Association between Alzheimer's Disease risk SNPs and episodic memory in South Asians from LASI-DAD

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Supplemental methods for genotyping and imputation

DNA extraction and genotyping was performed by MedGenome (Bangalore, Karnataka, India). A total of 960 LASI-DAD participants were genotyped using the Illumina Infinium Global Screening Array-24 (GSA) BeadChip, version 2.0 (Illumina, San Diego, CA). Quality control included a sex check, a relatedness check, and population structure analysis. Samples with a missing call rate greater than 5% were removed. Further, we removed SNPs that met any of the following criteria: SNPs with a missing call rate greater than 2%, greater than 0 discordant calls among 15 pairs of technical duplicates, greater than 0 discordant calls among 20 1000G Project control samples, sex differences in allelic frequency greater than 0.2, sex differences in heterozygosity greater than 0.3, more than one Mendelian error, and any positional duplicates. Among the 665,608 probes that were present on the array, 533,348 polymorphic probes (80.1%) were available to be used for imputation. We used the Michigan Imputation Server, Minimac 4, version 1.0 (Center for Statistical Genetics, University of Michigan, Ann Arbor, MI) to impute the LASI-DAD samples using the 1000G Project worldwide reference panel (phase 3, version 5).[1] Only SNPs with good imputation quality (r^2>0.8) were included in the analysis. Principal components analysis (PCA), performed using the SNPRelate R Package, Bioconductor 3.10 (University of Washington, Seattle, WA), was used to exclude outliers and select a set of 932 unrelated individuals for analysis.[2] The top 10 principal components (PCs) calculated within the selected analysis sample were used as model covariates in all analyses to adjust for population stratification.

Table S1. Alzheimer's disease risk SNPs from three large, replicated GWAS

Source GWAS	Source Table in the GWAS	SNP Index[f]	SNP	Chr	Position	Gene Index[g]	Gene	Genotyped or imputed in LASI-DAD	Imputation quality in LASI-DAD (R^2)
Lambert et al., 2013[3]	Table 2[a]	1	rs6656401	1	207692049	1	CR1	Genotyped	0.997
		2	rs6733839	2	127892810	2	BIN1	Genotyped	0.992
		3	rs10948363	6	47487762	3	CD2AP	Genotyped	0.996
		4	rs11771145	7	143110762	4	EPHA1	Genotyped	0.981
		5	rs9331896	8	27467686	5	CLU	Genotyped	0.998
		6	rs983392	11	59923508	6	MS4A6A	Genotyped	0.998
		7	rs10792832	11	85867875	7	PICALM	Genotyped	1.000
		8	rs4147929	19	1063443	8	ABCA7	Imputed	0.898
		9	rs9271192	6	32578530	9	HLA-DRB5-HLA-DRB1	Genotyped	1.000
		10	rs28834970	8	27195121	10	PTK2B	Genotyped	0.999
		11	rs11218343	11	121435587	11	SORL1	Genotyped	0.995
		12	rs10498633	14	92926952	12	SLC24A4-RIN3	Genotyped	0.993
		13	rs35349669	2	234068476	13	INPP5D	Genotyped	0.999
		14	rs190982	5	88223420	14	MEF2C	Genotyped	0.987
		15	rs2718058	7	37841534	15	NME8	Genotyped	0.999
		16	rs1476679	7	100004446	16	ZCWPW1	Genotyped	0.993
		17	rs10838725	11	47557871	17	CELF1	Genotyped	1.000
		18	rs17125944	14	53400629	18	FERMT2	Genotyped	0.995
		19	rs7274581	20	55018260	19	CASS4	Genotyped	0.980
Kunkle et al., 2019[4]	Table 1[b]	20	rs4844610	1	207802552	--	CR1	Imputed	0.903
		--	rs6733839	2	127892810	--	BIN1	Genotyped	0.992
		--	rs10933431	2	233981912	--	INPP5D	Imputed	0.674
		21	rs9271058	6	32575406	--	HLA-DRB1	Imputed	0.871
		22	rs75932628	6	41129252	20	TREM2	Genotyped	0.972
		23	rs9473117	6	47431284	--	CD2AP	Imputed	0.864
		24	rs12539172	7	100091795	--	NYAP1/ZCWPW1	Imputed	0.690
		25	rs10808026	7	143099133	--	EPHA1	Imputed	0.890
		26	rs73223431	8	27219987	--	PTK2B	Imputed	0.961
		--	rs9331896	8	27467686	--	CLU	Genotyped	0.998

		27	rs3740688	11	47380340	--	SPI1/CELF1	Imputed	0.959
		28	rs7933202	11	59936926	21	MS4A2	Imputed	0.943
		29	rs3851179	11	85868640	--	PICALM	Genotyped	0.999
		--	rs11218343	11	121435587	--	SORL1	Genotyped	0.995
		30	rs17125924	14	53391680	--	FERMT2	Imputed	0.952
		31	rs12881735	14	92932828	--	SLC24A4	Imputed	0.965
		32	rs3752246	19	1056492	--	ABCA7	Imputed	0.863
		33	rs6024870	20	54997568	--	CASS4	Imputed	0.696
		34	rs7920721	10	11720308	22	ECHDC3	Imputed	0.962
		35	rs138190086	17	61538148	23	ACE	Genotyped	0.993
	Table 2[c]	36	rs593742	15	59045774	--	ADAM10	Imputed	0.886
		37	rs7185636	16	19808163	24	IQCK	Imputed	0.931
		38	rs2830500	21	28156856	25	ADAMTS1	Imputed	0.882
		39	rs62039712	16	79355857	26	WWOX	Imputed	0.331
Jansen et al., 2019[5]	Table 1[d]	40	rs4575098	1	161155392	27	ADAMTS4	Imputed	0.719
		41	rs2093760	1	207786828	--	CR1	Imputed	0.959
		42	rs4663105	2	127891427	--	BIN1	Imputed	0.959
		43	rs10933431	2	233981912	--	INPP5D	Imputed	0.674
		44	rs184384746	3	57226150	28	HESX1	Imputed	0.005
		45	rs6448453	4	11026028	29	CLNK	Imputed	0.880
		46	rs6931277	6	32583357	--	HLA-DRB1	Genotyped	1.000
		47	rs187370608	6	40942196	--	TREM2	Imputed	0.762
		48	rs9381563	6	47432637	--	CD2AP	Imputed	0.829
		49	rs1859788	7	99971834	--	ZCWPW1	Genotyped	0.997
		50	rs7810606	7	143108158	--	EPHA1	Genotyped	0.995
		51	rs114360492	7	145950029	30	CNTNAP2	Imputed	0.213
		52	rs4236673	8	27464929	--	CLU/PTK2B	Imputed	0.963
		53	rs11257238	10	11717397	--	ECHDC3	Imputed	0.943
		54	rs2081545	11	59958380	--	MS4A6A	Imputed	0.962
		55	rs867611	11	85776544	--	PICALM	Imputed	0.959
		--	rs11218343	11	121435587	--	SORL1	Genotyped	0.995
		56	rs12590654	14	92938855	--	SLC24A4	Imputed	0.929
		57	rs442495	15	59022615	31	ADAM10	Imputed	0.899
		58	rs117618017	15	63569902	32	APH1B	Imputed	0.405

	59	rs59735493	16	31133100	33	KAT8	Imputed	0.803
	60	rs113260531	17	5138980	34	SCIMP	Imputed	0.885
	61	rs28394864	17	47450775	35	ABI3	Imputed	0.864
	62	rs76726049	18	56189459	36	ALPK2	Imputed	0.298
	63	rs111278892	19	1039323	--	ABCA7	Imputed	0.911
	64	rs76320948	19	46241841	37	AC074212.3	Not available	Not available
	65	rs3865444	19	51727962	38	CD33	Genotyped	0.998
	66	rs6014724	20	54998544	--	CASS4	Imputed	0.797
APOE[e]	67	rs429358 (ε4)	19	45411941	39	APOE	Genotyped	0.998
	68	rs7412 (ε2)	19	45412079	--	APOE	Genotyped	1.000

[a] All SNPs in this table are included except two SNPs (rs3865444 and rs8093731) that were not replicated in stage 2.
[b] All SNP in the "Previous genome-wide-significant loci still reaching significance" and "New genome-wide-significant loci reaching significance" sections are included except a SNP in the *APOE* gene region (rs429358).
[c] The SNPs that were considered novel loci and that were genome-wide-significant in the "Overall" phase (meta $p<5x10^{-8}$) are included. Three genome-wide-significant SNPs (rs114812713, rs138190086 and rs7920721) are excluded because they were not considered novel loci as discussed in the paper.
[d] All the SNPs that were significant in "Overall (phase 3)" are included except a SNP in the *APOE* gene region (rs41289512).
[e] *APOE* is listed separately as a well-known risk locus. Two SNPs that differentiate APOE ε4 and ε2 variants, respectively, are included.
[f] This column indicates all unique SNPs (-- indicates that it is a duplicated SNP).
[g] This column indicates all unique loci (-- indicates that it is a duplicated locus).

Table S2. Summary of known Alzheimer's disease risk SNPs in LASI-DAD

Source GWAS	# risk SNPs	# genotyped SNPs	# successfully imputed SNPs (Rsq>0.8)	# SNPs not available due to low imputation quality (Rsq<0.8)	# SNPs not available in 1000 Genomes Reference Panel
Lambert et al., 2013[3]	19	18	1	0	0
Kunkle et al., 2019[4]	24	6	14	4	0
Jansen et al., 2019[5]	28	5	14	8	1
APOE	2	2	0	0	0
All unique SNPs	68[a]	27	29	11	1

[a] Total number of risk SNPs is lower than the sum of risk SNPs across the three GWAS studies due to three SNPs overlapping among two GWAS studies and one SNP overlapping among all three GWAS studies.

Table S3. Comparison of observed risk allele frequency in LASI-DAD vs. reported risk allele frequency from published Alzheimer's disease GWAS

Index	Source GWAS	Gene	SNP	Chr	Position	AD Risk Allele	Risk-AF[a] (GWAS)	Risk-AF (LASI - DAD)	P-value[b]
1	Lambert et al., 2013[3]	CR1	rs6656401	1	207692049	A	0.197	0.066	**5.87E-23**
2		BIN1	rs6733839	2	127892810	T	0.409	0.414	7.56E-01
3		INPP5D	rs35349669	2	234068476	T	0.488	0.248	**3.85E-47**
4		MEF2C	rs190982	5	88223420	A	0.592	0.608	3.32E-01
5		HLA-DRB5-HLA-DRB1	rs9271192	6	32578530	C	0.276	0.251	9.89E-02
6		CD2AP	rs10948363	6	47487762	G	0.266	0.199	**4.84E-06**
7		NME8	rs2718058	7	37841534	A	0.627	0.867	**4.35E-50**
8		ZCWPW1	rs1476679	7	100004446	T	0.713	0.787	**8.19E-07**
9		EPHA1	rs11771145	7	143110762	G	0.662	0.700	**1.60E-02**
10		PTK2B	rs28834970	8	27195121	C	0.366	0.575	**9.01E-39**
11		CLU	rs9331896	8	27467686	T	0.621	0.717	**3.44E-09**
12		CELF1	rs10838725	11	47557871	C	0.316	0.494	**1.84E-30**
13		MS4A6A	rs983392	11	59923508	A	0.597	0.530	**4.23E-05**
14		PICALM	rs10792832	11	85867875	G	0.642	0.620	1.61E-01
15		SORL1	rs11218343	11	121435587	T	0.961	0.921	**7.84E-10**
16		FERMT2	rs17125944	14	53400629	C	0.092	0.120	**3.62E-03**
17		SLC24A4-RIN3	rs10498633	14	92926952	G	0.783	0.818	**1.04E-02**
18		ABCA7	rs4147929	19	1063443	A	0.190	0.201	4.05E-01
19		CASS4	rs7274581	20	55018260	T	0.917	0.988	**1.37E-14**
1	Kunkle et al., 2019[4]	CR1	rs4844610	1	207802552	A	0.187	0.064	**4.29E-21**
2		BIN1	rs6733839	2	127892810	T	0.407	0.414	6.65E-01
3		HLA -DRB1	rs9271058	6	32575406	A	0.270	0.277	6.60E-01
4		TREM2	rs75932628	6	41129252	T	0.008	0.001	**2.11E-02**
5		CD2AP	rs9473117	6	47431284	C	0.280	0.178	**9.46E-12**
6		EPHA1	rs10808026	7	143099133	C	0.801	0.728	**3.61E-08**
7		PTK2B	rs73223431	8	27219987	T	0.367	0.556	**6.63E-32**
8		CLU	rs9331896	8	27467686	T	0.613	0.717	**1.79E-10**
9		ECHDC3	rs7920721	10	11720308	G	0.389	0.331	**3.49E-04**

10		SPI1 h	rs3740688	11	47380340	T	0.552	0.638	**2.27E-07**
11		MS4A2	rs7933202	11	59936926	A	0.609	0.539	**1.72E-05**
12		PICALM	rs3851179	11	85868640	C	0.644	0.620	1.34E-01
13		SORL1	rs11218343	11	121435587	T	0.960	0.921	**3.20E-09**
14		FERMT2	rs17125924	14	53391680	G	0.093	0.121	**4.13E-03**
15		SLC24A4	rs12881735	14	92932828	T	0.779	0.819	**3.71E-03**
16		ADAM10	rs593742	15	59045774	A	0.705	0.474	**2.72E-52**
17		IQCK	rs7185636	16	19808163	T	0.820	0.688	**8.18E-25**
18		ACE	rs138190086	17	61538148	A	0.020	0.037	**3.63E-04**
19		ABCA7	rs3752246	19	1056492	G	0.182	0.197	2.53E-01
20		ADAMTS1	rs2830500	21	28156856	C	0.692	0.768	**9.11E-07**
1	Jansen	CR1	rs2093760	1	207786828	A	0.205	0.096	**7.68E-16**
2	et al.,	BIN1	rs4663105	2	127891427	C	0.415	0.492	**2.42E-06**
3	2019[5]	CLNK	rs6448453	4	11026028	A	0.252	0.234	2.04E-01
4		HLA-DRB1	rs6931277	6	32583357	A	0.847	0.900	**1.06E-05**
5		CD2AP	rs9381563	6	47432637	C	0.355	0.414	**2.30E-04**
6		ZCWPW1	rs1859788	7	99971834	G	0.690	0.723	**3.31E-02**
7		EPHA1	rs7810606	7	143108158	C	0.500	0.387	**1.08E-11**
8		CLU/PTK2B	rs4236673	8	27464929	G	0.609	0.718	**1.94E-11**
9		ECHDC3	rs11257238	10	11717397	C	0.375	0.327	**3.23E-03**
10		MS4A6A	rs2081545	11	59958380	C	0.619	0.503	**9.93E-13**
11		PICALM	rs867611	11	85776544	A	0.686	0.610	**7.73E-07**
12		SORL1	rs11218343	11	121435587	T	0.960	0.921	**3.20E-09**
13		SLC24A4	rs12590654	14	92938855	G	0.656	0.546	**3.52E-12**
14		ADAM10	rs442495	15	59022615	T	0.680	0.465	**2.16E-43**
15		KAT8	rs59735493	16	31133100	G	0.700	0.276	**2.01E-169**
16		SCIMP	rs113260531	17	5138980	A	0.120	0.037	**1.32E-14**
17		ABI3	rs28394864	17	47450775	A	0.473	0.174	**4.46E-72**
18		ABCA7	rs111278892	19	1039323	G	0.161	0.035	**1.17E-24**
19		CD33	rs3865444	19	51727962	C	0.680	0.817	**9.95E-19**
1	--	APOE	rs429358	19	45411941	C	0.141[1]	0.099	**2.79E-04**
2		APOE	rs7412	19	45412079	C	0.928[1]	0.954	**2.61E-03**

Risk-AF = Risk allele frequency

[a] Risk-AF is from Jansen, et al. 2019

[b] P-value is from a proportion t-test comparing the allele frequencies from GWAS vs. LASI-DAD. P-value ≤ 0.05 is indicated by bold text

Table S4. SNP associations with total learning score and delayed recall score

Index	Source GWAS	Gene	SNP	CHR	POS	Risk Allele	Risk Allele Frequency	Beta from GWAS[a]	Total Learning Score				Delayed Recall Score			
									Model 1		Model 2		Model 1		Model 2	
									Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
1	Lambert, et al., 2013[3]	CR1	rs6656401	1	207692049	A	0.066	0.166	-0.614	0.174	-0.475	0.258	-0.209	0.337	-0.144	0.484
2		BIN1	rs6733839	2	127892810	T	0.414	0.199	-0.425	0.059	**-0.445**	**0.034**	-0.178	0.096	-0.187	0.065
3		INPP5D	rs35349669	2	234068476	T	0.248	0.077	-0.077	0.767	-0.025	0.919	-0.156	0.209	-0.131	0.265
4		MEF2C	rs190982	5	88223420	A	0.608	0.073	-0.162	0.481	-0.267	0.212	-0.016	0.883	-0.062	0.552
5		HLA-DRB5-HLA-DRB1	rs9271192	6	32578530	C	0.251	0.104	-0.388	0.131	-0.244	0.307	-0.195	0.110	-0.134	0.247
6		CD2AP	rs10948363	6	47487762	G	0.199	0.095	**0.617**	**0.025**	**0.522**	**0.041**	**0.397**	**0.002**	**0.354**	**0.004**
7		NME8	rs2718058	7	37841534	A	0.867	0.073	0.145	0.649	0.146	0.623	0.169	0.268	0.174	0.231
8		ZCWPW1	rs1476679	7	100004446	T	0.787	0.094	-0.390	0.150	-0.229	0.363	-0.081	0.529	-0.017	0.886
9		EPHA1	rs11771145	7	143110762	G	0.700	0.105	0.108	0.655	0.180	0.422	0.001	0.993	0.033	0.757
10		PTK2B	rs28834970	8	27195121	C	0.575	0.095	-0.077	0.733	-0.063	0.764	-0.177	0.100	-0.167	0.103
11		CLU	rs9331896	8	27467686	T	0.717	0.151	-0.084	0.729	-0.108	0.630	0.109	0.343	0.099	0.365
12		CELF1	rs10838725	11	47557871	C	0.494	0.077	0.111	0.613	0.077	0.706	0.004	0.969	-0.003	0.974
13		MS4A6A	rs983392	11	59923508	A	0.530	0.105	0.158	0.472	0.166	0.418	0.096	0.361	0.099	0.318
14		PICALM	rs10792832	11	85867875	G	0.620	0.139	-0.301	0.180	-0.163	0.434	0.006	0.958	0.060	0.556
15		SORL1	rs11218343	11	121435587	T	0.921	0.261	**-0.825**	**0.046**	**-0.891**	**0.020**	**-0.559**	**0.005**	**-0.577**	**0.002**
16		FERMT2	rs17125944	14	53400629	C	0.120	0.131	-0.230	0.494	-0.293	0.350	-0.113	0.481	-0.144	0.344
17		SLC24A4-RIN3	rs10498633	14	92926952	G	0.818	0.094	0.098	0.734	0.096	0.722	0.170	0.211	0.160	0.216
18		ABCA7	rs4147929	19	1063443	A	0.201	0.140	0.554	0.062	**0.669**	**0.015**	0.236	0.095	**0.291**	**0.030**
19		CASS4	rs7274581	20	55018260	T	0.988	0.128	-1.347	0.188	-0.960	0.313	-0.598	0.223	-0.425	0.361
1	Kunkle, et al., 2019[4]	CR1	rs4844610	1	207802552	A	0.064	0.157	-0.595	0.217	-0.390	0.384	-0.204	0.378	-0.109	0.620
2		BIN1	rs6733839	2	127892810	T	0.414	0.182	-0.425	0.059	**-0.445**	**0.034**	-0.178	0.096	-0.187	0.065
3		HLA -DRB1	rs9271058	6	32575406	A	0.277	0.095	-0.399	0.134	-0.249	0.316	-0.201	0.113	-0.137	0.254
4		TREM2	rs75932628	6	41129252	T	0.001	0.732	2.278	0.491	3.063	0.320	-1.859	0.149	-1.600	0.190
5		CD2AP	rs9473117	6	47431284	C	0.178	0.086	0.568	0.064	0.482	0.091	**0.402**	**0.006**	**0.364**	**0.009**
6		EPHA1	rs10808026	7	143099133	C	0.728	0.105	-0.406	0.126	-0.389	0.114	-0.112	0.372	-0.108	0.364
7		PTK2B	rs73223431	8	27219987	T	0.556	0.095	-0.040	0.861	-0.075	0.725	-0.158	0.149	-0.168	0.106
8		CLU	rs9331896	8	27467686	T	0.717	0.128	-0.084	0.729	-0.108	0.630	0.109	0.343	0.099	0.365
9		ECHDC3	rs7920721	10	11720308	G	0.331	0.077	-0.097	0.688	0.084	0.711	-0.020	0.865	0.054	0.620
10		SPI1	rs3740688	11	47380340	T	0.638	0.083	-0.070	0.765	-0.067	0.756	-0.057	0.609	-0.050	0.632

11		MS4A2	rs7933202	11	59936926	A	0.539	0.117	-0.058	0.797	-0.026	0.902	0.017	0.874	0.031	0.762
12		PICALM	rs3851179	11	85868640	C	0.620	0.128	-0.283	0.207	-0.159	0.446	0.001	0.990	0.050	0.622
13		SORL1	rs11218343	11	121435587	T	0.921	0.223	**-0.825**	**0.046**	**-0.891**	**0.020**	**-0.559**	**0.005**	**-0.577**	**0.002**
14		FERMT2	rs17125924	14	53391680	G	0.121	0.131	-0.205	0.552	-0.261	0.414	-0.119	0.469	-0.147	0.344
15		SLC24A4	rs12881735	14	92932828	T	0.819	0.083	0.135	0.645	0.122	0.655	0.155	0.263	0.140	0.285
16		ADAM10	rs593742	15	59045774	A	0.474	0.073	-0.128	0.585	0.009	0.967	-0.156	0.162	-0.100	0.344
17		IQCK	rs7185636	16	19808163	T	0.688	0.083	**-0.585**	**0.017**	**-0.530**	**0.021**	-0.103	0.379	-0.085	0.445
18		ACE	rs138190086	17	61538148	A	0.037	0.278	0.770	0.189	0.912	0.094	0.168	0.551	0.223	0.404
19		ABCA7	rs3752246	19	1056492	G	0.197	0.140	0.505	0.098	**0.591**	**0.037**	0.200	0.169	0.243	0.078
20		ADAMTS1	rs2830500	21	28156856	C	0.768	0.073	**-0.663**	**0.020**	-0.499	0.059	**-0.443**	**0.001**	**-0.377**	**0.003**
1		CR1	rs2093760	1	207786828	A	0.096	0.024	-0.316	0.417	-0.134	0.711	-0.196	0.292	-0.115	0.515
2		BIN1	rs4663105	2	127891427	C	0.492	0.030	-0.393	0.078	**-0.434**	**0.036**	-0.178	0.092	**-0.196**	**0.050**
3		CLNK	rs6448453	4	11026028	A	0.234	0.014	0.377	0.175	0.280	0.279	0.136	0.303	0.101	0.419
4		HLA-DRB1	rs6931277	6	32583357	A	0.900	0.019	-0.126	0.729	-0.021	0.951	-0.122	0.482	-0.078	0.636
5		CD2AP	rs9381563	6	47432637	C	0.414	0.014	0.442	0.072	0.298	0.193	0.199	0.090	0.137	0.218
6		ZCWPW1	rs1859788	7	99971834	G	0.723	0.018	**-0.585**	**0.018**	-0.413	0.072	-0.095	0.418	-0.026	0.817
7		EPHA1	rs7810606	7	143108158	C	0.387	0.014	-0.090	0.694	-0.033	0.879	-0.074	0.497	-0.047	0.645
8		CLU/PTK2B	rs4236673	8	27464929	G	0.718	0.020	-0.136	0.582	-0.138	0.547	0.125	0.286	0.120	0.279
9		ECHDC3	rs11257238	10	11717397	C	0.327	0.013	-0.080	0.746	0.100	0.663	-0.009	0.942	0.065	0.561
10	Jansen, et al., 2019[5]	MS4A6A	rs2081545	11	59958380	C	0.503	0.017	0.185	0.403	0.178	0.388	0.161	0.127	0.157	0.118
11		PICALM	rs867611	11	85776544	A	0.610	0.020	-0.254	0.266	-0.104	0.626	0.043	0.696	0.101	0.327
12		SORL1	rs11218343	11	121435587	T	0.921	0.035	**-0.825**	**0.046**	**-0.891**	**0.020**	**-0.559**	**0.005**	**-0.577**	**0.002**
13		SLC24A4	rs12590654	14	92938855	G	0.546	0.014	0.006	0.980	0.124	0.572	-0.015	0.894	0.029	0.782
14		ADAM10	rs442495	15	59022615	T	0.465	0.013	-0.020	0.931	0.125	0.565	-0.146	0.188	-0.087	0.409
15		KAT8	rs59735493	16	31133100	G	0.276	0.013	0.537	0.055	0.394	0.131	0.139	0.296	0.080	0.527
16		SCIMP	rs113260531	17	5138980	A	0.037	0.019	0.073	0.906	-0.124	0.829	-0.307	0.300	-0.375	0.182
17		ABI3	rs28394864	17	47450775	A	0.174	0.012	0.550	0.085	0.420	0.158	0.190	0.210	0.142	0.323
18		ABCA7	rs111278892	19	1039323	G	0.035	0.019	0.153	0.812	0.138	0.817	0.217	0.474	0.205	0.475
19		CD33	rs3865444	19	51727962	C	0.817	0.013	0.314	0.273	0.297	0.266	0.098	0.475	0.086	0.507
1		APOE	rs429358	19	45411941	C	0.099	0.157[1]	-0.29	0.437	-0.200	0.572	-0.160	0.383	-0.120	0.487
2		APOE	rs7412	19	45412079	C	0.954	0.086[1]	-0.490	0.360	-0.190	0.702	-0.170	0.516	-0.040	0.877

P-value ≤ 0.05 is indicated by bold text

Effects sizes are calculated with respect to the Alzheimer's disease risk allele

[a] Effect sizes are from Jansen, et al. 2019

Table S5. Correlations between effect sizes from LASI-DAD and Alzheimer's disease GWAS

Correlation	Model	Lambert et. al, 2013[3]	Kunkle et. al,2019[4a]	Jansen et. al, 2019[5]
Total Learning Score	Model 1	-0.47*	-0.35	-0.76*
	Model 2	-0.54*	-0.43	-0.88*
Delayed Recall Score	Model 1	-0.50*	-0.35	-0.69*
	Model 2	-0.53*	-0.40	-0.71*

Model 1: Outcome ~ SNP + age + gender + PC1 ~ PC10
Model 2: Outcome ~ SNP + age + gender + education + PC1 ~ PC10
Asterisks indicate correlations with p-value < 0.05.
[a] Correlations for Kunkle et al. were analyzed after excluding two SNPs with low minor allele frequency (MAF<0.05): rs75932628 (*TREM2*) and rs138190086 (*ACE*).

Table S6. SNP-by-age interactions on total learning score and delayed recall score

Index	Source GWAS	Gene	SNP	CHR	POS	Risk Allele	Risk Allele Frequency	Total Learning Score				Delayed Recall Score			
								Model 1		Model 2		Model 1		Model 2	
								Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
1	Lambert, et al.	CR1	rs6656401	1	207692049	A	0.066	0.006	0.918	0.021	0.712	0.002	0.945	0.007	0.789
2		BIN1	rs6733839	2	127892810	T	0.414	-0.036	0.264	-0.031	0.307	-0.006	0.675	-0.004	0.770
3		INPP5D	rs35349669	2	234068476	T	0.248	-0.023	0.505	-0.010	0.754	0.004	0.806	0.009	0.577
4		MEF2C	rs190982	5	88223420	A	0.608	0.006	0.862	-0.002	0.953	0.001	0.933	-0.002	0.882
5		HLA-DRB5-HLA-DRB1	rs9271192	6	32578530	C	0.251	0.017	0.625	0.012	0.704	0.008	0.610	0.007	0.641
6		CD2AP	rs10948363	6	47487762	G	0.199	-0.017	0.650	-0.034	0.341	-0.008	0.644	-0.015	0.373
7		NME8	rs2718058	7	37841534	A	0.867	0.000	0.997	-0.005	0.911	-0.002	0.945	-0.004	0.837
8		ZCWPW1	rs1476679	7	100004446	T	0.787	0.037	0.313	0.043	0.218	0.002	0.916	0.004	0.814
9		EPHA1	rs11771145	7	143110762	G	0.700	-0.025	0.461	-0.016	0.612	-0.022	0.169	-0.018	0.242
10		PTK2B	rs28834970	8	27195121	C	0.575	**-0.067**	**0.031**	**-0.057**	**0.049**	-0.017	0.254	-0.012	0.385
11		CLU	rs9331896	8	27467686	T	0.717	-0.019	0.567	-0.013	0.680	-0.006	0.707	-0.004	0.799
12		CELF1	rs10838725	11	47557871	C	0.494	0.023	0.452	0.017	0.553	-0.010	0.513	-0.012	0.381
13		MS4A6A	rs983392	11	59923508	A	0.530	-0.010	0.749	-0.011	0.687	0.003	0.823	0.003	0.841
14		PICALM	rs10792832	11	85867875	G	0.620	0.001	0.986	-0.003	0.919	0.004	0.815	0.002	0.874
15		SORL1	rs11218343	11	121435587	T	0.921	0.021	0.759	0.025	0.689	-0.022	0.494	-0.021	0.480
16		FERMT2	rs17125944	14	53400629	C	0.120	0.003	0.948	-0.001	0.974	0.001	0.958	0.000	0.994
17		SLC24A4-RIN3	rs10498633	14	92926952	G	0.818	-0.003	0.944	-0.005	0.874	-0.012	0.486	-0.013	0.408
18		ABCA7	rs4147929	19	1063443	A	0.201	0.012	0.764	0.005	0.896	0.006	0.770	0.003	0.876
19		CASS4	rs7274581	20	55018260	T	0.988	-0.060	0.721	0.049	0.755	-0.003	0.974	0.041	0.595
1	Kunkle, et al.	CR1	rs4844610	1	207802552	A	0.064	-0.010	0.874	0.014	0.817	-0.008	0.789	0.001	0.970
2		BIN1	rs6733839	2	127892810	T	0.414	-0.036	0.264	-0.031	0.307	-0.006	0.675	-0.004	0.770
3		HLA -DRB1	rs9271058	6	32575406	A	0.277	0.018	0.618	0.012	0.706	0.009	0.606	0.007	0.645
4		TREM2	rs75932628	6	41129252	T	0.001	2.814	0.394	3.142	0.306	-0.083	0.782	-0.100	0.724
5		CD2AP	rs9473117	6	47431284	C	0.178	-0.017	0.697	-0.034	0.410	-0.006	0.797	-0.013	0.519
6		EPHA1	rs10808026	7	143099133	C	0.728	-0.001	0.983	-0.006	0.847	0.007	0.659	0.005	0.769
7		PTK2B	rs73223431	8	27219987	T	0.556	**-0.075**	**0.018**	**-0.060**	**0.042**	-0.021	0.170	-0.014	0.326
8		CLU	rs9331896	8	27467686	T	0.717	-0.019	0.567	-0.013	0.680	-0.006	0.707	-0.004	0.799

9		ECHDC3	rs7920721	10	11720308	G	0.331	0.001	0.986	0.004	0.912	-0.009	0.573	-0.008	0.603
10		SPI1	rs3740688	11	47380340	T	0.638	0.010	0.765	0.000	0.993	0.008	0.622	0.003	0.858
11		MS4A2	rs7933202	11	59936926	A	0.539	-0.017	0.582	-0.017	0.551	0.000	0.983	0.000	0.986
12		PICALM	rs3851179	11	85868640	C	0.620	0.003	0.926	-0.001	0.978	0.004	0.800	0.003	0.864
13		SORL1	rs11218343	11	121435587	T	0.921	0.021	0.759	0.025	0.689	-0.022	0.494	-0.021	0.480
14		FERMT2	rs17125924	14	53391680	G	0.121	-0.001	0.987	-0.004	0.928	-0.006	0.796	-0.007	0.756
15		SLC24A4	rs12881735	14	92932828	T	0.819	0.001	0.968	-0.002	0.952	-0.010	0.556	-0.012	0.465
16		ADAM10	rs593742	15	59045774	A	0.474	0.018	0.578	0.000	0.993	0.029	0.059	0.022	0.144
17		IQCK	rs7185636	16	19808163	T	0.688	-0.027	0.423	-0.031	0.312	-0.002	0.893	-0.004	0.774
18		ACE	rs138190086	17	61538148	A	0.037	0.061	0.500	0.078	0.354	-0.010	0.810	-0.002	0.957
19		ABCA7	rs3752246	19	1056492	G	0.197	0.003	0.939	0.000	0.996	-0.009	0.671	-0.010	0.608
20		ADAMTS1	rs2830500	21	28156856	C	0.768	-0.056	0.154	-0.052	0.154	**-0.043**	**0.020**	**-0.042**	**0.018**
1		CR1	rs2093760	1	207786828	A	0.096	-0.009	0.862	0.008	0.875	-0.013	0.598	-0.007	0.780
2		BIN1	rs4663105	2	127891427	C	0.492	-0.035	0.276	-0.035	0.243	-0.009	0.564	-0.009	0.547
3		CLNK	rs6448453	4	11026028	A	0.234	0.013	0.719	0.024	0.481	0.010	0.554	0.015	0.359
4		HLA-DRB1	rs6931277	6	32583357	A	0.900	-0.045	0.391	-0.053	0.270	0.005	0.853	0.001	0.976
5		CD2AP	rs9381563	6	47432637	C	0.414	-0.051	0.137	**-0.064**	**0.046**	-0.018	0.273	-0.024	0.130
6		ZCWPW1	rs1859788	7	99971834	G	0.723	0.040	0.241	0.044	0.164	0.002	0.885	0.004	0.769
7		EPHA1	rs7810606	7	143108158	C	0.387	0.001	0.972	-0.015	0.603	0.000	0.993	-0.006	0.639
8		CLU/PTK2B	rs4236673	8	27464929	G	0.718	-0.011	0.731	-0.007	0.821	-0.004	0.802	-0.002	0.879
9		ECHDC3	rs11257238	10	11717397	C	0.327	-0.004	0.907	0.000	0.998	-0.011	0.523	-0.009	0.566
10	Jansen, et al.	MS4A6A	rs2081545	11	59958380	C	0.503	-0.016	0.604	-0.010	0.728	-0.003	0.853	0.000	1.000
11		PICALM	rs867611	11	85776544	A	0.610	-0.019	0.561	-0.016	0.600	-0.001	0.941	0.000	0.986
12		SORL1	rs11218343	11	121435587	T	0.921	0.021	0.759	0.025	0.689	-0.022	0.494	-0.021	0.480
13		SLC24A4	rs12590654	14	92938855	G	0.546	0.058	0.067	0.043	0.145	0.019	0.203	0.013	0.358
14		ADAM10	rs442495	15	59022615	T	0.465	0.010	0.754	-0.003	0.915	0.024	0.113	0.019	0.201
15		KAT8	rs59735493	16	31133100	G	0.276	0.065	0.089	0.043	0.228	**0.037**	**0.041**	0.028	0.106
16		SCIMP	rs113260531	17	5138980	A	0.037	-0.080	0.288	-0.078	0.264	-0.013	0.721	-0.014	0.681
17		ABI3	rs28394864	17	47450775	A	0.174	**0.093**	**0.031**	**0.102**	**0.012**	0.021	0.285	0.024	0.203
18		ABCA7	rs111278892	19	1039323	G	0.035	-0.175	0.064	-0.140	0.111	-0.071	0.104	-0.058	0.163
19		CD33	rs3865444	19	51727962	C	0.817	-0.003	0.936	0.001	0.984	-0.006	0.744	-0.005	0.791
1	Kunkle et al.	APOE	rs429358	19	45411941	C	0.099	0.022	0.681	-0.019	0.713	0.022	0.397	0.005	0.827
2	None	APOE	rs7412	19	45412079	C	0.954	0.000	1.000	-0.029	0.656	0.010	0.760	-0.002	0.947

Note. Model 1: outcome ~ SNP * Age + sex + PC1 – PC10; Model 2: outcome ~ SNP * Age + sex + education + PC1 – PC10
P-value ≤ 0.05 is indicated by bold text. Beta is referring to interaction term and calculated with respect to the risk allele.

Table S7. Associations between SNPs in the *APOE* gene/promoter region and total learning or delayed recall score

SNP	Location	CHR	POS	Effect Allele	Non-effect Allele	Effect AF	Total Learning Score				Delayed Recall Score			
							Model 1		Model 2		Model 1		Model 2	
							Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
rs7256173	promoter	19	45407655	T	C	0.026	**-1.490**	**0.042**	-1.118	0.102	-0.647	0.063	-0.508	0.124
rs7259620	promoter	19	45407788	A	G	0.364	**-0.684**	**0.004**	**-0.613**	**0.005**	-0.154	0.171	-0.120	0.259
rs405509	promoter	19	45408836	G	T	0.409	**-0.506**	**0.028**	**-0.447**	**0.037**	-0.123	0.260	-0.095	0.358
rs440446	intronic	19	45409167	G	C	0.484	**-0.689**	**0.003**	**-0.583**	**0.007**	-0.181	0.101	-0.134	0.202
rs769450	intronic	19	45409608	C	A	0.021	0.556	0.487	0.265	0.722	0.388	0.307	0.268	0.457
rs769449	intronic	19	45410002	A	G	0.076	-0.587	0.171	-0.452	0.258	-0.210	0.304	-0.155	0.425
rs769450	intronic	19	45410444	A	G	0.310	**-0.599**	**0.014**	**-0.512**	**0.024**	-0.113	0.331	-0.071	0.518
rs555222732	intronic	19	45411722	A	G	0.002	1.238	0.702	0.551	0.856	0.085	0.956	-0.277	0.850
rs429358 (e4)	exonic	19	45411941	C	T	0.099	-0.290	0.437	-0.196	0.572	-0.155	0.383	-0.117	0.487
rs7412 (e2)	exonic	19	45412079	C	T	0.954	-0.491	0.360	-0.191	0.702	-0.167	0.516	-0.038	0.877

P-value ≤ 0.05 is indicated by bold text.

Model1: outcome ~ SNP + Age + Sex + PC1 – PC10; Model2: outcome ~ SNP + Age + Sex + Education + PC1 –PC10

Effect sizes are calculated with respect to the minor allele except the SNPs for e2 and e4, which are calculated with respect to the Alzheimer's disease risk allele.

Table S8. Interactions between SNPs and *APOE* e2/e4 on total learning score or delayed recall score

			Model 1						Model 2					
Interaction with rs429358 (ε4)			rs429358 (ε4)		SNP		SNP by rs429358 (ε4)		rs429358 (ε4)		SNP		SNP by rs429358 (ε4)	
Outcome	Predictor	N	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P
Total Learning Score	rs7256173	932	-0.602	0.117	**-1.690**	**0.028**	**6.173**	**0.009**	-0.498	0.165	-1.354	0.059[a]	**6.452**	**0.004**
	rs7259620	932	**-1.002**	**0.039**	**-0.912**	**0.000**	0.644	0.409	-0.884	0.051[a]	**-0.824**	**0.001**	0.706	0.333
	rs405509	932	**-1.180**	**0.037**	**-0.793**	**0.002**	0.915	0.123	**-1.122**	**0.033**	**-0.738**	**0.002**	0.997	0.072[a]
	rs440446	932	0.287	0.796	**-0.758**	**0.003**	-0.196	0.785	-0.345	0.740	**-0.711**	**0.003**	0.276	0.681
	rs769450	932	-0.723	0.117	**-0.831**	**0.002**	-0.013	0.988	-0.630	0.143	**-0.737**	**0.003**	0.160	0.838
Delayed Recall Score	rs7256173	932	-0.262	0.144	**-0.917**	**0.010**	**2.444**	**0.027**	-0.219	0.198	**-0.780**	**0.022**	**2.559**	**0.015**
	rs7259620	932	-0.395	0.082[a]	**-0.260**	**0.033**	0.340	0.352	-0.348	0.107	-0.223	0.055[a]	0.370	0.287
	rs405509	932	-0.404	0.126	-0.216	0.072[a]	0.277	0.320	-0.382	0.128	-0.193	0.091[a]	0.312	0.237
	rs440446	932	-0.120	0.818	-0.203	0.095[a]	0.034	0.919	-0.387	0.434	-0.182	0.114	0.233	0.467
	rs769450	932	-0.271	0.209	-0.201	0.108	0.074	0.850	-0.234	0.253	-0.162	0.172	0.150	0.689
Interaction with rs7412 (ε2)			rs7412 (ε2)		SNP		SNP by rs7412 (ε2)		rs7412 (ε2)		SNP		SNP by rs7412 (ε2)	
Outcome	Predictor	N	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P
Total Learning Score	rs7256173	932	-0.540	0.322	-0.896	0.229	1.568	0.658	-0.239	0.639	-0.592	0.394	0.896	0.786
	rs7259620	932	-1.605	0.082[a]	**-0.650**	**0.009**	1.100	0.210	-1.288	0.135	**-0.570**	**0.015**	1.092	0.183
	rs405509	932	-2.788	0.072[a]	**-0.615**	**0.012**	1.476	0.188	**-2.841**	**0.049**	**-0.509**	**0.026**	1.785	0.089[a]
	rs440446	932	**-3.491**	**0.027**	**-0.773**	**0.002**	1.873	0.083[a]	**-3.218**	**0.029**	**-0.633**	**0.006**	1.934	0.056[a]
	rs769450	932	-0.747	0.231	**-0.608**	**0.018**	2.026	0.106	-0.414	0.479	**-0.556**	**0.020**	1.766	0.132
Delayed Recall Score	rs7256173	932	-0.184	0.470	-0.668	0.054	-0.950	0.565	-0.065	0.789	-0.543	0.100	-1.221	0.436
	rs7259620	932	-0.629	0.145	-0.154	0.189	0.429	0.297	-0.503	0.221	-0.120	0.282	0.425	0.276
	rs405509	932	-1.358	0.061[a]	-0.149	0.190	0.802	0.127	**-1.381**	**0.045**	-0.104	0.335	0.927	0.063[a]
	rs440446	932	**-1.614**	**0.029**	-0.200	0.080	0.930	0.067[a]	**-1.503**	**0.033**	-0.141	0.194	**0.954**	**0.048**
	rs769450	932	-0.382	0.191	-0.103	0.388	0.861	0.143	-0.250	0.368	-0.081	0.478	0.753	0.178

P-value ≤ 0.05 is indicated by bold text

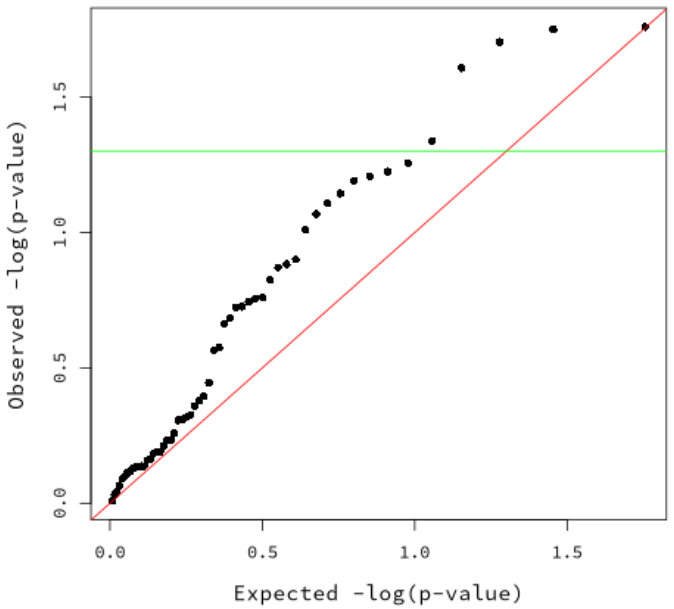
[a] Suggestive association at P-value <0.1

Model1: outcome ~ SNP * rs429358/rs7412 + Age + Sex + PC1 – PC10

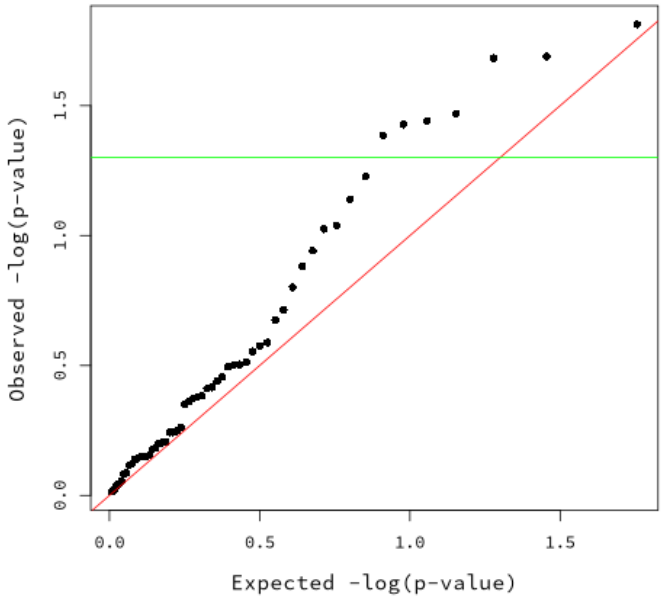
Model2: outcome ~ SNP * rs429358/rs7412 + Age + Sex + Education + PC1 –PC10

Effect sizes are calculated with respect to the minor allele, except the SNPs for ε2 and ε4, which are calculated with respect to the Alzheimer's disease risk allele

(a)


Observed -log(p-value)
Expected -log(p-value)
0.0
0.5
1.0
1.5

(b)


Observed -log(p-value)
Expected -log(p-value)
0.0
0.5
1.0
1.5

(c) (d)

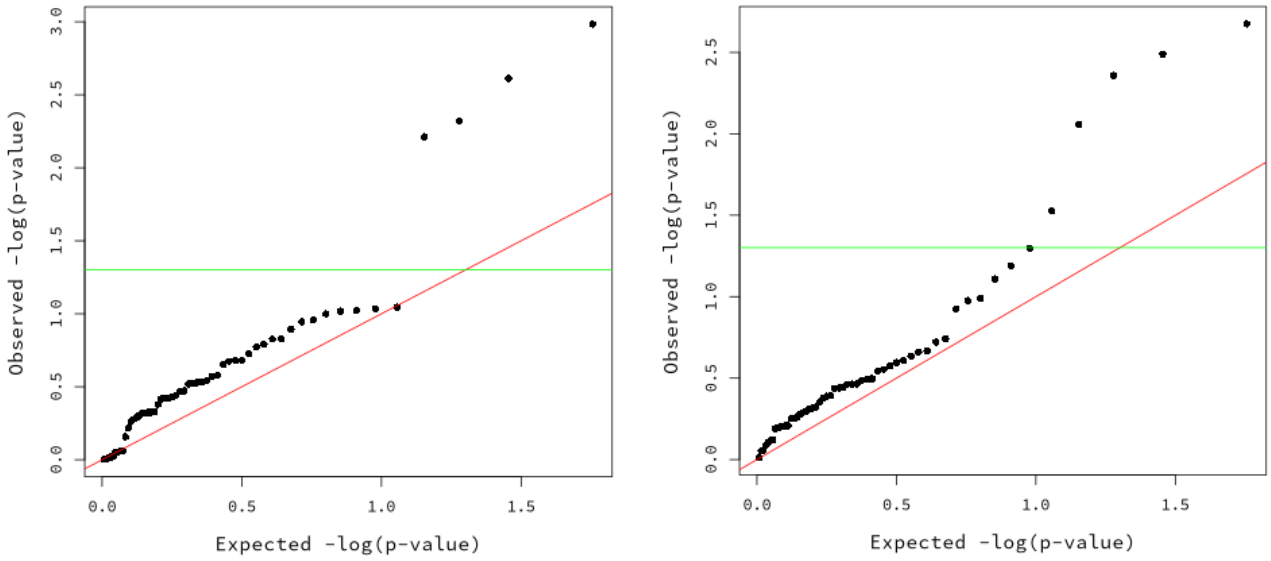
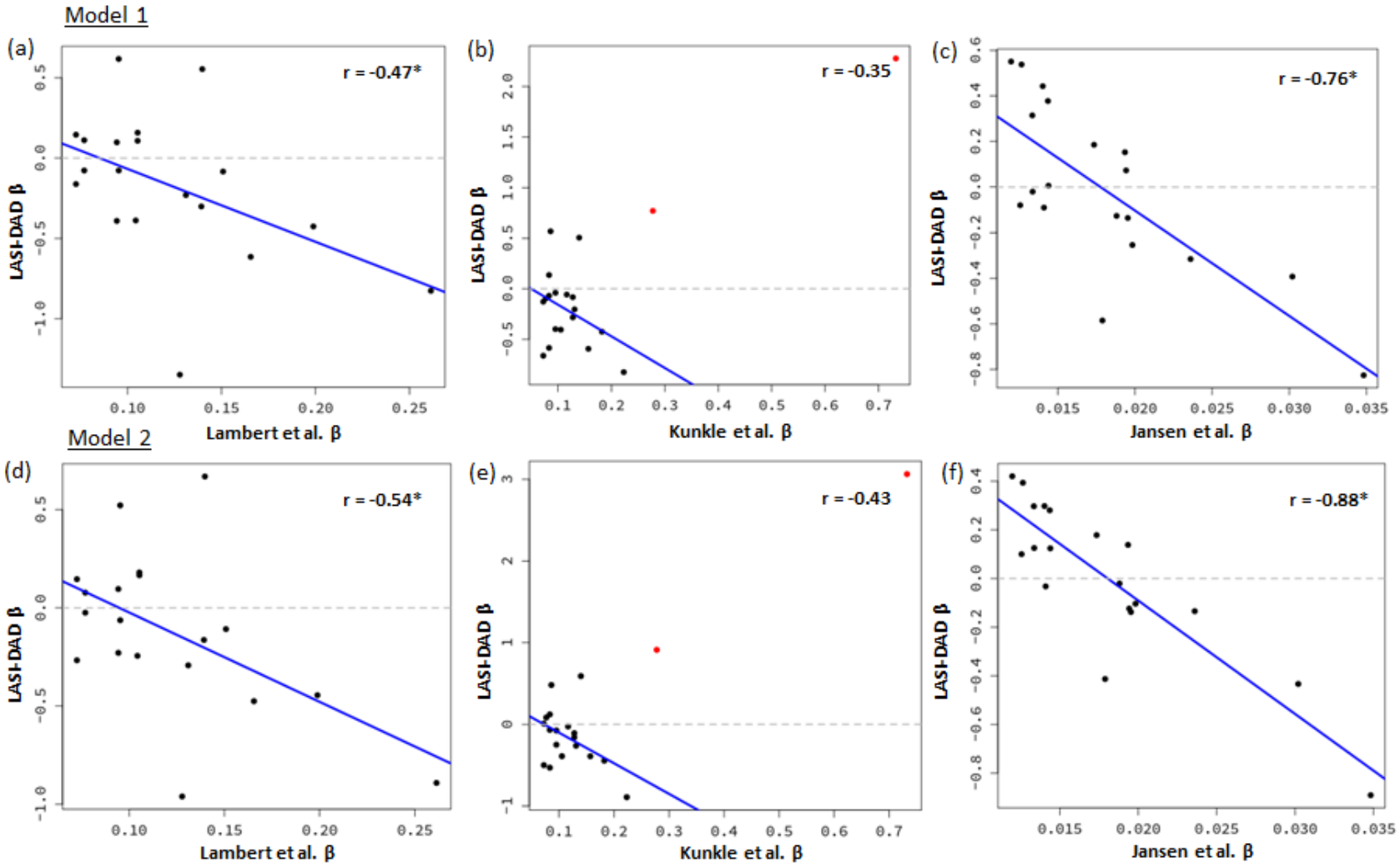


Figure S1. Q-Q plots for the association between cognitive measures and 56 known AD risk SNPs in LASI-DAD
Q-Q plot for total learning score in Model 1 (a) and Model 2 (b), and Q-Q plot for delayed recall score in Model 1 (c) and Model 2 (d)

Total Learning Score



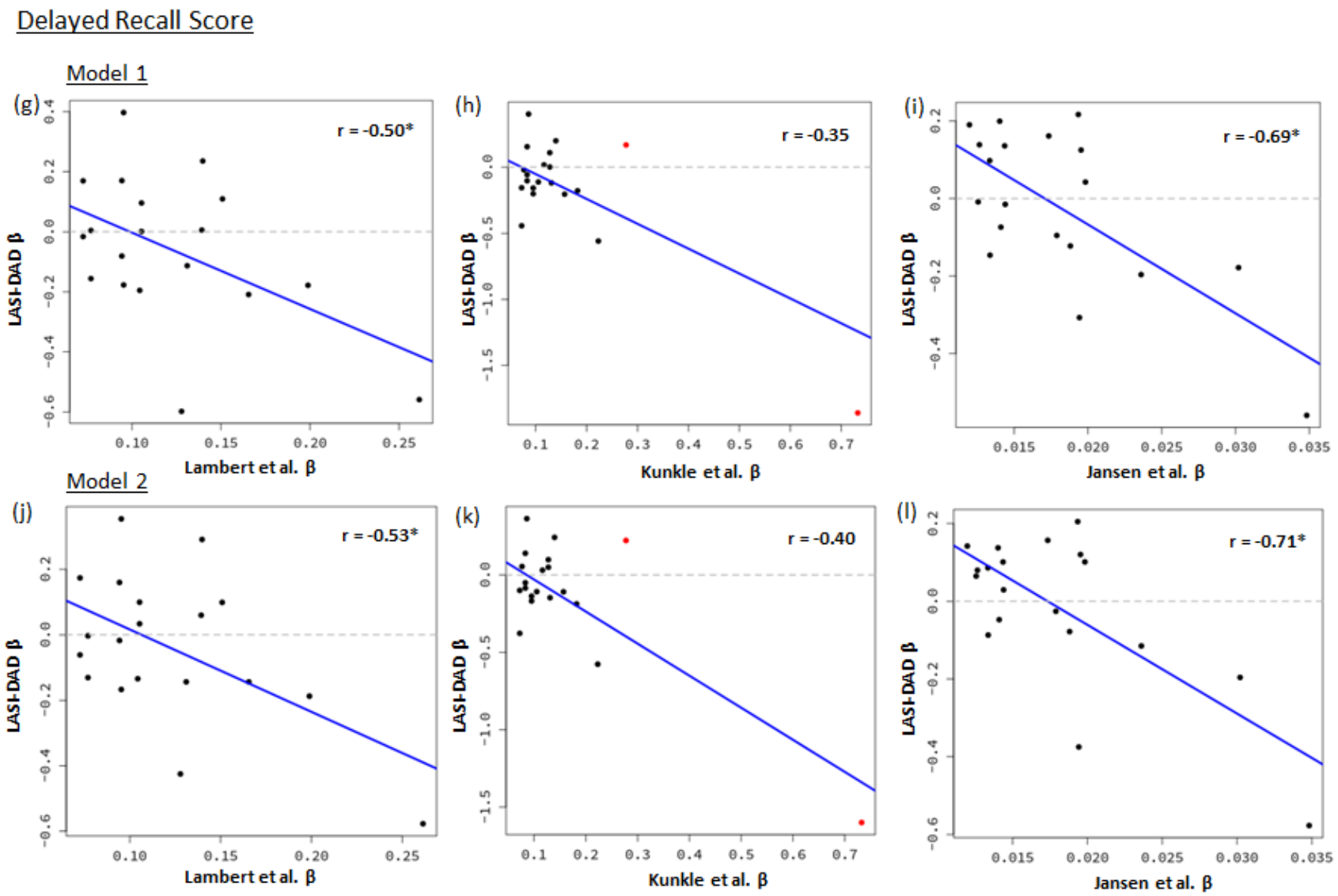
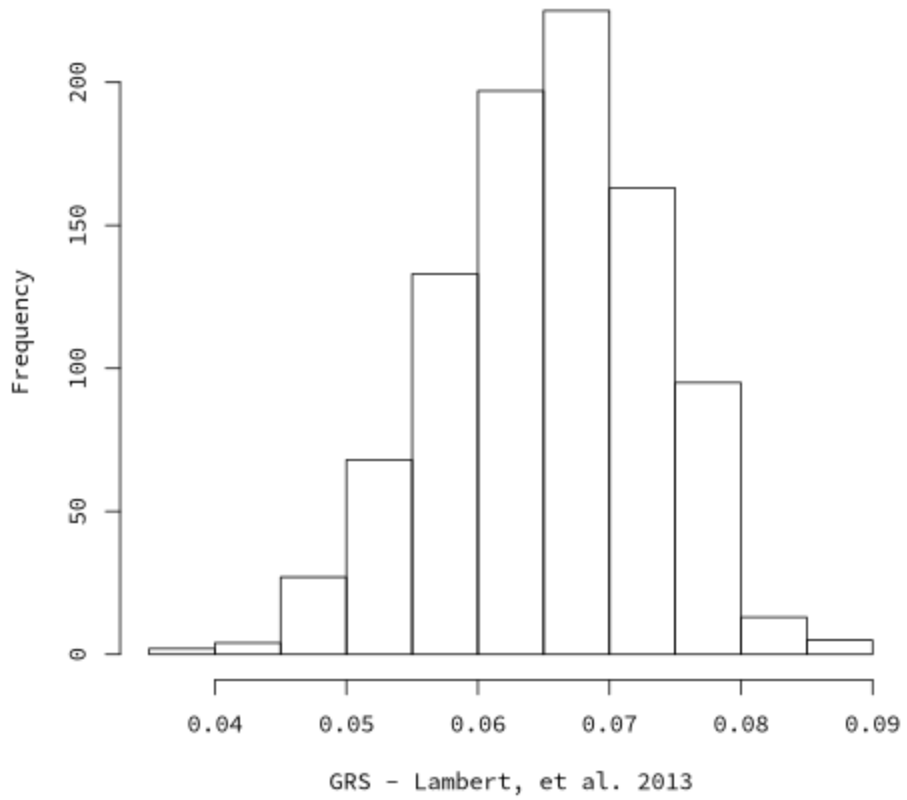
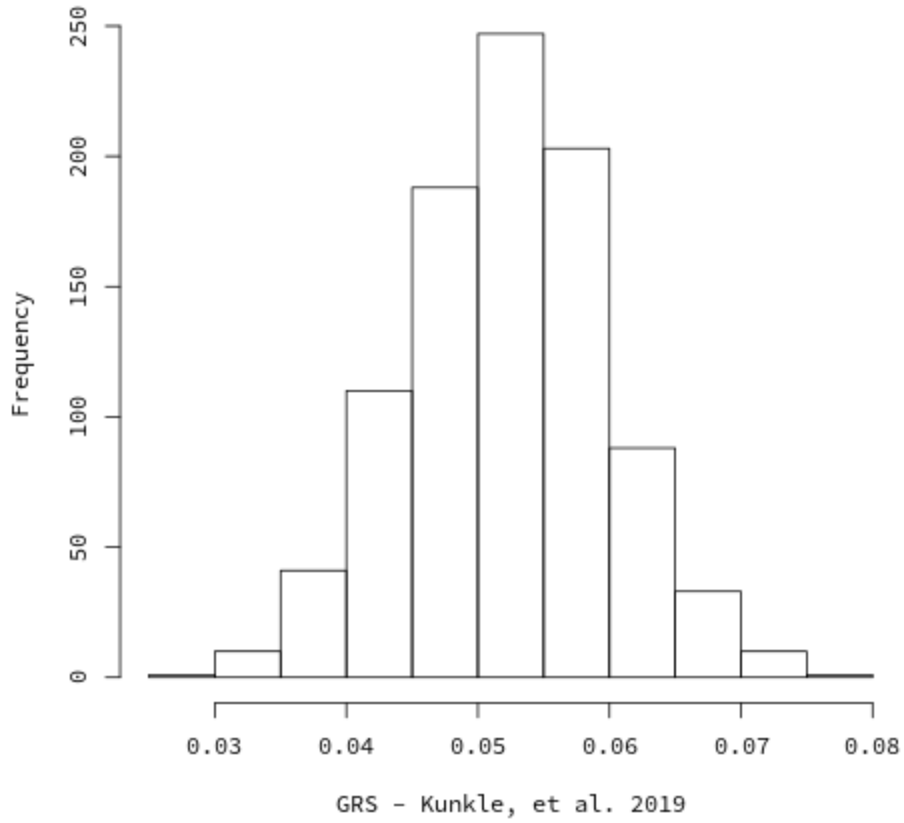


Figure S2. Scatterplots of estimated effect sizes for cognitive measures in LASI-DAD (Y axis) and effect sizes for Alzheimer's disease (AD) from published GWAS papers (X axis).

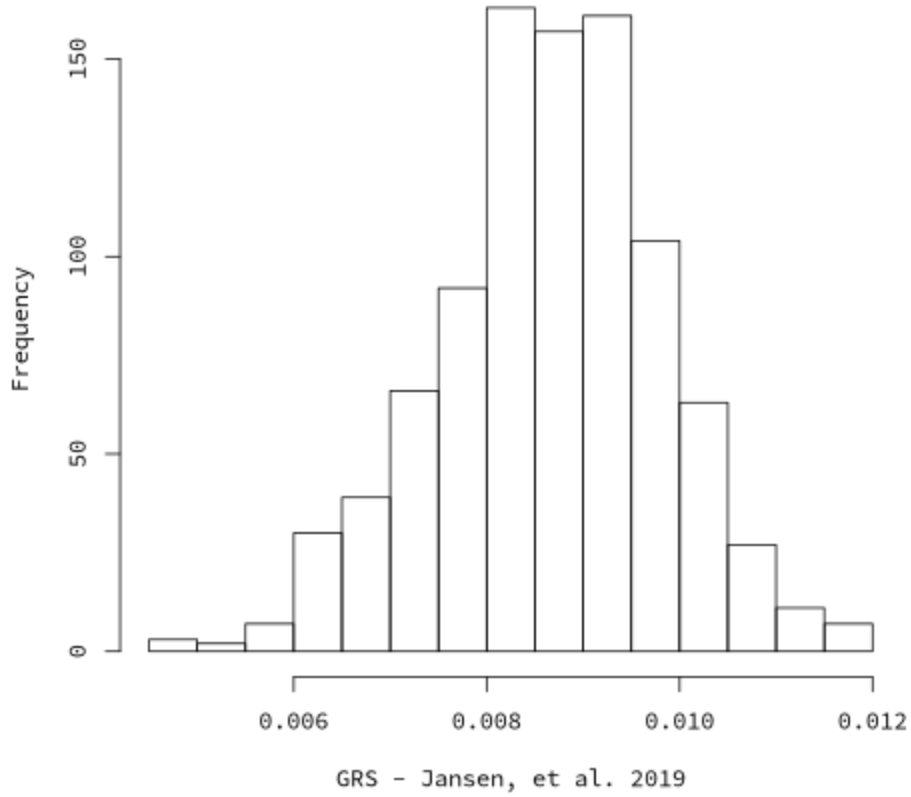
Scatterplot of estimated effect sizes for total learning score in Model 1 vs. effect sizes for AD reported from Lambert et al. (a), Kunkle et al. (b), and Jansen et al. (c).
Scatterplots of estimated effect sizes for total learning score in Model 2 vs. effect sizes for AD reported from Lambert et al. (d), Kunkle et al. (e), and Jansen et al. (f).
Scatterplots of estimated effect sizes for delayed recall score in Model 1 vs effect sizes for AD reported from Lambert et al. (g), Kunkle et al. (h), and Jansen et al. (i).
Scatterplots of estimated effect sizes for delayed recall score in Model 2 vs. effect sizes for AD reported from Lambert et al. (j), Kunkle et al. (k), and Jansen et al. (l).
The blue line represents the regression line and r is the corresponding correlation coefficient. An asterisk indicates p-value ≤ 0.05.
There are two SNPs (in red) with low minor allele frequency (MAF<0.05) from Kunkle et al. that appear to be high leverage points. Thus, Kunkle et al. correlations were calculated after excluding these outliers (rs75932628 [*TREM2*], rs138190086 [*ACE*]).



(a) GRS from Lambert et. al, 2013



(b) GRS from Kunkle et. al, 2019



(c) GRS from Jansen et. al, 2019

Figure S3. Histograms of the genetic risk scores (GRSs) in LASI-DAD

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