06 (-1.09, 0.98)	0.916	0.31 (-0.7, 1.33)	0.547	-0.04 (-1.08, 1.00)	0.938	0.33 (-0.68, 1.35)	0.519
ADNI	-1.62 (-3.14, -0.09)	0.0374	-1.34 (-2.83, 0.14)	0.0767	-1.65 (-3.18, -0.13)	0.0336	-1.36 (-2.85, 0.14)	0.0747
GSK	-0.26 (-1.43, 0.92)	0.668	-1.02 (-2.17, 0.13)	0.0810	-0.20 (-1.38, 0.97)	0.734	-0.96 (-2.12, 0.19)	0.100
LOAD	-3.46 (-4.66, -2.26)	1.51×10^{-8}	-2.71 (-3.88, -1.53)	6.24×10^{-6}	-3.41 (-4.61, -2.21)	2.52×10^{-8}	-2.65 (-3.83, -1.48)	9.71×10^{-6}
MIRAGE	-3.56 (-4.72, -2.4)	2.04×10^{-9}	-3.29 (-4.43, -2.16)	1.37×10^{-8}	-3.53 (-4.69, -2.37)	2.82×10^{-9}	-3.26 (-4.40, -2.12)	1.98×10^{-8}
TGEN2	0.21 (-1.46, 1.89)	0.802	0.65 (-0.99, 2.28)	0.440	0.11 (-1.57, 1.79)	0.898	0.57 (-1.07, 2.22)	0.495
UM/VU/MSSM	-2.42 (-3.62, -1.23)	7.50×10^{-5}	-2.87 (-4.05, -1.7)	1.60×10^{-6}	-2.34 (-3.55, -1.14)	1.38×10^{-4}	-2.79 (-3.96, -1.61)	3.59×10^{-6}
UPITT	-1.44 (-2.32, -0.56)	0.00133	-1.3 (-2.16, -0.44)	0.00300	-1.43 (-2.31, -0.55)	0.00147	-1.28 (-2.14, -0.42)	0.00355
PC1	12.83 (-0.15, 25.81)	0.0528	11.03 (-1.66, 23.72)	0.0885	12.8 (-0.21, 25.8)	0.0538	11.1 (-1.64, 23.8)	0.0878
PC2	17.88 (2.32, 33.45)	0.0244	17.95 (2.73, 33.16)	0.0208	17.4 (1.87, 33.0)	0.0281	17.6 (2.39, 32.8)	0.0233
PC3	9.59 (-15.01, 34.2)	0.445	6.52 (-17.53, 30.58)	0.595	8.59 (-16.0, 33.2)	0.494	5.72 (-18.3, 29.8)	0.641
F (df_1, df_2)	14.36 (13, 6739)		36.44 (14,6738)		9.418 (22, 6722)		23.05 (23, 6721)	
P	$<10^{-320}$		$<10^{-320}$		$<10^{-320}$		$<10^{-320}$	
Multiple R^2	0.02696		0.07038		0.03990		0.08311	
Adjusted R^2	0.02508		0.06845		0.03673		0.07994	

eTable 4. Risk-weighted burden analysis results for *APOE* and 9 LOAD candidate genes excluding two family datasets (MIRAGE, LOAD). Beta coefficients (β), 95% Confidence Intervals, and *P*-values are from four linear regression models of AAO examining weighted scores for the peak SNP LOAD risk associations in *APOE* and 9 LOAD candidate genes. Scores are the product of the odds ratio for LOAD risk for each SNP multiplied by minor allele dosage from imputed genotype probabilities.

	Model 1: Adjustment for PCs & Site		**Model 2: Adjustment for Model 1 + *APOE***		**Model 3: Adjustment for Model 1 + 9 LOAD Genes**		**Model 4: Adjustment for Model 1 + *APOE* + 9 LOAD Genes**	
	β (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*
(Intercept)	74.3 (73.5, 75.0)	$<10^{-320}$	76.1 (75.3, 76.8)	$<10^{-320}$	75.4 (74.2, 76.6)	$<10^{-320}$	77.2 (76.1, 78.4)	$<10^{-320}$
CR1 Score	--	--	--	--	-0.31 (-0.57, -0.06)	0.0170	-0.29 (-0.54, -0.05)	0.0207
BIN1 Score	--	--	--	--	-0.31 (-0.53, -0.09)	0.00571	-0.32 (-0.53, -0.10)	0.00399
CD2AP Score	--	--	--	--	-0.09 (-0.33, 0.15)	0.458	-0.17 (-0.40, 0.07)	0.165
EPHA1 Score	--	--	--	--	0.01 (-0.27, 0.30)	0.934	0.04 (-0.23, 0.32)	0.753
CLU Score	--	--	--	--	-0.0014 (-0.24, 0.24)	0.991	-0.0092 (-0.24, 0.22)	0.939
MS4A4A Score	--	--	--	--	-0.05 (-0.27, 0.17)	0.649	-0.06 (-0.28, 0.16)	0.578
PICALM Score	--	--	--	--	-0.27 (-0.50, -0.04)	0.0221	-0.27 (-0.49, -0.04)	0.0205
ABCA7 Score	--	--	--	--	-0.26 (-0.55, 0.03)	0.0833	-0.22 (-0.51, 0.06)	0.127
CD33 Score	--	--	--	--	-0.08 (-0.32, 0.16)	0.514	-0.14 (-0.38, 0.10)	0.241
APOE Score	--	--	-0.87 (-0.96, -0.78)	1.38×10^{-78}	--	--	-0.84 (-0.93, -0.74)	8.79×10^{-66}
ACT	9.60 (8.55, 10.7)	1.62×10^{-69}	8.92 (7.89, 9.95)	3.66×10^{-63}	9.70 (8.66, 10.7)	9.89×10^{-73}	9.04 (8.02, 10.1)	2.71×10^{-66}
ADC1	-1.8 (-2.65, -0.96)	3.01×10^{-5}	-1.99 (-2.82, -1.16)	2.35×10^{-6}	-1.74 (-2.57, -0.90)	4.59×10^{-5}	-1.91 (-2.73, -1.10)	4.45×10^{-6}
ADC2	-1.09 (-2.03, -0.16)	0.0223	-0.79 (-1.71, 0.12)	0.0893	-1.05 (-1.98, -0.13)	0.0255	-0.76 (-1.67, 0.14)	0.0972
ADC3	0.16 (-0.79, 1.10)	0.747	0.51 (-0.41, 1.43)	0.276	0.22 (-0.71, 1.15)	0.644	0.56 (-0.35, 1.47)	0.224
ADNI	-1.33 (-2.72, 0.06)	0.0617	-1.05 (-2.41, 0.31)	0.130	-1.26 (-2.64, 0.11)	0.0710	-0.98 (-2.32, 0.36)	0.151
GSK	0.33 (-0.60, 1.27)	0.485	-0.62 (-1.53, 0.30)	0.188	0.46 (-0.46, 1.38)	0.326	-0.45 (-1.36, 0.45)	0.325
OHSU	11.7 (10.2, 13.2)	7.36×10^{-55}	11.3 (9.83, 12.7)	1.60×10^{-53}	11.9 (10.5, 13.4)	1.94×10^{-58}	11.5 (10.1, 12.9)	6.47×10^{-57}
ROSMAP	11.3 (10.1, 12.4)	3.79×10^{-85}	10.5 (9.42, 11.6)	3.97×10^{-78}	11.4 (10.3, 12.5)	9.74×10^{-89}	10.6 (9.56, 11.7)	1.15×10^{-81}
TGEN2	0.26 (-1.34, 1.86)	0.754	0.69 (-0.87, 2.25)	0.388	0.53 (-1.04, 2.11)	0.508	0.94 (-0.60, 2.48)	0.232
UM/VU/MSSM	-0.38 (-1.26, 0.49)	0.390	-0.56 (-1.41, 0.29)	0.199	-1.90 (-2.99, -0.80)	7.16×10^{-4}	-2.46 (-3.53, -1.38)	7.36×10^{-6}
UPITT	-1.38 (-2.24, -0.51)	0.00180	-1.23 (-2.08, -0.39)	0.00410	-1.45 (-2.30, -0.60)	8.38×10^{-4}	-1.29 (-2.12, -0.46)	0.00239
PC1	21.5 (11.2, 31.8)	4.37×10^{-5}	22.0 (12.0, 32.1)	1.70×10^{-5}	-22.4 (-35.2, -9.55)	6.35×10^{-4}	-17.0 (-29.6, -4.47)	0.00790
PC2	33.9 (24.0, 43.9)	$2.99\times10^{-}$	31.8 (22.1, 41.6)	$1.56\times10^{-}$	6.47 (-4.37, 17.3)	0.242	6.46 (-4.12, 17.0)	0.232

		[11]		[10]				
PC3	-2.61 (-12.6, 7.39)	0.609	-1.43 (-11.2, 8.31)	0.774	-9.92 (-22.7, 2.82)	0.127	-6.82 (-19.3, 5.62)	0.282
F (df_1, df_2)	141.4 (14, 6780)		161.1 (15, 6779)		88.98 (23, 6031)		102 (24, 6030)	
P	$<10^{-320}$		$<10^{-320}$		$<10^{-320}$		$<10^{-320}$	
Multiple R^2	0.2259		0.2651		0.2534		0.2888	
Adjusted R^2	0.2243		0.2635		0.2505		0.2860	

eAppendix. Genome-wide analysis of Age-at-Onset in the ADGC.

Although known LOAD risk variants may modify age-at-onset (AAO) of Late-onset Alzheimer Disease (LOAD), it is possible that genomic variants without detectable effects on risk may also modify age-at-onset, through several possible mechanisms: modifying severity of the phenotype independently of risk; through still-undetected genetic interactions; etc. Here we examined results from association analyses of a genome-wide set of 2,324,889 genotyped and imputed SNPs with MAF > 0.02 in 6,143 LOAD cases from 10 case-control datasets of the ADGC.

Methods

We performed association analysis by way of linear regression in PLINK[1] on individual datasets assuming an additive model on log-transformed age-at-onset with covariate adjustment for population substructure. As in primary analyses, population substructure was estimated within each dataset by principal components (PC) analysis in EIGENSTRAT[2] using a subset of 21,109 SNPs common to all genotyping platforms, and the first three PCs were incorporated in our minimal model for covariate adjustment. An extended model adjusted for the first three PCs, sex, and the number of *APOE* ε4 alleles (0, 1, or 2) to account for the major AAO-modifying effects of *APOE*. Association statistics from individual datasets were combined in meta-analysis using the inverse-variance weighting as implemented in METAL,[3] applying a genomic control to each dataset. The genomic inflation factor (λ) for the genome-wide *meta*-analysis was less than 0.997 suggesting the absence of inflated associations (eFigure).

Due to the potential effects of ascertainment differences between the family-based, prospective, and case-control datasets, GWAS analyses of AAO were confined to only the case-control datasets and excluded family (NIA-LOAD, MIRAGE) and prospective (ACT, ROSMAP) studies; however the primary analysis of known risk variant effects on AAO included family-based and prospective datasets to examine AAO effects among the risk groups in which these variants were identified.

With this set of 6,219 cases, we expected to have 80% power at a genome-wide $\alpha=5.0\times10^{-8}$ to detect loci with as little effect as 1 year difference in AAO per allelic copy for very common variants (MAF>0.26), with power to detect 1.5 years difference in AAO per allelic copy for variants of even modest frequency (MAF>0.10).[4]

Variant associations were replicated in a novel replication dataset of cases from six newly available datasets. These included cases from three new waves (4-6) of cases and controls taken from the NIA Alzheimer's Disease Centers (ADC4-6) (waves 1-3 were described in detail in Naj et al. 2011),[5] comprising 304, 286, and 213 cases for waves 4, 5, and 6 respectively (ADC4, ADC5, ADC6), all of which were genotyped on the Illumina HumanOmniExpress-24 beadchip. We also examined cases from two waves of case-control data from the Texas Alzheimer's Research and Care Consortium (TARCC),[6] a new case-control dataset from the University of Miami/Vanderbilt University (UMVU), and a set of cases from the Universitätsklinikum des Saarlandes (UKS).[7] Data from the TARCC included 495 cases with complete AAO data collected at six different major medical research institutions (Baylor College of Medicine, Texas Tech University Health Sciences Center, University of North Texas Health Science Center, The University of Texas Health Sciences Center at San Antonio, The University of Texas Southwestern Medical Center, and Texas A & M Health Science Center). The first wave of samples examined including 323 cases genotyped on the Affymetrix 6.0 platform, and the second wave included 172 cases genotyped on the Illumina HumanOmniExpress-24 beadchip. Second wave TARCC (TARCC2) cases were genotyped together with 84 cases from the new UMVU dataset, and consequently underwent quality control together and were incorporated into analysis as a joint dataset (UMVU-TARCC2). Finally, we examined 596 clinically ascertained German cases with complete AAO data genotyped on the Illumina HumanHap550 beadchip from the UKS dataset. Affected individuals in all datasets met NINCDS-ADRDA criteria for probable or definite AD, and had AAO greater than 60 years. All replication datasets were imputed with IMPUTE2 using reference haplotypes from the March 2012 release of 1000 Genomes. We imputed our variants of interest in the original 15 ADGC datasets to the March 2012 release of 1000 Genomes and found no significant difference in the distribution of genotype probabilities between old and new imputations for the same samples among the original ADGC datasets. Variants underwent within-dataset association analysis and meta-analysis using the same approaches described for discovery data above.

In addition to association meta-analysis, we performed genetic burden analyses to determine the percent contribution to variation in AAO of the SNPs most strongly associated with AAO in each genomic region with more than one AAO single-variant association of $P<10^{-6}$. As the threshold *P*-value for follow-

up used here is much higher than the traditional threshold for statistical significance in GWAS ($\alpha=5\times10^{-8}$), we used only SNPs from regions where multiple SNPs were associated with $P<10^{-6}$ in order to reduce the likelihood of including false-positive associations, as the density of common variants (MAF>0.05) after imputation is likely to produce multiple adjacent strong associations due to the effects of linkage disequilibrium. Genetic burden analyses of AAO linearly modeled locus-specific effects as the product of the meta-analysis-estimated effect size (across-study change in AAO for each copy of the minor allele) and the dosage of the minor allele (scale 0-2; estimated from genotype-specific imputation probabilities), and were implemented in analyses of risk variants. Additional covariate adjustment in the burden model included covariates for population substructure from principal components analysis and dataset-specific effects. Genetic burden analyses of AAO with risk weighting were also performed on genome-wide association signals for AAO, as these associations may or may not be mediated by variant effects on risk.

Results

Because LOAD risk variants account for only a small portion of the variability of AAO, we performed a GWAS for AAO using the entire set of genotyped and imputed SNPs common to the 10 ADGC case-control datasets. eTable 5 reports the strongest SNP associations with AAO in 7 genomic regions containing multiple SNP associations of $P<10^{-5}$ (all SNP associations of $P<10^{-5}$ are reported in eTable 6).

Variation in the *APOE* region was most strongly associated with AAO (rs6857 in *PVRL2*; OR (95% CI): -2.61 (-2.89, -2.32), $P=5.26\times10^{-72}$), as expected. No variants outside of the *APOE* region were associated with genome-wide statistical significance ($P<5.0\times10^{-8}$). Among the stronger associations with AAO observed genome-wide outside of the *APOE* region, 38 SNPs were associated with AAO at $P<10^{-5}$ in or near the gene *MYO16*, which encodes atypical myosin XVI, located at 109.4 Megabases (Mb) on chromosome 13q33.3. The strongest association in *MYO16* was observed at rs9521011, where each copy of the A allele (MAF=0.47) delayed onset by approximately 0.73 years (9 months) [β (95% CI): 0.73 (0.47, 1.00); $P=7.62\times10^{-8}$], nearing genome-wide statistical significance ($P<5\times10^{-8}$). Several of the other potentially associated SNPs ($P<10^{-5}$) were either in introns of or intergenic SNPs near potential AAO candidate genes. These include 6 variants in the chromosome 8p22 (14.3 Mb) gene *SGCZ*, which encodes zeta-sarcoglycan. The strongest association for this gene was with rs7016159 [β (95% CI): -0.65 (-0.91, -0.38); $P=2.47\times10^{-6}$], which lowered AAO by approximately half a year per copy of the T allele (MAF=0.32). Two variants located on chromosome 11q13.3 in *CPT1A* (encoding the mitochondrial protein carnitine palmitoyltransferase 1A in liver); among these, the SNP rs3019613 lowered AAO by approximately eleven months for each G allele (MAF=0.14) [β (95% CI): 0.89 (0.51, 1.27); $P=8.52\times10^{-6}$], located in *PTPRD* which encodes protein tyrosine phosphatase receptor type D. The strongest difference in AAO by genotype was observed for variants in an intergenic region on chromosome 9p13.3 (34.7Mb), with 12 SNP associations of $P<10^{-5}$. The most strongly associated of these variants, rs1735611 [β (95% CI): 2.76 (1.61, 3.91); $P=2.49\times10^{-6}$], delayed AAO by approximately 2 years and 9 months for each copy of the T allele (MAF=0.02), on par with the effect observed for *APOE* region variants in this study though not attaining genome-wide statistical significance.

We also performed analyses adjusting for dosage of the *APOE* ε4 allele, and observed several strong associations ($P<10^{-5}$), although these did not meet genome-wide statistical significance ($P<5.0\times10^{-8}$) (eTable 7). SNP associations at *MYO16*, *SGCZ*, *CPT1A*, and the chromosome 9p13.3 intergenic region were observed with similar effects as in the minimally-adjusted model, with statistical significance of these associations weakened only modestly but remaining at $P<10^{-5}$. Several additional genomic regions demonstrated multiple SNPs associations of $P<10^{-5}$. These included variants in or near *BCHE* (encoding butyrylcholinesterase) on chromosome 3q26.1 and *TNIP3* (encoding a protein interacting with a Tumor Necrosis Factor (TNF)-α induced protein) on chromosome 4q27. The strongest association in the *BCHE* region is immediately downstream of the gene at rs3914191 [β (95% CI): 1.16 (0.70, 1.61); $P=5.71\times10^{-7}$], for which each copy of the T allele (MAF=0.09) delays onset by approximately 1 year and 2 months. Likewise, the strongest association in the *TNIP3* region is at rs62321501 [β (95% CI): 1.78 (0.99, 2.56); $P=8.76\times10^{-6}$], where each copy of the A allele (MAF=0.03) delays onset by approximately 1 year and 9 months.

We examined associations of these variants in a novel replication dataset comprising cases from 6 newly available datasets. While associations of *APOE* region variants with AAO were replicated strongly (eTable 7), no other associations observed under a minimal model of covariate adjustment replicated with nominal statistical significance (P<0.05). However, in replication analyses under an extended model including covariate adjustment for the *APOE* ε4 allele,

several intergenic variants upstream of *BCHE* with modest but not statistically significant associations (e.g., rs28642690, β (95% CI): 1.17 (0.66, 1.68), $P=6.95\times10^{-6}$) demonstrated nominally-significant associations ($P<0.05$) in the replication data (e.g, rs28642690, β (95% CI): 0.17 (0.016, 0.31), $P=0.0297$).

Examining the genetic burden on AAO of variants in the seven genomic regions associated at $P<10^{-5}$ (eTable 8), we found similar levels of genetic burden from non-risk variants on AAO as observed among risk variants affecting AAO, that those variants contribute 2.2% of AAO variation compared to a contribution of 3.7% of *APOE* ε4 dosage to AAO variation in the same modeling. Slight differences in the availability of genotypes modified the dataset-specific effects, which accounted for almost 7.6% of the variation in AAO ($R^2=0.0786$) in our analyses. The independent contribution of dosage of the *APOE* ε4 allele to genetic burden is 4.6% of AAO variation ($R^2=0.1217$), similar to that observed in risk variant modeling. The cumulative effect of the variants most significantly associated with AAO over fifteen genomic regions is 1.9% ($R^2=0.0954$), and together with *APOE*, these variants account for approximately 6.3% of genetic variation in AAO ($R^2=0.1391$). Excluding study-specific effects, *APOE* ε4 dosage accounts for 4.9% of the remaining variation while AAO-associated variants account for another 2.1%, which when combined, contribute approximately 6.8% of the variation in AAO. The risk-weighted burden analysis (eTable 9) demonstrates that very little of the effect on variation in AAO from these SNPs is mediated through LOAD risk.

Summary

A preliminary analysis of genome-wide association with AAO identified novel potential candidate loci associated with AAO but not with LOAD risk, though none were associated with genome-wide statistical significance ($P<5.0\times10^{-8}$). Additionally, burden analyses on variants at these novel loci demonstrated that the variation explained by SNPs strongly associated with AAO but not LOAD risk was approximately half the AAO variation accounted for by *APOE*.

Several of the variants most strongly associated with AAO in our genome-wide analysis are in or near regions implicated in genome-wide linkage scans of AAO. AAO associations on chromosome 8p22 (~14.3Mb) overlapped chromosome 8 linkage signals to AAO (LOD≈2.00) observed in 277 affected sibling pairs (ASPs) from the NIMH-AD Genetics Consortium,[8] and variants on chromosome 9p13.3 (~34.7Mb) overlapped a region with similarly modest linkage (LOD≈2.00) with AAO observed in both NIMH-AD sibling pairs and 341 UK sibling pairs.[8] To our knowledge, these subjects are not included in datasets used in the current analysis. However, many previous linkage and association signals for AAO were not observed in our analyses. For instance, we were unable to confirm the strongest non-*APOE* association with AAO from a previous GWAS, rs1466662 (previous study $P=4.95\times10^{-7}$) in the gene *DCHS2* on chromosome 4q31.3 ($P=0.497$).[9]

Among variants with the strongest observed associations for AAO ($P<10^{-5}$), several are in loci that may be functionally related to Alzheimer disease, including *MYO16* and *CPT1A*. The myosin protein encoded by *MYO16*, is involved in the regulation of cellular events in neurons, including neuronal morphogenesis,[10] through its role in the phosphoinositide 3-kinase (PI3K) signaling pathway.[11] *CPT1A* encodes the liver isoform (A) of the mitochondrial protein carnitine palmitoyltransferase 1, and knock-down mutations in *CPT1A* are associated with elevated ApoA-I levels,[12] which preserve cognitive function[13] and correlate with reduced risk of dementia and Alzheimer disease.[14-16] *CPT1A* expression is also downregulated with natural aging.[17]

Here we identified several potential novel candidate loci with smaller effects on AAO of LOAD than those of *APOE,* suggesting that AAO is governed in part by a strong polygenic effect combined with the strong major gene effect of *APOE*, however, these findings require additional confirmation in more independent datasets of sufficient size to be able to detect effects on AAO as small as 1.5 years difference.

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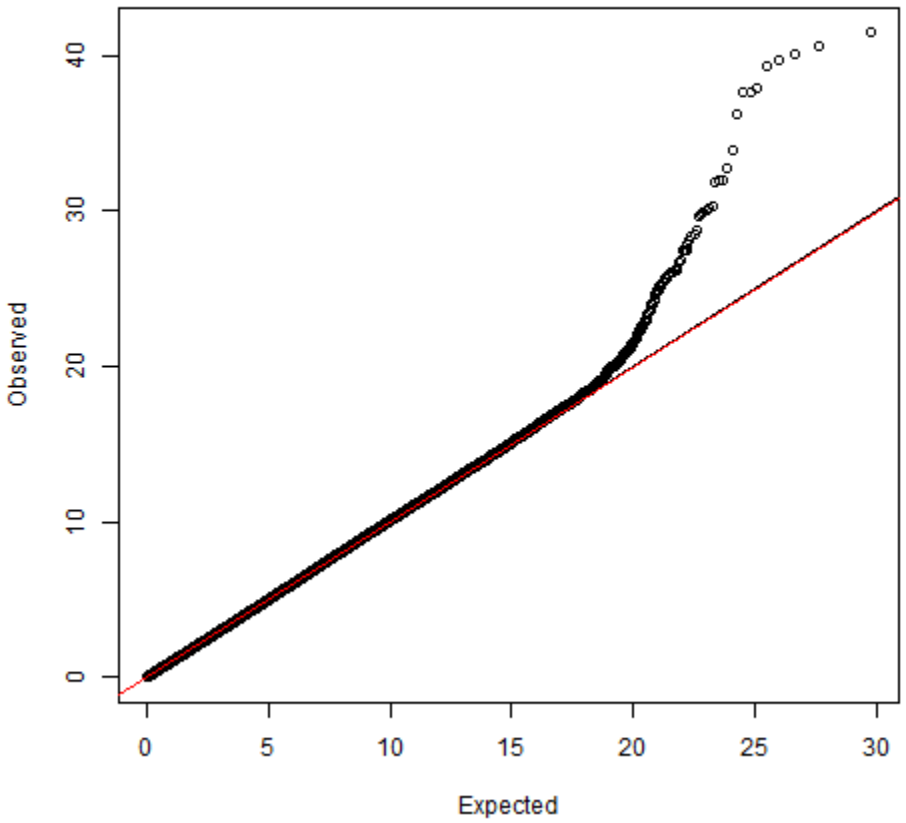
eFigure. Genomic Inflation for Discovery Genome-wide Association Analysis of AAO.



Quantile-quantile plots of observed (y-axis) vs. expected (x-axis) *P*-values for AAO of LOAD in 10 ADGC case-control datasets.

eTable 5. Genome-wide association results by genomic region for age-at-onset of LOAD. Association signals presented are the SNPs with the strongest associations within each locus or region with multiple SNPs demonstrating associations of $P \leq 10^{-5}$ in meta-analysis across 10 ADGC case-control datasets with age-at-onset information on cases. Loci or regions with only one SNP association of $P \leq 10^{-5}$ are excluded. SNPs examined included those present in a minimum of 7 out of 10 ADGC case-control datasets. Minimal adjustment in each dataset included the first three population substructure principal components (PCs) from EIGENSTRAT.

SNP	CH:MB	Nearest Gene	MA	MAF	# SNPs in region at $P<10^{-6}$	AAO (Minimal Adjustment Model)			AAO (Extended Adjustment Model)			LOAD Risk (from Naj et al.)	
						β (95% CI)	*P*	Het *P*	*β* (95% CI)	*P*	Het *P*	OR (95% CI)	*P*
rs6857	19:45.4	*PVRL2*	T	0.35	113	-2.61 (-2.89, -2.32)	5.26×10^{-72}	0.325	-1.01 (-1.48, -0.54)	2.92×10^{-5}	0.0742	3.30 (3.11, 3.49)	7.46×10^{-357}
rs9521011	13:109.4	*MYO16*	A	0.47	38	0.73 (0.47, 1.00)	7.62×10^{-8}	0.971	0.70 (0.44, 0.96)	1.82×10^{-7}	0.958	1.02 (0.98, 1.06)	0.398
rs12956834	18:59.1	*CDH20*	A	0.22	4	-0.82 (-1.15, -0.48)	1.62×10^{-6}	0.970	-0.83 (-1.16, -0.51)	5.78×10^{-7}	0.871	0.97 (0.92, 1.02)	0.223
rs7016159	8:14.3	*SGCZ*	T	0.32	6	-0.65 (-0.91, -0.38)	2.47×10^{-6}	0.213	-0.60 (-0.87, -0.34)	6.61×10^{-6}	0.197	1.02 (0.97, 1.06)	0.409
rs17356611	9:34.7	--	T	0.02	12	2.76 (1.61, 3.91)	2.49×10^{-6}	0.594	2.82 (1.70, 3.94)	7.55×10^{-7}	0.531	0.98 (0.80, 1.19)	0.821
rs3019613	11:68.6	*CPT1A*	G	0.14	2	0.89 (0.51, 1.27)	4.58×10^{-6}	0.135	0.87 (0.50, 1.25)	4.60×10^{-6}	0.091	1.04 (0.97, 1.10)	0.294
rs231790	2:204.7	--	G	0.49	5	-0.61 (-0.88, -0.35)	5.32×10^{-6}	0.401	-0.57 (-0.83, -0.31)	1.61×10^{-5}	0.295	0.99 (0.95, 1.03)	0.577
rs11743156	5:86.1	--	C	0.43	4	-0.58 (-0.83, -0.33)	5.36×10^{-6}	0.688	-0.51 (-0.75, -0.27)	3.81×10^{-5}	0.708	0.99 (0.95, 1.04)	0.775

CH:MB, chromosome:position (in mega base pairs, build 19); MA, minor allele; MAF, minor allele frequency; *β*, Beta coefficient for AAO from meta-analysis (# years difference in AAO per copy of the minor allele); OR, odds ratio; 95% CI, 95% Confidence Interval; P, P-value; Het *P*, *P*-value for heterogeneity across studies.

eTable 8. Burden analysis results for *APOE* and SNPs associated with AAO at $P<10^{-6}$ from 7 genomic regions. Beta coefficients (β), 95% Confidence Intervals, and P-values are from four linear regression models of AAO examining weighted scores for the peak SNP associations in *APOE* and the SNPs most significantly associated with AAO ($P<10^{-6}$) in seven genomic regions. Scores are the minor allele dosage for each SNP derived from imputed genotype probabilities. Prospective datasets (ACT, ROSMAP) and family datasets (NIA-LOAD, MIRAGE) are excluded from this analysis.

	Model 1: Adjustment for PCs & Site		**Model 2: Adjustment for Model 1 + APOE**		**Model 3: Adjustment for Model 1 + 15 SNPs**		**Model 4: Adjustment for Model 1 + APOE + 15 SNPs**	
	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***
(Intercept)	74.2 (73.5, 75.0)	$< 10^{-320}$	76.0 (75.2, 76.8)	$< 10^{-320}$	80.4 (78.8, 82.0)	$< 10^{-320}$	82.0 (80.4, 83.5)	$< 10^{-320}$
rs11743156	--	--	--	--	-0.0021 (-0.0032, -0.001)	1.55×10^{-4}	-0.0020 (-0.003, -0.0009)	2.38×10^{-4}
rs12956834	--	--	--	--	-0.0006 (-0.0011, -0.0002)	1.77E-03	-0.0006 (-0.001, -0.0002)	0.00168
rs17356611	--	--	--	--	-0.0068 (-0.0102, -0.0033)	1.16×10^{-4}	-0.0068 (-0.0102, -0.0035)	7.07×10^{-5}
rs231790	--	--	--	--	-0.0027 (-0.0042, -0.0012)	3.04×10^{-4}	-0.0024 (-0.0039, -0.001)	9.22×10^{-4}
rs3019613	--	--	--	--	-0.002 (-0.0029, -0.0012)	1.04×10^{-6}	-0.0019 (-0.0027, -0.0011)	5.39×10^{-6}
rs7016159	--	--	--	--	-0.0019 (-0.0027, -0.001)	1.20×10^{-5}	-0.0018 (-0.0026, -0.001)	2.06×10^{-5}
rs9521011	--	--	--	--	-0.0018 (-0.0025, -0.0011)	8.74×10^{-7}	-0.0017 (-0.0024, -0.001)	1.17×10^{-6}
APOE	--	--	-3.11 (-3.45, -2.77)	4.97×10^{-70}	--	--	-3.04 (-3.38, -2.70)	2.19×10^{-68}
ADC1	-1.77 (-2.63, -0.91)	5.87×10^{-5}	-1.96 (-2.8, -1.12)	5.15×10^{-6}	-1.68 (-2.54, -0.83)	1.13×10^{-4}	-1.87 (-2.70, -1.04)	1.09×10^{-5}
ADC2	-1.06 (-2.01, -0.1)	0.0304	-0.76 (-1.69, 0.18)	0.112	-1 (-1.95, -0.06)	0.0381	-0.71 (-1.63, 0.21)	0.131
ADC3	0.19 (-0.77, 1.16)	0.692	0.54 (-0.39, 1.48)	0.256	-4.52 (-6.23, -2.81)	2.25×10^{-7}	-4.02 (-5.69, -2.36)	2.31×10^{-6}
ADNI	-1.23 (-2.64, 0.19)	0.0895	-0.96 (-2.34, 0.42)	0.172	-1.23 (-2.63, 0.17)	0.0849	-0.97 (-2.34, 0.40)	0.165
GenADA	0.36 (-0.59, 1.31)	0.454	-0.58 (-1.52, 0.35)	0.219	0.26 (-0.69, 1.2)	0.594	-0.67 (-1.59, 0.26)	0.156
OHSU	11.7 (10.3, 13.2)	2.38×10^{-54}	11.28 (9.85, 12.71)	6.19×10^{-53}	7.33 (5.58, 9.09)	3.04×10^{-16}	7.07 (5.36, 8.78)	6.61×10^{-16}
TGEN2	0.46 (-1.16, 2.08)	0.579	0.86 (-0.72, 2.45)	0.285	0.38 (-1.23, 1.98)	0.647	0.78 (-0.79, 2.35)	0.331
UM/VU/MSSM	-0.33 (-1.22, 0.56)	0.465	-0.51 (-1.38, 0.36)	0.250	-0.30 (-1.19, 0.58)	0.499	-0.48 (-1.34, 0.38)	0.275
UPITT	-1.34 (-2.22, -0.46)	0.00275	-1.21 (-2.06, -0.35)	0.00586	-1.38 (-2.25, -0.51)	0.00191	-1.25 (-2.10, -0.40)	3.99×10^{-3}
PC1	20.5 (9.96, 31.0)	1.38×10^{-4}	21.2 (10.9, 31.4)	5.45×10^{-5}	20.4 (9.97, 30.8)	1.28×10^{-4}	21.1 (10.9, 31.2)	5.05×10^{-5}

PC2	31.6 (21.4, 41.8)	1.49×10^{-9}	29.4 (19.5, 39.4)	7.58×10^{-9}	30.9 (20.8, 41.0)	2.35×10^{-9}	28.8 (18.9, 38.7)	1.12×10^{-8}
PC3	-2.92 (-13.1, 7.29)	0.575	-2.19 (-12.15, 7.77)	0.667	-1.18 (-11.3, 8.94)	0.819	-0.59 (-10.5, 9.29)	0.907
F (df_1, df_2)	43.33 (12,6160)		66.77 (13,6159)		35.27 (19,6153)		50.87 (20,6152)	
P	$< 10^{-320}$		$< 10^{-320}$		$< 10^{-320}$		$< 10^{-320}$	
Multiple R^2	0.07784		0.1235		0.09820		1.42E-01	
Adjusted R^2	0.07604		0.1217		0.09544		0.1391	

eTable 9. Risk-weighted burden analysis results for *APOE* and SNPs associated with AAO at $P<10^{-6}$ from 7 genomic regions. Beta coefficients (β), 95% Confidence Intervals, and P-values are from four linear regression models of AAO examining weighted scores for the peak SNP associations in *APOE* and the SNPs most significantly associated with AAO ($P<10^{-6}$) in seven genomic regions. Scores are the product of the odds ratio for LOAD risk for each SNP multiplied by minor allele dosage from imputed genotype probabilities. Prospective (ACT, ROSMAP) and family datasets (NIA-LOAD, MIRAGE) are excluded from this analysis.

	Model 1: Adjustment for PCs & Site		**Model 2: Adjustment for Model 1 + APOE**		**Model 3: Adjustment for Model 1 + 15 SNPs**		**Model 4: Adjustment for Model 1 + APOE + 15 SNPs**	
	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***
(Intercept)	74.2 (73.5, 75.0)	$< 10^{-320}$	76.0 (75.2, 76.8)	$< 10^{-320}$	80.4 (78.8, 82.0)	$< 10^{-320}$	81.95 (80.4, 83.5)	$< 10^{-320}$
rs11743156 Score	--	--	--	--	-0.0021 (-0.0032, -0.001)	1.55×10^{-4}	-0.002 (-0.003, -0.0009)	2.38×10^{-4}
rs12956834 Score	--	--	--	--	-0.0006 (-0.0011, -0.0002)	0.00177	-0.0006 (-0.001, -0.0002)	0.00168
rs17356611 Score	--	--	--	--	-0.0068 (-0.0102, -0.0033)	1.16×10^{-4}	-0.0068 (-0.0102, -0.0035)	7.07×10^{-5}
rs231790 Score	--	--	--	--	-0.0027 (-0.0042, -0.0012)	3.04×10^{-4}	-0.0024 (-0.0039, -0.001)	9.22×10^{-4}
rs3019613 Score	--	--	--	--	-0.002 (-0.0029, -0.0012)	1.04×10^{-6}	-0.0019 (-0.0027, -0.0011)	5.39×10^{-6}
rs7016159 Score	--	--	--	--	-0.0019 (-0.0027, -0.001)	1.20×10^{-5}	-0.0018 (-0.0026, -0.001)	2.06×10^{-5}
rs9521011 Score	--	--	--	--	-0.0018 (-0.0025, -0.0011)	8.74×10^{-7}	-0.0017 (-0.0024, -0.001)	1.17×10^{-6}
APOE Score	--	--	-0.87 (-0.96, -0.77)	4.97×10^{-70}	--	--	-0.85 (-0.94, -0.75)	2.19×10^{-68}
ADC1	-1.77 (-2.63, -0.91)	5.87×10^{-5}	-1.96 (-2.80, -1.12)	5.15×10^{-6}	-1.68 (-2.54, -0.83)	1.13×10^{-4}	-1.87 (-2.70, -1.04)	$1.09\text{E}\times10^{-5}$
ADC2	-1.06 (-2.01, -0.10)	0.0304	-0.76 (-1.69, 0.18)	0.112	-1.00 (-1.95, -0.06)	0.0381	-0.71 (-1.63, 0.21)	0.131
ADC3	0.19 (-0.77, 1.16)	0.692	0.54 (-0.39, 1.48)	0.256	-4.52 (-6.23, -2.81)	2.25×10^{-7}	-4.02 (-5.69, -2.36)	2.31×10^{-6}
ADNI	-1.23 (-2.64, 0.19)	0.0895	-0.96 (-2.34, 0.42)	0.172	-1.23 (-2.63, 0.17)	0.0849	-0.97 (-2.34, 0.40)	0.165
GenADA	0.36 (-0.59, 1.31)	0.454	-0.58 (-1.52, 0.35)	0.219	0.26 (-0.69, 1.20)	0.0594	-0.67 (-1.59, 0.26)	0.156
OHSU	11.7 (10.3, 13.2)	2.38×10^{-54}	11.3 (9.85, 12.7)	6.19×10^{-53}	7.33 (5.58, 9.09)	3.04×10^{-16}	7.07 (5.36, 8.78)	6.61×10^{-16}
TGEN2	0.46 (-1.16, 2.08)	0.579	0.86 (-0.72, 2.45)	0.285	0.38 (-1.23, 1.98)	0.647	0.78 (-0.79, 2.35)	0.331
UM/VU/MSSM	-0.33 (-1.22, 0.56)	0.465	-0.51 (-1.38, 0.36)	0.250	-0.30 (-1.19, 0.58)	0.499	-0.48 (-1.34, 0.38)	0.275
UPITT	-1.34 (-2.22, -0.46)	0.00275	-1.21 (-2.06, -0.35)	0.00586	-1.38 (-2.25, -0.51)	0.00191	-1.25 (-2.10, -0.40)	0.00399
PC1	20.5 (9.96, 31.0)	1.38×10^{-4}	21.2 (10.9, 31.4)	5.45×10^{-5}	20.4 (9.97, 30.8)	1.28×10^{-4}	21.1 (10.9, 31.2)	5.05E-05
PC2	31.6 (21.4, 41.8)	1.49×10^{-9}	29.4 (19.5, 39.4)	7.58×10^{-9}	30.9 (20.8, 41.0)	2.35×10^{-9}	28.8 (18.9, 38.7)	1.12×10^{-8}

PC3	-2.92 (-13.1, 7.29) 0.575	-2.19 (-12.2, 7.77) 0.667	-1.18 (-11.3, 8.94) 0.819	-0.59 (-10.5, 9.29) 0.907
F (df_1, df_2)	43.33 (12,6160)	66.77 (13, 6159)	35.27 (19, 6153)	50.87 (20, 6152)
P	$< 10^{-320}$	$< 10^{-320}$	$< 10^{-320}$	$< 10^{-320}$
Multiple R^2	0.07784	0.1235	0.09822	0.1419
Adjusted R^2	0.07604	0.1217	0.09544	0.1391