Supplemental Online Content

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

eAppendix. Additional acknowledgments

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eMethods.

EADB-core analysis

The sample and variant quality controls as well as the imputation procedure have already been described in [1]. For each sample, the *APOE* genotype was defined as (i) the clinical *APOE* genotype if available or (ii) the imputed *APOE* genotype. Indeed, the SNPs rs429358 and rs7412 had a good imputation quality (R^2) in the resulting TOPMed imputations with a R^2 of 0.991 and 0.999 respectively. For each sample, it was required that the genotype probability (GP) for both SNPs was ≥0.8, otherwise the sample was excluded from the analysis. In total, 15,519 samples had their APOE genotype derived from the imputations. Finally, all the samples who were part of the CGPS cohort were also excluded to avoid any overlap in the meta-analysis. As a result, 19,873 AD cases and 21,160 controls were selected for the analysis. The V236E and R251G SNPs had a R^2 of 0.763 and 0.707 in the imputations and thus were retained for the analyses. Tests of the association between AD status and the V236E and R251G genotypes were conducted with the SNPTEST software[2] (v2.5.6) using a logistic regression and an additive genetic model. The genotype probabilities were analyzed using the newml method adjusting for sex, 20 firsts principal components (PCs) and the genotyping center. Non-*APOE* stratified association were additionally covaried by ε2 and ε4 dosages.

GERAD analysis

The sample and variant quality controls as well as the imputation procedure have already been described in [1]. For each sample, the *APOE* genotype was defined as (i) the clinical *APOE* genotype if available or (ii) the imputed *APOE* genotype. Indeed, the SNPs rs429358 and rs7412 had a good imputation quality (R^2) in the resulting TOPMed imputations with a R^2 of 0.863 and 0.934 respectively. For each sample, it was required that the genotype probability (GP) for both SNPs was ≥0.8, otherwise the sample was excluded from the analysis. In total, 1,314 samples had their APOE genotype derived from the imputations. As a result, 2,989 AD cases and 7,007 controls were selected for the analysis. The V236E and R251G SNPs had a R^2 of 0.794 and 0.823 in the imputations and thus were retained for the analyses. Tests of the association between AD status and the V236E and R251G genotypes were conducted with the SNPTEST software[2] (v2.5.6) using a logistic regression and an additive genetic

model. The genotype probabilities were analyzed using the newml method adjusting for sex, PC2 and PC3. Non-*APOE* stratified association were additionally covaried by ε2 and ε4 dosages.

DemGene analysis

The sample and variant quality controls as well as the imputation procedure have already been described in [1]. Since no *APOE* genotype was available in the clinical information, the imputed *APOE* genotype was used. Indeed, the SNPs rs429358 and rs7412 had a good imputation quality (R^2) in the resulting TOPMed imputations with a R^2 of 0.992 and 0.998 respectively. For each sample, it was required that the genotype probability (GP) for both SNPs was ≥0.8, otherwise the sample was excluded from the analysis. As a result, 1,687 AD cases and 5,911 controls were selected for the analysis. Only the V236E SNP had a R^2>0.7 (0.931) in the imputations and thus was retained for the analyses. Tests of the association between AD status and the V236E genotype were conducted with the SNPTEST software[2] (v2.5.6) using a logistic regression and an additive genetic model. The genotype probabilities were analyzed using the newml method adjusting for sex, PC1, PC2, PC3, PC5, PC8, PC9, PC10 and PC11. Non-*APOE* stratified association were additionally covaried by ε2 and ε4 dosages.

EADI analysis

The sample and variant quality controls as well as the imputation procedure have already been described in [1]. For each sample, the *APOE* genotype was defined as (i) the clinical *APOE* genotype if available or (ii) the imputed *APOE* genotype. Indeed, the SNPs rs429358 and rs7412 had a good imputation quality (R^2) in the resulting TOPMed imputations with a R^2 of 0.923 and 0.906 respectively. For each sample, it was required that the genotype probability (GP) for both SNPs was ≥0.8, otherwise the sample was excluded from the analysis. In total, 119 samples had their *APOE* genotype derived from the imputations. As a result, 2,397 AD cases and 6,331 controls were selected for the analysis. Only the R251G SNP had a R^2>0.7 (0.721) in the imputations and thus was retained for the analyses. Tests of the association between AD status and the R251G genotype were conducted with the SNPTEST software[2] (v2.5.6) using a logistic regression and an additive genetic model. The genotype probabilities were analyzed using the newml method adjusting for sex and the firsts 3 PCs. Non-*APOE* stratified association were additionally covaried by ε2 and ε4 dosages.

GR@ACE/DEGESCO analysis

The sample and variant quality controls as well as the imputation procedure have already been described in [3]. Since no *APOE* genotype was available in the clinical information, the imputed *APOE* genotype was used. Indeed, the SNPs rs429358 and rs7412 had a good imputation quality (R^2) in the resulting TOPMed imputations with a R^2 of 0.999 and 0.999 respectively. For each sample, it was required that the genotype probability (GP) for both SNPs was ≥0.8, otherwise the sample was excluded from the analysis. In total, 15,894 samples had their *APOE* genotype derived from the imputations. As a result, 7,355 AD cases and 8,539 controls were selected for the analysis. Only the R251G SNP had a R^2>0.7 (0.763) in the imputations and thus was retained for the analyses. Tests of the association between AD status and the R251G genotype were conducted with the SNPTEST software[2] (v2.5.6) using a logistic regression and an additive genetic model. The genotype probabilities were analyzed using the newml method adjusting for sex and the firsts 4 PCs. Non-*APOE* stratified association were additionally covaried by ε2 and ε4 dosages.

CCHS & CGPS analysis

We included individuals from two similar studies of the Danish general population: The Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS). Individuals were randomly selected from the national Danish Civil Registration System to reflect the adult population aged 20-100+ years. These studies combined included a total of 104,087 of whom 2,092 developed dementia during the follow-up period. We sequenced the exonic parts of the *APOE* gene in the CCHS, and nine amino acid changing rare variants with frequency ≥2/10,000 (allele frequency ≥0.01%) were further directly genotyped in the CGPS as previously described[4]. Individuals with missing ε2 or ε4 exact genotypes were removed from the analyses. Information on the AD diagnosis was collected from the national Danish Patient Registry with data on all patient contacts from all clinical hospital departments in Denmark since 1977, and from the national Danish Causes of Death Registry with data on causes of all deaths in Denmark, as reported by hospitals and general practitioners since 1977. AD was World Health Organization International Classification of Diseases (ICD) 8th and 10th revision ICD8 290.10 and ICD10 F00 and G30. AD association with V236E and R251G genotype were tested with logistic

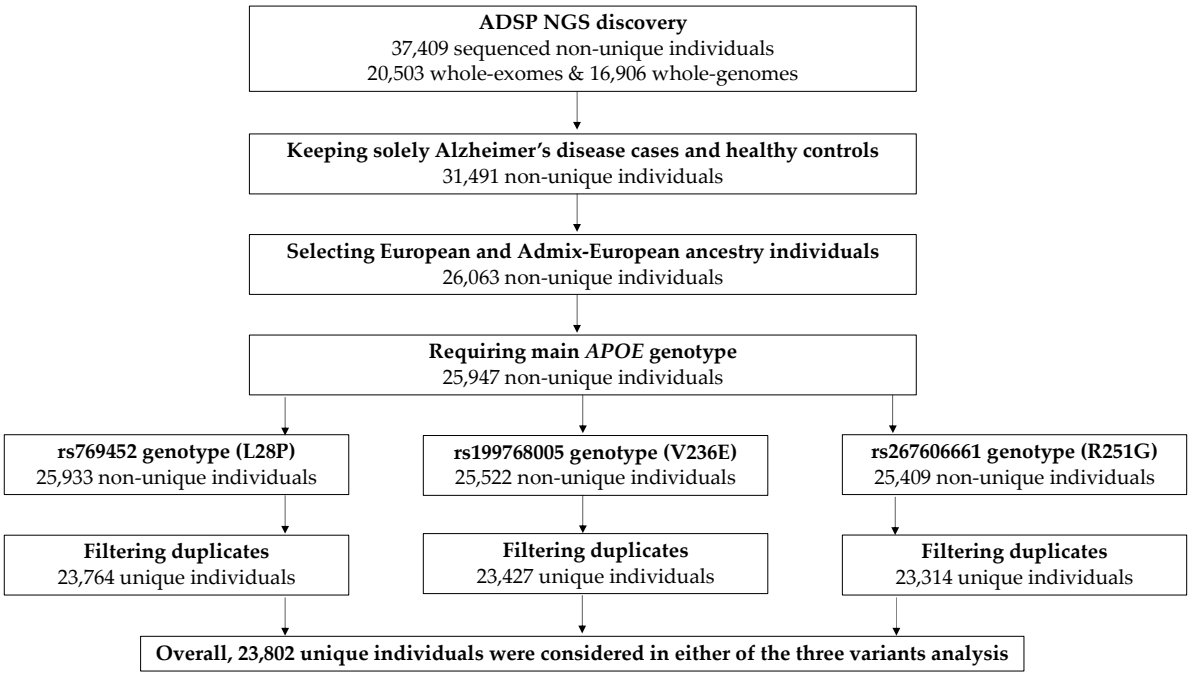
regression adjusted for age, sex, ε2 and ε4 dosages in the overall analyses. Plink2 (v2.00a2LM)[5] using the glm flag covarying for age and sex was used for ε33 and ε43 stratified analyses.

UK Biobank proxy-AD analysis

We analyzed the intermediate whole-exome sequencing "200k WES" released from the UK Biobank which included 200,643 individual genotypes. The imputed data were not used since the imputation of the two variants was deemed both having an Information Score below 0.7. The proxy-AD was defined following the approach proposed in Bellenguez et al.[1], where the proxy-AD variable is a binary outcome with a case being any individual with self-AD (ICD10 codes defined in Jansen et al.[6]), or having a self-reported first degree relative with AD (mother, father, or siblings). Individuals with sex discordance[7], missing *APOE* ε2 or *APOE* ε4 WES genotype, or who withdraw consent were removed from the analysis. A total of 28,484 AD and AD-proxy cases, 157,436 controls remained for analysis. Proxy-AD association with V236E and R251G genotypes were tested with SAIGE software[8] (v 0.44.6.5) using the saddle point approximation and adjusting for relatedness, Age, Sex and the first 20 principal components accounting for ancestry[7], non-*APOE* stratified analyses were additionally covaried by ε2 and ε4 dosages. Parameter estimates and standard error were adjusted by a factor of 2 to account for the use of the proxy-AD phenotype[9].

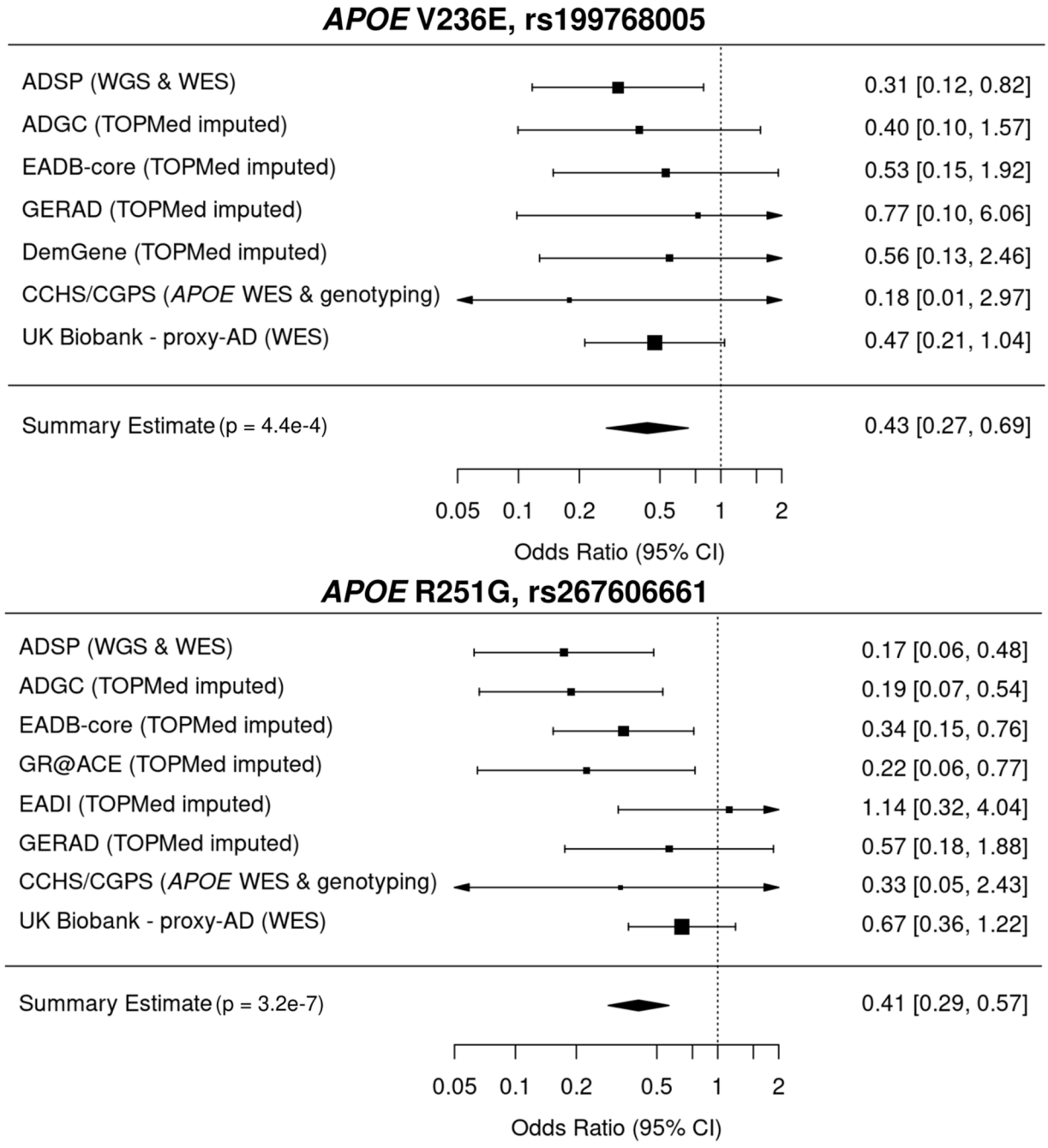
eFigure 1. Flowchart describing the number of individuals remaining at each filtering steps

When filtering for duplicates, concordance of genotype call for each variant was confirmed and the whole-genome version was prioritized, when available, for ancestry principal component computations.



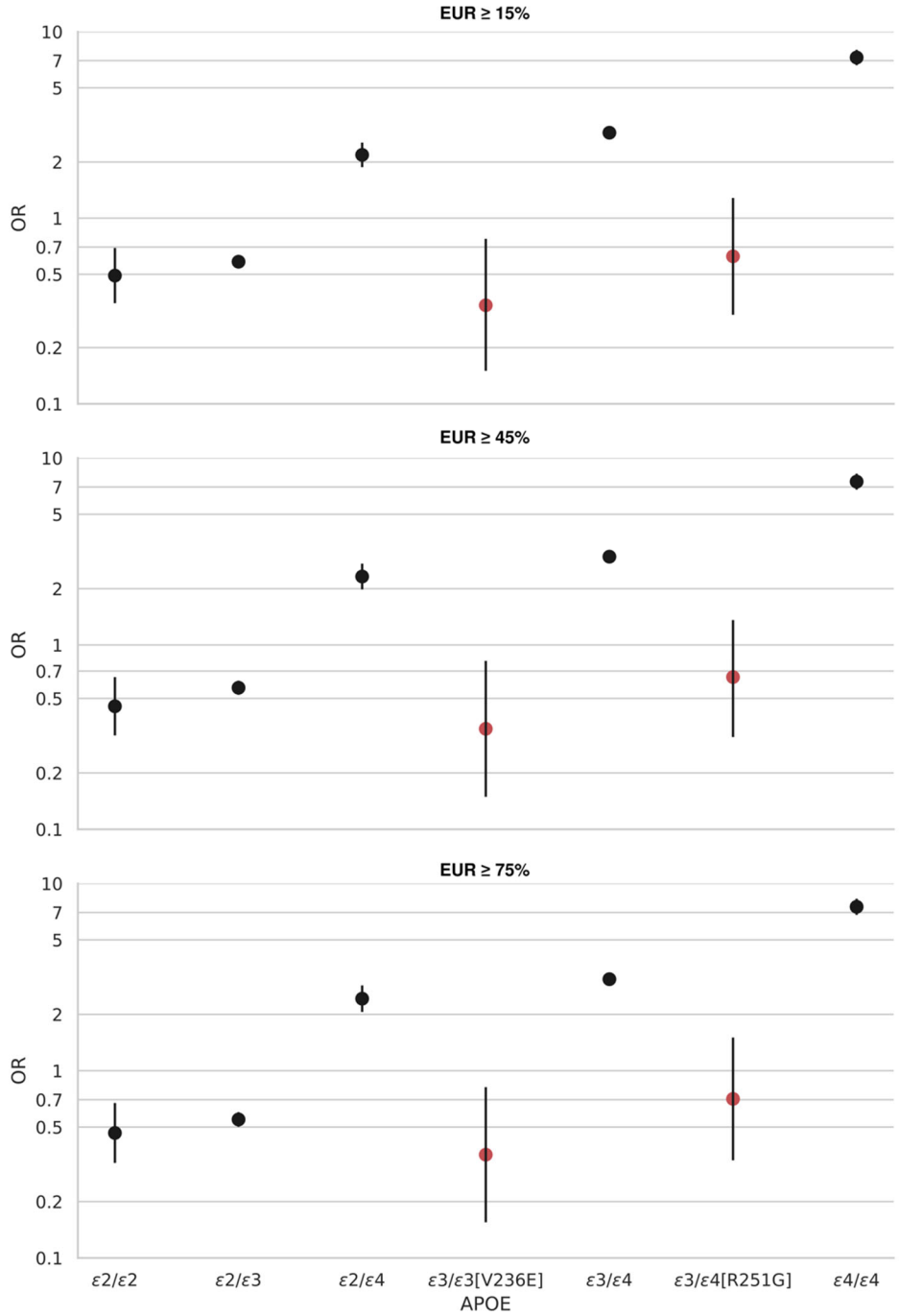
eFigure 2. V236E and R251G are associated with decreased AD risk across dataset in *APOE*-stratified sensitivity analyses

Top panel presents V236E association in ε3/ε3-stratified analyses and bottom panel shows R251G association in ε3/ε4-stratified analyses.



eFigure 3. *APOE* ε3/ε3[V236E] individuals have a lower AD risk than *APOE* ε2/ε3 individuals and *APOE* ε3/ε4[R251G] have a risk equivalent to ε2/ε3 carriers despite carrying 1 ε4 allele, regardless of the EUR ancestry cutoff for admixed Europeans and Europeans

OR: Odds ratio.



eTable 1. Queried cohort overview to identify admixed and European ancestry individuals in the ADSP discovery and ADGC internal replication

Cohort/Project	Genotyping Platform	Cohort-Platform ID	Sample (N)	Data Repository and Access ID
ADSP WES	Whole Exome Sequencing	ADSP_WES	20503	NIAGADS DSS (NG00067.v5) / NACC
ADSP WGS	Whole Genome Sequencing	ADSP_WGS	16906	NIAGADS DSS (NG00067.v5) / NACC
ACT	Illumina Human 660W-Quad	ACT	2790	NIAGADS (NG00034) / dbGaP (phs000234)
ADC1	Illumina Human 660W-Quad	ADC1	2731	NIAGADS (NG00022) / NACC
ADC2	Illumina Human 660W-Quad	ADC2	928	NIAGADS (NG00023) / NACC
ADC3	Illumina Human OmniExpress	ADC3	1526	NIAGADS (NG00024) / NACC
ADC4	Illumina Human OmniExpress	ADC4	1054	NIAGADS (NG00068) / NACC
ADC5	Illumina Human OmniExpress	ADC5	1224	NIAGADS (NG00069) / NACC
ADC6	Illumina Human OmniExpress	ADC6	1333	NIAGADS (NG00070) / NACC
ADC7	Illumina Infinium Human OmniExpressExome	ADC7	1462	NIAGADS (NG00071) / NACC
ADDNEUROMED	Illumina Human 610-Quad	ADM_Q	315	Synapse AddNeuroMed (syn4907804)
	Illumina Human OmniExpress	ADM_O	329	Synapse AddNeuroMed (syn4907804)
ADGC-ExomeChip	Illumina HumanExome BeadChip v1.0 at CHOP	CHOP	5180	NIAGADS (NG00081) / NACC
	Illumina HumanExome BeadChip v1.0 at Miami	MIA	1923	NIAGADS (NG00080) / NACC
	Illumina HumanExome BeadChip v1.0 at Northshore	NS	5998	NIAGADS (NG00079) / NACC
	Illumina HumanExome BeadChip v1.0 at WashU	WU	868	NIAGADS (NG00085) / NACC
ADNI	Illumina Human 610-Quad	ADNI_Q	757	LONI ADNI
	Illumina Human OmniExpress	ADNI_OE	361	LONI ADNI
	Illumina Omni 2.5	ADNI_O25	812	LONI ADNI
	Illumina Human OmniExpress	ADNI_DOD	204	LONI ADNIDOD
ADNI3	Illumina Global Screening Array (GSA)	ADNI3	327	LONI ADNI
IIDP African Americans	Illumina Human 1M-Duo	IIDP_AA	1175	NIAGADS (NG00047)
IIDP Yorubans	Illumina Human 1M-Duo	IIDP_YOR	1264	NIAGADS (NG00047) / cf. gaaindata.org/partner/IIDP
CIDR	Illumina Human Omni1-Quad	CIDR	3101	NIAGADS (NG00015) / dbGAP (phs000160)

GenADA	Affymetrix 500K	GSK	1571	dbGaP (phs000219)
LATC	Illumina Multi-Ethnic – BU	LATC	63	RADC Rush / Latino CORE Study
NIA-LOAD	Illumina Human 610-Quad	LOAD	5220	NIAGADS (NG00020)
MARS	Illumina Multi-Ethnic – BU	MARS	708	RADC Rush / Minority Aging Research Study
MAYO	Illumina Human Hap300	MAYO_1	2099	Synapse AMP-AD (syn5591675)
MAYO2	Illumina Omni 2.5	MAYO_2	314	Synapse AMP-AD (syn5550404)
MIRAGE	Illumina Human CNV370-Duo	MIRAGE_370	397	NIAGADS (NG00031)
	Illumina Human 610-Quad	MIRAGE_610	1105	NIAGADS (NG00031)
MTC	Illumina Human OmniExpress	MTC	542	NIAGADS (NG00096)
OHSU	Illumina Human CNV370-Duo	OHSU	647	NIAGADS (NG00017)
ROSMAP	Affymetrix GeneChip 6.0 - Broad Institute	ROSMAP_1B	1126	RADC Rush / Synapse AMP-AD (syn3219045)
	Affymetrix GeneChip 6.0 - TGen	ROSMAP_1T	582	RADC Rush / Synapse AMP-AD (syn3219045)
	Illumina Human OmniExpress 12 - Chop	ROSMAP_2C	382	RADC Rush / Synapse AMP-AD (syn7824841)
	Illumina Multi-Ethnic - BU	ROSMAP_3BU	494	RADC Rush
TARCC	Affymetrix 6.0	TARCC	2718	NIAGADS (NG00097) / TARCC study
TGEN2	Affymetrix 6.0	TGEN	1599	NIAGADS (NG00028)
UPITT	Illumina Human Omni1-Quad	UPITT	2440	NIAGADS (NG00026)
UM-VU-MSSM	Illumina Human 1M-Duo, Illumina 1M	UVM_A	1153	NIAGADS (NG00042)
	Affymetrix 6.0	UVM_B	864	NIAGADS (NG00042)
	Illumina Human 550K. Illumina Human 610-Quad	UVM_C	445	NIAGADS (NG00042)
WASHU	Illumina Human 610-Quad	WASHU_1	670	NIAGADS (NG00030)
WASHU2	Illumina Human OmniExpress	WASHU_2	235	NIAGADS (NG00087)
WHICAP	Illumina Human OmniExpress	WHICAP	647	NIAGADS (NG00093)

eTable 2. Overview of ADSP studies with whole-exome sequencing (WES) and/or whole-genome sequencing (WGS) available at NIAGADS DSS (NG00067)

Study	Accession Number	Related Datasets
Accelerating Medicines Partnership- Alzheimer's Disease (AMP-AD)	sa000011	NG00067 – ADSP Umbrella
Cache County Study	sa000014	NG00067 – ADSP Umbrella
University of Pittsburgh- Kamboh WGS	sa000012	NG00067 – ADSP Umbrella
CurePSP and Tau Consortium PSP WGS	sa000016	NG00067 – ADSP Umbrella
NIH, CurePSP and Tau Consortium PSP WGS	sa000015	NG00067 – ADSP Umbrella
UCLA Progressive Supranuclear Palsy	sa000017	NG00067 – ADSP Umbrella
NACC Genentech WGS	sa000013	NG00067 – ADSP Umbrella
Alzheimer's Disease Sequencing Project (ADSP)	sa000001	NG00067 – ADSP Umbrella
Alzheimer's Disease Neuroimaging Initiative (ADNI)	sa000002	NG00067 – ADSP Umbrella
Alzheimer's Disease Genetics Consortium: African Americans (ADGC AA)	sa000003	NG00067 – ADSP Umbrella
The Familial Alzheimer Sequencing (FASe) project	sa000004	NG00067 – ADSP Umbrella
Brkanac – Family-based genome scan for AAO of LOAD	sa000005	NG00067 – ADSP Umbrella
HIHG Miami Families with AD	sa000006	NG00067 – ADSP Umbrella
Washington Heights/Inwood Columbia Aging Project (WHICAP)	sa000007	NG00067 – ADSP Umbrella
Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight ADRC)	sa000008	NG00067 – ADSP Umbrella
Corticobasal degeneration Study (CBD)	sa000009	NG00067 – ADSP Umbrella
Progressive Supranuclear Palsy Study (PSP)	sa000010	NG00067 – ADSP Umbrella

eTable 3. Demographic characteristics of the cohorts queried for discovery and internal replication samples

AFR: African, AMR: American (central and south; admixed), EAS: East Asian, SAS South Asian, EUR: European, otherwise ADMIX: admixed of these super ancestry categories.

			Ancestry						Diagnosis		Sex - Females		Age	
	Cohort	N total	AFR N	ADMIX N	AMR N	EAS N	SAS N	EUR N	CN N	AD N	CN N(%)	AD N(%)	CN μ(σ)	AD μ(σ)
Discovery	ADSP WES	20503	3171	3174	125	7	2	14024	9617	8723	6101(63.4)	5394(61.8)	82.0(8.5)	75.7(8.8)
	ADSP WGS	16906	2240	4012	58	68	19	10509	6717	6434	4510(67.1)	3896(60.6)	78.2(8.5)	74.1(10.5)
Replication	ACT	2790	70	64	7	73	0	2576	1833	713	1000(54.6)	462(64.8)	82.9(6.5)	82.1(6.6)
	ADC1	2731	92	58	47	20	0	2514	603	1946	354(58.7)	1039(53.4)	79.8(10.8)	70.7(9.5)
	ADC2	928	0	2	0	0	0	926	124	707	87(70.2)	366(51.8)	80.1(9.2)	72.9(7.1)
	ADC3	1526	0	5	0	0	0	1521	482	858	305(63.3)	468(54.5)	79.6(9.6)	72.5(10.3)
	ADC4	1054	6	10	1	0	0	1037	420	452	257(61.2)	237(52.4)	79.2(8.7)	72.6(9.0)
	ADC5	1224	0	1	0	0	0	1223	579	415	376(64.9)	226(54.5)	82.0(8.9)	74.1(8.7)
	ADC6	1333	0	2	0	0	0	1331	352	567	238(67.6)	304(53.6)	80.1(8.9)	66.9(12.0)
	ADC7	1462	0	4	0	0	0	1458	763	536	493(64.6)	281(52.4)	78.0(7.9)	72.8(7.7)
	ADDNEURO	644	0	2	0	0	0	642	186	256	105(56.5)	164(64.1)	76.4(6.6)	73.0(6.7)
	ADGC-ExomeChip	13969	55	197	12	32	0	13673	5250	7830	3136(59.7)	4585(58.6)	79.6(9.0)	73.0(9.1)
	ADNI	2134	63	69	21	30	5	1945	606	761	260(42.9)	330(43.4)	78.5(7.8)	74.1(7.4)
	ADNI3	327	4	12	1	4	0	306	228	24	142(62.3)	10(41.7)	72.5(6.1)	72.7(9.5)
	CIDR	3101	93	2780	70	0	0	158	1505	1530	1033(68.6)	986(64.4)	74.5(9.4)	75.5(9.6)
	GSK	1571	0	1	1	0	0	1569	773	798	497(64.3)	459(57.5)	73.4(7.9)	72.5(8.6)
	IIDP AA	1175	815	359	0	0	0	1	1001	172	663(66.2)	107(62.2)	83.3(5.3)	83.6(6.7)
	IIDP YOR	1264	1253	10	0	0	0	1	1145	104	732(63.9)	79(76.0)	82.6(5.9)	77.9(7.2)
	LATC	63	13	23	24	0	0	0	15	2	15(100.0)	2(100.0)	77.4(5.4)	78.0(0.0)
	MARS	708	423	275	1	0	0	1	463	79	392(84.7)	54(68.4)	79.6(6.1)	77.3(7.1)
	MAYO	2413	7	24	2	4	0	2335	1225	948	642(52.4)	546(57.6)	75.5(6.5)	74.0(6.0)
	MIRAGE	1502	1	28	2	0	0	1471	738	601	436(59.1)	366(60.9)	72.1(7.3)	68.8(8.6)
	MTC	542	5	29	12	0	0	496	202	272	130(64.4)	157(57.7)	71.7(8.9)	72.6(9.3)
	NIA-LOAD	5220	112	642	13	8	0	4445	2091	2351	1278(61.1)	1546(65.8)	70.6(12.6)	73.6(7.8)
	OHSU	647	3	2	0	1	0	635	379	201	205(54.1)	127(63.2)	85.7(7.5)	85.0(6.9)
	ROSMAP	2584	13	50	28	9	0	2451	1102	951	795(72.1)	690(72.6)	85.4(7.4)	84.1(6.5)
	TARCC	2718	75	218	821	7	2	1557	1124	908	788(70.1)	502(55.3)	70.1(9.8)	70.1(8.9)
	TGEN2	1599	0	9	1	0	1	1512	573	1005	255(44.5)	640(63.7)	80.8(8.7)	72.8(8.0)
	UM-VU-MSSM	2462	5	16	0	0	0	2441	1195	1206	724(60.6)	778(64.5)	74.1(8.2)	74.2(7.9)
	UPITT	2440	7	8	1	0	0	2355	896	1406	563(62.8)	908(64.6)	75.6(6.2)	73.2(6.6)
	WASHU	670	0	0	0	0	0	670	202	429	125(61.9)	239(55.7)	77.9(8.7)	74.0(9.6)
	WASHU2	235	10	1	0	0	0	224	116	68	65(56.0)	38(55.9)	73.7(8.6)	74.0(8.1)
	WHICAP	647	0	7	0	0	0	640	554	85	335(60.5)	60(70.6)	82.7(6.7)	84.1(7.5)

eTable 4. Missense variants on the *APOE* canonical transcript reported in gnomADv.3.1

Pos: position on chromosome 19 in build hg38, AF: alternate allele frequency, AC: allele count, AN: allele number, Hom: Homozygote count. Only the first ten missense variants in terms of allele frequency in gnomAD are reported here (AC > 20).

				HGVs		Overall gnomAD.v3.1				African/African-American				Latino/Admixed American				European (non-Finnish)			
Pos (hg38)	rsIDs	Ref	Alt	new	standard	AC	AN	AF	Hom	AC	AN	AF	Hom	AC	AN	AF	Hom	AC	AN	AF	Hom
44908684	rs429358	T	C	p.Cys130Arg	p.Cys112Arg	23875	151972	0.157101	1998	8917	41390	0.215439	950	1718	15280	0.112435	90	9371	67924	0.137963	676
44908822	rs7412	C	T	p.Arg176Cys	p.Arg158Cys	11838	152004	0.07788	546	4335	41402	0.104705	247	640	15262	0.041934	17	5401	67956	0.079478	224
44908783	rs769455	C	T	p.Arg163Cys	p.Arg145Cys	978	152126	0.006429	15	869	41444	0.020968	15	83	15274	0.005434	0	5	67996	7.35E-05	0
44907853	rs769452	T	C	p.Leu46Pro	p.Leu28Pro	293	152188	0.001925	0	11	41454	0.000265	0	14	15282	0.000916	0	168	68034	0.002469	0
44909057	rs199768005	T	A	p.Val254Glu	p.Val236Glu	72	152080	0.000473	0	16	41424	0.000386	0	0	15272	0	0	52	67984	0.000765	0
44907807	rs201672011	G	A	p.Glu31Lys	p.Glu13Lys	72	152186	0.000473	0	10	41458	0.000241	0	48	15282	0.003141	0	5	68024	7.35E-05	0
44908799	rs376170967	G	A	p.Arg168His	p.Arg150His	62	152122	0.000408	0	58	41452	0.001399	0	3	15262	0.000197	0	1	67994	1.47E-05	0
44909101	rs267606661	C	G	p.Arg269Gly	p.Arg251Gly	46	152200	0.000302	0	5	41450	0.000121	0	7	15280	0.000458	0	33	68022	0.000485	0
44908730	rs267606664	G	A	p.Gly145Asp	p.Gly127Asp	22	152152	0.000145	0	3	41458	7.24E-05	0	1	15284	6.54E-05	0	17	67992	0.00025	0
44908915	rs749750245	C	T	p.Arg207Cys	p.Arg189Cys	21	151884	0.000138	1	0	41406	0	0	21	15254	0.001377	1	0	67920	0	0

eTable 5. Demographic characteristics per cohort in ADSP discovery and ADGC internal replication after ancestry selection, quality control, and duplicates removal

Dx: diagnosis, AAD: age-at death, AAL: age-at-last-exam, AAE: age-at-exam (and Dx), AAO: age-at-onset.

				Sex	Age	Age Type			
	Cohort	Dx	N	Females (%)	μ(σ)	AAD μ(σ) [%]	AAL μ(σ) [%]	AAE μ(σ) [%]	AAO μ(σ) [%]
Discovery	ADSP WES	AD	6485	59.7%	75.5(8.8)	75.0(-)[0.0%]	79.7(11.7)[0.0%]	77.4(8.5)[5.9%]	75.4(8.8)[93.9%]
		CN	6592	60.2%	84.0(7.5)	88.5(6.0)[14.7%]	83.2(7.5)[85.0%]	-	-
	ADSP WGS	AD	5383	58.9%	74.2(10.6)	69.0(-)[0.0%]	86.2(4.1)[0.1%]	78.7(8.5)[15.6%]	73.4(10.8)[83.4%]
		CN	5342	65.3%	78.7(8.1)	85.1(7.3)[14.2%]	77.6(7.8)[81.0%]	-	-
Internal replication	ACT	AD	232	64.7%	81.0(5.6)	-	82.1(5.9)[21.1%]	-	80.8(5.5)[78.9%]
		CN	835	55.7%	78.7(5.7)	80.8(5.6)[60.7%]	75.4(4.2)[39.3%]	-	-
	ADC1	AD	548	51.3%	66.1(10.3)	73.3(6.5)[0.5%]	76.0(-)[0.2%]	77.1(6.9)[1.8%]	65.8(10.3)[97.4%]
		CN	205	64.4%	73.2(11.1)	82.4(8.0)[10.7%]	72.1(10.9)[89.3%]	-	-
	ADC2	AD	205	51.7%	72.0(6.7)	-	-	-	72.0(6.7)[100.0%]
		CN	60	70.0%	76.0(9.4)	89.5(7.6)[13.3%]	73.9(7.8)[86.7%]	-	-
	ADC3	AD	250	54.8%	68.1(11.0)	-	-	67.0(-)[0.4%]	68.1(11.0)[99.6%]
		CN	227	67.0%	73.6(7.6)	82.0(6.7)[9.7%]	72.7(7.1)[90.3%]	-	-
	ADC4	AD	123	56.9%	70.7(10.4)	-	94.0(-)[0.8%]	-	70.5(10.3)[99.2%]
		CN	219	61.6%	75.5(8.7)	83.5(9.4)[16.4%]	73.9(7.6)[83.6%]	-	-
	ADC5	AD	132	59.1%	73.6(8.6)	-	76.0(-)[0.8%]	-	73.6(8.6)[99.2%]
		CN	212	65.1%	75.7(7.8)	86.2(7.9)[12.3%]	74.3(6.6)[87.7%]	-	-
	ADC6	AD	205	56.6%	63.5(11.5)	-	90.0(-)[0.5%]	-	63.3(11.4)[99.5%]
		CN	146	67.1%	74.6(7.7)	81.3(9.9)[11.6%]	73.7(6.9)[88.4%]	-	-
	ADC7	AD	279	50.9%	70.6(7.3)	-	-	-	70.6(7.3)[100.0%]
		CN	376	67.3%	73.7(7.1)	82.6(10.0)[7.2%]	73.0(6.4)[92.8%]	-	-
	ADNI	AD	62	50.0%	75.5(7.3)	-	-	75.5(7.3)[100.0%]	-
		CN	104	9.6%	72.3(6.6)	-	72.3(6.6)[100.0%]	-	-
	CIDR	AD	731	64.7%	73.6(10.4)	-	-	-	73.6(10.4)[100.0%]
		CN	448	70.1%	67.9(9.0)	-	67.9(9.0)[100.0%]	-	-
	GSK	AD	788	57.7%	72.5(8.6)	-	85.2(6.4)[1.9%]	-	72.3(8.5)[98.1%]
		CN	770	64.3%	73.4(7.9)	-	73.4(7.9)[100.0%]	-	-
	NIA-LOAD	AD	976	67.0%	73.8(7.6)	-	78.8(8.6)[0.4%]	87.2(3.8)[0.4%]	73.8(7.5)[99.2%]
		CN	1342	62.2%	65.5(11.1)	82.0(8.4)[1.4%]	65.3(10.9)[98.6%]	-	-
	ROSMAP	AD	407	71.5%	83.9(6.5)	-	89.2(1.2)[2.0%]	83.8(6.5)[96.8%]	86.6(5.7)[1.2%]
		CN	638	75.1%	83.4(7.5)	85.8(7.3)[28.7%]	82.5(7.3)[71.3%]	-	-
	TGEN2	AD	835	64.0%	72.4(7.8)	71.7(7.7)[69.6%]	-	73.2(5.2)[0.5%]	75.9(7.6)[13.3%]
		CN	484	44.0%	80.0(8.6)	80.0(8.6)[78.5%]	80.3(9.1)[0.6%]	-	-
	UM-VU-MSSM	AD	858	65.0%	75.0(8.3)	75.1(8.6)[7.8%]	79.4(10.0)[3.1%]	-	74.9(8.2)[89.0%]
		CN	1125	61.6%	73.8(8.1)	80.2(11.6)[11.6%]	72.9(7.1)[88.1%]	-	-
	UPITT	AD	1137	64.7%	73.4(6.6)	-	78.2(7.9)[8.2%]	-	73.0(6.4)[91.2%]
		CN	868	63.4%	75.5(6.1)	-	75.5(6.1)[100.0%]	-	-

eTable 6. *APOE* missense variants rs769452-C (*APOE*[L28P]), rs199768005-A (*APOE*[V236E]), and rs267606661-G (*APOE*[R251G]) allelic breakdown by *APOE* main genotype

Based on the allelic distribution in the discovery sequencing data, we inferred that the rs769452 alternate allele (C) is in-phase with the *APOE*-ε4 allele, the rs199768005 alternate allele (A) is in-phase with the *APOE*-ε3 allele, and the rs267606661 alternate allele (C) is in-phase with the *APOE*-ε4 allele. The complete linkage disequilibrium between any of these variants and *APOE* genotype is rarely broken even in UK Biobank (200k WES individuals) and Rasmussen et al[4] (100k individuals). This is expected given the proximity of these rare variants with the two variants determining *APOE* genotype (417 bp is the maximum distance between any of these variants and rs429358 or rs7412). CN: cognitively normal, AD: Alzheimer's disease, N: number of individuals. X/Y/Z annotation, X refers to the number of homozygotes for the reference allele, Y to the number of heterozygotes, and Z to the number of homozygotes for the alternate allele. Cells with variant carriers are shaded and number of heterozygotes is highlighted in bold.

			APOE ε2/ε2		*APOE* ε2/ε3		*APOE* ε3/ε3		*APOE* ε2/ε4		*APOE* ε3/ε4		*APOE* ε4/ε4	
Sample	**SNP**	**N total**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**
ADSP Discovery	rs769452	23621/144/0	73/0/0	28/0/0	1467/0/0	580/0/0	7424/0/0	5310/0/0	191/**2**/0	256/**2**/0	2521/**35**/0	4841/**74**/0	191/**4**/0	739/**27**/0
	rs199768005	23414/20/0	72/0/0	26/0/0	1452/0/0	572/0/0	7361/**14**/0	5230/**3**/0	191/0/0	255/0/0	2499/**3**/0	4832/0/0	188/0/0	736/0/0
	rs267606661	28009/29/0	71/0/0	29/0/0	1450/0/0	567/0/0	7325/0/0	5169/0/0	191/**1**/0	253/0/0	2493/**13**/0	4827/**5**/0	188/**2**/0	730/**5**/0
ADGC Replication	rs199768005	13907/13/0	48/0/0	7/0/0	863/0/0	218/0/0	4076/**9**/0	1773/**1**/0	174/0/0	181/0/0	1551/**1**/0	2413/0/0	130/0/0	1096/0/0
	rs267606661	16218/35/0	53/0/0	9/0/0	902/0/0	290/0/0	4418/0/0	2266/0/0	193/**1**/0	215/0/0	1697/**13**/0	3045/**4**/0	156/**1**/0	1371/**12**/0

eTable 7. V236E and R251G association in primary and secondary analyses, nonstratified and *APOE* stratified

In stratified analysis, V236E and R251G are associated with a decreased AD risk in the discovery sample and R251G association significantly replicates in an independent sample. In non-stratified analyses, V236E and R251G are also associated with a decreased AD risk adjusted by *APOE* ε2 and ε4 dosages. The primary and secondary analyses presented below were run in the ADSP discovery and ADGC internal replication samples.
N: Number of individuals, MAC: Minor allele count, OR: odds ratio, β: beta parameter estimate of the age-at-onset analysis, HR: hazard ratio, 95% CI: 95% confidence interval, P: p-value.

		AD Case-Control Regression				AD Age-at-onset Regression				Competing Risk Regression			
	Sample	N	MAC	OR [95% CI]	P	N	MAC	β [95% CI]	P	N	MAC	HR [95% CI]	P
V236E in ε3ε3	*ADSP Discovery*	12604	17	0.31 [0.12; 0.82]	0.02	4671	3	13.27 [1.92; 24.62]	0.02	11803	17	0.36 [0.13; 0.98]	0.04
	ADGC Replication	5741	10	0.40 [0.1; 1.57]	0.19	1291	1	3.67 [-16.36; 23.69]	0.72	5149	10	0.58 [0.09; 3.86]	0.57
	Meta-analysis	**18345**	**27**	**0.34 [0.15; 0.75]**	**7.3E-03**	**5962**	**4**	**10.93 [1.06; 20.81]**	**0.03**	**16952**	**27**	**0.40 [0.17; 0.97]**	**0.04**
R251G in ε3ε4	*ADSP Discovery*	7335	18	0.17 [0.06; 0.48]	7.8E-04	4318	4	3.94 [-4.31; 12.2]	0.35	6731	17	0.27 [0.1; 0.69]	6.6E-03
	ADGC Replication	4630	16	0.19 [0.07; 0.54]	1.7E-03	2511	2	10.27 [-1.45; 21.99]	0.09	4040	13	0.26 [0.09; 0.78]	0.02
	Meta-analysis	**11965**	**34**	**0.18 [0.09; 0.37]**	**4.4E-06**	**6829**	**6**	**6.04 [-0.71; 12.79]**	**0.08**	**10771**	**30**	**0.26 [0.13; 0.54]**	**2.9E-04**
V236E in all APOE	*ADSP Discovery*	23427	20	0.23 [0.09; 0.56]	1.4E-03	10377	3	13.41 [2.99; 23.82]	0.01	21774	20	0.26 [0.09; 0.73]	0.01
	ADGC Replication	11652	10	0.35 [0.08; 1.51]	0.16	4372	1	3.41 [-13.41; 20.24]	0.69	10279	10	0.53 [0.08; 3.46]	0.5
	Meta-analysis	**35079**	**30**	**0.26 [0.12; 0.56]**	**5.4E-04**	**14749**	**4**	**10.64 [1.78; 19.49]**	**0.02**	**32053**	**30**	**0.30 [0.12; 0.76]**	**0.01**
R251G in all APOE	*ADSP Discovery*	23314	26	0.20 [0.08; 0.49]	3.7E-04	10304	9	2.68 [-3.58; 8.93]	0.4	21656	25	0.44 [0.24; 0.8]	7.8E-03
	ADGC Replication	14134	29	0.29 [0.12; 0.7]	5.8E-03	5906	12	-0.14 [-5.2; 4.92]	0.96	12633	25	0.87 [0.54; 1.41]	0.57
	Meta-analysis	**37448**	**55**	**0.24 [0.13; 0.45]**	**8.0E-06**	**16210**	**21**	**0.97 [-2.96; 4.91]**	**0.63**	**34289**	**50**	**0.67 [0.46; 0.97]**	**0.04**

eTable 8. Nonstratified sensitivity analyses at various European ancestry cutoffs

Three representative thresholds are shown: 15%, 45%, and 75% corresponding respectively to the threshold used in the main analysis (15%), a first generation admix individual (45%), and the cut off for EUR super ancestry assignment (75%). Overall, the results are similar for the three cutoffs and the main findings remain unchanged.

N: Number of individuals, MAC: Minor allele count, OR: odds ratio, β: beta, parameter estimate for age-at-onset analysis, HR: hazard ratio, 95% CI: 95% confidence interval.

			AD Case-Control Regression				AD Age-at-onset Regression				Competing Risk Regression			
Sample		EUR (≥%)	N	MAC	OR [95% CI]	P	N	MAC	β [95% CI]	P	N	MAC	HR [95% CI]	P
ADSP Discovery	*L28P*	15	23764	144	1.12[0.77; 1.62]	0.56	10570	96	1.59[-0.30; 3.48]	0.1	22093	137	1.13[0.91; 1.39]	0.26
		45	21038	139	1.10[0.75; 1.61]	0.62	9629	93	1.62[-0.31; 3.56]	0.1	19469	132	1.12[0.91; 1.38]	0.3
		75	18278	120	0.98[0.65; 1.49]	0.93	8747	80	1.16[-0.94; 3.26]	0.28	16943	113	1.06[0.85; 1.31]	0.62
	V236E	15	23427	20	0.23[0.09; 0.56]	1.4E-03	10377	3	13.41[2.99; 23.82]	0.01	21774	20	0.26[0.09; 0.73]	0.01
		45	20705	20	0.23[0.09; 0.58]	1.7E-03	9440	3	13.39[2.94; 23.84]	0.01	19154	20	0.26[0.09; 0.75]	0.01
		75	17961	20	0.24[0.10; 0.60]	2.3E-03	8571	3	13.10[2.61; 23.59]	0.01	16644	20	0.27[0.10; 0.78]	0.01
	R251G	15	23314	26	0.20[0.08; 0.49]	3.7E-04	10304	9	2.68[-3.58; 8.93]	0.40	21656	25	0.44[0.24; 0.8]	7.8E-03
		45	20609	24	0.19[0.07; 0.48]	5.0E-04	9372	9	2.81[-3.46; 9.09]	0.38	19053	23	0.47[0.26; 0.85]	0.01
		75	17885	23	0.17[0.06; 0.45]	3.4E-04	8515	9	2.89[-3.41; 9.20]	0.37	16563	22	0.46[0.26; 0.82]	8.8E-03
ADGCI Replication	*V236E*	15	11652	10	0.35[0.08; 1.51]	0.16	4372	1	3.41[-13.41; 20.24]	0.69	10279	10	0.53[0.08; 3.46]	0.5
		45	11652	10	0.35[0.08; 1.51]	0.16	4372	1	3.41[-13.41; 20.24]	0.69	10279	10	0.53[0.08; 3.46]	0.5
		75	11647	10	0.35[0.08; 1.51]	0.16	4369	1	3.42[-13.40; 20.25]	0.69	10275	10	0.53[0.08; 3.46]	0.5
	R251G	15	14134	29	0.29[0.12; 0.70]	5.8E-03	5906	12	-0.14[-5.2; 4.92]	0.96	12633	25	0.87[0.54; 1.41]	0.57
		45	13603	29	0.28[0.12; 0.68]	4.8E-03	5572	12	-0.17[-5.18; 4.84]	0.95	12109	25	0.86[0.53; 1.38]	0.53
		75	12954	28	0.30[0.12; 0.74]	9.0E-03	5174	12	-0.04[-5.02; 4.94]	0.99	11471	24	0.84[0.53; 1.35]	0.48
Meta-analysis	***V236E***	**15**	**35079**	**30**	**0.26[0.12; 0.56]**	**5.4E-04**	**14749**	**4**	**10.64[1.78; 19.49]**	**0.02**	**32053**	**30**	**0.30[0.12; 0.76]**	**0.01**
		45	**32357**	**30**	**0.26[0.12; 0.56]**	**6.8E-04**	**13812**	**4**	**10.61[1.74; 19.49]**	**0.02**	**29433**	**30**	**0.31[0.12; 0.77]**	**0.01**
		75	**29608**	**30**	**0.27[0.12; 0.58]**	**8.6E-04**	**12940**	**4**	**10.39[1.49; 19.29]**	**0.02**	**26919**	**30**	**0.32[0.13; 0.80]**	**0.01**
	R251G	**15**	**37448**	**55**	**0.24[0.13; 0.45]**	**8.0E-06**	**16210**	**21**	**0.97[-2.96; 4.91]**	**0.63**	**34289**	**50**	**0.67[0.46; 0.97]**	**0.04**
		45	**34212**	**53**	**0.23[0.12; 0.44]**	**8.9E-06**	**14944**	**21**	**0.99[-2.92; 4.91]**	**0.62**	**31162**	**48**	**0.68[0.47; 0.98]**	**0.04**
		75	**30839**	**51**	**0.23[0.12; 0.45]**	**1.3E-05**	**13689**	**21**	**1.09[-2.82; 5.00]**	**0.59**	**28034**	**46**	**0.66[0.46; 0.96]**	**0.03**

eTable 9. Sensitivity analysis, including all dementia in the CCHS and CGPS data set, slightly strengthens the V236E and R251G associations with decreased AD risk

Changes compared with Table 2 are highlighted in grey.

		AD Case-Control Regression Non-stratified				AD Case-Control Regression *APOE*-Stratified			
	Sample	N	MAC	OR [95% CI]	P	N	MAC	OR [95% CI]	P
V236E (all APOE (left) and ε3/ε3 only (right))	*ADSP*	23,427	20	0.23 [0.09; 0.56]	1.4E-03	12,604	17	0.31 [0.12; 0.82]	0.020
	ADGC imputed	11,652	10	0.35 [0.08; 1.51]	0.16	5,741	10	0.40 [0.1; 1.57]	0.19
	EADB-core	41,033	27.17	0.59 [0.19; 1.80]	0.34	21,650	21.28	0.53 [0.15; 1.92]	0.30
	GERAD	9,996	17.72	0.37 [0.07; 1.90]	0.18	5,219	9.43	0.77 [0.10; 6.06]	0.78
	DemGene	7,598	58.68	0.21 [0.05; 0.90]	8.5E-03	3,773	35.88	0.56 [0.13; 2.46]	0.40
	CCHS & CGPS	105,625	240	0.25 [0.06; 1.02]	0.053	58,732	191	0.09 [0.01; 1.54]	0.097
	UKB proxy-AD	185,741	277	0.45 [0.23; 0.89]	0.021	109,120	219	0.47 [0.21; 1.04]	0.063
	Meta-analysis	**385,072**	**650.57**	**0.35 [0.23; 0.53]**	**5.7E-07**	**216,839**	**503.59**	**0.43 [0.27; 0.68]**	**3.3E-04**
R251G (all APOE (left) and ε3/ε4 only (right))	*ADSP*	23,314	26	0.20 [0.08; 0.49]	3.7E-04	7,335	18	0.17 [0.06; 0.48]	7.8E-04
	ADGC imputed	14,134	29	0.29 [0.12; 0.70]	5.8E-03	4,630	16	0.19 [0.07; 0.54]	1.7E-03
	EADB-core	41,033	59.16	0.51 [0.26; 0.99]	0.049	12,393	40.27	0.34 [0.15; 0.76]	7.8E-03
	GR@ACE	15,894	21.27	0.35 [0.12; 1.01]	0.049	4,049	17.81	0.22 [0.06; 0.77]	0.011
	EADI	8,728	19.21	0.68 [0.22; 2.09]	0.49	1,994	13.32	1.14 [0.32; 4.04]	0.84
	GERAD	9,996	23.17	0.50 [0.17; 1.47]	0.18	2,933	16.82	0.57 [0.18; 1.88]	0.34
	CCHS & CGPS	105,628	106	0.42 [0.13; 1.37]	0.15	26,913	76	0.41 [0.10; 1.74]	0.23
	UKB proxy-AD	185,735	335	0.57 [0.34; 0.98]	0.041	43,820	262	0.67 [0.36; 1.22]	0.19
	Meta-analysis	**404,462**	**618.81**	**0.44 [0.33; 0.59]**	**3.5E-08**	**104,067**	**460.22**	**0.41 [0.29; 0.58]**	**2.7E-07**

eTable 10. Sensitivity analysis, excluding the UK Biobank proxy-AD phenotype from the meta-analysis, results in slight worsening of the *P* values of the V236E and R251G associations with decreased AD risk

Changes compared with Table 2 are highlighted in grey.

		AD Case-Control Regression Non-stratified				AD Case-Control Regression *APOE*-Stratified			
	Sample	N	MAC	OR [95% CI]	P	N	MAC	OR [95% CI]	P
V236E (all APOE (left) and ε3/ε3 only (right))	*ADSP*	23,427	20	0.23 [0.09; 0.56]	1.4E-03	12,604	17	0.31 [0.12; 0.82]	0.020
	ADGC imputed	11,652	10	0.35 [0.08; 1.51]	0.16	5,741	10	0.40 [0.1; 1.57]	0.19
	EADB-core	41,033	27.17	0.59 [0.19; 1.80]	0.34	21,650	21.28	0.53 [0.15; 1.92]	0.30
	GERAD	9,996	17.72	0.37 [0.07; 1.90]	0.18	5,219	9.43	0.77 [0.10; 6.06]	0.78
	DemGene	7,598	58.68	0.21 [0.05; 0.90]	8.5E-03	3,773	35.88	0.56 [0.13; 2.46]	0.40
	CCHS & CGPS	104,084	240	0.45 [0.11; 1.84]	0.23	57,955	191	0.18 [0.01; 2.97]	0.27
	Meta-analysis	**197,790**	**373.57**	**0.33 [0.20; 0.55]**	**2.4E-05**	**106,942**	**284.59**	**0.41 [0.23; 0.74]**	**2.8E-03**
R251G (all APOE (left) and ε3/ε4 only (right))	*ADSP*	23,314	26	0.20 [0.08; 0.49]	3.7E-04	7,335	18	0.17 [0.06; 0.48]	7.8E-04
	ADGC imputed	14,134	29	0.29 [0.12; 0.70]	5.8E-03	4,630	16	0.19 [0.07; 0.54]	1.7E-03
	EADB-core	41,033	59.16	0.51 [0.26; 0.99]	0.049	12,393	40.27	0.34 [0.15; 0.76]	7.8E-03
	GR@ACE	15,894	21.27	0.35 [0.12; 1.01]	0.049	4,049	17.81	0.22 [0.06; 0.77]	0.011
	EADI	8,728	19.21	0.68 [0.22; 2.09]	0.49	1,994	13.32	1.14 [0.32; 4.04]	0.84
	GERAD	9,996	23.17	0.50 [0.17; 1.47]	0.18	2,933	16.82	0.57 [0.18; 1.88]	0.34
	CCHS & CGPS	104,087	105	0.41 [0.10; 2.72]	0.23	26,437	75	0.33 [0.05; 2.43]	0.28
	Meta-analysis	**217,186**	**512.81**	**0.39 [0.27; 0.56]**	**1.2E-07**	**77,154**	**197.22**	**0.32 [0.21; 0.49]**	**1.1E-07**

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