Supplementary Online Content

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eReferences.

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

eMethods.

Phenotype Ascertainment

Cohorts and Phenotype Ascertainment

In the current study, we used twenty-two case/control, family-based, and longitudinal, late-onset Alzheimer's Disease (AD) cohorts available through public repositories (**Table1**)[1–15]. We further included three independent cohorts from the Knight Alzheimer's Disease Research Center at Washington University in St. Louis, the University of Washington, Seattle, and the University of Pennsylvania. These cohorts provided cross-sectional Aβ CSF measures and are here referred to, jointly, as the CRU sample[16]. Participants or their caregivers provided consents in the original studies. Details on phenotype ascertainment are described elsewhere[12,16]. Briefly, all individuals with a diagnosis of AD met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable or possible late onset AD[17], or met Diagnosis and Statistical Manual of Mental Disorders IV-V (DSMIV-V) criteria[18–20], or had a clinical dementia rating (CDR® Dementia Staging Instrument[21]) > 0.5. Some cohorts verified AD diagnoses by means of neuropathology, using Braak staging[22], CERAD scoring[23], or National Institute on Aging Reagan (NIA-Reagan) 1997 criteria[24]. Cognitively normal subjects (controls) did not have AD according to the above clinical criteria for AD, did not have a diagnosis of MCI, and had a CDR of 0 and/or Mini-Mental State Examination (MMSE[25]) > 25. In the MIRAGE cohort, control status was evaluated through a Modified Telephone Interview of Cognitive Status score ≥ 86 (a telephone version of the MMSE)[26]. For the three independent cohorts making up the CRU sample[16], subjects were evaluated as cognitively normal if their CDR was equal to 0.

Further, the National Alzheimer's Coordinating Center (NACC), Rush University Religious Orders Study/Memory and Aging Project (ROSMAP), and Alzheimer's Disease Neuroimaging Initiative (ADNI), are longitudinal cohorts that evaluate clinical status (control, mild cognitive impairment (MCI), demented) and presumed disease etiology at repeated examinations. Additionally, deceased subjects are assessed for neuropathology. Where possible, in NACC, a final diagnoses of MCI or possible/probable/definite AD was obtained using NIA Alzheimer's Association (NIA-AA) 2011 criteria[27,28]. In all three cohorts, AD diagnoses were verified by neuropathology as middle or high AD likelihood following NIA-Reagan 1997 criteria (moderate to frequent neuritic plaques and Braak stage III-VI)[24]. In concordance with the category "possible AD dementia with evidence of the AD pathophysiological process" from the NIA-AA 2011

criteria[27], we attributed possible AD diagnoses to subjects who met clinical criteria for non-AD dementia but also met AD neuropathological criteria. In concordance with the NIA-AA 2011/2012 framework[28,29], we also evaluated neuropathology in MCI subjects to verify presumed AD etiology. Controls were not re-evaluated based on neuropathology data. Subjects that reverted from dementia to control status during longitudinal follow-up were excluded. Additional cohort-specific details are listed below.

NACC

Genotyping waves 1 through 7 from the Alzheimer's Disease Centers (ADC1-7) include subjects ascertained and evaluated by the clinical and neuropathological cores of 32 NIA-funded ADCs. NACC coordinates the collection of these phenotypes, implements diagnoses (cognitively normal, cognitively impaired but not MCI, MCI, demented; and presumed disease etiology) and then provides all data to researchers under the form of the Minimum Data Set (MDS), Uniform Data Set (UDS)[30–32], and Neuropathology data set (NP)[33]. The MDS represents an older subset of the NACC data and only contains cross-sectional data, while the more recent UDS provides longitudinal phenotypes and covariates. Since 2015, the UDS was updated to incorporate the NIA-AA 2011 criteria for MCI and AD[11,28]. In the current study, we used the UDS and NP for which data was collected between September 2005 and June 2019. The ADC1-7 data sets covered 7,627 subjects in the UDS and 2,629 subjects in the MDS.

Subjects that had a diagnosis of Down syndrome, central nervous system neoplasm, bipolar disorder, schizophrenia, alcohol-induced dementia, or substance-abuse-induced dementia, were excluded. Subjects carrying mutations of dominantly inherited AD or frontotemporal lobar degeneration (FTLD) were also excluded. Subjects with a final diagnosis of MCI or dementia, for which the etiology was unknown or not due to AD, were excluded. Subjects with a final diagnosis of "cognitively impaired but not MCI" were excluded, unless they had a baseline diagnosis of cognitively normal. In that case, these subjects were retained as controls with their age frozen at their latest diagnosis of cognitively normal.

ROSMAP

In ROSMAP, subjects were diagnosed at each visit: as possible/probable AD according to NINCDS-ADRDA criteria[17]; as MCI when judged to have cognitive impairment but not meeting dementia criteria according to the clinician; or as control when there was no cognitive impairment or the subject did not meet dementia criteria[34,35]. At time of death, a final clinical diagnosis was made by an expert neurologist, followed by case conference consensus review (blinded to postmortem data)[36].

ADNI

In ADNI, subjects were diagnosed at regular visits: as possible/probable AD according to NINCDS-ADRDA criteria[17]; as MCI according to Petersen/Winblad criteria; or as control when not demented, not MCI, CDR = 0, and MMSE > 28. Since 2018, ADNI has also released the first set of neuropathology assessments that follow the NACC NP framework. After AD neuropathology verification, remaining demented or MCI subjects with a presumed non-AD etiology were excluded.

Genetic Data Quality Control and Processing

Genetic Data

Genetic data were available across twenty-two cohorts for a total of 35,760 subjects (**Table1**) and were processed using Plink v1.9. Genotypes were available from commercially available high-density single-nucleotide polymorphism (SNP) genotyping microarrays (Illumina or Affymetrix). The numbers of remaining samples after each quality control (QC) or processing step are listed in **eTable2**. For each cohort, subjects with autosome missingness (≥ 5%) and sex problems (discordance between genetic sex and demographic sex, or deviation of expected X-chromosome homozygosity/heterozygosity) were excluded.

Ancestry Determination

Individual ancestries were determined using SNPweights v.2.12 with populations from the 1000 Genomes Consortium as a reference[37,38]. By applying an ancestry percentage cut-off ≥ 75%, the samples were stratified into the five super populations, South-Asians (SAS), East-Asians (EAS), Americans (AMR), Africans (AFR) and Europeans (EUR) (**eFigure1**). Subjects with a genetic ancestry that differed from their ethnicity, as provided in cohort demographics, were excluded. Most remaining samples were of European ancestry. To obtain the largest and most homogeneous sample, the ancestry of subjects belonging to the European population was further determined according to three major ethnicities, that is, Northwestern European (NWE), Southeastern European (SEE), and Ashkenazi Jewish (AJE), using reference populations available from SNPweights v.2.1.2[37]. European subjects were stratified into the above-mentioned ethnicities by applying an ancestry percentage cut-off ≥ 50% (**eFigure1**). Most remaining samples were of NWE ancestry.

Relationship Determination

Across all cohorts (and ethnicities) the relatedness of subjects (after QC indicated above) was evaluated through identity-by-descent (IBD) analysis (using directly genotyped SNPs that were shared across all

genetic datasets with a call rate > 99% and minor allele frequency (MAF) > 1%). Duplicates (IBD > 0.95) with discordant diagnoses were excluded. For the remaining duplicates, only a single subject was retained in the cohort that had the highest detail of ascertainment. In case of related subjects (IBD > 0.25), only a single subject was retained per relatedness cluster, prioritizing first younger cases followed by older controls. For statistical analyses, the removal of related subjects was evaluated separately for each respective analysis. For mega-analyses, which combine all cohorts into a single group, related subjects were excluded across all cohorts, while for meta-analyses this was only performed within cohorts.

Principal Component Analysis

To identify population substructure, principal component analyses (PCA) were performed on directly genotyped pruned SNPs (R^2 < 0.1) of unrelated subjects with NWE ancestry (**eFigure2**). PCAs were set to derive ten principal components (PCs) using Plink v.1.9. For statistical analyses, PCAs were performed across all cohorts, to obtain PCs for mega-analyses (SNPs with call rate > 99%, MAF > 1%, and no deviation from Hardy-Weinberg Equilibrium (HWE) in controls (P<10-5)), or per cohort, to obtain PCs for meta-analyses (SNPs with call rate > 99%, MAF > 1%, and no deviation from HWE in controls (P<10-5)). PCs were then projected to related subjects.

Imputation Processing

Only subjects from European ancestry were processed for the purpose of imputation. For each cohort, SNPs were removed prior to imputation for any of the following reasons: a call rate ≤95%, MAF ≤1%, deviating more than 10% from the MAF reported in the 1000 Genomes European population, differential missingness between cases and controls (P<5x10-5), deviation from HWE in controls (P<5x10-5), tri-allelic genotypes, allele mismatches compared to the 1000Genomes reference sequence, and A/T or C/G polymorphisms. All the genetic datasets per cohort were phased and imputed using the Michigan Imputation Server[39], considering the Haplotype Reference Consortium r1.1. 2016 European panel[40].

APOE and KL-VS genotypes

KL-VS status was available from rs9536314, directly genotyped or imputed with a minimal imputation score of 0.998. *APOE* status was available from cohort demographics or imputed with a minimal imputation R^2 quality score of 0.7 for both rs7412 and rs429358.

CRU Sample

Genotypes in the CRU sample were only available as pre-imputed data, using the HapMAP release 22 (CEU) as a reference, rather than raw SNP data[16]. For this reason, these data could not be processed in the same unified way as the other cohorts investigated in this study. As a result, the CRU sample was processed separately, using the same procedures as listed above with the exception that the genotype status (genotyped/imputed) of any given SNP was not known.

Statistical Analyses – Additional Model Criteria

Meta-Analysis Heterogeneity testing

Cohort heterogeneity was evaluated using Cochran's Q test and if significant ($P<0.05$), meta-analyses were performed using random effects.

Case/Control Analysis

Case/control meta-analyses, for each respective *APOE*4- and age-stratum, included only cohorts with a minimum of n=50 subjects, and required the presence of both cases and controls. In the 80+ age range, the ADC1-7 cohorts were combined into a single "NACC" cohort to avoid small individual cohort sample sizes. For cases that only had age-at-death (AAD) available, the final ages used for regression analysis were subtracted by 10 years in order to approximate age-at-onset (AAO). This reflects expected mean delays between AAO and AAD for AD patients[41], and is consistent with the derived age covariate for AD cohorts provided by the Alzheimer's Disease Genetics Consortium (ADGC) on NIAGADS[42]. Where available in the ADNI and ROSMAP cohorts (which provide conversion information but not AAO) the age-at-examination (AAE) variable followed a prioritization of age-at-MCI-diagnosis > age-at-dementia-diagnosis. This was done to most closely approximate AAO.

Conversion Risk Analysis

Competing risk regression (CRR) is a type of time-to-event analysis that estimates the marginal probability of an event occurring in the presence of other competing events[43,44]. This is relevant in late-onset AD cohorts where subjects are generally in their last quartile of life and death (competing risk) may occur prior to conversion events, which causes bias in risk estimates. For CRR models, subjects were required to have an age-at-baseline-visit of at least 60 years and no age-at-onset lower than 60 years. Conversions were defined as the first diagnosis of MCI or AD (first model), or AD (second model), and included subjects with a final diagnosis of AD. Non-converting or deceased controls (first model), or controls and MCI (second model), were censored at their last available age. Time-to-event or -censoring

was standardized to the minimum required baseline age of 60 years (e.g. a conversion at age 85 provided a time-to-event value of 25 years). Model restrictions on minimal study time considered actual follow-up time to the last examination. Further delay between last examination and death did not add to follow-up time. For CRR meta-analyses, the ADC1-7 cohorts were combined into a single "NACC" cohort to avoid small individual cohort sample sizes.

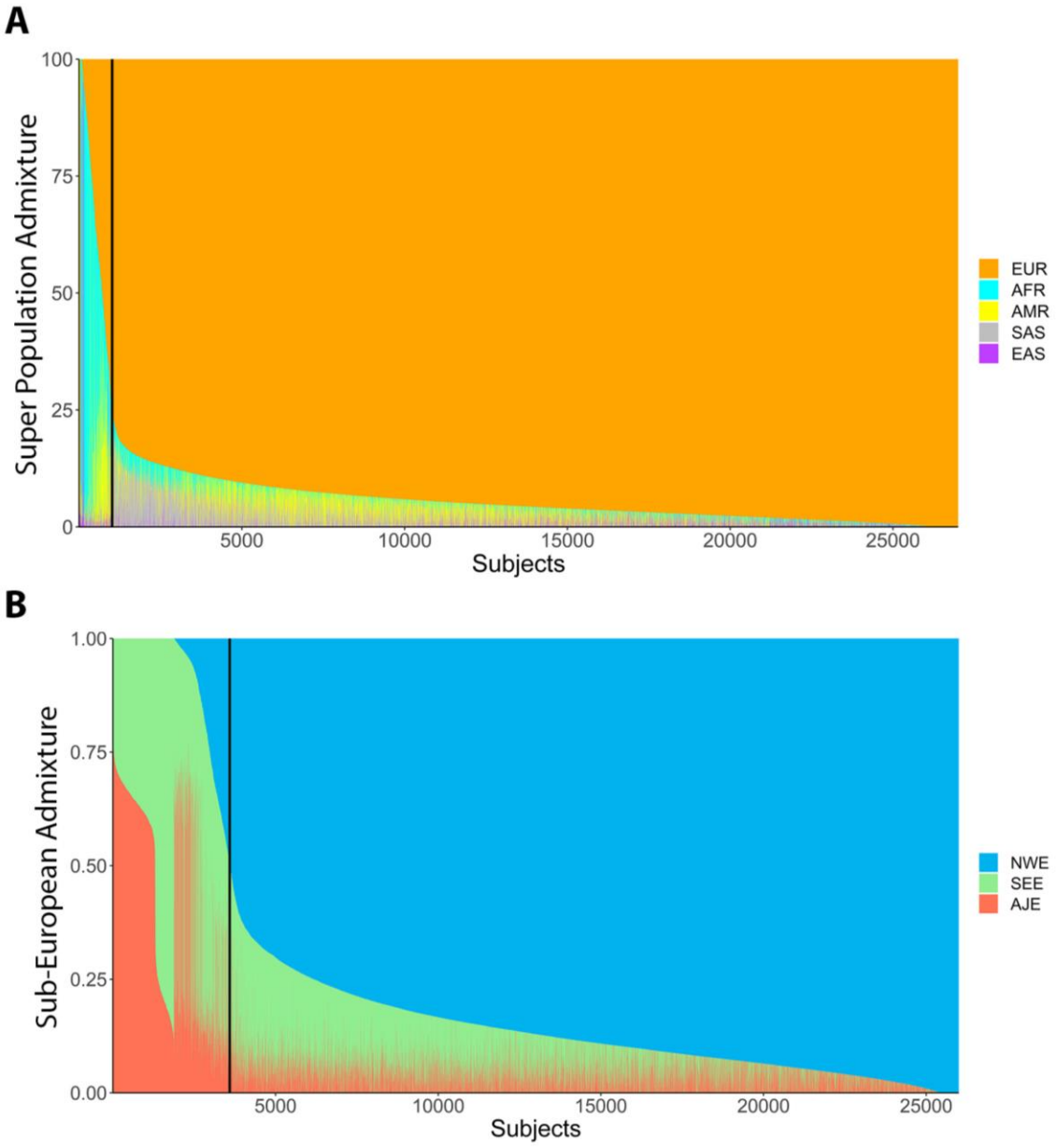
Aβ association Analysis

For associations with Aβ CSF in the CRU sample, a mega-analysis was performed across the participating cohorts. Cohort was included as a covariate in the mega-analysis, which was preferred over meta-analysis to avoid small individual cohort sample sizes. Only two out of three cohorts met inclusion criteria.

Association of APOE4 with Alzheimer's Disease Risk and Age-at-Onset

We evaluated whether relative risk for AD due to *APOE*4 was different between the age ranges 60-80 and 80+ years. This was performed in a case/control logistic regression mega-analysis, co-varying for *APOE*4, age-range, and age-range***APOE*4, while adjusting for sex, the first three genetic PCs, and cohort. We also evaluated the association of *APOE*4 with age-at-onset in cases. This was performed in the full 60+ years case group by means of a multiple linear regression mega-analysis of log-transformed ages-at-onset, covarying for *APOE*4, while adjusting for sex, the first three genetic PCs, and cohort.

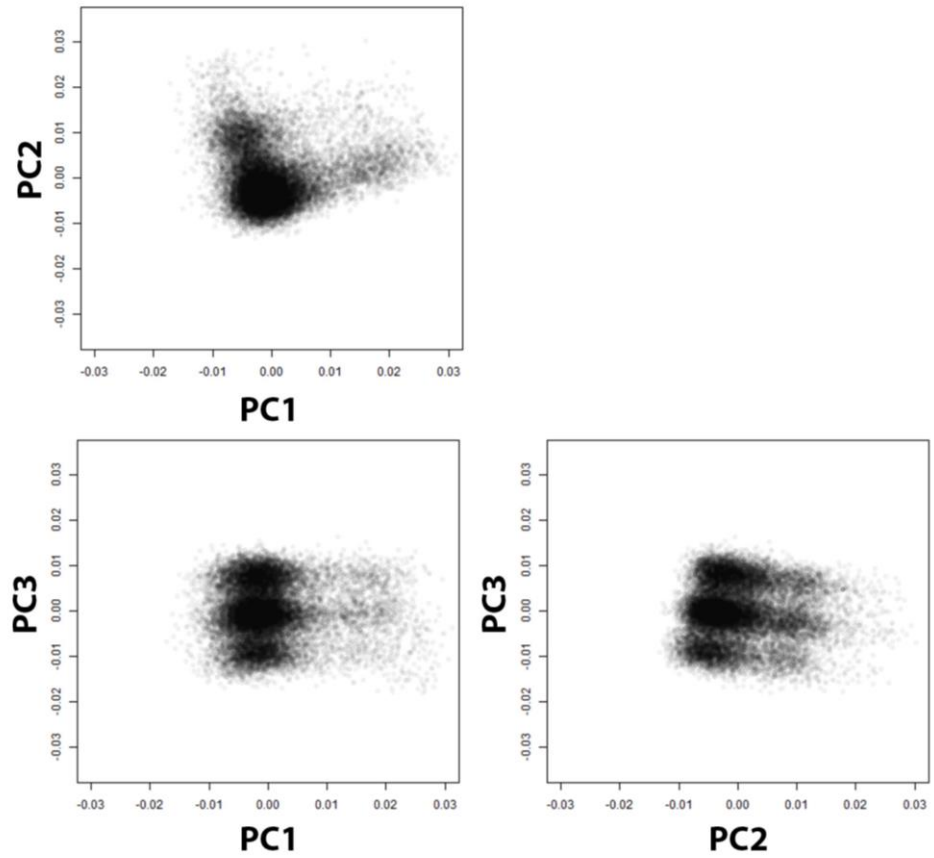
eFigures



eFigure 1. Admixture plots for A) the five major super populations and B) three major sub-European populations across all 22 case-control cohorts.

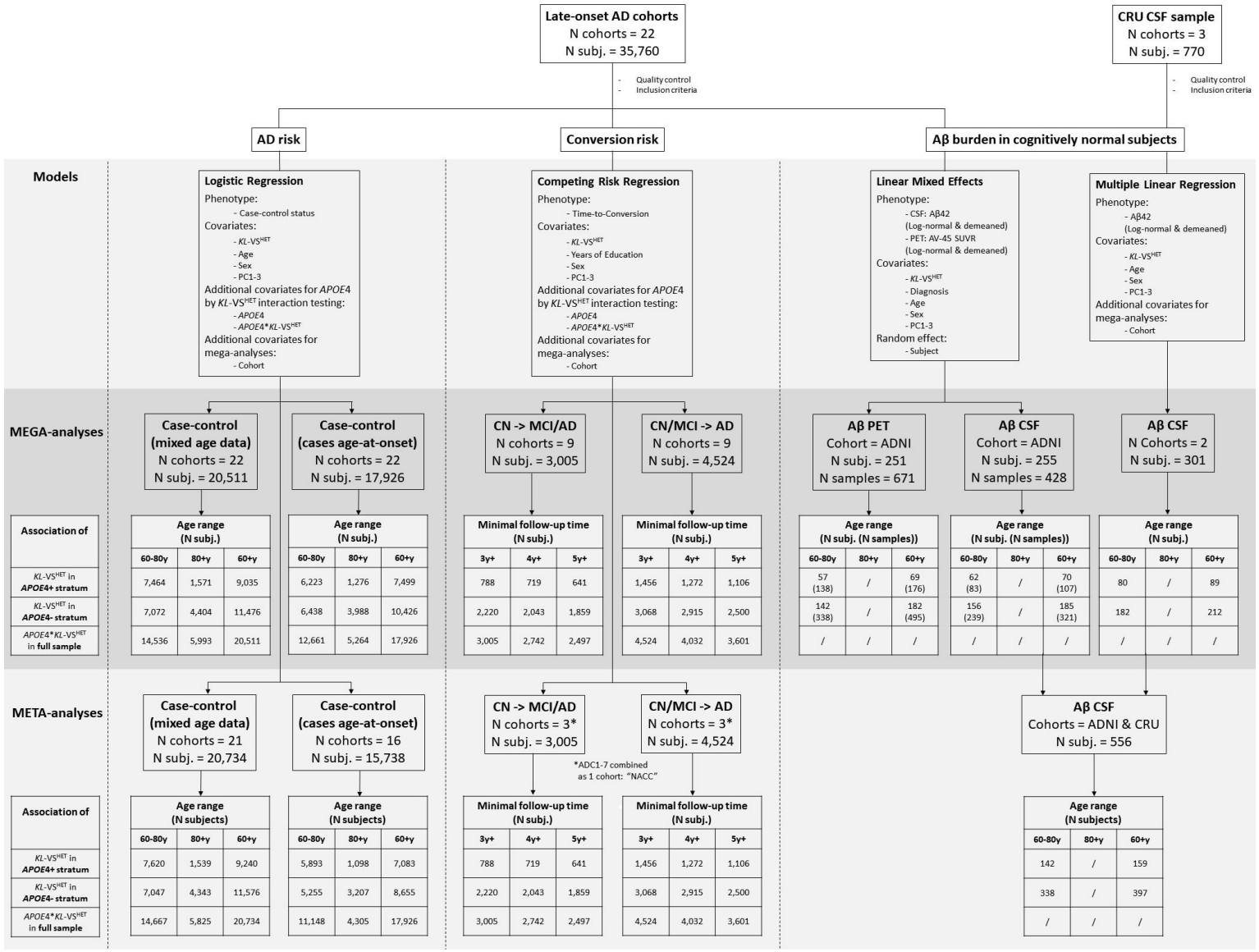
Black vertical lines mark the cut-off for EUR ancestry [75%] in (A) and NWE ancestry [50%] in (B).

Abbreviations: EUR, European; AFR, African; AMR; American; SAS, Southern Asian; EAS; Eastern Asian; NWE; Northwestern European; SEE; Southeastern European; AJE, Ashkenazi Jewish.

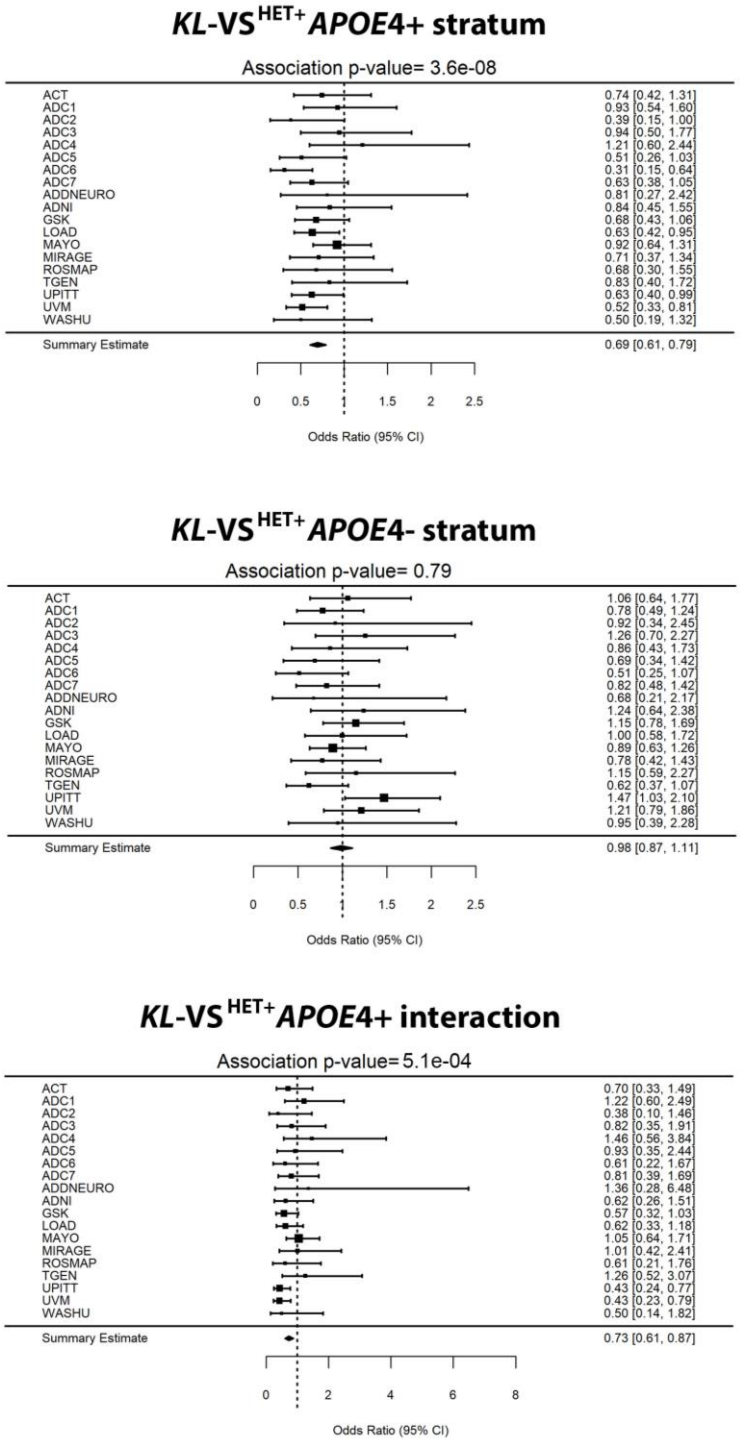


eFigure 2. First three principal components of the genetic population structure in Northwestern European subjects across all 22 case-control cohorts.

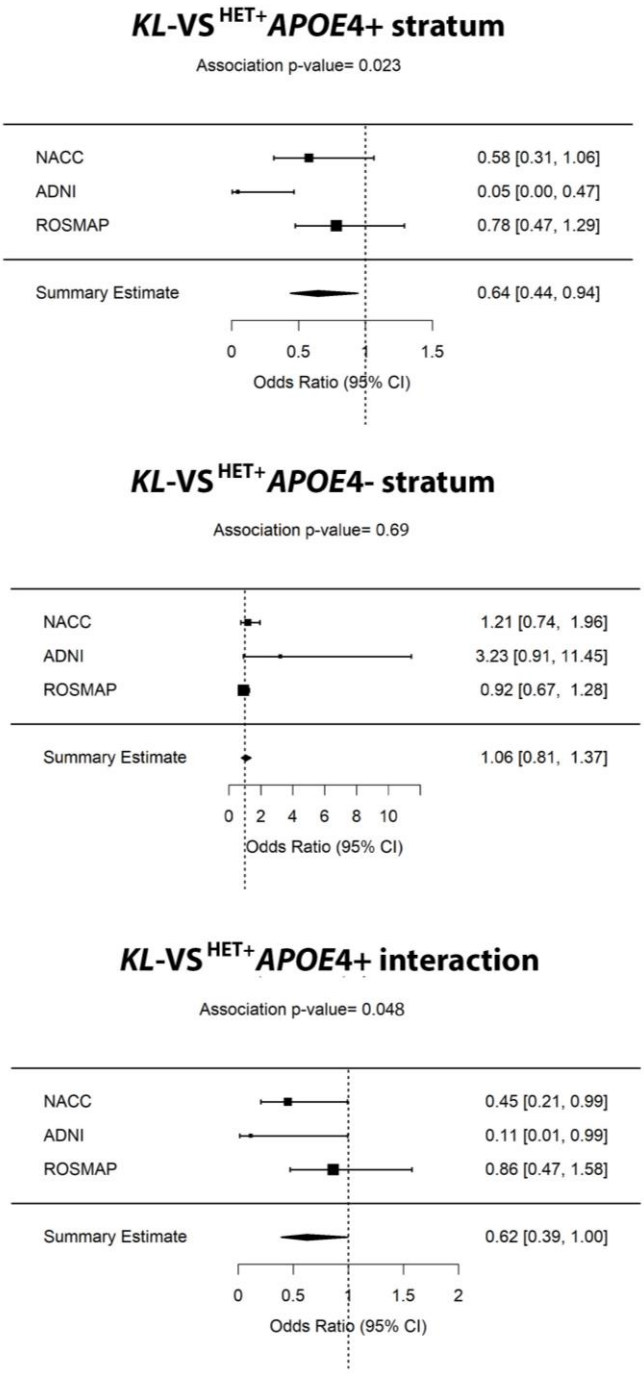
Abbreviations: PC, principal component.



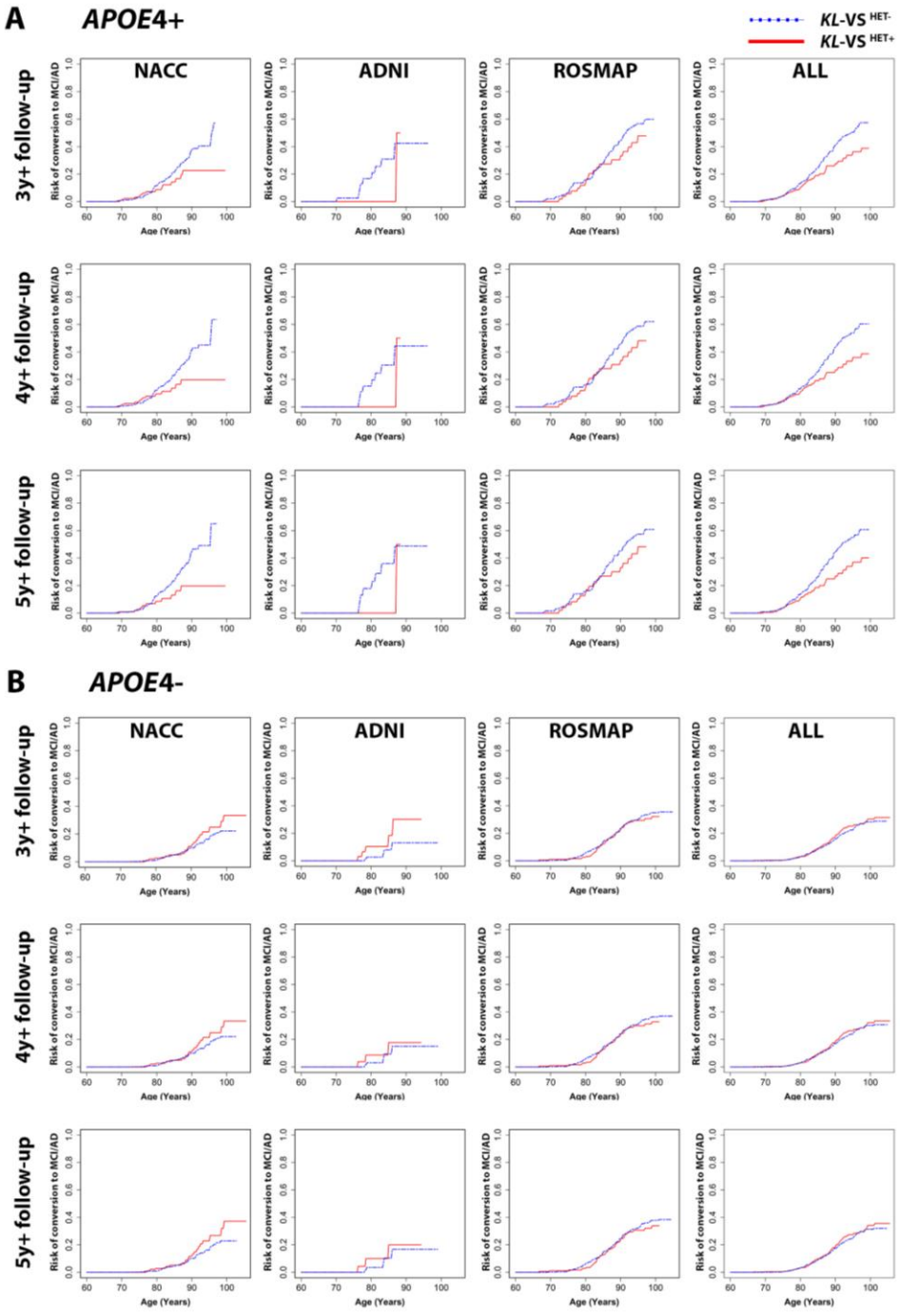
eFigure 3. Schematic overview of datasets and performed analyses.



eFigure 4. Forest plots for the association of *KL*-VS^{HET+} with Alzheimer's disease case-control status in 60-80 year old subjects. Separate forest plots are shown for the *APOE*4+ stratum (top), the *APOE*4- stratum (middle), and the formal interaction between *APOE*4+ and *KL*-VS^{HET+} (bottom).



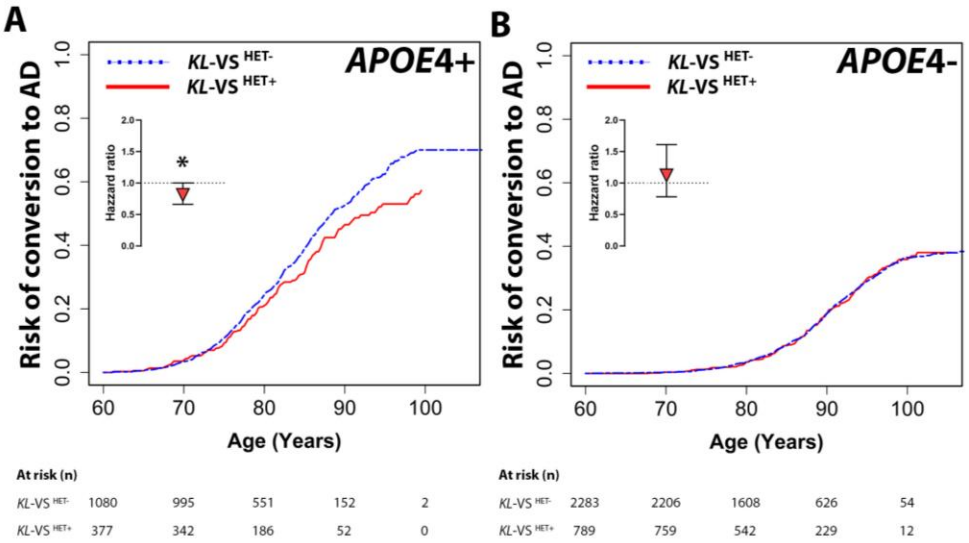
eFigure 5. Forest plots for the association of *KL*-VS^{HET+} with risk of conversion to mild cognitive impairment or Alzheimer's disease in subjects with a minimum of three years follow-up time. Separate forest plots are shown for the *APOE*4+ stratum (top), the *APOE*4- stratum (middle), and the formal interaction between *APOE*4+ and *KL*-VS^{HET+} (bottom).



eFigure 6. Cohort-specific risk of conversion to mild cognitive impairment or Alzheimer's disease by *KL*-VS heterozygosity status in A) *APOE*4+ and B) *APOE*4- subjects.

Each row indicates the minimum study follow-up time for subjects included in the respective analyses.

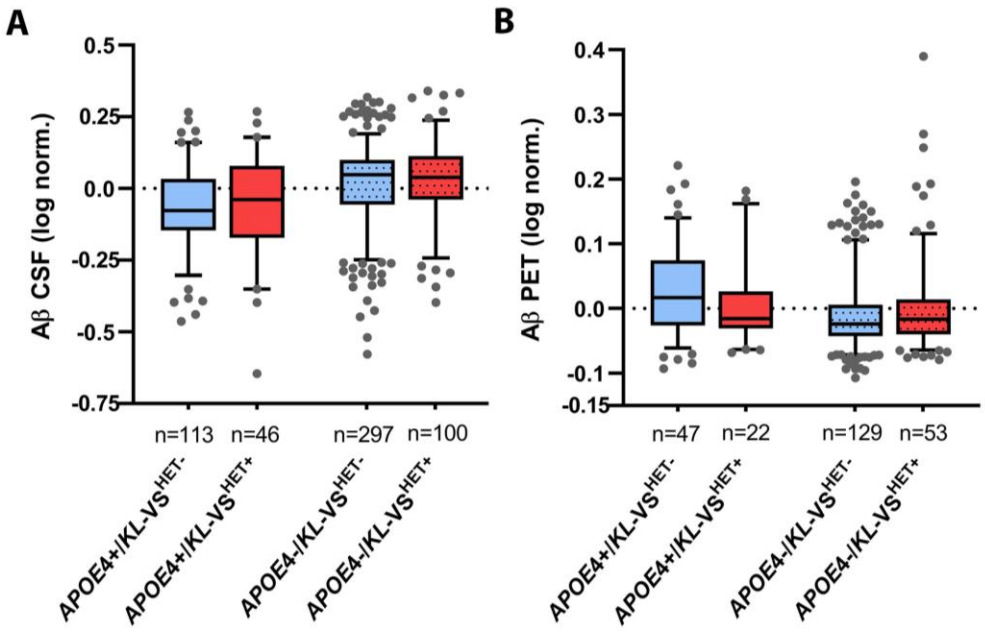
Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's Disease; HET+, heterozygous carriers; HET-, non-heterozygous carriers; y, years.



eFigure 7. Risk of conversion to Alzheimer's disease by *KL*-VS heterozygosity status in A) *APOE*4+ and B) *APOE*4- subjects.

Graphs shows risk of conversion from either a control or MCI baseline diagnosis to AD. Insets show hazard ratio (red triangle) and 95% confidence interval (error bars). Asterisk (*) marks significant effect of *KL*-VS^{HET+} ($P<0.05$).

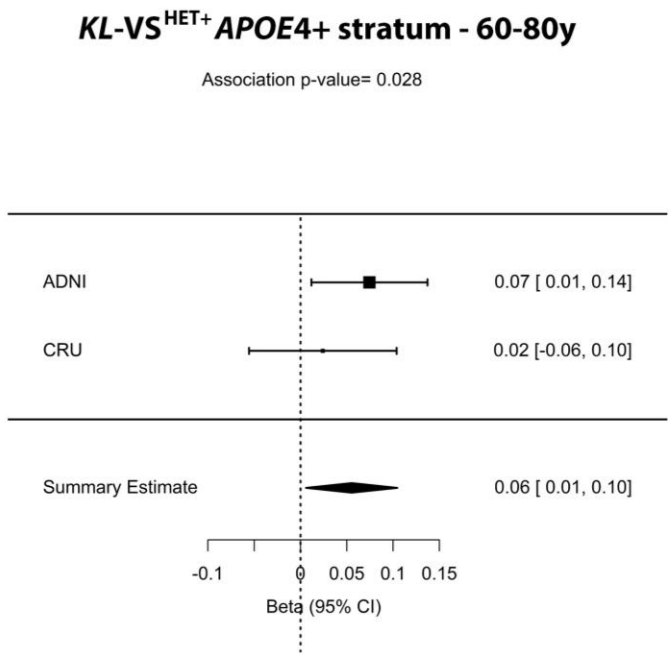
Abbreviations: AD, Alzheimer's Disease; HR, hazard ratio; HET+, heterozygous carriers; HET-, non-heterozygous carriers.

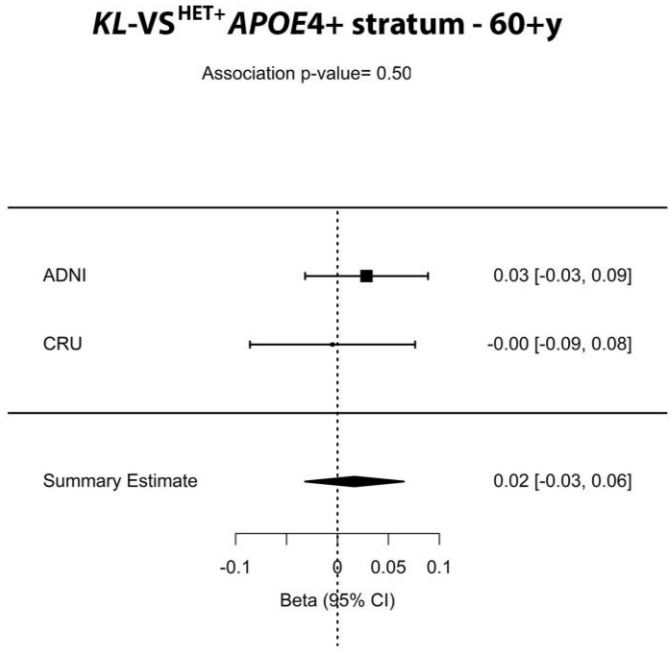


eFigure 8. Association of *KL*-VS heterozygosity status with amyloid beta levels in 60+ years old controls stratified by *APOE*4 status, as measured from A) CSF samples and B) PET imaging.

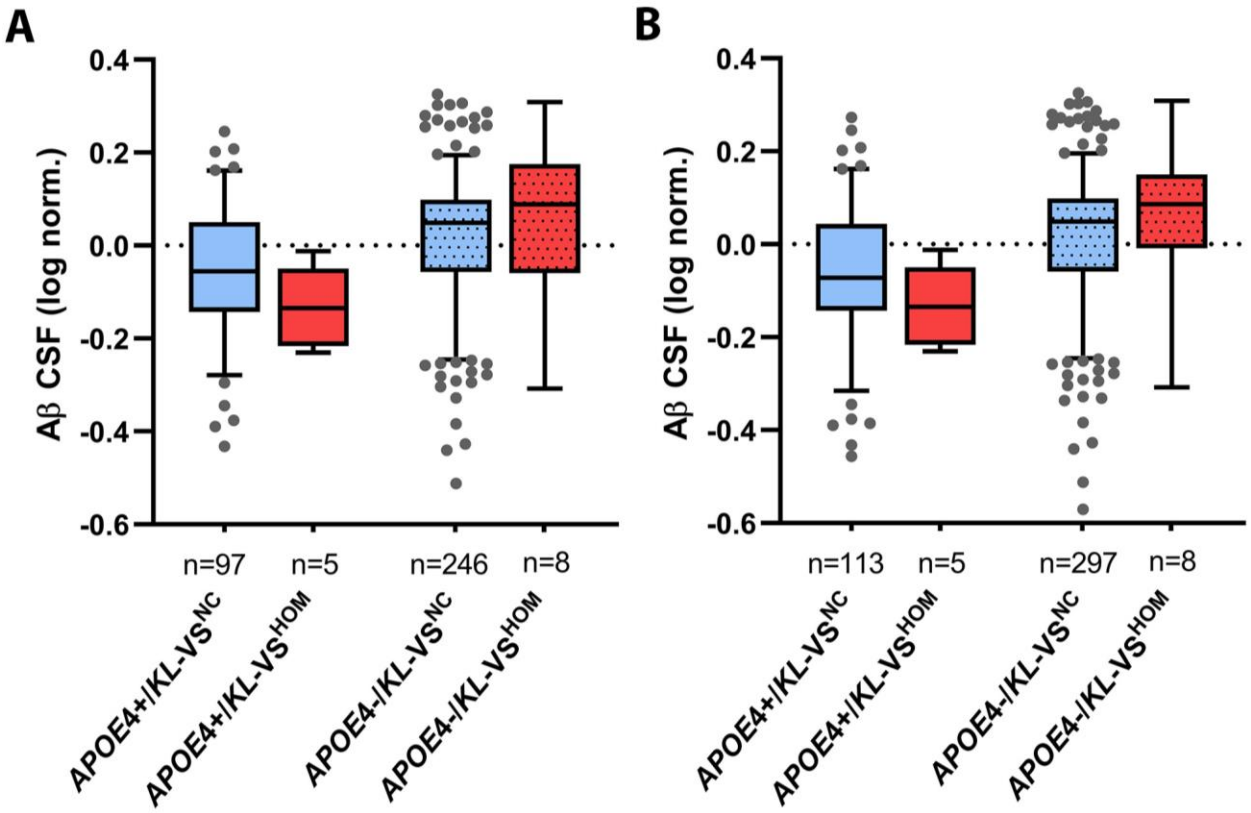
Box plot error bars show 95-percentile range. Gray circles indicate values outside of the 95-percentile range. There were no significant differences among *KL*-VS^{HET+} and *KL*-VS^{HET-} carriers in either *APOE*4+ or *APOE*4- groups. N on x-axes indicates number of subjects per group.

Abbreviations: CSF, cerebrospinal fluid; PET, positron emission tomography; Aβ, amyloid beta; HET+, heterozygous carriers; HET-, non-heterozygous carriers.





eFigure 9. Forest plots for the association of *KL*-VS^{HET+} with amyloid beta CSF in *APOE*4+ controls of ages A) 60-80 and B) 60+ years.



eFigure 10. Association of *KL*-VS^{HOM} , in contrast to *KL*-VS^{NC}, with amyloid beta levels as measured from CSF samples, in A) 60-80 and B) 60+ years old controls, stratified by *APOE*4 status.

Box plot error bars show 95-percentile range. Gray circles indicate values outside of the 95-percentile range. There were no significant differences between *KL*-VS^{HOM} and *KL*-VS^{NC} carriers in either *APOE*4+ or *APOE*4- groups. N on x-axes indicates number of subjects per group. **A)** *KL*-VS^{HOM} association with Aβ in *APOE4*+ group: Beta=-0.04 [-0.11,0.04]; P=0.31); *KL*-VS^{HOM} association with Aβ in *APOE*4- group: Beta=0.03 [-0.03,0.09]; P=0.36). **B)** *KL*-VS^{HOM} association with Aβ in *APOE*4+ group: Beta=-0.04 [-0.12,0.04]; P=0.36); *KL*-VS^{HOM} association with Aβ in *APOE*4- group: Beta=0.03 [-0.02,0.09]; P=0.26).

Abbreviations: CSF, cerebrospinal fluid; Aβ, amyloid beta; HOM, homozygous carriers; NC, non-carriers.

eTables

Cohort	Platform(s)
ACT	Illumina Human 660W-Quad
ADC1	Illumina Human 660W-Quad
ADC2	Illumina Human 660W-Quad
ADC3	Illumina Human OmniExpress
ADC4	Illumina Human OmniExpress
ADC5	Illumina Human OmniExpress
ADC6	Illumina Human OmniExpress
ADC7	Illumina Infinium Human OmniExpressExome
ADDNEUROMED	Illumina Human 610-Quad Illumina Human OmniExpress
ADNI	Illumina Omni 2.5 Illumina Human 610-Quad Illumina Human OmniExpress
ADOD	Illumina Human OmniExpress
GenADA	Affymetrix 500K
NIA-LOAD	Illumina Human 610-Quad
MAYO	Illumina Human Hap300
MAYO2	Illumina Omni 2.5
MIRAGE	Illumina Human CNV370-Duo Illumina Human 610-Quad
OHSU	Illumina Human CNV370-Duo
ROSMAP	Affymetrix 6.0 Illumina Human OmniExpress
TGEN2	Affymetrix 6.0
UPITT	Illumina Human Omni1-Quad
UM/VU/MSSM	Illumina Human 550K. Illumina Human 610-Quad Illumina Human 1M-Duo Affymetrix 6.0
WASHU	Illumina Human 610-Quad
CRU	Illumina Human 610-Quad Illumina Human OmniExpress

eTable 1. SNP microarray platforms per cohort.

Cohorts	1. All genotyped subjects	2. Genotype missingness <95%	3. No sex problems/missingness	4. No ancestry discordance	5. No duplicate discordance	6. Filter to CN/AD	7. *APOE* genotype available	8. AGE available	9. AGE 60y+	10. Retain unique non-duplicate	11. European (EU)	12. Northwestern EU (NWE)	13. Retain unique unrelated
ACT	2790	2790	2790	2788	2786	2535	2315	2315	2314	2308	2308	2147	2132
ADC1	2731	2731	2731	2725	2724	2503	2503	2503	2216	2216	2051	1790	1790
ADC2	928	928	926	926	924	826	826	826	819	819	815	705	705
ADC3	1526	1526	1525	1524	1524	1337	1337	1337	1236	1232	1228	1037	1036
ADC4	1054	1054	1054	1054	1053	841	841	841	809	808	796	630	629
ADC5	1224	1224	1223	1223	1219	972	972	972	963	961	959	807	807
ADC6	1333	1333	1333	1333	1333	882	882	882	675	672	672	535	535
ADC7	1462	1462	1462	1462	1461	1290	1290	1290	1290	1290	1285	1035	1035
ADDNEURO	644	644	594	594	593	441	441	441	433	433	431	239	239
ADNI	1930	1929	1925	1912	1912	1274	1274	1274	1251	949	849	725	724
ADOD	204	204	204	204	204	96	96	96	96	96	79	72	72
GSK	1571	1571	1571	1570	1570	1570	1558	1558	1464	1462	1460	1386	1371
LOAD	5220	5220	5205	5200	5194	4537	4537	4534	3993	3666	3072	2760	1693
MAYO	2099	2058	2058	2058	2055	2054	2052	2052	2052	1908	1876	1760	1738
MAYO2	314	314	276	276	273	160	160	160	150	130	129	122	122
MIRAGE	1502	1502	1500	1500	1499	1235	1233	1217	1217	1169	1140	784	481
OHSU	647	641	641	641	641	592	591	591	589	340	334	316	316
ROSMAP	2090	2068	2066	2065	2065	1469	1469	1448	1447	1447	1446	1379	1379
TGEN	1599	1523	1523	1523	1523	1523	1523	1092	1037	979	977	949	946
UPITT	2440	2376	2376	2374	2371	2227	2227	2218	2218	2192	2174	1691	1664
UVM	1782	1782	1777	1777	1777	1614	1610	1609	1603	1570	1552	1198	1198
WASHU	670	670	669	669	669	649	649	538	522	348	348	316	316
ALL	35760	35550	35429	35398	35370	30627	30386	29794	28394	26995	25981	22383	20928

eTable 2. Case-control sample sizes per cohort after sequential quality control and filtering steps (detailed in the titles above each column).

	Association between *KL*-VS^{HET+} and AD risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**
60-80	***APOE4* +**	1716/5748 (30.0/25.1)	**0.73 (0.64-0.83)**	**8.5E-07**	6198/8338 (27.3/25.2)	**0.74 (0.62-0.88)**	**5.3E-04**
	APOE4 -	4482/2590 (26.2/25.6)	0.99 (0.88-1.11)	0.90			
80+	*APOE4* +	728/843 (26.4/26.6)	0.97 (0.76-1.25)	0.88	3897/2096 (25.8/26.9)	0.91 (0.69-1.21)	0.53
	APOE4 -	3151/1253 (25.7/27.1)	1.08 (0.93-1.26)	0.33			
Full Sample	***APOE4* +**	2444/6591 (28.9/25.3)	**0.78 (0.70-0.87)**	**1.3E-05**	10077/10434 (26.7/25.6)	**0.77 (0.67-0.89)**	**4.3E-04**
	APOE4 -	7633/3843 (26.0/26.1)	1.02 (0.93-1.12)	0.62			

eTable 3. Association of *KL*-VS^{HET+} with Alzheimer's disease case-control status in age- and *APOE*4-strata, determined by MEGA-analysis.

Abbreviations: CN, control; AD, Alzheimer's disease; HET+, heterozygous carriers; OR, odds ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and AD risk by *APOE4* status			Interaction between *KL*-VS^{HET+} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**
60-80	***APOE4* +**	1293/4600 (31.9/24.8)	**0.64 (0.55-0.74)**	**4.0E-09**	4589/6559 (27.4/25.1)	**0.67 (0.55-0.82)**	**1.5E-04**
	APOE4 -	3296/1959 (25.9/25.7)	1.01 (0.87-1.16)	0.91			
80+	*APOE4* +	573/525 (25.8/28.2)	1.12 (0.84-1.51)	0.24	2978/1327 (25.4/27.1)	1.08 (0.76-1.53)	0.67
	APOE4 -	2405/802 (25.1/26.3)	1.13 (0.92-1.38)	0.29			
Full Sample	***APOE4* +**	1913/5170 (29.8/25.2)	**0.73 (0.64-0.83)**	**2.0E-06**	7744/7994 (26.6/25.4)	**0.74 (0.62-0.88)**	**7.4E-04**
	APOE4 -	5831/2824 (25.6/25.7)	1.03 (0.92-1.15)	0.65			

eTable 4. Association of *KL*-VS^{HET+} with Alzheimer's disease case-control status in age- and *APOE*4-strata, determined by META-analysis and using only age-at-onset data for cases.

Abbreviations: CN, control; AD, Alzheimer's disease; HET+, heterozygous carriers; OR, odds ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and AD risk by *APOE4* status			Interaction between *KL*-VS^{HET+} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**
60-80	***APOE4* +**	1722/4501 (30.0/24.7)	**0.67 (0.58-0.77)**	**2.7E-08**	6215/6446 (27.2/25.0)	**0.65 (0.54-0.80)**	**2.2E-05**
	APOE4 -	4493/1945 (26.2/25.7)	1.02 (0.89-1.17)	0.78			
80+	*APOE4* +	729/547 (26.3/28.5)	1.07 (0.80-1.43)	0.69	3884/1380 (25.8/27.2)	1.02 (0.73-1.43)	0.90
	APOE4 -	3155/833 (25.7/26.3)	1.08 (0.89-1.30)	0.44			
Full Sample	***APOE4* +**	2451/5048 (28.9/25.1)	**0.74 (0.65-0.84)**	**2.5E-06**	10099/7826 (26.7/25.4)	**0.72 (0.61-0.85)**	**9.7E-05**
	APOE4 -	7648/2778 (26.0/25.8)	1.04 (0.93-1.16)	0.52			

eTable 5. Association of *KL*-VS^{HET+} with Alzheimer's disease case-control status in age- and *APOE*4-strata, determined by MEGA-analysis and using only age-at-onset data for cases.

Abbreviations: CN, control; AD, Alzheimer's disease; HET+, heterozygous carriers; OR, odds ratio; CI, confidence interval.

Cohorts	1. All genotyped subjects	2. DX available (ADC 1-7 -> UDS)	3. Genotype missingness <95%	4. No sex problems/missingness	5. No ancestry discordance	6. No duplicate discordance	7. *APOE* genotype available	8. Years of Education available	9. Retain unique non-duplicate	10. European (EU)	11. Northwestern EU (NWE)	12. Retain unique unrelated	13. Age at basline 60+ y	Fits CRR model 1 criteria (3y+)	Fits CRR model 2 criteria (3y+)
ADC1	2731	717	717	717	716	715	715	708	707	596	508	398	398	198	237
ADC2	928	741	741	741	741	739	739	738	738	734	611	549	549	73	126
ADC3	1526	1104	1104	1104	1103	1103	1103	1089	1085	1082	884	772	772	250	311
ADC4	1054	1054	1054	1054	1054	1053	1053	1048	1048	1029	802	663	663	252	353
ADC5	1224	1223	1223	1223	1223	1219	1219	1212	1211	1209	1029	873	873	398	517
ADC6	1333	1326	1326	1326	1326	1326	1326	1322	1320	1317	1073	776	776	214	419
ADC7	1462	1461	1461	1461	1461	1460	1460	1458	1457	1452	1164	1049	1049	481	582
ADNI	1930	1927	1926	1925	1912	1912	1911	1911	1536	1381	1149	1024	1024	234	582
ROSMAP	2090	2046	2024	2024	2023	2023	2023	2022	2022	2021	1937	1798	1798	908	1402
ALL	14278	11966	11943	11942	11559	11550	11549	11508	11124	10821	9157	7902	7902	3008	4529

eTable 6. Sample sizes per conversion risk cohort after sequential quality control and filtering steps.

Model 1 refers to conversion from CN to MCI/AD status. Model 2 refers to conversion from CN/MCI to AD status.

Abbreviations: CN, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; y, years.

	Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	***APOE4* +**	612/176 (29.6/20.5)	**0.64 (0.44-0.94)**	**0.023**	2558/450 (26.2/24.9)	**0.62 (0.39-1.00)**	**0.048**
	APOE4 -	1946/274 (25.2/27.7)	1.06 (0.81-1.37)	0.69			
4+ years	***APOE4* +**	549/170 (30.2/20.0)	**0.61 (0.41-0.90)**	**0.013**	2324/438 (26.2/24.4)	**0.60 (0.37-097)**	**0.036**
	APOE4 -	1775/268 (25.0/27.2)	1.04 (0.80-1.36)	0.77			
5+ years	***APOE4* +**	484/157 (30.6/19.7)	**0.60 (0.40-1.25)**	**0.015**	2085/415 (26.3/24.6)	**0.59 (0.36-0.97)**	**0.04**
	APOE4 -	1601/258 (25.0/27.5)	1.05 (0.80-1.38)	0.75			

eTable 7. Association of *KL*-VS^{HET+} with risk of conversion to mild cognitive impairment or Alzheimer's disease, stratified by *APOE*4 status, determined by META-analysis.

For meta-analyses, the ADC1-7 cohorts were combined as the "NACC" cohort to avoid small individual samples sizes.

Abbreviations: CN, control; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; HR, hazard ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status			Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	***APOE4* +**	612/176 (29.6/20.5)	**0.68 (0.56-0.82)**	**0.039**	2558/450 (26.2/24.9)	*0.63 (0.50-0.80)*	*0.052*
	APOE4 -	1946/274 (25.2/27.7)	1.06 (0.93-1.21)	0.67			
4+ years	***APOE4* +**	549/170 (30.2/20.0)	**0.64 (0.52-0.77)**	**0.021**	2324/438 (26.2/24.4)	**0.61 (0.48-0.78)**	**0.040**
	APOE4 -	1775/268 (25.0/27.2)	1.03 (0.90-1.18)	0.83			
5+ years	***APOE4* +**	484/157 (30.6/19.7)	**0.60 (0.49-0.74)**	**0.014**	2085/415 (26.3/24.6)	**0.59 (0.46-0.75)**	**0.033**
	APOE4 -	1601/258 (25.0/27.5)	1.01 (0.92-1.10)	0.76			

eTable 8. Association of *KL*-VS^{HET+} with risk of conversion to mild cognitive impairment or Alzheimer's disease, stratified by *APOE*4 status, determined by MEGA-analysis.

Abbreviations: CN, control; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; HR, hazard ratio; CI, confidence interval.

	Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	***APOE4 +***	891/566 (28.3/22.1)	**0.81 (0.66-1.00)**	**0.047**	3410/1119 (26.4/23.8)	0.79 (0.59-1.06)	0.12
	APOE4 -	2519/553 (25.7/25.5)	1.12 (0.78-1.61)	0.99			
4+ years	***APOE4 +***	789/484 (28.8/21.9)	**0.79 (0.63-0.98)**	**0.033**	3046/991 (26.3/23.9)	*0.75 (0.55-1.02)*	*0.064*
	APOE4 -	2257/507 (25.4/25.8)	1.03 (0.84-1.25)	0.79			
5+ years	***APOE4 +***	691/415 (29.5/21.7)	**0.75 (0.59-0.95)**	**0.019**	2729/872 (26.6/24.5)	**0.68 (0.49-0.95)**	**0.02**
	APOE4 -	2042/458 (25.6/27.1)	1.05 (0.86-1.30)	0.61			

eTable 9. Association of *KL*-VS^{HET+} with risk of conversion to Alzheimer's disease, stratified by *APOE*4 status, determined by META-analysis.

For meta-analyses, the ADC1-7 cohorts were combined as the "NACC" cohort to avoid small individual samples sizes.

Abbreviations: CN, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; HR, hazard ratio; CI, confidence interval.

	Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	***APOE4 +***	891/566 (28.3/22.1)	**0.71 (0.79-0.87)**	**0.023**	3410/1119 (26.4/23.8)	*0.75 (0.65-0.87)*	*0.054*
	APOE4 -	2519/553 (25.7/25.5)	1.01 (0.91-1.11)	0.94			
4+ years	***APOE4 +***	789/484 (28.8/21.9)	**0.72 (0.63-0.81)**	**0.019**	3046/991 (26.3/23.9)	*0.71 (0.61-0.83)*	*0.054*
	APOE4 -	2257/507 (25.4/25.8)	1.03 (0.93-1.14)	0.78			
5+ years	***APOE4 +***	691/415 (29.5/21.7)	**0.61 (0.63-0.81)**	**0.0086**	2729/872 (26.6/24.5)	**0.65 (0.54-0.76)**	**0.009**
	APOE4 -	2042/458 (25.6/27.1)	1.05 (0.95-1.17)	0.61			

eTable 10. Association of *KL*-VS^{HET+} with risk of conversion to Alzheimer's disease, stratified by *APOE*4 status, determined by MEGA-analysis.

Abbreviations: CN, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; HR, hazard ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and AD risk by *APOE4* status			Interaction between *KL*-VS^{HET+} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**
60-80	***APOE4* +**	1701/5729 (31.0/25.7)	**0.70 (0.61-0.80)**	**6.4E-08**	6057/8265 (28.0/25.9)	**0.73 (0.61-0.88)**	**6.2E-04**
	APOE4 -	4356/2536 (26.8/26.1)	0.98 (0.87-1.11)	0.79			
80+	*APOE4* +	700/805 (26.7/27.1)	1.00 (0.78-1.29)	0.99	3683/1992 (26.4/27.7)	0.92 (0.69-1.24)	0.60
	APOE4 -	3012/1212 (26.4/28.0)	1.10 (0.94-1.29)	0.28			
Full Sample	***APOE4* +**	2437/6577 (29.8/26.0)	**0.75 (0.67-0.85)**	**1.5E-06**	9876/10354 (27.4/26.3)	**0.77 (0.66-0.89)**	**4.6E-04**
	APOE4 -	7494/3804 (26.6/26.7)	1.01 (0.92-1.11)	0.87			

eTable 11. Association of *KL*-VS^{HET+}, in contrast to *KL*-VS^{NC}, with Alzheimer's disease case-control status in age- and *APOE*4-strata, determined by META-analysis.

Abbreviations: CN, control; AD, Alzheimer's disease; HET+, heterozygous carriers; NC, non-carriers; OR, odds ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and AD risk by *APOE4* status			Interaction between *KL*-VS^{HET+} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**
60-80	***APOE4* +**	1271/4487 (32.4/25.5)	**0.64 (0.55-0.76)**	**8.0E-09**	4493/6400 (28.2/25.7)	**0.67 (0.55-0.83)**	**1.8E-04**
	APOE4 -	3222/1913 (26.5/26.1)	1.01 (0.87-1.16)	0.91			
80+	*APOE4* +	562/512 (26.3/28.9)	1.13 (0.84-1.52)	0.41	2910/1286 (25.8/27.9)	1.07 (0.76-1.52)	0.70
	APOE4 -	2348/563 (25.7/27.2)	1.14 (0.93-1.39)	0.21			
Full Sample	***APOE4* +**	1876/5044 (30.4/25.9)	**0.73 (0.64-0.83)**	**3.6E-06**	7572/7791 (27.2/26.1)	**0.74 (0.62-0.88)**	**7.5E-04**
	APOE4 -	5696/2747 (26.2/26.5)	1.03 (0.92-1.16)	0.60			

eTable 12. Association of *KL*-VS^{HET+}, in contrast to *KL*-VS^{NC}, with Alzheimer's disease case-control status in age- and *APOE*4-strata, determined by META-analysis and using only age-at-onset data for cases.

Abbreviations: CN, control; AD, Alzheimer's disease; HET+, heterozygous carriers; NC, non-carriers; OR, odds ratio; CI, confidence interval.

	Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	***APOE4* +**	602/171 (30.1/21.1)	**0.65 (0.45-0.96)**	**0.029**	2498/439 (26.9/25.5)	*0.64 (0.40-1.02)*	*0.060*
	APOE4 -	1896/268 (25.8/28.4)	1.15 (0.76-1.72)	0.51			
4+ years	***APOE4* +**	539/165 (30.8/20.6)	**0.62 (0.42-0.92)**	**0.017**	2253/427 (26.9/25.1)	**0.61 (0.38-0.99)**	**0.045**
	APOE4 -	1714/262 (25.6/27.9)	1.10 (0.75-1.59)	0.63			
5+ years	***APOE4* +**	476/152 (31.1/20.4)	**0.61 (0.41-0.92)**	**0.019**	2034/404 (27.0/25.2)	**0.61 (0.37-0.99)**	**0.047**
	APOE4 -	1558/252 (25.7/28.2)	1.15 (0.72-1.82)	0.55			

eTable 13. Association of *KL*-VS^{HET+}, in contrast to *KL*-VS^{NC}, with risk of conversion to mild cognitive impairment or Alzheimer's disease, stratified by *APOE*4 status, determined by META-analysis.

For meta-analyses, the ADC1-7 cohorts were combined as the "NACC" cohort to avoid small individual samples sizes.

Abbreviations: CN, control; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; NC, non-carriers; HR, hazard ratio; CI, confidence interval.

	Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	*APOE4 +*	874/545 (28.8/22.9)	*0.82 (0.67-1.01)*	*0.060*	3334/1088 (27.0/24.9)	0.81 (0.60-1.08)	0.15
	APOE4 -	2460/543 (26.3/26.0)	0.95 (0.82-1.20)	0.96			
4+ years	***APOE4 +***	774/463 (29.3/22.9)	**0.80 (0.64-1.00)**	**0.0497**	2979/961 (26.9/24.7)	*0.76 (0.56-1.04)*	*0.088*
	APOE4 -	2205/498 (26.0/26.3)	1.02 (0.84-1.25)	0.82			
5+ years	***APOE4 +***	678/397 (29.5/21.7)	**0.76 (0.60-0.97)**	**0.028**	2672/848 (27.2/25.2)	**0.70 (0.50-0.97)**	**0.033**
	APOE4 -	1994/451 (26.2/27.5)	1.05 (0.85-1.29)	0.63			

eTable 14. Association of *KL*-VS^{HET+}, in contrast to *KL*-VS^{NC}, with risk of conversion to Alzheimer's disease, stratified by *APOE4* status, determined by META-analysis.

For meta-analyses, the ADC1-7 cohorts were combined as the "NACC" cohort to avoid small individual samples sizes.

Abbreviations: CN, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; NC, non-carriers; HR, hazard ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and Aβ CSF by *APOE4* status				Association between *KL-VS*$^{HET+}$ and Aβ PET by *APOE4* status		
Age	**Model**	**Stratum**	**N (*KL*-VS^{HET+} %)**	**Beta (95% CI)**	**P-value**	**N (*KL*-VS^{HET+} %)**	**Beta (95% CI)**	**P-value**
60-80y	KL-VS^{HET+} vs KL-VS^{HET-}	***APOE4* +**	142 (28.2)	**0.06 (0.01,0.10)**	**0.028**	57 (33.3)	**-0.04 (-0.07,-0.00)**	**0.040**
		APOE4 -	338 (24.9)	0.04 (-0.02,0.09)	0.22	142 (29.6)	-0.00 (-0.02,0.01)	0.69
	KL-VS^{HET+} vs KL-VS^{NC}	***APOE4* +**	137 (29.2)	**0.05 (0.00,0.10)**	**0.038**	56 (33.9)	**-0.04 (-0.07,-0.00)**	**0.039**
		APOE4 -	330 (25.4)	0.04 (-0.02,0.10)	0.22	141 (29.1)	-0.00 (-0.02,0.01)	0.68
60+y	KL-VS^{HET+} vs KL-VS^{HET-}	*APOE4* +	159 (28.9)	0.02 (-0.03,0.06)	0.50	69 (31.9)	-0.02 (-0.05,0.02)	0.31
		APOE4 -	397 (25.2)	0.02 (-0.03,0.07)	0.44	182 (29.1)	0.01 (-0.01,0.03)	0.24
	KL-VS^{HET+} vs KL-VS^{NC}	*APOE4* +	154 (29.9)	0.01 (-0.03,0.06)	0.57	68 (32.4)	-0.02 (-0.05,0.02)	0.30
		APOE4 -	386 (25.9)	0.02 (-0.03,0.08)	0.40	179 (29.6)	0.01 (-0.01,0.03)	0.28

eTable 15. Association of *KL*-VS^{HET+}, in contrast to *KL*-VS^{HET-} or *KL*-VS^{NC}, with Aβ levels in cognitively normal subjects, stratified by *APOE*4 status, determined by META-analysis.

Abbreviations: Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography; HET+, heterozygous carriers; HET-, non-heterozygous carriers; NC, non-carriers; CI, confidence interval.

		Association between *KL*-VS^{HOM} and AD risk by *APOE4* status			Interaction between *KL*-VS^{HOM} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HOM} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HOM} %))**	**OR (95% CI)**	**P-value**
60-80	*APOE4 +*	1202/4306 (3.1/3.4)	1.14 (0.78-1.71)	0.50	4509/6233 (3.0/3.3)	1.23 (0.74-2.11)	0.42
	APOE4 -	3307/1927 (3.0/3.0)	0.89 (0.62-1.27)	0.53			
80+	*APOE4 +*	536/598 (2.6/3.4)	1.39 (0.65-3.04)	0.40	2877/1532 (3.3/4.2)	0.95 (0.41-2.24)	0.91
	APOE4 -	2341/913 (3.4/4.7)	1.32 (0.88-1.96)	0.17			
Full Sample	*APOE4 +*	1738/4925 (2.9/3.4)	1.19 (0.85-1.69)	0.31	7386/7765 (3.1/3.5)	1.10 (0.72-1.70)	0.66
	APOE4 -	5648/2840 (3.1/3.6)	1.05 (0.80-1.36)	0.73			

eTable 16. Association of *KL*-VS^{HOM}, in contrast to *KL*-VS^{NC}, with Alzheimer's disease case-control status in age- and *APOE*4-strata, determined by MEGA-analysis.

Abbreviations: CN, control; AD, Alzheimer's disease; HOM, homozygous carriers; NC, non-carriers; OR, odds ratio; CI, confidence interval.

		Association between *KL*-VS^{HOM} and AD risk by *APOE4* status			Interaction between *KL*-VS^{HOM} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HOM} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HOM} %))**	**OR (95% CI)**	**P-value**
60-80	*APOE4* +	1206/3388 (3.1/3.2)	1.12 (0.70-1.85)	0.64	4522/4834 (3.0/3.2)	1.24 (0.68-2.36)	0.490
	APOE4 -	3316/1446 (3.0/3.1)	0.86 (0.57-1.29)	0.48			
80+	*APOE4* +	537/391 (2.6/3.3)	1.54 (0.63-3.80)	0.34	2882/1005 (3.3/4.4)	0.93 (0.35-2.52)	0.89
	APOE4 -	2345/614 (3.4/5.0)	1.45 (0.90-2.31)	0.12			
Full Sample	*APOE4* +	1743/3779 (2.9/3.2)	1.25 (0.83-1.93)	0.30	7404/5839 (3.1/3.4)	1.12 (0.68-1.89)	0.66
	APOE4 -	5661/2060 (3.2/3.7)	1.07 (0.79-1.45)	0.65			

eTable 17. Association of *KL*-VS^{HOM}, in contrast to *KL*-VS^{NC}, with Alzheimer's disease case-control status in age- and *APOE*4-strata, determined by MEGA-analysis and using only age-at-onset data for cases.

Abbreviations: CN, control; AD, Alzheimer's disease; HOM, homozygous carriers; NC, non-carriers; OR, odds ratio; CI, confidence interval.

	Association between *KL*-VS^{HOM} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HOM} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN/CON (N (*KL*-VS^{HOM} %))**	**HR (95% CI)**	**P-value**	**CN/CON (N (*KL*-VS^{HOM} %))**	**HR (95% CI)**	**P-value**
3+ years	*APOE4* +	431/140 (2.3/3.6)	1.32 (1.07-1.64)	0.18	1887/338 (3.2/3.3)	1.53 (1.13-2.07)	0.16
	APOE4 -	1456/198 (3.4/3.0)	0.84 (0.68-1.02)	0.38			
4+ years	*APOE4* +	383/136 (2.6/3.7)	1.28 (1.03-1.59)	0.26	1702/331 (3.2/3.3)	1.44 (1.07-1.94)	0.22
	APOE4 -	1319/195 (3.3/3.1)	0.88 (0.72-1.07)	0.50			
5+ years	*APOE4* +	336/126 (2.4/4.0)	1.30 (1.05-1.61)	0.21	1536/313 (3.3/3.5)	1.45 (1.08-1.95)	0.21
	APOE4 -	1200/187 (3.6/3.2)	0.88 (0.72-1.07)	0.50			

eTable 18. Association of *KL*-VS^{HOM}, in contrast to *KL*-VS^{NC}, with risk of conversion to mild cognitive impairment or Alzheimer's disease, stratified by *APOE*4 status, determined by MEGA-analysis.

Abbreviations: CN, control; AD, Alzheimer's disease; CON, converted subject; HOM, homozygous carriers; NC, non-carriers; HR, hazard ratio; CI, confidence interval.

	Association between *KL*-VS^{HOM} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HOM} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN+MCI/CON (N (*KL*-VS^{HOM} %))**	**HR (95% CI)**	**P-value**	**CN+MCI/CON (N (*KL*-VS^{HOM} %))**	**HR (95% CI)**	**P-value**
3+ years	*APOE4* +	639/441 (2.7/4.8)	1.14 (1.03-1.27)	0.18	2510/853 (3.0/3.6)	1.35 (1.11-1.65)	0.13
	APOE4 -	1871/412 (3.2/2.4)	0.88 (0.75-1.03)	0.44			
4+ years	***APOE4* +**	562/378 (2.7/5.6)	**1.26 (1.15-1.38)**	**0.013**	2246/754 (3.0/4.0)	*1.44 (1.18-1.76)*	*0.063*
	APOE4 -	1684/376 (3.1/2.4)	0.91 (0.77-1.07)	0.56			
5+ years	***APOE4* +**	487/325 (2.7/5.5)	**1.26 (1.14-1.39)**	**0.023**	2006/659 (3.0/3.8)	*1.47 (1.18-1.83)*	*0.079*
	APOE4 -	1519/334 (3.2/2.1)	0.88 (0.73-1.06)	0.50			

eTable 19. Association of *KL*-VS^{HOM}, in contrast to *KL*-VS^{NC}, with risk of conversion to Alzheimer's disease, stratified by *APOE4* status, determined by MEGA-analysis.

Abbreviations: CN, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; CON, converted subject; HOM, homozygous carriers; NC, non-carriers; HR, hazard ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and AD risk by *APOE4* status			Interaction between *KL*-VS^{HET+} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**
60-80	***APOE34/44***	1596/5649 (31.0/25.0)	**0.68 (0.59-0.77)**	**1.9E-08**	6048/8244 (27.5/25.2)	**0.71 (0.58-0.87)**	**7.8E-04**
	APOE4 -	4452/2595 (26.2/25.5)	0.98 (0.87-1.11)	0.79			
80+	*APOE34/44*	648/761 (25.6/26.3)	0.96 (0.70-1.32)	0.81	3707/1988 (25.7/26.9)	0.93 (0.69-1.26)	0.63
	APOE4 -	3090/1253 (25.8/27.1)	1.09 (0.93-1.28)	0.28			
Full Sample	***APOE34/44***	2277/6451 (29.3/25.3)	**0.74 (0.67-0.84)**	**2.7E-06**	9892/10330 (26.8/25.6)	**0.75 (0.64-0.88)**	**4.7E-04**
	APOE4 -	7670/3906 (26.0/26.0)	1.01 (0.91-1.11)	0.91			

eTable 20. Association of *KL*-VS^{HET+} with Alzheimer's disease case-control status in age- and *APOE*4-strata, but excluding *APOE*24 carriers, determined by META-analysis.

Abbreviations: CN, control; AD, Alzheimer's disease; HET+, heterozygous carriers; OR, odds ratio; CI, confidence interval.

	Association between *KL*-VS^{HET+} and AD risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and AD risk by *APOE4* status		
Ages	**Stratum**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**	**CN/AD (N (*KL*-VS^{HET+} %))**	**OR (95% CI)**	**P-value**
60-80	***APOE34/44***	1195/4416 (32.6/24.9)	**0.62 (0.53-0.72)**	**1.0E-09**	4491/6375 (27.7/25.1)	**0.65 (0.52-0.80)**	**4.3E-05**
	APOE4 -	3296/1959 (25.9/25.7)	1.01 (0.87-1.16)	0.91			
80+	*APOE34/44*	518/477 (25.1/28.1)	1.16 (0.85-1.58)	0.35	2923/1279 (25.1/27.0)	1.12 (0.78-1.61)	0.53
	APOE4 -	2405/802 (25.1/26.3)	1.13 (0.92-1.38)	0.29			
Full Sample	***APOE34/44***	1755/4937 (30.1/25.3)	**0.73 (0.64-0.83)**	**1.2E-06**	7586/7761 (26.6/25.4)	**0.73 (0.61-0.87)**	**4.7E-04**
	APOE4 -	5831/2824 (25.6/25.7)	1.03 (0.92-1.15)	0.65			

eTable 21. Association of *KL*-VS^{HET+} with Alzheimer's disease case-control status in age- and *APOE*4-strata, but excluding *APOE*24 carriers, determined by META-analysis and using only age-at-onset data for cases.

Abbreviations: CN, control; AD, Alzheimer's disease; HET+, heterozygous carriers; OR, odds ratio; CI, confidence interval.

	Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	***APOE34/44***	559/166 (29.5/20.5)	**0.61 (0.41-0.91)**	**0.014**	2505/440 (26.1/25.0)	**0.61 (0.38-0.99)**	**0.047**
	APOE4 -	1946/274 (25.2/27.7)	1.06 (0.81-1.37)	0.69			
4+ years	***APOE34/44***	502/161 (30.1/19.9)	**0.60 (0.39-0.90)**	**0.013**	2260/429 (26.1/24.5)	**0.60 (0.3-0.98)**	**0.040**
	APOE4 -	1775/268 (25.0/27.2)	1.04 (0.80-1.36)	0.77			
5+ years	***APOE34/44***	442/150 (30.8/19.3)	**0.58 (0.38-0.89)**	**0.013**	2043/408 (26.3/24.5)	**0.58 (0.35-0.97)**	**0.039**
	APOE4 -	1601/258 (25.0/27.5)	1.05 (0.80-1.38)	0.75			

eTable 22. Association of *KL*-VS^{HET+} with risk of conversion to mild cognitive impairment or Alzheimer's disease, stratified by *APOE*4 status but excluding *APOE*24 carriers, determined by META-analysis.

For meta-analyses, the ADC1-7 cohorts were combined as the "NACC" cohort to avoid small individual samples sizes.

Abbreviations: CN, control; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; HR, hazard ratio; CI, confidence interval.

	Association between *KL*-VS^{HET+} and conversion risk by *APOE4* status				Interaction between *KL*-VS^{HET+} and conv. risk by *APOE4* status		
Study Time	**Stratum**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**	**CN+MCI/CON (N (*KL*-VS^{HET+} %))**	**HR (95% CI)**	**P-value**
3+ years	*APOE34/44*	817/539 (28.2/22.4)	*0.83 (0.67-1.02)*	*0.080*	3336/1092 (26.3/24.0)	0.81 (0.60-1.08)	0.15
	APOE4 -	2519/553 (25.7/25.5)	1.12 (0.78-1.61)	0.99			
4+ years	*APOE34/44*	723/459 (28.5/22.2)	*0.80 (0.64-1.01)*	*0.061*	2980/966 (26.1/24.1)	*0.76 (0.55-1.04)*	*0.091*
	APOE4 -	2257/507 (25.4/25.8)	1.03 (0.84-1.25)	0.79			
5+ years	***APOE34/44***	631/394 (29.4/21.8)	**0.76 (0.59-0.98)**	**0.032**	2673/852 (26.5/24.6)	**0.69 (0.49-0.97)**	**0.03**
	APOE4 -	2042/458 (25.6/27.1)	1.05 (0.86-1.30)	0.61			

eTable 23. Association of *KL*-VS^{HET+} with risk of conversion to Alzheimer's disease, stratified by *APOE*4 status but excluding *APOE*24 carriers, determined by META-analysis.

For meta-analyses, the ADC1-7 cohorts were combined as the "NACC" cohort to avoid small individual samples sizes.

Abbreviations: CN, control; MCI, mild cognitive impairment; AD, Alzheimer's disease; CON, converted subject; HET+, heterozygous carriers; HR, hazard ratio; CI, confidence interval.

		Association between *KL*-VS^{HET+} and Abeta CSF by *APOE4* status			Association between *KL-VS* $^{HET+}$ and Abeta PET by APOE4 status		
Age	**Stratum**	**N (*KL*-VS^{HET+} %)**	**Beta (95% CI)**	**P-value**	**N (*KL*-VS^{HET+} %)**	**Beta (95% CI)**	**P-value**
60-80y	***APOE34/44***	132 (26.5)	**0.06 (0.00,0.11)**	**0.036**	53 (30.2)	**-0.04 (-0.08,-0.00)**	**0.048**
	APOE4 -	338 (24.9)	0.04 (-0.02,0.09)	0.22	142 (29.6)	-0.00 (-0.02,0.01)	0.69
60+	*APOE34/44*	149 (27.5)	0.01 (-0.04,0.06)	0.73	64 (28.1)	-0.02 (-0.06,0.02)	0.36
	APOE4 -	397 (25.2)	0.02 (-0.03,0.07)	0.44	182 (29.1)	0.01 (-0.01,0.03)	0.24

eTable 24. Association of *KL*-VS^{HET+} with Aβ levels in cognitively normal subjects, stratified by *APOE*4 status but excluding *APOE*24 carriers, determined by META-analysis.

Abbreviations: Aβ, amyloid beta; CSF, cerebrospinal fluid; PET, positron emission tomography; HET+, heterozygous carriers; HET-, non-heterozygous carriers; CI, confidence interval.

References

1. Weiner MW, Aisen PS, Clifford RJJ, et al. The Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans. *Alzheimers Dement*. 2010;6(3):202-211. doi:10.1016/j.jalz.2010.03.007.The

2. A. Bennett D, A. Schneider J, S. Buchman A, L. Barnes L, A. Boyle P, S. Wilson R. Overview and Findings from the Rush Memory and Aging Project. *Curr Alzheimer Res*. 2012;9(6):646-663. doi:10.2174/156720512801322663

3. Green RC, Cupples LA, Go R, et al. Risk of Dementia Among White and African American Relatives of Patients With Alzheimer Disease. *JAMA*. 2002;287(3):329-336.

4. Lee JH, Cheng R, Graff-radford N, Foroud T. Analyses of the National Institute on Aging Late-Onset Alzheimer's Disease Family Study: Implication of Additional Loci. *Arch Neurol*. 2008;65(11):1518-1526. doi:10.1001/archneur.65.11.1518.Analyses

5. Kamboh MI, Minster RL, Demirci FY, et al. Association of CLU and PICALM variants with Alzheimer's disease. *Neurobiogy of Aging*. 2012;33(3):518-521. doi:10.1016/j.neurobiolaging.2010.04.015

6. Weiner MW, Veitch DP, Hayes J, et al. Injury and Disease Linkages Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in veterans, using the Alzheimer's Disease Neuroimaging Initiative. *Alzheimer's Dement*. 2014;10(3):S226-S235. doi:10.1016/j.jalz.2014.04.005

7. Li H, Wetten S, Li L, et al. Candidate Single-Nucleotide Polymorphisms From a Genomewide Association Study of Alzheimer Disease. *Arch Intern Med*. 2008;65(1):45-53.

8. Lovestone S, Francis P, Kloszewska I, et al. AddNeuroMed - The european collaboration for the discovery of novel biomarkers for alzheimer's disease. *Ann N Y Acad Sci*. 2009;1180:36-46. doi:10.1111/j.1749-6632.2009.05064.x

9. Allen M, Carrasquillo MM, Funk C, et al. Human whole genome genotype and transcriptome data for Alzheimer's and other neurodegenerative diseases. *Sci Data*. 2016;3:160089. doi:10.1038/sdata.2016.89

10. Carrasquillo MM, Zou F, Pankratz VS, et al. Genetic variation in PCDH11X is associated with

susceptibility to late onset Alzheimer's disease. *Nat Genet*. 2009;41(2):192-198. doi:10.1038/ng.305.Genetic

11. Besser L, Kukull W, Knopman DS, et al. Version 3 of the national Alzheimer's coordinating center's uniform data set. *Alzheimer Dis Assoc Disord*. 2018;32(4):351-358. doi:10.1097/WAD.0000000000000279

12. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet*. 2019;51(3):414-430. doi:10.1038/s41588-019-0358-2

13. Naj AC, Jun G, Beecham GW, et al. Common variants in MS4A4/MS4A6E, CD2uAP, CD33, and EPHA1 are associated with late-onset Alzheimer's disease. *Nat Genet*. 2011;43(5):436-441. doi:10.1038/ng.801.Common

14. Beecham GW, Martin ER, Li Y, et al. Genome-wide Association Study Implicates a Chromosome 12 Risk Locus for Late-Onset Alzheimer Disease. *Am J Hum Genet*. 2009;84(1):35-43. doi:10.1016/j.ajhg.2008.12.008

15. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer Disease Incidence A Prospective Cohort Study. *Arch Neurol*. 2002;59:1737-1746.

16. Cruchaga C, Kauwe JSK, Harari O, et al. GWAS of cerebrospinal fluid tau levels identifies novel risk variants for Alzheimer's disease. *Neuron*. 2013;78(2):256-268. doi:10.1016/j.neuron.2013.02.026.GWAS

17. Mckhann G, Drachman D, Folstein M, Katzman R, Price D, Mckhann G. Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS-ADRDA Work Group Under the Auspices of Derpartment of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:27-28. doi:10.1212/01.wnl.0000400650.92875.cf

18. Bell CC. DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. *JAMA*. 1994;272(10):828-829.

19. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th edn. *Am Psychiatr Assoc*. 2013.

20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 4th edn.

Am Psychiatr Assoc. 1994.

21. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140(6):566-572. doi:10.1192/bjp.140.6.566

22. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82:239-259. doi:10.1109/ICINIS.2015.10

23. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessement of Alzheimer's disease. *Neurology*. 1991;41:479-486. doi:10.1017/CBO9781107415324.004

24. Windows M, Corporation M, Hori K, Sakajiri A. Editorial on Consensus Recommendations for the Postmortem Diagnosis of Alzheimer Disease from the National Institute on Aging and the Reagan Institute Working Group on Diagnositic Criteria for the Neuropathological Assessment of Alzheimr Disease. *J Neuropathol Exp Neurol*. 1997;56(10):1095-1097.

25. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State" A Practical Method for Grading the Cognitive State of Patients for the Clinician. *J Psychiatr Res*. 1975;12:189-198. doi:10.3744/snak.2003.40.2.021

26. Roccaforte WH, Burke WJ, Bayer BL, Wengel SP. Validation of a Telephone Version of the Mini-Mental State Examination. *J Am Geriatr Soc*. 1992;40:697-702. https://seirei-univ.repo.nii.ac.jp/?action=repository_action_common_download&item_id=821&item_no=1&attribute_id=20&file_no=1.

27. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005.The

28. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008.The

29. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging – Alzheimer's Association

guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's Dement*. 2012;8(1):1-13. doi:10.1016/j.jalz.2011.10.007

30. Morris JC, Weintraub S, Chui HC, et al. The Uniform Data Set (UDS): Clinical and cognitive variables and descriptive data from Alzheimer disease centers. *Alzheimer Dis Assoc Disord*. 2006;20(4):210-216. doi:10.1097/01.wad.0000213865.09806.92

31. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS) The Neuropsychologic Test Battery. *Alzheimer Dis Assoc Disord*. 2009;23(2):91-101. https://www.alz.washington.edu.

32. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) Database: The Uniform Data Set. *Alzheimer Dis Assoc Disord*. 2007;21(3):249-258. doi:10.1097/WAD.0b013e318142774e

33. Besser LM, Kukull WA, Teylan MA, et al. The revised national Alzheimer's coordinating center's neuropathology form-available data and new analyses. *J Neuropathol Exp Neurol*. 2018;77(8):717-726. doi:10.1093/jnen/nly049

34. Bennett DA, Schneider JA, Buchman AS, De Leon CM, Bienias JL, Wilson RS. The rush memory and aging project: Study design and baseline characteristics of the study cohort. *Neuroepidemiology*. 2005;25(4):163-175. doi:10.1159/000087446

35. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002;59(2):198-205. doi:10.1212/WNL.59.2.198

36. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69(24):2197-2204. doi:10.1212/01.wnl.0000271090.28148.24

37. Chen CY, Pollack S, Hunter DJ, Hirschhorn JN, Kraft P, Price AL. Improved ancestry inference using weights from external reference panels. *Bioinformatics*. 2013;29(11):1399-1406. doi:10.1093/bioinformatics/btt144

38. Auton A, Abecasis GR, Altshuler DM, et al. A global reference for human genetic variation. *Nature*. 2015;526(7571):68-74. doi:10.1038/nature15393

39. Das S, Forer L, Schönherr S, et al. Next-generation genotype imputation service and methods. *Nat*

Genet. 2016;48(10):1284-1287. doi:10.1038/ng.3656

40. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nat Genet*. 2016;48(10):1279-1283. doi:10.1038/ng.3643

41. Wattmo C, Londos E, Minthon L. Risk factors that affect life expectancy in alzheimer's disease: A 15-year follow-up. *Dement Geriatr Cogn Disord*. 2014;38(5-6):286-299. doi:10.1159/000362926

42. Kuzma A, Valladares O, Cweibel R, et al. NIAGADS: The NIA Genetics of Alzheimer's Disease Data Storage Site. *Alzheimer's Dement*. 2016;12(11):1200-1203. doi:10.1016/j.jalz.2016.08.018

43. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144

44. Scrucca L, Santucci A, Aversa F. Regression modeling of competing risk using R: An in depth guide for clinicians. *Bone Marrow Transplant*. 2010;45(9):1388-1395. doi:10.1038/bmt.2009.359