Supplemental Online Content

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eTable 16. Sensitivity Case-Control Regression Analyses Mirroring the Table, Considering Stratifications Across Global Population Ancestry Proportion Greater Than 75%
eReferences

eMethods

In the current study, we used data from a variety of cohorts and sequencing projects related to AD[1-23]. All available genetic/phenotypic data were jointly harmonized with the purpose of performing phenotype/covariate harmonization. Details are provided below.

Phenotype Ascertainment

Cohorts and Phenotype Ascertainment

Details on phenotype ascertainment are described elsewhere[1–6]. 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 definite, probable, or possible late onset AD[7], or met Diagnosis and Statistical Manual of Mental Disorders IV-V (DSMIV-V) criteria[8–10], or had a clinical dementia rating (CDR® Dementia Staging Instrument[11]) > 0.5. Some cohorts verified AD diagnoses by means of neuropathology, using Braak staging[12], CERAD scoring[13], or National Institute on Aging Reagan (NIA-Reagan) 1997 criteria[14]. Cognitively normal subjects did not have AD according to the above clinical AD criteria, did not have a diagnosis of mild-cognitive impairment (MCI), and had a CDR of 0 and/or Mini-Mental State Examination (MMSE[15]) > 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)[16].

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 provide detailed information regarding clinical status (control, 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[17,18]. 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)[14]. In concordance with the category "possible AD dementia with evidence of the AD pathophysiological process" from the NIA-AA 2011 criteria[17], 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[18,19], we also evaluated neuropathology in MCI subjects to verify presumed AD etiology (cf. page 5). 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) and a subset of the ADSP projects 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)[20–22], and Neuropathology data set (NP)[23]. 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[18,24]. In the current study, we used the UDS and NP for which data was collected between September 2005 and March 2022, to determine phenotypes for subjects in ADC1-7, ADSP WES/WGS, and ADGC Exome arrays.

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, not due to AD, or only secondary due to AD (and without AD neuropathological information), were excluded. Subjects with a final diagnosis of "cognitively impaired but not MCI", but having no other neurological disorder, were kept as controls, considering that this more consistently matched control criteria in many of the other cohorts considered in this study.

ROSMAP

In ROSMAP, subjects were diagnosed at each visit: as possible/probable AD according to NINCDS-ADRDA criteria[7]; 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[25,26]. At time of death, a final clinical diagnosis was made by an expert neurologist, followed by case conference consensus review (blinded to postmortem data)[27].

ADNI

In ADNI, subjects were diagnosed at regular visits: as possible/probable AD according to NINCDS-ADRDA criteria[7]; as MCI according to Petersen/Winblad criteria; or as control when not demented, not MCI, CDR = 0, and MMSE > 28. Neuropathology assessments followed the NACC NP framework.

Phenotype Harmonization

The available sample contained many subjects that were genotyped multiple times across different studies. This largely reflected efforts from the ADGC, ADSP, and AMP-AD, to perform next generation sequencing (NGS) on existing cohort samples for the purpose of rare variant discovery and AD gene prioritization. In other instances, participants were recruited in different studies at different times. Therefore, to handle potential duplicate discordance and phenotype heterogeneity, we implemented a cross-sample phenotype harmonization procedure aiming to standardize pathology-verified diagnoses where possible, share unique missing information across all duplicate entries of a given subject, resolve longitudinal changes in diagnosis, and flag subjects with unresolvable duplicate discordance for exclusion.

Duplicate samples were identified by determining genetic cryptic relatedness (cf. below), but for the purpose of sample cross-referencing did not include known identical twins in LOAD and ROSMAP samples. First, duplicate samples were flagged as discordant if their age-at-death information differed by more than 2 years or if pathology measures (Braak or neuritic plaque density) differed. Across all cohorts, where possible, 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)[14]. Additionally, when only either neuritic plaque or Braak information was available and in line with NIA-Reagan 1997 middle or high AD likelihood criteria, and/or the cohort/project demographics provided a diagnosis of definite AD, the subject was considered to have pathology-verified AD status. Cognitively normal (CN) subjects with evidence of AD pathology were kept as CN. Further, if at least one entry across duplicate samples indicated a diagnosis of Down syndrome, central nervous system neoplasm, bipolar disorder, schizophrenia, alcohol-induced dementia, substance-abuse-induced dementia, neurological (not including Parkinson's disease) or systemic disease despite being cognitively normal, or carrying mutations of dominantly inherited AD or frontotemporal lobar degeneration (FTLD), then all duplicate samples were marked as such and flagged for exclusion. Extending on the above, all genetic samples were checked for the presence of known pathogenic mutations on *APP, PSEN1, PSEN2* and *MAPT*, whereby carriers and their duplicate samples were flagged for exclusion.

Then, duplicate samples with differing age entries (i.e. longitudinal changes) were evaluated. Reversions from AD or dementia to MCI status, or from MCI to cognitively normal (CN) status, were permitted, but reversions from AD or non-AD dementia to CN status were flagged for exclusion. "Reversions" from AD to non-AD dementia status were permitted, unless pathology (cf. above) indicated the presence of AD pathology, thereby marking the subject as AD. Vice versa, "conversions" from non-AD

dementia to AD status were permitted, unless pathology (cf. above) indicated no presence of AD pathology, thereby marking the subject as non-AD dementia. All other types of conversions were directly permitted. Then, duplicate samples for which the diagnoses at the oldest shared age entries differed, or for which diagnoses differed but age was consistent (i.e. apparent cross-sectional discordances), were evaluated. Discordances between AD and non-AD dementia status were resolved on the basis of pathology (cf. above) or flagged as discordant if no pathology data was available. Discordances between CN and AD status, or CN and non-AD dementia status, were resolved as respectively AD or non-AD dementia when those dementia diagnoses corresponded to a unique age-at-onset (of symptoms) without other available age information (i.e. indicating that a conversion likely occurred after the subject was lost to follow-up in the cohort that last observed a CN status), or, were flagged as discordant if duplicate entries shared the same age-at-examination and age-at-last-exam. Discordances between CN and MCI status, or MCI and AD status, or MCI and non-AD dementia status, were resolved as respectively MCI, AD, or non-AD dementia (i.e. keeping the most severe diagnosis).

Finally, once all clinical diagnostic and pathological data were unified across duplicate entries, pathological criteria were applied once more to obtain the final diagnoses. Where possible, 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)[14]. In concordance with the category "possible AD dementia with evidence of the AD pathophysiological process" from the NIA-AA 2011 criteria[17], 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[18,19], we also evaluated neuropathology in MCI subjects to verify presumed AD etiology and considered subjects as cases if AD pathology, following NIA-Reagan 1997 criteria (cf. above), was present (i.e. marking high likelihood of AD etiology). Controls were not re-evaluated based on neuropathology data.

Beyond cross-referencing clinical diagnostic and pathological data across subjects, other covariates were considered for cross-referencing or sharing in case of missingness across duplicate entries. These included age-at-onset of cognitive symptoms, age-at-examination providing clinical diagnosis, at-at-last exam, age-at-death, sex, race, ethnicity, *APOE* genotype provided from demographics, *APOE* genotype provided from whole-genome sequencing, and *APOE* genotype provided from whole-exome sequencing. Duplicate entries with discordant sex or race information were flagged for exclusion.

Genetic Data Quality Control and Processing

Genetic Data Harmonization and Standard Quality Control

Genotypes were available from commercial high-density single-nucleotide polymorphism (SNP) genotyping microarrays (Illumina or Affymetrix), Exome microarrays, Exome sequencing (ES), or Genome sequencing (GS) (**eTable 1-2**). Genotype samples had their genetic variants lifted to hg38 using liftOver if not released in hg38[28]. Autosomal variants were extracted from the SNP array data and further processed in several stages. First, SNP array data were processed by the Genotype Harmonizer with CEU and TSI HapMap populations as the reference panel, to perform automatic strand alignment[29]. Then, multi-allelic SNPs, SNPs located on common copy number or segmental duplication regions, and duplicated or monomorphic SNPs, were removed. The list of multi-allelic SNPs or SNPs located on common copy number and segmental duplication regions was created using Tri-Typer[30]. The list of CNV and segmental duplication regions was curated from the Eichler lab (eichlerlab.gs.washington.edu/database.html)[31] and the gnomAD website (gnomad.broadinstitute.org/downloads)[32]. All respective genotype data sets were then iteratively merged with each other, applying strand flipping and variant ID updating as applicable, to ultimately obtain parsimonious data sets that could be merged for cross-sample relationship determination and principal component analyses (cf. below).

Genetic data were then further processed using Plink v1.9. For each sample platform, subjects with autosome missingness (≥ 5%) and sex problems (discordance between genetic sex and demographic sex, or deviation of expected X-chromosome homozygosity/heterozygosity) were flagged for exclusion.

Ancestry Determination

Individual ancestries were determined using SNPweights v.2.1 with populations from the 1000 Genomes Consortium as a reference[33,34]. By applying an ancestry percentage cut-off ≥ 75%, the samples were stratified into the five super populations, South-Asians (SAS), East-Asians (EAS), Amerindians (AMR), Africans (AFR) and Europeans (EUR) (**eFigure 2**). When multiple samples were available for a single unique individual, the ancestry was inferred from the sample with the highest genetic coverage.

Genetic Relationship Determination using King

Across all cohorts the relatedness of subjects (after QC indicated above) was evaluated through identity-by-descent (IBD) analysis (using directly genotyped non-palindromic SNPs that shared across all genetic datasets with a call rate > 95%, minor allele frequency (MAF) > 1%). This outcome was used for

duplicate tracking across samples, which in turn was used to enable phenotype harmonization, and to identify first-degree related samples, which in turn was used to retain only one individual per relatedness cluster in *APOE* dosage and genotype association analyses.

APOE genotype assessment in ADSP WES/WGS

In ADSP WGS, the rs429358 and rs7412 variants showed low genotype missingness across subjects, reflecting good variant quality metrics. In ADSP WES, there was a high genotype missingness at rs7412 (32.5%). This resulted from a low read depth and genotype quality in some of the different WES capture kits that were used in the ADSP WES[2]. We therefore sought to re-call both variants in order to fill out missing *APOE* information where possible. We first inferred the variants' genotype using data called by the ADSP, which required a read depth read depth (DP) >=10 and genotype quality (GQ) >= 20. We then further inferred the variants' genotype if DP and GQ were respectively greater than or equal to 6 and 20, observing at least 20% alternate allele reads to call a heterozygote (e.g. *APOE**3/4).

After this first round of *APOE* genotype ascertainment, some individuals still had either the rs7412 or rs429358 genotype missing (i.e., only one of the two variants could be called using the above criteria), making it impossible to infer their *APOE* genotype from the ADSP NGS data alone. Many of these remaining individuals however had a reported *APOE* genotype in their demographics that could be used to complete the missing information in a second additional round of *APOE* genotype ascertainment. This approach was preferred over relying solely on the *APOE* genotype in the demographics, since the genotype calls on the ADSP NGS data are expected to provide higher accuracy compared to other commonly used *APOE* direct genotyping methods[36]. To illustrate, consider the example where one of these remaining individuals in the sequencing data was homozygous for the reference allele at rs429358, which would suggest the subject is *APOE**3/3, but had a missing genotype at rs7412. In this case, from the ADSP NGS data, we know that this individual is not carrying an *APOE**4 allele, but we cannot determine the presence or absence of an *APOE**2 allele. We then turned to the information from the *APOE* genotype provided in the demographics to infer the most likely *APOE* genotype. For the current example, if the individual has a provided *APOE* genotype that was 2/2, 2/3, or 3/3, then the information in the ADSP NGS data is deemed concordant with the provided *APOE* genotype (that is, rs429358 is always the reference allele for those provided *APOE* genotypes) and we used the provided *APOE* genotype. However, if the provided *APOE* genotype was 4/4 or 3/4, then we would correct it to *APOE**3/3, because the ADSP NGS information clearly indicated there was no *APOE**4 genotype call (similarly a provided *APOE**2/4 genotype would be corrected to *APOE**2/3). This can be generalized as: for remaining individuals with DP>=6 and

GQ>=20 at rs429358, the ADSP NGS data at rs429358 was used to change, when discordant, the provided *APOE**3 genotype to *APOE**4, or vice-versa. One additional extension to this step was implemented for the few scenarios where the ADSP NGS data called two rs429358 alleles (i.e. *APOE**4/4) but the allelic distribution indicated that the reference allele was still observed (e.g. 1 REF allele and 7 ALT alleles). In these situations, if the provided *APOE* genotype indicated the presence of *APOE**3, then the genotype was corrected to *APOE**3/4 (reasoning there is sufficient evidence to support the presence of an *APOE**3 genotype). The extra checks described in this paragraph were also applied to subjects in the first QC round (prior paragraph), who had 6<=DP<10 and GQ>=20 for both rs429358 and rs7412.

As a quality check, using these thresholds, we did not observe any discordance in the inferred *APOE* genotype across 3,499 duplicates between the ADSP WGS and ADSP WES.

APOE genotype consensus harmonization and imputation

We used the consensus *APOE* genotyping approach as described in Belloy et al. 2022[37], namely, to prioritize first WGS/WES *APOE**2/3/4 genotypes if available (and if only either rs429358 or rs7412 is available from WGS/WES, to use those genotype data to verify the provided/demographic *APOE**2/3/4 genotypes); second to use provided/demographic *APOE**2/3/4 genotypes; and third, in subjects without WGS/WES information, to exclude those for whom the provided/demographic and imputed (R2>0.8) *APOE**2/3/4 genotypes are discordant. Regarding imputation, SNP array data were used to perform genotype imputation with regard to the TOPMed imputation reference panel[38,39], which was performed per SNP array and per sample groups of >75% European ancestry, >75% African ancestry, >75% Amerindian ancestry, or admixed samples where all global ancestries where <75%. The final step to ensure the highest quality of *APOE**2/3/4 genotypes was to verify and harmonize *APOE* genotype information across available duplicate samples.

Race and Ethnicity Ascertainment

Race and ethnicity (Hispanic versus non-Hispanic) information was directly available for a large fraction of samples (87.4% and 79.9% respectively). In many instances, this missing race information could be inferred from the respective cohorts/studies that contributed the samples (and often corresponds to White samples). Missing ethnicity information similarly reflected that related cohort/studies mainly recruited non-Hispanic samples and as such, we considered missing ethnicity information as samples being non-Hispanic. Based on prior observations of higher European ancestry in non-Hispanic Whites and higher African ancestry in non-Hispanic Blacks, and in an attempt to reduce potential ambiguity about

missing race status in available genetic samples, we used ancestry information in some individuals to inform on race status. For Non-Hispanic White (NHW) individuals, 18.4% of samples included in the final association analyses did not have race information directly available in cohort covariate files, but these subjects showed a global European ancestry >75%. For Non-Hispanic Black (NHB) individuals, 11.3% of samples included in the final association analyses did not have race information directly available in cohort covariate files, but these subjects showed a global African ancestry >75%. For Hispanic (HISP) individuals, ethnicity information was always available and indicated Hispanic status. Within HISP subjects, for Hispanic White (HW) individuals, 62.9% of samples included in the final association analyses did not have race information directly available in cohort covariate files, but these subjects showed a global European ancestry >75%, and, for Hispanic Black (HB) individuals, 87.2% of samples included in the final association analyses did not have race information directly available in cohort covariate files, but these subjects showed a global African ancestry >75%.

Statistical Analyses

Design of statistical analyses and General model criteria

All association analyses with AD risk (primary) or survival (secondary) adjusted for sex, array/batch/center, and global European, African, and Amerindian ancestry. Other technical covariates were considered in respective sensitivity analyses. Age adjustment in case-control analyses was not performed, given that the current AD genetic samples often showed younger ages for cases than controls due to the use of age-at-onset information (**eTable3**), which violates the assumption for age adjustment (which is that older age is associated with increased AD incidence). In prior work, we showed that age adjustment in such scenarios leads to significantly decreased power for genetic association analyses[40]. To avoid concern given the lack of age adjustment (which may be relevant particularly for HISP where ages in controls was on average higher than ages in controls), secondary survival analyses provide alternative insight into *APOE* genotype associations with AD by directly integrating age-at-onset data.

All association analyses evaluated the effect *APOE**2 dosage, *APOE**4 dosage, or *APOE* genotype with regard to *APOE**33 as the reference. Dosage effects were evaluated as a scalar, additive genetic model. All interaction between *APOE* dosage or genotype with sex were evaluated through formal interaction tests (i.e. an *APOE*-by-SEX variable in the association model in addition to *APOE* and sex variables). Differences across race/ethnicity groups were evaluated through heterogeneity tests, using the following formulation: Z-value = $(Beta_{Group1} - Beta_{Group2})/\sqrt{(SE_{Group1}^2 + SE_{Group2}^2)}$. P-values were then determined

using the normal distribution with a two-sided hypothesis in R using the following formulation: P-value = 2*pnorm(q=Z-value, lower.tail=FALSE).

Age information

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]. In cohorts that provide conversion information but not AAO, age-at-examination (AAE) was used and followed a prioritization of age-at-MCI-diagnosis > age-at-dementia-diagnosis (incident) > age-at-dementia diagnosis (prevalent). This was done to most closely approximate AAO. For the remaining control samples, age-at-last-examination (AAL) was used. After implementing these criteria, samples were filtered to have a minimal age of 55 years. Some samples were censored at ages 90+, for which we assumed the age was 90.

Multivariate Case-Control Logistic Regression Analyses

Case-control analyses were conducted using the standard *glm* function in R (v.4.2.1). In age-stratified analyses, the oldest age window was 90+, meaning that there was no concern for the use of samples censored at ages 90+.

Multivariate Cox Proportional Hazards Regression Analyses

Survival analyses were conducted using the *coxph* and *Surv* functions from the "survival" package in R (v.4.2.1). In these time-to-event analyses, events were defined at AAO (or best approximation) for individuals who developed AD (i.e. conversion to AD). Controls were right-censored at AAD or AAL. Left censoring was set at age 55 years. Individuals with ages censored at 90+ were removed from analyses.

Meta-Analysis

Meta-analyses were conducted using the *metagen* function from the "meta" package in R (v.4.2.1).

eAppendix. Additional Contributions

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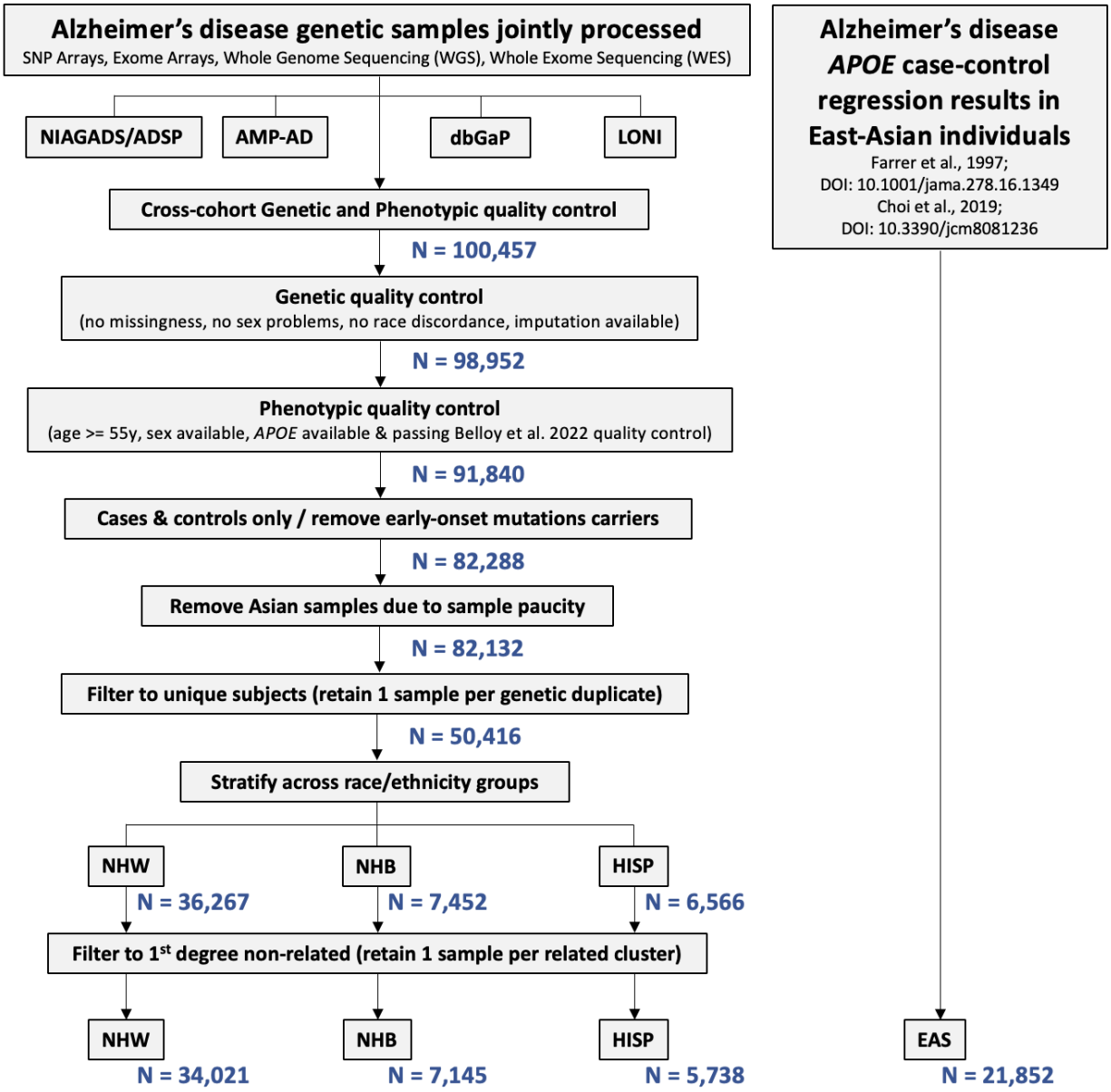
Rosenberg, MD), P30 AG049638 (PI Suzanne Craft, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P30 AG062715-01 (PI Sanjay Asthana, MD, FRCP), P50 AG005681 (PI John Morris, MD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD). MARS & LATC: We thank all Minority Aging Research Study and Latino Core participants and the Rush Alzheimer's Disease Center staff. This database was funded by the NIH/NIA grants R01AG22018 (MARS) and P30AG 072975 (ADC). GenADA: The genotypic and associated phenotypic data used in the study "Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease (GenADA)" were provided by the GlaxoSmithKline, R&D Limited. ROSMAP: ROSMAP study data were provided by the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago. Data collection was supported through funding by NIA grants P30AG10161, R01AG15819, R01AG17917, R01AG30146, R01AG36836, U01AG32984, U01AG46152, the Illinois Department of Public Health, and the Translational Genomics Research Institute. AddNeuroMed: The AddNeuroMed data are from a public-private partnership supported by EFPIA companies and SMEs as part of InnoMed (Innovative Medicines in Europe), an Integrated Project funded by the European Union of the Sixth Framework program priority FP6-2004-LIFESCIHEALTH-5. Clinical leads responsible for data collection are Iwona Kłoszewska (Lodz), Simon Lovestone (London), Patrizia Mecocci (Perugia), Hilkka Soininen (Kuopio), Magda Tsolaki (Thessaloniki), and Bruno Vellas (Toulouse), imaging leads are Andy Simmons (London), Lars-Olad Wahlund (Stockholm) and Christian Spenger (Zurich) and bioinformatics leads are Richard Dobson (London) and Stephen Newhouse (London). ADNI: Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering and through generous contributions from the following: AbbVie. Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica. Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir. Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals. Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech. Inc.; Fujirebio; GE HealtControlsare; IXICO Ltd; Janssen Alzheimer Immunotherapy Research & Development. LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co. Inc.; Meso Scale Diagnostics. LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health. The grantee organization is the Northern California Institute for Research

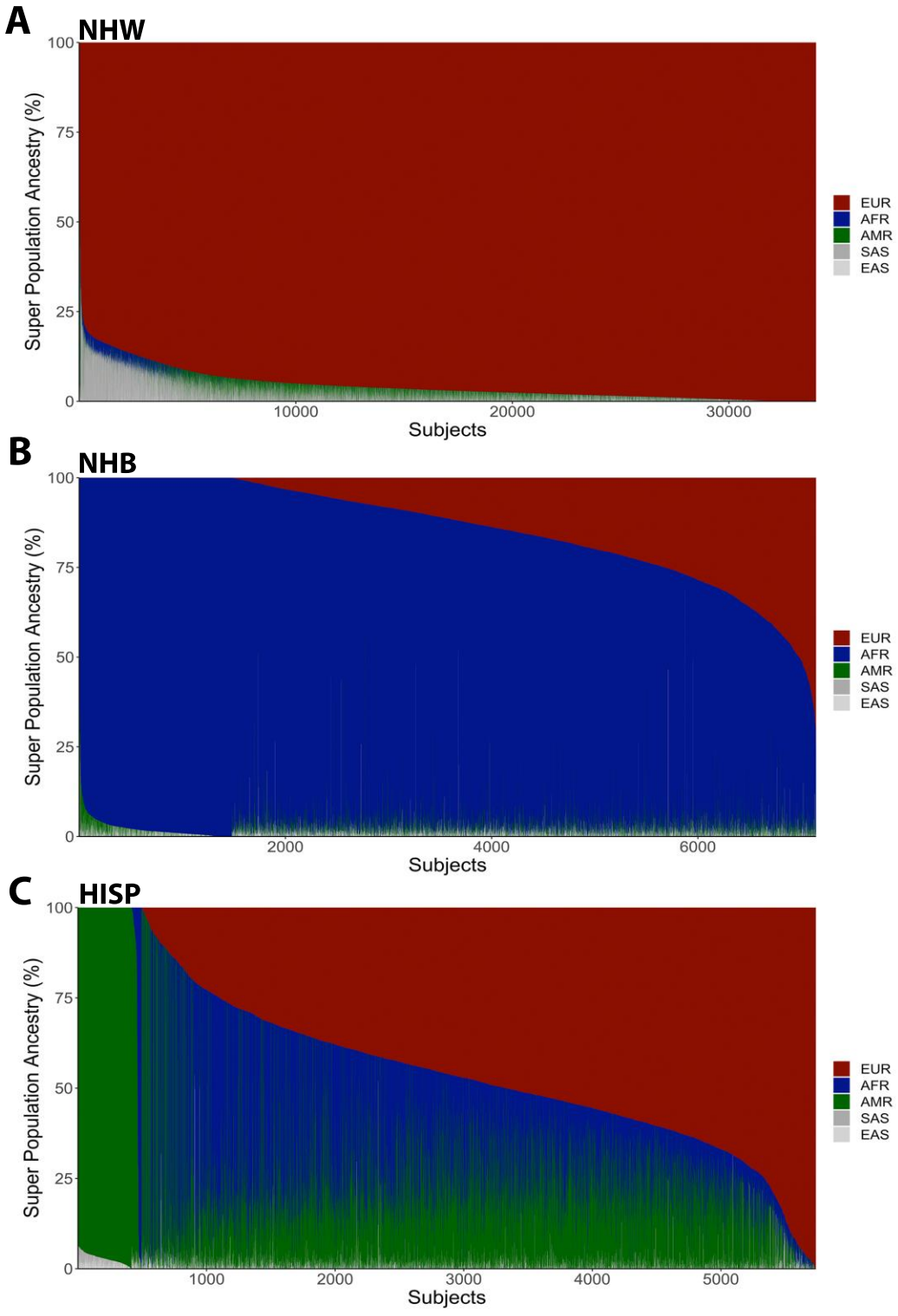
and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. NCRAD: Biological samples used in this study were stored at study investigators' institutions and at the National Cell Repository for Alzheimer's Disease (NCRAD) at Indiana University, which receives government support under a cooperative agreement grant (U24 AG21886) awarded by the National Institute on Aging (NIA).

eFigure 1. Flow Chart of Sample/Participant Filtering for *APOE* Association Analyses With Alzheimer's Disease Risk



The Belloy et al. 2022 quality control procedure is described in the supplementary methods and in the original study.[37]

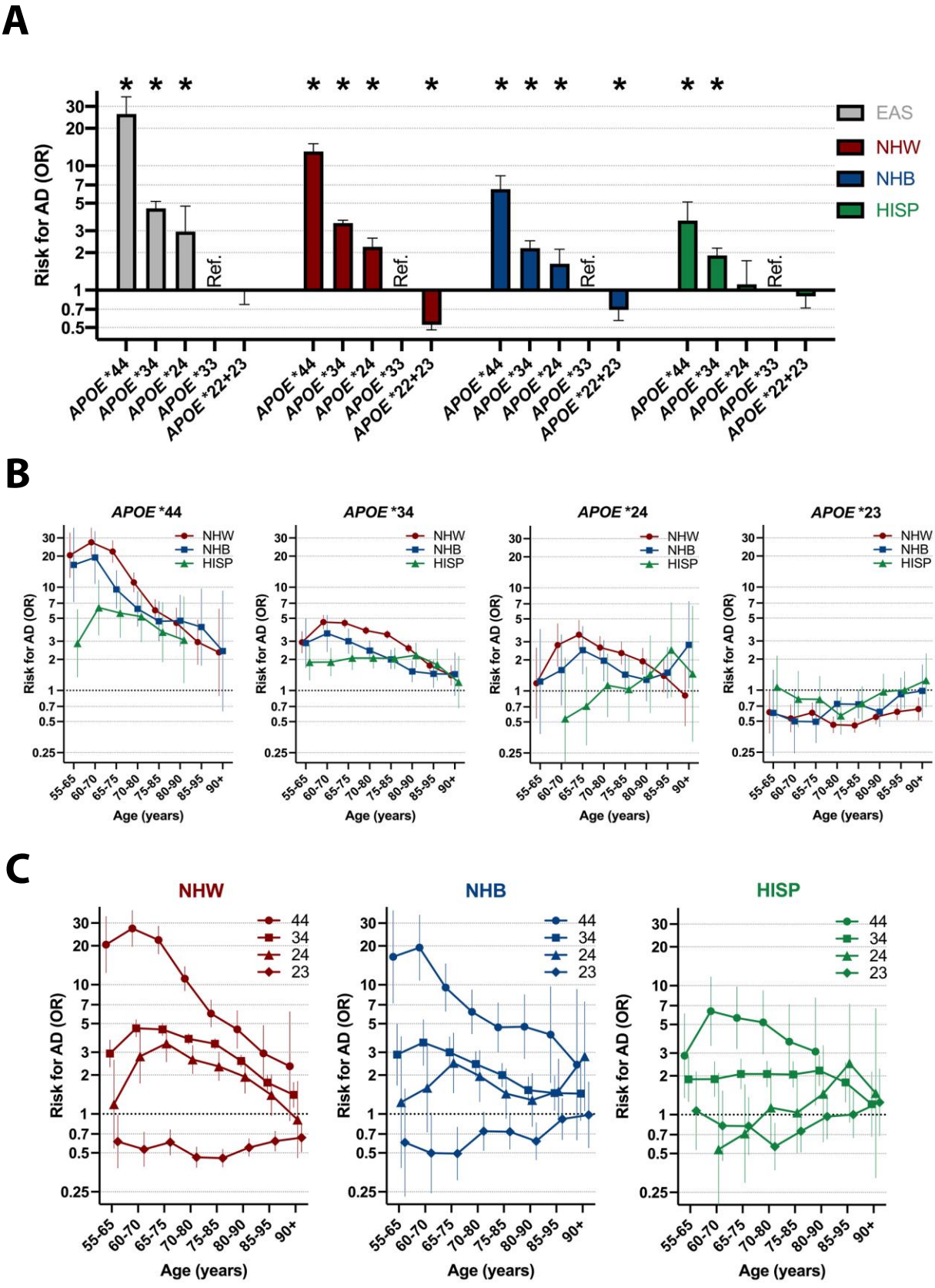
eFigure 2. Admixture Plots Across the Five Major Super Populations, for Participants Included in Association Analyses



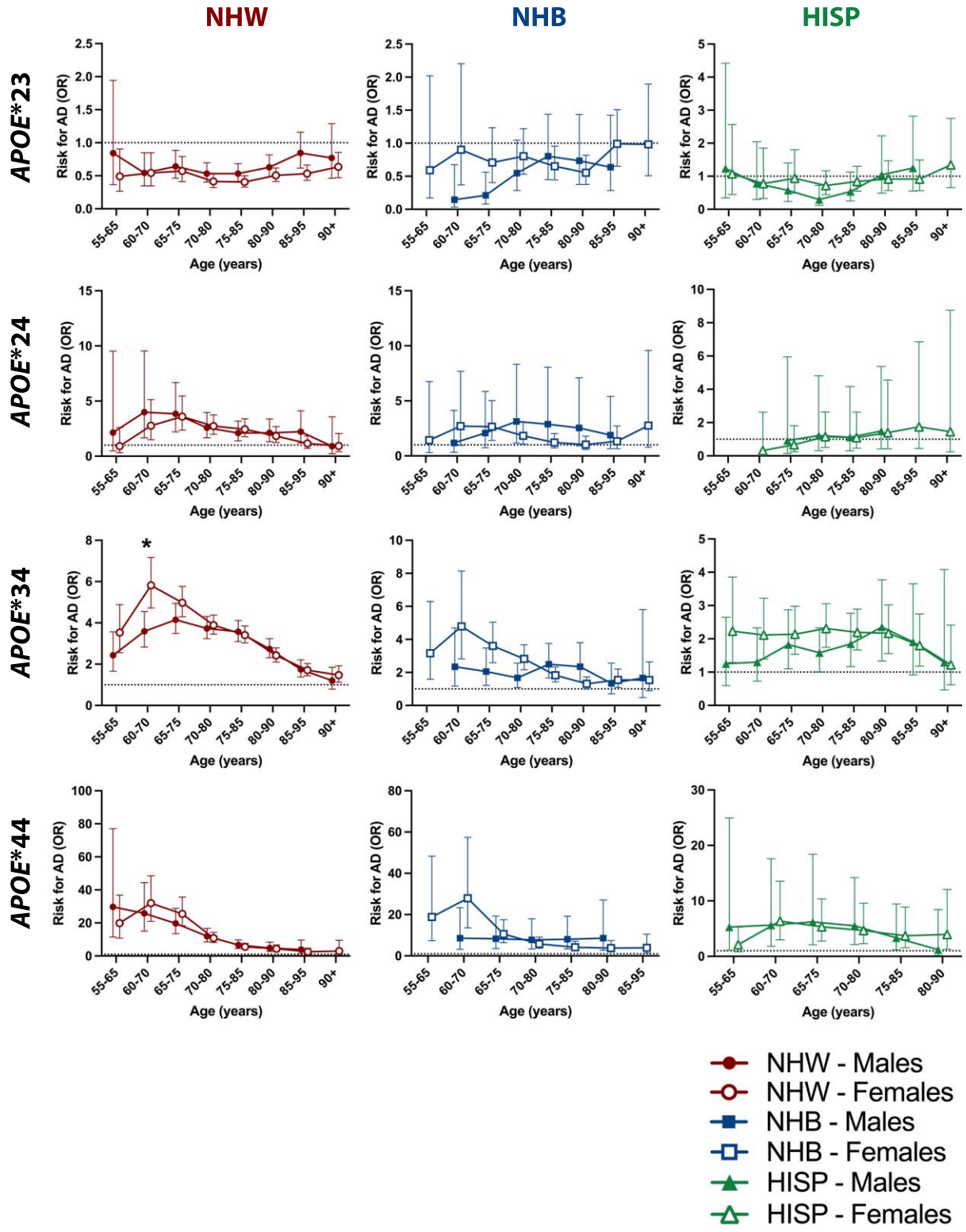
(A) Non-Hispanic White (NHW), (B) Non-Hispanic Black (NHB), (C) Hispanic (HISP).

Abbreviations: EUR, European; AFR, African; AMR; Amerindian; SAS, South Asian; EAS; East Asian.

eFigure 3. Alternative Visualizations of Case-Control Regression Results Presented in Figure 1

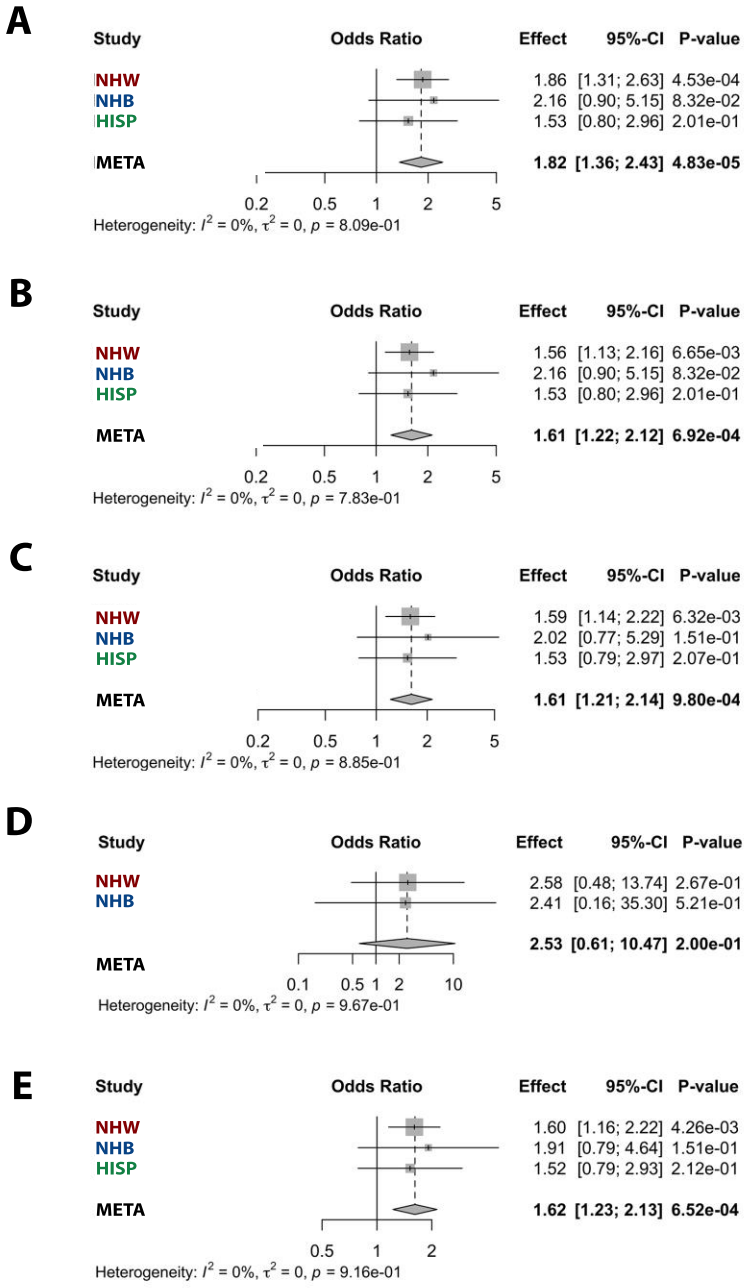


eFigure 4. Sex-and-Age Stratified Results for *APOE* Genotype Case-Control Regression Analyses Across Non-Hispanic White (NHW), Non-Hispanic Black (NHB), and Hispanic (HISP) Individuals



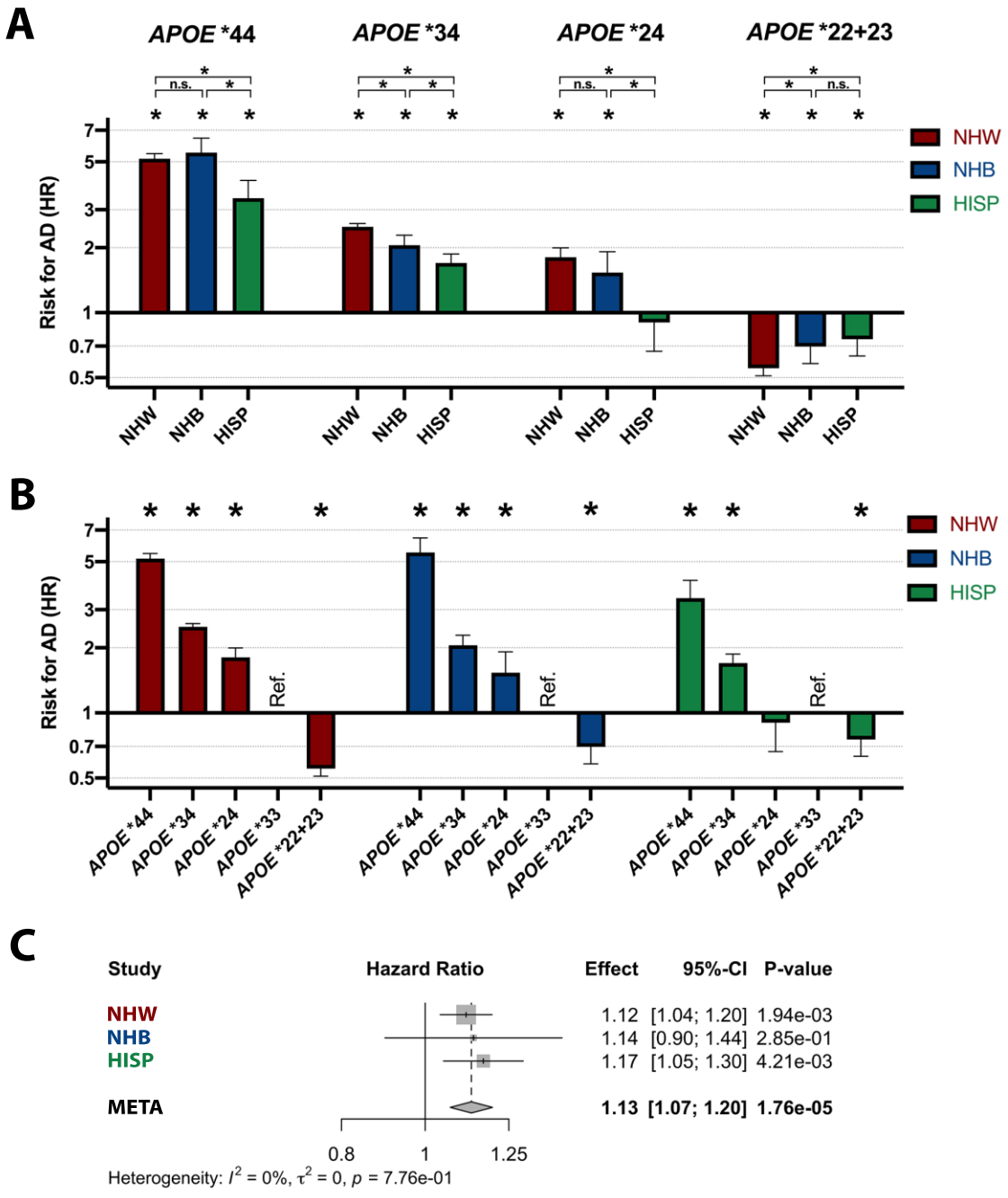
Star marks significant sex difference.

eFigure 5. *APOE**34-by-Sex Interaction Effect in Case-Control Regression Analyses for Individuals 60 to 70 Years of Age Is Preserved Across Sensitivity Analyses



A) Excluding subjects with pathology. B) Additionally adjusting for pathology verification status. C) Using only samples from cohorts with a clinical/hospital or autopsy/brainbank ascertainment design, while additionally adjusting for pathology verification status. D) Using only samples from cohorts with a community/population-based ascertainment design, while additionally adjusting for pathology verification status (HISP not included due to sample paucity). E) Additionally adjusting for ascertainment design and pathology verification status.

eFigure 6. Survival Analyses Results, Through Cox Regression, Across *APOE* Genotypes, for Non-Hispanic White (NHW), Non-Hispanic Black (NHB), and Hispanic (HISP) Individuals



For exact summary statistics corresponding to this figure, please cf. eTable 13. **(A-B)** Compared to case-control regression results presented in Figure 1A, the current figure shows more pronounced *APOE**22+23 effects in HISP individuals and loss of *APOE**24 and *APOE**44 significant differences across NHW and NHB. (C) In line with results present in Figure 1C, the *APOE**34-by-sex interaction was consistent across race/ethnicity groups and was even more significant upon meta-analysis compared the outcome of case-control regression analyses.

eTable 1. Overview of Genotyping Platforms Across All Available AD-Related Genetic Data

Cohort/Study	Genotyping Platform	Cohort-Platform ID	Sample count	Data Repository
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)
ADNI	Illumina Human 610-Quad	ADNI_1	757	LONI ADNI
	Illumina Human OmniExpress	ADNI_2	361	LONI ADNI
	Illumina Global Screening Array (GSA)	ADNI_3	327	LONI ADNI
	Illumina Omni 2.5	ADNI_O25	812	LONI ADNI
	Whole Genome Sequencing - Illumina	ADNI_WGS	812	LONI ADNI
ADNI-DOD	Illumina Human OmniExpress	ADNI_DOD	204	LONI ADNIDOD
ADSP Exome-Arrays	Illumina HumanExome BeadChip v1.0 - CHOP	CHOP	5180	NIAGADS (NG00081) / NACC
	Illumina HumanExome BeadChip v1.0 - Miami	MIA	1923	NIAGADS (NG00080) / NACC
	Illumina HumanExome BeadChip v1.0 - Northshore	NS	5998	NIAGADS (NG00079) / NACC
	Illumina HumanExome BeadChip v1.0 - WashU	WU	868	NIAGADS (NG00085) / NACC
ADSP WES	Whole Exome Sequencing	ADSP_WES	20503	NIAGADS DSS (NG00067.v3) / NACC
ADSP WGS	Whole Genome Sequencing	ADSP_WGS	16906	NIAGADS DSS (NG00067.v5) / NACC
Indianapolis African-American	Illumina Human 1M-Duo	IIDP_AA	1175	NIAGADS (NG00047)
Indianapolis Yoruba	Illumina Omni 2.5	IIDP_YOR	1264	dbGaP (phs000378)
CIDR	Illumina Human Omni1-Quad	CIDR	3101	NIAGADS (NG00015) / dbGAP (phs000496)
GenADA	Affymetrix 500K	GSK	1571	dbGaP (phs000219)
HBTRC	Illumina Human Hap650Y	HBTRC_ILL	338	Synapse AMP-AD (syn3159435)
	Illumina Human Hap650Y	HBTRC_PERL	402	Synapse AMP-AD (syn3159435)

LATC	Illumina Multi-Ethnic – BU	LATC	63	RADC Rush (contact:Gregory_Klein@rush.edu)
NIA-LOAD	Illumina Human 610-Quad	LOAD	5220	NIAGADS (NG00020)
MARS	Illumina Multi-Ethnic – BU	MARS	708	RADC Rush (contact:Gregory_Klein@rush.edu)
MAYO	Illumina Human Hap300	MAYO_1	2099	Synapse AMP-AD (syn5591675) / NIAGADS (NG00029)
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 (contact:Gregory_Klein@rush.edu) / Synapse AMP-AD
	Affymetrix GeneChip 6.0 - TGen	ROSMAP_1T	582	RADC Rush (contact:Gregory_Klein@rush.edu) / Synapse AMP-AD
	Illumina Human OmniExpress 12 - Chop	ROSMAP_2C	382	RADC Rush (contact:Gregory_Klein@rush.edu) / Synapse AMP-AD
	Illumina Multi-Ethnic - BU	ROSMAP_3BU	494	RADC Rush (contact:Gregory_Klein@rush.edu)
TARCC	Affymetrix 6.0	TARCC	625	NIAGADS (NG00097)
	Illumina Multi-Ethnic – BU	TARCC_full	2718	TARCC (contact: Bruce.Jones@UTSouthwestern.edu)
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 WES or WGS Available Through 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. Overview of Participant Demographics Across Race and Ethnicity and *APOE* Genotype Strata

Group & *APOE* stratum		Diagnosis		Pathology		Sex	Age	Global Ancestry		
Name	Participants after QC (N)	Type	(N (%))	Available (N (%))	AD Path. (N (%))	Female (N (%))	Age (Mean (SD))	EUR% (Mean (SD))	AFR% (Mean (SD))	AMR% (Mean (SD))
Non-Hispanic White (NHW)										
All	34,021	CN	17,058 (50.1 %)	2,070 (12.1 %)	314 (15.2 %)	10,183 (59.7 %)	79.4 (8.8)	95.4 % (5.2 %)	0.6 % (1.9 %)	1.6 % (2.6 %)
		AD	16,963 (49.9 %)	6,639 (39.1 %)	6,639 (100 %)	9,982 (58.8 %)	74.5 (8.7)	95.6 % (4.8 %)	0.6 % (1.7 %)	1.6 % (2.5 %)
***APOE* *22**	133	CN	105 (78.9 %)	22 (21.0 %)	2 (9.1 %)	55 (52.4 %)	81.9 (8.3)	96.0 % (4.2 %)	0.6 % (1.5 %)	1.2 % (1.8 %)
		AD	28 (21.1 %)	9 (32.1 %)	9 (100 %)	13 (46.4 %)	79.1 (9.5)	95.8 % (4.0 %)	0.4 % (1.0 %)	1.6 % (1.7%)
***APOE* *23**	2,886	CN	2,185 (75.7 %)	317 (14.5 %)	44 (13.9 %)	1,329 (60.8 %)	80.8 (8.7)	95.5 % (5.2 %)	0.6 % (2.1 %)	1.6 % (2.3 %)
		AD	701 (24.3 %)	240 (34.2 %)	240 (100 %)	409 (58.3 %)	79.1 (9.5)	95.6 % (5.1 %)	0.6 % (1.7 %)	1.5 % (2.3 %)
***APOE* *33**	741	CN	10,647 (61.9 %)	1,349 (12.7 %)	202 (14.5 %)	6,345 (59.6 %)	79.8 (8.8)	95.2 % (5.2 %)	0.6 % (1.7 %)	1.6 % (2.6 %)
		AD	6,552 (38.1 %)	2,491 (38.0 %)	2,491 (100 %)	3,929 (60.0 %)	76.8 (9.3)	95.1 % (5.1 %)	0.7 % (1.6 %)	1.5 % (2.4 %)
***APOE* *24**	17,199	CN	319 (43.0 %)	32 (10.0 %)	4 (12.5 %)	204 (63.9 %)	78.7 (8.5)	95.5 % (6.8 %)	0.7 % (3.7 %)	1.8 % (4.8 %)
		AD	422 (57.0 %)	180 (42.7 %)	180 (100 %)	267 (63.3 %)	75.4 (7.5)	96.0 % (4.2 %)	0.5 % (2.0 %)	1.6 % (2.0 %)
***APOE* *34**	10,807	CN	3,533 (32.7 %)	333 (9.4 %)	57 (17.1 %)	2,084 (59.0 %)	77.7 (8.6)	95.7 % (5.0 %)	0.5 % (1.9 %)	1.6 % (2.4 %)
		AD	7,274 (67.3 %)	2,906 (40.0 %)	2,906 (100 %)	4,275 (58.8 %)	73.4 (7.6)	95.8 % (4.7 %)	0.5 % (1.7 %)	1.6 % (2.5 %)
***APOE* *44**	2,255	CN	269 (11.9 %)	17 (6.3 %)	5 (29.4 %)	166 (61.7 %)	74.7 (8.0)	96.1 % (6.6 %)	0.6 % (3.8 %)	1.8 % (3.2 %)
		AD	1,986 (88.1 %)	813 (40.9 %)	813 (100 %)	1,089 (54.8 %)	69.2 (6.8)	96.2 % (4.3 %)	0.4 % (1.9 %)	1.7 % (2.5 %)
Non-Hispanic Black (NHB)										
All	7,145	CN	5,134 (71.9 %)	38 (0.7 %)	5 (13.2 %)	3,627 (70.6 %)	79.2 (8.0)	13.8 % (13.9 %)	83.3 % (14.6 %)	1.6 % (2.8 %)
		AD	2,011 (28.1 %)	197 (9.8 %)	197 (100 %)	1,433 (71.3 %)	76.4 (8.4)	16.2 % (14.3 %)	80.8 % (14.7 %)	1.8 % (3.3 %)
***APOE* *22**	65	CN	55 (84.6 %)	0 (0.0 %)	-	37 (67.3 %)	80.0 (8.9)	11.9 % (15.1 %)	85.1 % (15.9 %)	1.5 % (2.3 %)
		AD	10 (15.4 %)	0 (0.0 %)	-	7 (70.0 %)	83.1 (5.6)	8.0 % (8.3 %)	89.1 % (8.6 %)	1.7 % (2.0 %)
***APOE* *23**	1,012	CN	854 (84.4 %)	7 (0.8 %)	0 (0.0 %)	581 (68.0 %)	79.4 (8.1)	14.5 % (13.9 %)	82.6 % (14.4 %)	1.6 % (3.2 %)
		AD	158 (15.6 %)	16 (10.1 %)	16 (100 %)	110 (69.6 %)	79.6 (8.2)	16.8 % (13.6 %)	80.1 % (15.0 %)	1.9 % (3.9 %)
***APOE* *33**	3,095	CN	2,464 (79.6 %)	21 (0.9 %)	3 (14.3 %)	1,762 (71.5 %)	79.7 (7.9)	14.1 % (14.5 %)	82.9 % (15.3 %)	1.6 % (2.7 %)
		AD	631 (20.4 %)	47 (7.4 %)	47 (100 %)	455 (72.1 %)	78.8 (8.1)	15.8 % (14.5 %)	81.2 % (14.9 %)	1.8 % (3.1 %)
***APOE* *24**	334	CN	231 (69.2 %)	5 (2.2 %)	0 (0.0 %)	164 (71.0 %)	78.6 (8.1)	12.8 % (13.4 %)	84.7 % (13.6 %)	1.4 % (2.0 %)
		AD	103 (30.8 %)	8 (7.8 %)	8 (100 %)	71 (68.9 %)	77.2 (8.1)	13.6 % (14.1 %)	82.9 % (15.1 %)	1.9 % (2.3 %)
***APOE* *34**	2,233	CN	1,391 (62.3 %)	5 (0.4 %)	2 (40.0 %)	978 (70.3 %)	78.6 (8.1)	13.2 % (13.0 %)	83.9 % (13.7 %)	1.7 % (3.0 %)
		AD	842 (37.7 %)	94 (11.2 %)	94 (100 %)	598 (71.0 %)	75.5 (8.1)	16.3 % (14.3 %)	80.7 % (14.6 %)	1.7 % (3.7 %)
***APOE* *44**	406	CN	139 (34.2 %)	0 (0 %)	-	105 (75.5 %)	76.3 (8.1)	13.3 % (12.2 %)	84.1 % (12.3 %)	1.4 % (2.2 %)
		AD	267 (65.8 %)	32 (12.0 %)	32 (100 %)	192 (71.9 %)	71.3 (7.7)	17.5 % (14.3 %)	79.6 % (14.5 %)	1.8 % (2.2 %)
Hispanic White + Black + Other (HISP)										
All	5,738	CN	3,549 (61.9 %)	16 (0.5 %)	3 (18.8 %)	2,460 (69.3 %)	74.6 (8.7)	42.1 % (23.7 %)	23.7 % (21.8 %)	32.9 % (28.6 %)
		AD	2,189 (38.1 %)	49 (2.2 %)	49 (100 %)	1,455 (66.5 %)	76.6 (9.0)	46.9 % (21.5 %)	29.6 % (21.3 %)	22.3 % (19.3 %)
***APOE* *22**	24	CN	15 (62.5 %)	0 (0.0 %)	-	9 (60.0 %)	79.4 (8.6)	45.2 % (20.0 %)	32.0 % (24.6 %)	21.6 % (19.5 %)
		AD	9 (37.5 %)	0 (0.0 %)	-	8 (88.9 %)	79.7 (7.0)	32.8 % (24.4 %)	52.8 % (31.7 %)	11.6 % (12.6 %)
***APOE* *23**	482	CN	330 (68.5 %)	2 (0.6 %)	0 (0.0 %)	236 (71.5 %)	76.6 (9.0)	42.0 % (23.8 %)	28.6 % (24.1 %)	28.0 % (26.7 %)
		AD	151 (31.5 %)	2 (1.3 %)	2 (100 %)	107 (70.4 %)	79.7 (9.7)	45.2 % (20.1 %)	35.1 % (22.8 %)	18.7 % (14.4 %)
***APOE* *33**	3,517	CN	2,376 (67.6%)	12 (0.5 %)	3 (25.0 %)	1,641 (69.1 %)	74.7 (8.7)	42.2 % (24.2 %)	21.8 % (21.2 %)	34.7 % (29.4 %)
		AD	1,141 (32.4 %)	24 (2.1 %)	24 (100 %)	751 (65.8 %)	77.4 (9.0)	47.8 % (21.8 %)	27.6 % (20.3 %)	23.4 % (20.6 %)
***APOE* *24**	101	CN	57 (56.4 %)	0 (0.0 %)	-	44 (77.2 %)	74.4 (7.9)	41.0 % (21.6 %)	35.9 % (24.7 %)	22.0 % (20.9 %)
		AD	44 (43.6 %)	0 (0.0 %)	-	26 (59.1 %)	80.0 (7.7)	41.4 % (18.4 %)	41.8 % (22.6 %)	15.5 % (10.1 %)
***APOE* *34**	1,426	CN	712 (49.9 %)	2 (0.3 %)	0 (0.0 %)	489 (68.7 %)	73.6 (8.3)	41.8 % (22.1 %)	26.2 % (21.5 %)	30.6 % (27.1 %)
		AD	714 (50.1 %)	20 (2.8 %)	20 (100 %)	481 (67.4 %)	75.3 (8.7)	46.5 % (21.8 %)	30.0 % (21.6 %)	22.1 % (19.2 %)
***APOE* *44**	188	CN	59 (31.4 %)	0 (0.0 %)	-	41 (69.5 %)	70.2 (7.8)	41.3 % (21.7 %)	28.4 % (22.7 %)	28.9 % (25.0 %)
		AD	129 (68.6 %)	3 (2.3 %)	3 (100 %)	82 (63.6 %)	71.5 (7.4)	46.0 % (19.9 %)	33.1 % (21.2 %)	20.1 % (14.0 %)

eTable 4. Overview of Participant Demographics Across the Cohort-Platform Technical Covariate

	NHW		NHB		HISP	
Cohort-Platform ID	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**
ACT	1,522	558	68	26	4	1
ADC1	292	1,206	21	17	8	18
ADC2	72	537	0	0	0	0
ADC3	297	563	0	0	7	6
ADC4	269	325	0	1	1	4
ADC5	358	324	0	0	0	0
ADC6	204	317	0	0	0	0
ADC7	372	281	0	0	0	0
ADM_O	111	123	0	0	0	0
ADM_Q	62	111	0	0	0	0
ADNI_1	21	53	1	4	1	1
ADNI_DOD	78	NA	5	NA	4	NA
ADNI_OE	1	2	0	0	0	0
ADNI3	197	20	5	0	8	1
ADSP_WES_Baylor	968	727	0	0	2	50
ADSP_WES_Broad	1,015	399	0	1	0	1
ADSP_WES_CU_IGM	590	55	858	125	479	196
ADSP_WES_MGI	211	127	0	10	2	0
ADSP_WES_Otogenetics	8	67	0	0	0	2
ADSP_WES_UM_HIHG	2	10	444	473	2	1
ADSP_WES_UW_GenomeSciences	NA	1	NA	0	NA	0
ADSP_WES_WashU	185	322	0	0	4	40
ADSP_WGS_BAYLOR	74	41	0	0	473	532
ADSP_WGS_BROAD	426	548	0	2	110	49
ADSP_WGS_GENENTECH	2	10	0	0	0	0
ADSP_WGS_ILLUMINA	400	313	7	3	5	4
ADSP_WGS_MACROGEN	NA	1	NA	0	NA	0
ADSP_WGS_NYGC	298	850	2	16	2	6
ADSP_WGS_USUHS	1,644	1,902	1,139	626	917	150
ADSP_WGS_WASHU	32	42	479	445	62	15
CHOP	459	535	3	5	1	0
CIDR	0	0	0	0	888	821
GSK	750	664	0	0	0	0
HBTRC_ILL	45	85	0	0	0	0
HBTRC_PERL	76	151	0	0	0	0
IIDP_AA	0	0	702	56	0	0
IIDP_YOR	0	0	980	85	0	0
LATC	0	NA	9	NA	0	NA
LOAD	466	369	33	21	30	148
MARS	0	0	346	43	1	2
MAYO_1	953	684	3	8	0	0
MAYO_2	87	2	0	0	0	0
MIA	59	333	0	3	0	0
MIRAGE_370	36	21	0	0	0	1
MIRAGE_610	214	48	0	1	0	5
MTC	116	176	0	0	0	0
NS	14	33	0	0	0	0
OHSU	205	57	1	0	0	0
ROSMAP_1B	392	270	0	0	0	0
ROSMAP_1T	75	86	0	0	4	2
ROSMAP_2C	148	72	0	0	3	2
ROSMAP_3BU	172	63	4	5	28	18
TARCC	18	94	0	0	0	0
TARCC_full	409	488	17	23	503	112
TGEN	369	706	0	0	0	1
UPITT	819	1,086	2	1	0	0
UVM_A	600	145	0	0	0	0
UVM_B	322	200	0	0	0	0
UVM_C	109	288	3	5	0	0
WASHU	140	261	0	0	0	0
WASHU2	5	8	0	0	0	0
WHICAP	155	25	0	0	0	0
WU	134	178	2	6	0	0

The technical covariate represents the subdivision of publicly available array-based cohorts/studies across respective arrays, as well as the subdivision of ADSP WES/WGS across respective sequencing platforms.

eTable 5. Overview of Participant Demographics and Ascertainment Design Across Cohorts

		NHW		NHB		HISP	
Cohort	**Ascertainment design**	**CN**	**AD**	**CN**	**AD**	**CN**	**AD**
ACT	Community/Population	1,703	701	68	26	4	1
ADC	non-Community/Population	3,671	5,552	921	625	41	52
ADM	non-Community/Population	173	234	0	0	0	0
ADNI	non-Community/Population	630	584	29	14	24	17
ARIC	Community/Population	18	36	0	0	0	0
CCS	Community/Population	205	0	0	0	0	0
CHAP	Community/Population	201	25	0	0	0	0
CHS	Community/Population	530	216	0	0	2	1
CIDR	non-Community/Population	0	0	0	0	1,290	1,274
ERF	non-Community/Population	74	86	0	0	0	0
FHS	Community/Population	407	153	0	0	0	0
GAA	Community/Population	0	0	175	204	0	0
GDF	Community/Population	204	50	2	4	0	0
GSK	non-Community/Population	750	664	0	0	0	0
HBTRC	Community/Population	121	236	0	0	0	0
IIDP_AA	Community/Population	0	0	981	159	0	0
IIDP_YOR	Community/Population	0	0	980	85	0	0
KGAD	non-Community/Population	210	132	0	11	2	0
LATC	non-Community/Population	0	0	9	0	0	0
LOAD	non-Community/Population	700	749	35	28	30	151
MARS	Community/Population	0	0	370	66	1	3
MAYO	non-Community/Population	1,112	776	3	8	0	0
MIA	non-Community/Population	80	438	530	362	0	1
MIRAGE	non-Community/Population	250	396	34	91	0	55
MSBB	non-Community/Population	23	166	2	16	1	6
MTC	non-Community/Population	116	176	0	0	0	0
NCRD	non-Community/Population	0	317	0	1	0	0
NS	non-Community/Population	14	33	0	0	0	0
OHSU	non-Community/Population	205	57	1	0	0	0
PRHS	non-Community/Population	0	0	0	0	886	115
RAS	non-Community/Population	0	39	0	0	0	0
ROSMAP	Community/Population	991	887	22	19	37	22
RS	Community/Population	750	268	0	0	0	0
STEP	non-Community/Population	34	96	0	0	0	0
TARCC	non-Community/Population	427	591	17	23	503	112
TGEN	non-Community/Population	369	706	0	0	0	1
TOR	non-Community/Population	0	89	0	0	0	0
UCLA	non-Community/Population	13	3	0	0	1	0
UPITT	non-Community/Population	819	1,289	2	1	0	0
UPN	-	4	17	0	0	0	0
UVM	non-Community/Population	1,031	633	3	5	0	0
VAN	non-Community/Population	2	14	56	38	0	0
WASHU	non-Community/Population	279	447	2	6	0	0
WHICAP	Community/Population	942	107	892	219	727	378
	non-Community/Population	10,982	14,267	1,644	1,229	2,778	1,784
	Community/Population	6,072	2,679	3,490	782	771	405

Original cohorts in ADSP were identified from sample IDs and pooled with array-based samples, when contributed by respective, matching cohorts. Ascertainment design was annotated based on review of cohorts in a manner similar to Farrer et al. 1997, which used a trichotomous classification scheme based on one of the following recruitment settings: community/population (com), clinic/hospital (clin), or autopsy/brain bank (aut). For the current study, we pooled clin and aut samples into one group: non-community/population (non-com). This is consistent with the primary analyses presented in Farrer et al. 1997, Table 3, which has been a common reference in the field for cross-race/ethnicity differences of *APOE* genotype associations with AD risk (cf. eTable10-11 for related sensitivity analyses).

eTable 6. Case-Control Regression Results Across *APOE* Strata Corresponding to Figure 1a

	East-Asian (EAS)			Non-Hispanic Whites (NHW)			Non-Hispanic Blacks (NHB)			Hispanic (HISP)		
Group/Model	**No. carriers**	**OR (95% CI)**	**P-value**	**No. carriers**	**OR (95% CI)**	**P-value**	**No. carriers**	**OR (95% CI)**	**P-value**	**No. carriers**	**OR (95% CI)**	**P-value**
***APOE* across race/ethnicity**												
***APOE* genotype**												
APOE *22+23	1,230	0.97 [0.77, 1.23]	0.80	3,019	0.53 [0.48, 0.58]	**2.44E-40**	1,077	0.69 [0.57, 0.84]	**2.56E-04**	506	0.89 [0.72, 1.10]	0.29
APOE *33	15,904	Ref.	-	17,199	Ref.	-	3,095	Ref.	-	3,517	Ref.	-
APOE *24	157	2.96 [1.85, 4.73]	**6.05E-06**	741	2.23 [1.90, 2.62]	**6.39E-23**	334	1.63 [1.24, 2.13]	**4.06E-04**	101	1.11 [0.72, 1.72]	0.63
APOE *34	4,164	4.54 [3.99, 5.17]	**3.11E-115**	10,807	3.46 [3.27, 3.65]	**<1.0E-300**	2,233	2.18 [1.90, 2.49]	**9.82E-30**	1,426	1.90 [1.65, 2.18]	**8.39E-20**
APOE *44	397	26.13 [19.06, 35.82]	**1.81E-91**	2,255	13.04 [11.31, 15.04]	**1.16E-273**	406	6.49 [5.07, 8.31]	**1.10E-49**	188	3.62 [2.56, 5.11]	**2.55E-13**

eTable 7. Case-Control Regression Results Across *APOE* Dosages and Strata for Hispanic Individuals (HISP), Stratified Into Hispanic Whites (HW) and Hispanic Blacks (HB)

	Hispanic (HISP)					
	Whites (HW)			Blacks (HB)		
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value
***APOE* across race/ethnicity**						
***APOE* *4 and *APOE* *2 dosage**						
APOE *2 dosage	120	1.21 [0.79, 1.88]	0.38	108	1.07 [0.67, 1.69]	0.78
APOE *33	791	Ref.	-	545	Ref.	-
APOE *4 dosage	566	2.07 [1.68, 2.57]	**1.79E-11**	479	2.08 [1.65, 2.62]	**5.67E-10**
***APOE* genotype**						
APOE *22	4	1.81 [0.17, 19.19]	0.62	4	2.09 [0.2, 22.29]	0.54
APOE *23	91	1.18 [0.74, 1.87]	0.49	77	0.99 [0.60, 1.64]	0.98
APOE *33	791	Ref.	-	545	Ref.	-
APOE *24	25	1.37 [0.57, 3.28]	0.48	27	1.04 [0.46, 2.34]	0.92
APOE *34	450	2.36 [1.80, 3.08]	**3.82E-10**	366	2.25 [1.67, 3.03]	**8.45E-08**
APOE *44	91	3.08 [1.78, 5.35]	**6.16E-05**	86	3.56 [1.97, 6.44]	**2.63E-05**

eTable 8. Sensitivity Case-Control Regression Analyses Corresponding to Table 1, Using Clinically Determined Phenotypes Only

	Non-Hispanic						Hispanic			Race/ethnicity effect		
	Whites (NHW)			Blacks (NHB)			Whites + Blacks + Other (HISP)			NHW vs. NHB	NHW vs. HISP	NHB vs. HISP
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	P-value	P-value	P-value
***APOE* across race/ethnicity**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	2,960	0.61 [0.55, 0.68]	**2.61E-19**	1,375	0.72 [0.59, 0.87]	**5.35E-04**	603	0.91 [0.74, 1.11]	0.33	0.15	**7.83E-04**	0.10
APOE *33	13,359	Ref.	-	3,027	Ref.	-	3,481	Ref.	-	-	-	-
APOE *4 dosage	9,522	3.27 [3.10, 3.45]	**<1.0E-300**	2,829	2.31 [2.08, 2.57]	**4.33E-55**	1,690	1.89 [1.68, 2.11]	**1.95E-27**	**7.51E-09**	**1.80E-16**	**0.010**
***APOE* genotype**												
APOE *22	102	0.53 [0.32, 0.89]	**0.017**	65	0.82 [0.40, 1.66]	0.58	24	1.01 [0.41, 2.50]	0.98	0.34	0.225	0.72
APOE *23	2,329	0.59 [0.53, 0.67]	**5.47E-19**	989	0.68 [0.55, 0.84]	**2.68E-04**	478	0.89 [0.71, 1.11]	0.29	0.27	**1.48E-03**	0.08
APOE *33	13,359	Ref.	-	3,027	Ref.	-	3,481	Ref.	-	-	-	-
APOE *24	529	1.96 [1.62, 2.37]	**4.02E-12**	321	1.65 [1.25, 2.17]	**4.19E-04**	101	1.12 [0.72, 1.74]	0.61	0.31	**0.022**	0.15
APOE *34	7,568	3.22 [3.02, 3.44]	**2.06E-278**	2,134	2.08 [1.82, 2.39]	**1.69E-25**	1,404	1.88 [1.64, 2.16]	**4.97E-19**	**2.04E-08**	**4.30E-12**	0.30
APOE *44	1,425	11.91 [10.20, 13.90]	**3.03E-216**	374	6.15 [4.78, 7.92]	**2.07E-45**	185	3.57 [2.53, 5.05]	**5.42E-13**	**1.20E-05**	**4.70E-10**	**0.013**
***APOE* across race/ethnicity & sex**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage, males	1,483	0.61 [0.53, 0.70]	**2.78E-12**	426	0.61 [0.42, 0.88]	**8.00E-03**	176	0.72 [0.49, 1.06]	0.092	0.54	0.86	0.55
APOE *33, males	5,312	Ref.	-	853	Ref.	-	1,113	Ref.	-	-	-	-
APOE *4 dosage, males	3,790	3.22 [2.96, 3.51]	**5.52E-161**	819	2.45 [1.99, 3.03]	**7.44E-17**	537	1.83 [1.49, 2.24]	**5.09E-09**	**0.018**	**4.63E-07**	0.050
APOE *2 dosage, females	1,790	0.56 [0.49, 0.65]	**1.53E-15**	949	0.77 [0.61, 0.95]	**0.018**	427	0.99 [0.78, 1.25]	0.90	**0.020**	**6.85E-05**	0.13
APOE *33, females	8,047	Ref.	-	2,174	Ref.	-	2,368	Ref.	-	-	-	-
APOE *4 dosage, females	2,960	3.32 [3.10, 3.56]	**1.94E-256**	2,010	2.27 [2.01, 2.57]	**1.27E-39**	1,153	1.93 [1.67, 2.22]	**4.56E-20**	**1.11E-07**	**7.14E-12**	0.080
APOE *2 dosage, sex effect (male ref.)	3,760	0.87 [0.72, 1.06]	0.17	1,375	1.10 [0.76, 1.58]	0.62	603	1.25 [0.83, 1.88]	0.29	0.28	0.12	0.64
APOE *4 dosage, sex effect (male ref.)	9,522	0.97 [0.88, 1.08]	0.60	2,829	0.92 [0.73, 1.17]	0.51	1,690	1.05 [0.83, 1.33]	0.69	0.69	0.57	0.46
***APOE* genotype**												
APOE *22, males	48	0.56 [0.26, 1.21]	0.14	21	0.70 [0.18, 2.65]	0.60	7	0.22 [0.02, 2.34]	0.21	0.78	0.45	0.40
APOE *23, males	930	0.68 [0.57, 0.81]	**2.67E-05**	309	0.56 [0.38, 0.84]	**5.52E-03**	138	0.77 [0.51, 1.15]	0.20	0.40	0.60	0.30
APOE *33, males	5,312	Ref.	-	853	Ref.	-	1,113	Ref.	-	-	-	-
APOE *24, males	192	1.99 [1.45, 2.73]	**2.01E-05**	96	1.95 [1.14, 3.35]	**0.015**	31	1.39 [0.63, 3.07]	0.42	0.95	0.41	0.49
APOE *34, males	2,984	3.03 [2.73, 3.36]	**7.50E-98**	623	2.11 [1.60, 2.77]	**8.99E-08**	444	1.72 [1.35, 2.20]	**1.61E-05**	**0.015**	**3.53E-05**	0.28
APOE *44, males	614	12.80 [9.95, 16.46]	**9.30E-88**	100	7.72 [4.55, 13.08]	**3.36E-14**	62	3.86 [2.07, 7.17]	**2.01E-05**	0.090	**4.44E-04**	0.10
APOE *22, females	54	0.53 [0.26, 1.09]	0.084	44	0.88 [0.38, 2.05]	0.77	17	1.57 [0.57, 4.34]	0.38	0.37	**3.68E-04**	0.39
APOE *23, females	1,399	0.54 [0.46, 0.63]	**9.62E-16**	680	0.73 [0.57, 0.93]	**1.22E-02**	340	0.93 [0.72, 1.22]	0.62	**0.037**	**0.031**	0.18
APOE *33, females	8,047	Ref.	-	2,174	Ref.	-	2,368	Ref.	-	-	-	-
APOE *24, females	337	1.96 [1.55, 2.49]	**3.06E-08**	225	1.56 [1.12, 2.16]	**8.08E-03**	70	1.04 [0.61, 1.76]	0.90	0.258	**0.031**	0.20
APOE *34, females	4,584	3.38 [3.11, 3.68]	**2.93E-182**	1,511	2.08 [1.77, 2.45]	**4.50E-19**	960	1.96 [1.65, 2.31]	**5.97E-15**	**1.50E-07**	**1.03E-08**	0.60
APOE *44, females	811	11.55 [9.46, 14.09]	**4.79E-128**	274	5.84 [4.37, 7.81]	**1.33E-32**	123	3.52 [2.31, 5.38]	**5.67E-09**	**1.51E-04**	**6.56E-07**	0.054
APOE*22, sex effect (male ref.)	102	1.05 [0.37, 2.97]	0.93	65	1.29 [0.27, 6.05]	0.75	24	8.24 [0.63, 108.00]	0.11	0.83	0.15	0.23
APOE*23, sex effect (male ref.)	2,329	0.83 [0.66, 1.05]	0.11	989	1.27 [0.79, 2.02]	0.32	478	1.21 [0.75, 1.96]	0.44	0.11	0.17	0.89
APOE*24, sex effect (male ref.)	529	0.97 [0.66, 1.44]	0.88	321	0.81 [0.45, 1.49]	0.50	101	0.76 [0.29, 1.94]	0.56	0.63	0.63	0.90
APOE*34, sex effect (male ref.)	7,568	1.05 [0.92, 1.19]	0.47	2,134	1.00 [0.74, 1.36]	0.99	1,404	1.14 [0.85, 1.54]	0.38	0.79	0.60	0.55
APOE*44, sex effect (male ref.)	1,425	0.76 [0.56, 1.04]	0.082	374	0.79 [0.45, 1.39]	0.41	185	0.92 [0.44, 1.92]	0.82	0.92	0.65	0.75

Samples with pathology data or pathology-verified diagnoses were excluded. Compared to case-control regression results presented in Table 1, the current table shows lost significant associations in orange-shaded cells. Note the loss of significant *APOE**2, *APOE**23, and *APOE**24 association differences across Non-Hispanic White (NHW) and Non-Hispanic Black (NHB), but the overall conserved pattern (more protective in NHW).

eTable 9. Sensitivity Case-Control Regression Analyses Corresponding to Table 1, Additionally Adjusting for Pathology Verification Status

	Non-Hispanic						Hispanic			Race/ethnicity effect		
	Whites (NHW)			Blacks (NHB)			Whites + Blacks + Other (HISP)			NHW vs. NHB	NHW vs. HISP	NHB vs. HISP
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	P-value	P-value	P-value
***APOE* across race/ethnicity**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	3,760	0.56 [0.51, 0.61]	**2.66E-35**	1,411	0.72 [0.60, 0.87]	**5.80E-04**	607	0.90 [0.74, 1.10]	0.32	**1.39E-02**	**2.02E-05**	0.11
APOE *33	17,199	Ref.	-	3,095	Ref.	-	3,517	Ref.	-	-	-	-
APOE *4 dosage	13,803	3.48 [3.32, 3.66]	**<1.0E-300**	2,973	2.36 [2.13, 2.62]	**7.75E-59**	1,715	1.90 [1.69, 2.13]	**4.39E-28**	**2.74E-11**	**7.81E-22**	**5.69E-03**
***APOE* genotype**												
APOE *22	133	0.41 [0.26, 0.64]	**9.47E-05**	65	0.82 [0.40, 1.66]	0.58	24	1.01 [0.41, 2.50]	0.98	0.11	0.078	0.71
APOE *23	2,886	0.54 [0.49, 0.60]	**3.15E-33**	1,012	0.69 [0.56, 0.84]	**3.03E-04**	482	0.89 [0.71, 1.10]	0.28	**0.046**	**7.80E-05**	0.10
APOE *33	17,199	Ref.	-	3,095	Ref.	-	3,517	Ref.	-	-	-	-
APOE *24	741	2.18 [1.84, 2.57]	**5.15E-20**	334	1.59 [1.21, 2.09]	**9.09E-04**	101	1.12 [0.72, 1.74]	0.61	0.054	**5.49E-03**	0.19
APOE *34		3.46 [3.26, 3.66]	**<1.0E-300**	2,233	2.14 [1.87, 2.45]	**9.79E-28**	1,426	1.89 [1.65, 2.17]	**1.41E-19**	**2.35E-10**	**3.11E-15**	0.21
APOE *44	2,255	12.94 [11.20, 14.95]	**4.76E-265**	406	6.38 [4.97, 8.19]	**7.83E-48**	188	3.60 [2.55, 5.09]	**3.36E-13**	**1.57E-06**	**2.10E-11**	**8.60E-03**
***APOE* across race/ethnicity & sex**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage, males	1,483	0.63 [0.55, 0.73]	**3.76E-10**	441	0.64 [0.45, 0.91]	**0.013**	177	0.73 [0.50, 1.07]	0.11	0.97	0.49	0.61
APOE *33, males	6,925	Ref.	-	878	Ref.	-	1,125	Ref.	-	-	-	-
APOE *4 dosage, males	5,718	3.48 [3.23, 3.76]	**7.16E-228**	865	2.55 [2.06, 3.14]	**2.26E-18**	552	1.86 [1.52, 2.27]	**1.96E-09**	**5.80E-03**	**1.09E-08**	**0.033**
APOE *2 dosage, females	2,277	0.51 [0.45, 0.57]	**1.05E-27**	970	0.76 [0.61, 0.95]	**0.015**	430	0.98 [0.77, 1.24]	0.85	**1.31E-03**	**1.37E-06**	0.13
APOE *33, females	10,274	Ref.	-	2,217	Ref.	-	2,392	Ref.	-	-	-	-
APOE *4 dosage, females	8,085	3.51 [3.3, 3.74]	**<1.0E-300**	2,108	2.31 [2.05, 2.61]	**6.16E-42**	1,163	1.94 [1.68, 2.23]	**2.12E-20**	**1.91E-09**	**2.66E-14**	0.060
APOE *2 dosage, sex effect (male ref.)	3,760	0.85 [0.72, 1.00]	0.055	1,411	1.05 [0.74, 1.50]	0.78	607	1.22 [0.81, 1.84]	0.33	0.29	0.10	0.59
APOE *4 dosage, sex effect (male ref.)	13,803	0.94 [0.86, 1.04]	0.24	2,973	0.91 [0.72, 1.15]	0.43	1,715	1.05 [0.82, 1.33]	0.71	0.77	0.43	0.41
***APOE* genotype**												
APOE *22, males	65	0.51 [0.27, 0.95]	**0.034**	21	0.69 [0.18, 2.62]	0.59	7	0.22 [0.02, 2.33]	0.21	0.68	0.49	0.40
APOE *23, males	1,148	0.62 [0.53, 0.72]	**1.65E-09**	321	0.59 [0.40, 0.88]	**8.80E-03**	139	0.78 [0.52, 1.17]	0.23	0.85	0.29	0.34
APOE *33, males	6,925	Ref.	-	878	Ref.	-	1,125	Ref.	-	-	-	-
APOE *24, males	270	2.26 [1.72, 2.98]	**6.44E-09**	99	1.93 [1.13, 3.28]	**0.015**	31	1.39 [0.63, 3.08]	0.41	0.60	0.26	0.50
APOE *34, males	4,448	3.33 [3.04, 3.64]	**4.62E-148**	657	2.23 [1.70, 2.93]	**6.70E-09**	456	1.75 [1.37, 2.24]	**8.01E-06**	**6.29E-03**	**1.58E-06**	0.19
APOE *44, males	1,000	14.23 [11.30, 17.93]	**2.45E-112**	109	8.09 [4.79, 13.67]	**5.76E-15**	65	4.03 [2.17, 7.48]	**9.84E-06**	0.053	**1.78E-04**	0.092
APOE *22, females	68	0.35 [0.18, 0.67]	**1.48E-03**	44	0.89 [0.38, 2.07]	0.78	17	1.58 [0.57, 4.35]	0.38	0.083	**0.014**	0.39
APOE *23, females	1,738	0.50 [0.44, 0.56]	**1.99E-26**	691	0.73 [0.57, 0.93]	**0.010**	343	0.93 [0.71, 1.20]	0.57	**5.67E-03**	**2.65E-05**	0.19
APOE *33, females	10,274	Ref.	-	2,217	Ref.	-	2,392	Ref.	-	-	-	-
APOE *24, females	471	2.14 [1.74, 2.65]	**1.28E-12**	235	1.49 [1.08, 2.06]	**0.016**	70	1.04 [0.61, 1.77]	0.88	0.064	**0.013**	0.26
APOE *34, females	6,359	3.59 [3.33, 3.87]	**2.62E-241**	1,576	2.11 [1.80, 2.48]	**3.62E-20**	970	1.97 [1.66, 2.33]	**2.59E-15**	**4.37E-09**	**1.69E-10**	0.55
APOE *44, females	1,255	12.29 [10.19, 14.83]	**8.46E-152**	297	6.06 [4.54, 8.08]	**2.41E-34**	123	3.52 [2.30, 5.37]	**5.80E-09**	**5.54E-05**	**1.17E-07**	**0.038**
APOE*22, sex effect (male ref.)	133	0.76 [0.31, 1.86]	0.55	65	1.30 [0.28, 6.12]	0.74	24	8.27 [0.63, 108.66]	0.11	0.56	0.086	0.23
APOE*23, sex effect (male ref.)	2,886	0.83 [0.68, 1.02]	0.073	1,012	1.19 [0.76, 1.86]	0.46	482	1.18 [0.73, 1.90]	0.50	0.16	0.19	0.98
APOE*24, sex effect (male ref.)	741	0.92 [0.65, 1.30]	0.64	334	0.79 [0.43, 1.43]	0.43	101	0.76 [0.29, 1.94]	0.56	0.66	0.70	0.94
APOE*34, sex effect (male ref.)	10,807	1.01 [0.90, 1.13]	0.93	2,233	0.96 [0.71, 1.31]	0.81	1,426	1.14 [0.85, 1.53]	0.38	0.80	0.43	0.43
APOE*44, sex effect (male ref.)	2,255	0.73 [0.55, 0.98]	**0.034**	406	0.80 [0.45, 1.40]	0.43	188	0.90 [0.43, 1.87]	0.77	0.80	0.62	0.80

The additional covariate marked “1” for samples with pathology data or pathology-verified diagnoses versus “0” for those without. Compared to case-control regression results presented in Table 1, the current table shows lost significant associations in orange-shaded cells. Note that overall the results are highly similar to those presented in Table 1.

eTable 10. Sensitivity Case-Control Regression Analyses Corresponding to Table 1 and eTable 10, Using Only Samples From Cohorts With a Given Ascertainment Design

Non-Com Samples

	Non-Hispanic						Hispanic			Race/ethnicity effect		
	Whites (NHW)			Blacks (NHB)			Whites + Blacks + Other (HISP)			NHW vs. NHB	NHW vs. HISP	NHB vs. HISP
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	P-value	P-value	P-value
***APOE* across race/ethnicity**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	2,415	0.53 [0.47, 0.59]	**1.08E-26**	509	0.59 [0.44, 0.79]	**3.37E-04**	434	0.86 [0.67, 1.1]	0.23	0.47	**4.07E-04**	0.051
APOE *33	11,806	Ref.	-	1,059	Ref.	-	2,792	Ref.	-	-	-	-
APOE *4 dosage	11,608	3.80 [3.59, 4.02]	**<1.0E-300**	1,450	3.01 [2.60, 3.48]	**3.84E-50**	1,416	2.04 [1.8, 2.32]	**5.73E-28**	**3.33E-03**	**2.62E-18**	**8.37E-05**
***APOE* genotype**												
APOE *22	75	0.30 [0.16, 0.55]	**1.04E-04**	21	0.64 [0.21, 1.96]	0.49	17	0.94 [0.32, 2.83]	0.92	0.23	0.071	0.63
APOE *23	1,760	0.53 [0.46, 0.60]	**5.55E-24**	343	0.55 [0.40, 0.76]	**2.79E-04**	337	0.84 [0.64, 1.10]	0.20	0.75	**1.70E-03**	**0.049**
APOE *33	11,806	Ref.	-	1,059	Ref.	-	2,792	Ref.	-	-	-	-
APOE *24	580	2.34 [1.93, 2.84]	**8.71E-18**	145	1.50 [1.03, 2.19]	**4.06E-04**	80	1.05 [0.64, 1.74]	0.84	**0.041**	**3.52E-03**	0.26
APOE *34	8,914	3.86 [3.61, 4.13]	**<1.0E-300**	1,053	2.80 [2.31, 3.39]	**9.82E-30**	1,164	2.04 [1.74, 2.38]	**6.15E-19**	**1.79E-03**	**2.12E-13**	**0.012**
APOE *44	2,114	14.52 [12.35, 17.08]	**6.37E-230**	252	10.06 [7.06, 14.33]	**1.10E-49**	172	4.13 [2.85, 5.98]	**6.87E-14**	0.064	**1.13E-09**	**6.62E-04**

Com Samples

	Non-Hispanic						Hispanic			Race/ethnicity effect		
	Whites (NHW)			Blacks (NHB)			Whites + Blacks + Other (HISP)			NHW vs. NHB	NHW vs. HISP	NHB vs. HISP
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	P-value	P-value	P-value
***APOE* across race/ethnicity**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	1,343	0.64 [0.55, 0.75]	**1.45E-08**	902	0.84 [0.66, 1.07]	0.15	173	1.02 [0.70, 1.48]	0.92	0.067	**0.025**	0.39
APOE *33	5,383	Ref.	-	2,036	Ref.	-	725	Ref.	-	-	-	-
APOE *4 dosage	2,185	2.05 [1.83, 2.29]	**5.14E-36**	1,523	1.72 [1.47, 2.01]	**1.46E-11**	299	1.21 [0.92, 1.60]	**1.72E-01**	0.078	**5.92E-04**	**0.031**
***APOE* genotype**												
APOE *22	58	0.73 [0.38, 1.40]	0.34	44	1.00 [0.40, 2.52]	0.99	7	1.10 [0.21, 5.77]	0.91	0.58	0.650	0.92
APOE *23	1,125	0.60 [0.51, 0.71]	**2.88E-09**	669	0.80 [0.61, 1.05]	0.10	145	1.01 [0.67, 1.53]	0.95	0.077	**0.021**	0.35
APOE *33	5,383	Ref.	-	2,036	Ref.	-	725	Ref.	-	-	-	-
APOE *24	160	1.57 [1.10, 2.25]	**0.014**	189	1.70 [1.14, 2.54]	**9.23E-03**	21	1.17 [0.47, 2.93]	0.74	0.77	0.56	0.46
APOE *34	1,884	2.04 [1.80, 2.32]	**4.48E-28**	1,180	1.55 [1.27, 1.90]	**1.93E-05**	262	1.24 [0.91, 1.69]	0.18	**0.024**	**3.62E-03**	0.23
APOE *44	141	4.59 [3.06, 6.89]	**1.62E-13**	154	3.56 [2.40, 5.29]	**2.83E-10**	16	1.25 [0.43, 3.65]	0.68	0.38	**0.026**	0.072

Upper Table) Samples from cohorts with a clinical/hospital or autopsy/brainbank ascertainment design (i.e. a non-community/population-based (non-com). **Lower Table)** Samples from cohorts with a community/population-based ascertainment design (com). All analyses were adjusted for pathology verification status as in eTable9 (which helps account for differences across clinical/hospital and autopsy/brainbank ascertainment designs). Compared to case-control regression results presented in Table 1, the current tables show new significant associations in green-shaded cells, and lost significant associations in orange-shaded cells. Overall, the general pattern of Table 1 and eTable9 is similar here, but note the less pronounced differences and loss of significances across NHW and NHB in non-com samples (upper table). Many significances were also lost in com analyses, but sample sizes (and thus power) were substantially decreased, so interpretation of race/ethnicity differences is better guided by judging effect size differences (the same holds true to a lesser extent for non-com samples).

eTable 11. Sensitivity Case-Control Regression Analyses Corresponding to Table 1 and eTable 10, Additionally Adjusting for Ascertainment Design

	Non-Hispanic						Hispanic			Race/ethnicity effect		
	Whites (NHW)			Blacks (NHB)			Whites + Blacks + Other (HISP)			NHW vs. NHB	NHW vs. HISP	NHB vs. HISP
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	P-value	P-value	P-value
***APOE* across race/ethnicity**												
***APOE**4 and *APOE**2 dosage**												
*APOE**2 dosage	3,758	0.57 [0.52, 0.62]	**3.60E-33**	1,411	0.72 [0.60, 0.87]	**5.27E-04**	607	0.90 [0.74, 1.11]	0.33	**0.022**	**3.35E-05**	0.10
*APOE**33	17,189	Ref.	-	3,095	Ref.	-	3,517	Ref.	-	-	-	-
*APOE**4 dosage	13,793	3.33 [3.17, 3.50]	**<1.0E-300**	2,973	2.36 [2.12, 2.61]	**2.24E-58**	1,715	1.89 [1.69, 2.12]	**1.08E-27**	**3.86E-09**	**4.82E-19**	**5.33E-03**
***APOE* genotype**												
*APOE**22	133	0.44 [0.28, 0.69]	**3.28E-04**	65	0.81 [0.40, 1.65]	0.56	24	1.00 [0.41, 2.48]	0.99	0.15	0.11	0.72
*APOE**23	2,885	0.55 [0.50, 0.61]	**1.22E-31**	1,012	0.68 [0.56, 0.84]	**2.83E-04**	482	0.89 [0.71, 1.11]	0.29	0.061	**1.07E-04**	0.090
*APOE**33	17,189	Ref.	-	3,095	Ref.	-	3,517	Ref.	-	-	-	-
*APOE**24	740	2.13 [1.80, 2.52]	**9.55E-19**	334	1.60 [1.22, 2.11]	**7.30E-04**	101	1.13 [0.73, 1.75]	0.59	0.081	**7.80E-03**	0.18
*APOE**34	10,798	3.31 [3.12, 3.50]	**<1.0E-300**	2,233	2.13 [1.86, 2.45]	**1.98E-27**	1,426	1.89 [1.64, 2.17]	**2.22E-19**	**7.87E-09**	**2.38E-13**	0.22
*APOE**44	2,255	12.24 [10.58, 14.15]	**2.73E-250**	406	6.44 [5.01, 8.27]	**4.07E-48**	188	3.58 [2.53, 5.06]	**4.73E-13**	**1.37E-05**	**1.30E-10**	**7.04E-03**

Ascertainment was classified as non-community/population-based (non-com) versus community/population-based (com) (cf. eTable5), using non-com ascertained samples as the reference. Analyses were additionally adjusted for pathology verification status as in eTable9. Compared to case-control regression results presented in Table 1, the current table shows lost significant associations in orange-shaded cells. Note the loss of significant *APOE**23 and *APOE**24 association differences across Non-Hispanic Whites (NHW) and Non-Hispanic Blacks (NHB), but the overall conserved pattern (more protective in NHW). Note that overall the results are highly similar to those presented in Table 1.

eTable 12. Sensitivity Case-Control Regression Analyses Corresponding to Table 1, Removing Samples in Which Race and Ethnicity Status Was Not Directly Provided From Cohort Demographic Files

	Non-Hispanic					
	Whites (NHW)			Blacks (NHB)		
Group/Model	**No. carriers**	**OR (95% CI)**	**P-value**	**No. carriers**	**OR (95% CI)**	**P-value**
***APOE* across race/ethnicity**						
***APOE* *4 and *APOE* *2 dosage**						
APOE *2 dosage	3,096	0.55 [0.50, 0.61]	**2.28E-33**	1,234	0.72 [0.59, 0.86]	**4.84E-04**
APOE *33	14,102	Ref.	-	2,720	Ref.	-
APOE *4 dosage	11,146	3.30 [3.13, 3.48]	**<1.0E-300**	2,684	2.44 [2.20, 2.72]	**5.65E-61**
***APOE* genotype**						
APOE *22	108	0.42 [0.26, 0.67]	**3.41E-04**	60	0.70 [0.33, 1.47]	0.35
APOE *23	2,391	0.53 [0.48, 0.59]	**4.73E-32**	875	0.69 [0.56, 0.85]	**4.48E-04**
APOE *33	14,102	Ref.	-	2,720	Ref.	-
APOE *24	597	2.39 [2.00, 2.87]	**1.78E-21**	299	1.67 [1.26, 2.20]	**2.88E-04**
APOE *34	8,828	3.35 [3.15, 3.56]	**<1.0E-300**	2,017	2.20 [1.92, 2.53]	**3.67E-29**
APOE *44	1,721	10.84 [9.25, 12.71]	**1.72E-189**	368	6.93 [5.34, 9.00]	**5.96E-48**

Compared to case-control regression results presented in Table 1, the current table shows very similar findings for the respective race/ethnicity groups, except for potentially a slightly decreased *APOE**4 effect in NHW.

eTable 13. Survival Analyses Results, Through Cox Regression, Across *APOE* Dosages and Genotypes, and Additionally Stratified Across Sex, for Non-Hispanic White (NHW), Non-Hispanic Black (NHB), and Hispanic (HISP) Individuals

	Non-Hispanic						Hispanic			Race/ethnicity effect		
	Whites (NHW)			Blacks (NHB)			Whites + Blacks + Other (HISP)			NHW vs. NHB	NHW vs. HISP	NHB vs. HISP
Group/Model	No. carriers	HR (95% CI)	P-value	No. carriers	HR (95% CI)	P-value	No. carriers	HR (95% CI)	P-value	P-value	P-value	P-value
***APOE* across race/ethnicity**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	3,516	0.57 [0.53, 0.61]	**1.63E-47**	1,362	0.73 [0.62, 0.86]	**2.07E-04**	558	0.78 [0.67, 0.91]	**1.23E-03**	**9.11E-03**	**2.94E-04**	0.56
APOE *33	16,121	Ref.	-	3,003	Ref.	-	3,372	Ref.	-	-	-	-
APOE *4 dosage	13,531	2.32 [2.27, 2.38]	**<1.0E-300**	2,902	2.23 [2.07, 2.40]	**1.24E-101**	1,673	1.78 [1.65, 1.92]	**9.19E-50**	0.31	**6.09E-11**	**2.71E-05**
***APOE* genotype**												
APOE *22	122	0.41 [0.28, 0.61]	**7.97E-06**	62	0.79 [0.42, 1.48]	0.46	22	0.89 [0.45, 1.79]	0.75	0.086	0.058	0.80
APOE *23	2,685	0.56 [0.52, 0.61]	**2.33E-44**	975	0.69 [0.57, 0.83]	**1.06E-04**	438	0.75 [0.62, 0.90]	**2.05E-03**	**0.043**	**4.88E-03**	0.55
APOE *33	16,121	Ref.	-	3,003	Ref.	-	3,372	Ref.	-	-	-	-
APOE *24	709	1.81 [1.63, 2.00]	**1.14E-30**	325	1.53 [1.23, 1.91]	**1.47E-04**	98	0.90 [0.66, 1.23]	0.51	0.19	**2.76E-05**	**6.08E-03**
APOE *34	10,581	2.50 [2.41, 2.59]	**<1.0E-300**	2,174	2.05 [1.84, 2.29]	**2.25E-39**	1,387	1.70 [1.54, 1.87]	**2.64E-27**	**6.35E-04**	**1.75E-13**	**0.011**
APOE *44	2,241	5.16 [4.88, 5.46]	**<1.0E-300**	403	5.52 [4.73, 6.44]	**4.76E-104**	188	3.39 [2.80, 4.10]	**4.05E-36**	0.43	**3.25E-05**	**9.80E-05**
***APOE* across race/ethnicity & sex**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage, males	1,410	0.61 [0.55, 0.69]	**1.58E-16**	425	0.69 [0.51, 0.94]	**0.018**	167	0.68 [0.50, 0.94]	**0.018**	0.47	0.54	0.95
APOE *33, males	6,588	Ref.	-	863	Ref.	-	1,089	Ref.	-	-	-	-
APOE *4 dosage, males	5,626	2.20 [2.12, 2.28]	**<1.0E-300**	848	2.05 [1.78, 2.35]	**7.73E-24**	543	1.66 [1.45, 1.89]	**9.16E-14**	0.34	**6.07E-05**	**0.031**
APOE *2 dosage, females	2,106	0.55 [0.49, 0.60]	**1.41E-31**	937	0.75 [0.62, 0.92]	**6.08E-03**	391	0.81 [0.68, 0.98]	**0.026**	**5.47E-03**	**2.09E-04**	0.59
APOE *33, females	9,533	Ref.	-	2,140	Ref.	-	2,283	Ref.	-	-	-	-
APOE *4 dosage, females	7,905	2.42 [2.34, 2.49]	**<1.0E-300**	2,054	2.32 [2.12, 2.53]	**1.63E-79**	1,130	1.87 [1.70, 2.05]	**5.29E-39**	0.39	**3.74E-07**	**9.69E-04**
APOE *2 dosage, sex effect (male ref.)	3,516	1.01 [0.89, 1.15]	0.87	1,362	1.04 [0.76, 1.41]	0.81	521	1.08 [0.91, 1.3]	0.37	0.87	0.53	0.81
APOE *4 dosage, sex effect (male ref.)	13,531	1.04 [0.99, 1.09]	0.14	2,902	1.10 [0.94, 1.29]	0.24	1,561	1.11 [0.95, 1.3]	0.19	0.47	0.41	0.95
***APOE* genotype**												
APOE *22, males	60	0.48 [0.28, 0.82]	**6.67E-03**	20	0.46 [0.15, 1.46]	0.19	7	0.45 [0.06, 3.24]	0.43	0.95	0.95	0.99
APOE *23, males	1,091	0.60 [0.53, 0.68]	**3.32E-15**	310	0.69 [0.49, 0.98]	**0.036**	129	0.69 [0.49, 0.96]	**0.027**	0.49	0.48	0.99
APOE *33, males	6,588	Ref.	-	863	Ref.	-	1,089	Ref.	-	-	-	-
APOE *24, males	259	1.60 [1.36, 1.89]	**2.61E-08**	95	1.62 [1.09, 2.42]	**0.018**	31	0.93 [0.57, 1.53]	0.78	0.95	**0.041**	0.09
APOE *34, males	4,371	2.25 [2.13, 2.37]	**1.12E-186**	645	1.87 [1.52, 2.29]	**1.65E-09**	447	1.54 [1.29, 1.83]	**1.12E-06**	0.086	**3.96E-05**	0.15
APOE *44, males	996	4.70 [4.32, 5.11]	**1.97E-282**	108	4.67 [3.49, 6.26]	**4.40E-25**	65	2.95 [2.13, 4.08]	**7.48E-11**	0.97	**6.60E-03**	**0.039**
APOE *22, females	62	0.38 [0.21, 0.67]	**8.50E-04**	42	1.11 [0.52, 2.36]	0.78	15	1.07 [0.51, 2.26]	0.85	**0.025**	**0.029**	0.95
APOE *23, females	1,594	0.54 [0.48, 0.60]	**5.29E-30**	665	0.70 [0.56, 0.88]	**1.77E-03**	309	0.76 [0.61, 0.96]	**0.018**	**0.036**	**5.36E-03**	0.59
APOE *33, females	9,533	Ref.	-	2,140	Ref.	-	2,283	Ref.	-	-	-	-
APOE *24, females	450	1.98 [1.75, 2.26]	**8.21E-26**	230	1.52 [1.16, 1.99]	**2.11E-03**	67	0.90 [0.60, 1.35]	0.60	0.080	**2.62E-04**	**0.033**
APOE *34, females	6,210	2.68 [2.56, 2.81]	**<1.0E-300**	1,529	2.14 [1.88, 2.44]	**2.45E-31**	940	1.81 [1.61, 2.04]	**8.25E-23**	**1.29E-03**	**1.22E-09**	0.057
APOE *44, females	1,245	5.53 [5.13, 5.96]	**<1.0E-300**	295	6.01 [5.00, 7.22]	**1.53E-81**	123	3.70 [2.92, 4.68]	**3.00E-27**	0.41	**1.50E-03**	**1.50E-03**
APOE*22, sex effect (male ref.)	122	0.85 [0.39, 1.86]	0.69	62	2.50 [0.64, 9.82]	0.19	21	2.13 [1.01, 4.48]	**0.046**	0.18	0.10	0.84
APOE*23, sex effect (male ref.)	2,685	0.94 [0.79, 1.10]	0.42	975	0.98 [0.65, 1.47]	0.91	404	1.08 [0.87, 1.34]	0.49	0.84	0.30	0.67
APOE*24, sex effect (male ref.)	709	1.19 [0.96, 1.46]	0.11	325	0.96 [0.60, 1.55]	0.88	96	0.90 [0.60, 1.35]	0.60	0.43	0.23	0.83
APOE*34, sex effect (male ref.)	10,581	1.12 [1.04, 1.20]	**1.94E-03**	2,174	1.14 [0.90, 1.44]	0.28	1,285	1.17 [1.05, 1.30]	**4.21E-03**	0.88	0.48	0.84
APOE*44, sex effect (male ref.)	2,241	1.01 [0.91, 1.12]	0.85	403	1.20 [0.86, 1.67]	0.28	180	1.15 [0.78, 1.70]	0.47	0.32	0.51	0.88

Compared to case-control regression results in Table 1, this table shows new significant associations in green-shaded cells, and lost significant associations in orange-shaded cells. Note more pronounced *APOE**23 effects in HISP individuals. Note loss of *APOE**4 dosage and *APOE**44 differences across NHW and NHB.

eTable 14. Case-Control Regression Results Across *APOE* Dosage and Strata, for Hispanic Individuals, Stratified Into Global Ancestry Quartiles

	Hispanic (HISP) across global European ancestry											
	EUR% < 25			EUR% > 25			EUR% > 50			EUR% > 75		
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value
***APOE* across admixture**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	133	0.86 [0.53, 1.39]	0.54	485	0.92 [0.74, 1.15]	0.46	240	0.75 [0.54, 1.04]	0.082	39	0.73 [0.33, 1.61]	0.44
APOE *33	725	Ref.	-	2,834	Ref.	-	1,571	Ref.	-	270	Ref.	-
APOE *4 dosage	309	2.14 [1.63, 2.81]	**3.84E-08**	1,430	1.85 [1.63, 2.10]	**6.10E-22**	695	1.92 [1.61, 2.29]	**5.45E-13**	120	2.65 [1.67, 4.22]	**3.77E-05**
***APOE* genotype**												
APOE *22	6	3.39 [0.51, 22.52]	0.21	19	0.80 [0.28, 2.29]	0.68	7	0.16 [0.01, 2.38]	0.18	2	0.38 [0.00, 32.5]	0.67
APOE *23	101	0.71 [0.41, 1.23]	0.22	389	0.93 [0.73, 1.17]	0.53	199	0.79 [0.56, 1.11]	0.17	33	0.75 [0.33, 1.73]	0.50
APOE *33	370	Ref.	-	2,834	Ref.	-	1,571	Ref.	-	270	Ref.	-
APOE *24	26	1.00 [0.41, 2.43]	1.00	77	1.11 [0.68, 1.84]	0.67	34	1.08 [0.50, 2.31]	0.85	4	0.11 [0.01, 1.95]	0.13
APOE *34	251	2.35 [1.69, 3.26]	**3.48E-07**	1,194	1.81 [1.56, 2.11]	**1.29E-14**	578	1.86 [1.50, 2.31]	**1.79E-08**	103	3.04 [1.73, 5.36]	**1.20E-04**
APOE *44	32	3.57 [1.60, 7.94]	**1.85E-03**	159	3.63 [2.48, 5.31]	**3.39E-11**	83	4.06 [2.36, 6.98]	**3.89E-07**	13	5.59 [1.42, 21.99]	**0.014**

	Hispanic (HISP) across global African ancestry											
	AFR% < 25			AFR% > 25			AFR% > 50			AFR% > 75		
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value
***APOE* across admixture**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	271	0.77 [0.56, 1.07]	0.12	347	0.96 [0.75, 1.25]	0.78	146	1.38 [0.93, 2.04]	0.11	35	2.14 [0.88, 5.21]	0.095
APOE *33	2,104	Ref.	-	1,462	Ref.	-	463	Ref.	-	82	Ref.	-
APOE *4 dosage	833	2.11 [1.78, 2.50]	**3.15E-18**	910	1.68 [1.44, 1.96]	**3.98E-11**	310	1.92 [1.46, 2.52]	**2.83E-06**	61	2.80 [1.40, 5.60]	**3.55E-03**
***APOE* genotype**												
APOE *22	9	0.48 [0.07, 3.31]	0.46	15	1.39 [0.48, 4.03]	0.55	9	2.03 [0.49, 8.39]	0.33	3	24.5 [1.32, 453.49]	**0.032**
APOE *23	227	0.78 [0.56, 1.11]	0.17	265	0.92 [0.69, 1.22]	0.57	105	1.39 [0.88, 2.20]	0.15	25	1.52 [0.49, 4.68]	0.47
APOE *33	2,104	Ref.	-	1,462	Ref.	-	463	Ref.	-	82	Ref.	-
APOE *24	35	1.01 [0.46, 2.24]	0.98	67	1.19 [0.71, 2.02]	0.51	32	1.21 [0.56, 2.61]	0.63	7	3.15 [0.53, 18.80]	0.21
APOE *34	719	2.11 [1.73, 2.57]	**1.86E-13**	731	1.64 [1.36, 1.99]	**3.11E-07**	238	1.82 [1.30, 2.55]	**4.67E-04**	46	3.62 [1.52, 8.62]	**3.74E-03**
APOE *44	79	4.48 [2.61, 7.70]	**5.33E-08**	112	3.03 [1.95, 4.72]	**8.22E-07**	40	4.42 [1.94, 10.04]	**3.92E-04**	8	5.63 [0.85, 37.31]	0.073

	Hispanic (HISP) across global Amerindian ancestry											
	AMR% < 25			AMR% > 25			AMR% > 50			AMR% > 75		
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value
***APOE* across admixture**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	436	0.90 [0.72, 1.13]	0.38	190	0.80 [0.53, 1.22]	0.30	55	0.68 [0.26, 1.76]	0.42	45	0.46 [0.14, 1.51]	0.20
APOE *33	2,071	Ref.	-	1,580	Ref.	-	559	Ref.	-	448	Ref.	-
APOE *4 dosage	1,171	1.84 [1.61, 2.11]	**1.26E-18**	604	1.81 [1.49, 2.20]	**3.30E-09**	172	2.26 [1.56, 3.27]	**1.48E-05**	138	2.10 [1.39, 3.17]	**4.19E-04**
***APOE* genotype**												
APOE *22	19	1.03 [0.39, 2.75]	0.95	5	0.96 [0.10, 8.96]	0.97	-	-	-	-	-	-
APOE *23	340	0.88 [0.69, 1.13]	0.33	158	0.78 [0.50, 1.22]	0.28	50	0.70 [0.26, 1.83]	0.46	41	0.47 [0.14, 1.58]	0.22
APOE *33	2,071	Ref.	-	1,580	Ref.	-	559	Ref.	-	448	Ref.	-
APOE *24	77	1.14 [0.71, 1.86]	0.58	27	0.96 [0.37, 2.51]	0.93	4	0.00 [0.00, Inf]	0.99	3	0.00 [0.00, Inf]	0.99
APOE *34	954	1.76 [1.49, 2.07]	**3.10E-11**	516	1.95 [1.54, 2.47]	**2.86E-08**	156	2.35 [1.53, 3.62]	**1.02E-04**	125	2.35 [1.45, 3.79]	**4.97E-04**
APOE *44	140	4.02 [2.65, 6.10]	**6.00E-11**	61	2.57 [1.41, 4.68]	**2.08E-03**	12	4.15 [1.25, 13.80]	**0.020**	10	2.69 [0.65, 11.11]	0.17

Note there was overall no clear pattern whereby global European, African, or Amerindian ancestry (when considering significant associations only) could explain why HISP showed less pronounced *APOE* effects on AD risk compared to NHW and NHB. One notable observation was an increasing effect of *APOE**44 on AD risk with increasing global EUR ancestry. However, even at >75% EUR ancestry, the *APOE**44 effect was only about half of what was observed in NHW (who are primarily >75% EUR (cf. eFigure2)), indicating an overall diminished *APOE**44 effect in HISP. A potentially interesting finding was that with higher AMR ancestry, the *APOE**44 effect was the most diminished (although based on few samples) and the *APOE**2 dosage effect became the most protective (although not significant).

Table 15. Case-Control Regression Results Across *APOE* Dosage and Strata, for Non-Hispanic Black Individuals, Stratified Into Global Ancestry Quartiles

	Non-Hispanic Black (NHB) across global European ancestry														
	EUR% < 25			EUR% > 25			EUR% > 50			EUR% > 75			EUR% > 90		
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value
***APOE* across admixture**															
***APOE* *4 and *APOE* *2 dosage**															
APOE *2 dosage	868	0.73 [0.58, 0.91]	**6.43E-03**	241	0.67 [0.44, 1.01]	0.056	21	1.27 [0.31, 5.31]	0.74	0	-	-	0	-	-
APOE *33	1,910	Ref.	-	546	Ref.	-	72	Ref.	-	0	Ref.	-	0	Ref.	-
APOE *4 dosage	1,886	2.23 [1.96, 2.53]	**7.75E-34**	525	3.09 [2.44, 3.92]	**1.33E-20**	58	5.58 [2.43, 12.82]	**5.15E-05**	0	-	-	0	-	-
***APOE* genotype**															
APOE *22	44	0.96 [0.42, 2.19]	0.92	11	0.00 [0.00, Inf]	0.98	1	0.00 [0.00, Inf]	1.00	0	-	-	0	-	-
APOE *23	601	0.67 [0.52, 0.86]	**1.94E-03**	179	0.76 [0.49, 1.17]	0.21	13	2.84 [0.49, 16.53]	0.24	0	-	-	0	-	-
APOE *33	1,910	Ref.	-	546	Ref.	-	72	Ref.	-	0	Ref.	-	0	Ref.	-
APOE *24	223	1.85 [1.34, 2.54]	**1.75E-04**	51	1.62 [0.82, 3.18]	0.16	7	7.24 [1.11, 47.4]	**0.039**	0	-	-	0	-	-
APOE *34	1,424	2.08 [1.76, 2.46]	**1.47E-17**	391	2.70 [1.99, 3.66]	**1.72E-10**	44	5.59 [2.09, 14.95]	**5.97E-04**	0	-	-	0	-	-
APOE *44	239	5.54 [4.04, 7.59]	**1.79E-26**	83	12.86 [6.86, 24.09]	**1.56E-15**	7	38.96 [2.06, 737.98]	**0.015**	0	-	-	0	-	-

	Non-Hispanic Black (NHB) across global African ancestry														
	AFR% < 25			AFR% > 25			AFR% > 50			AFR% > 75			AFR% > 90		
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value
***APOE* across admixture**															
***APOE* *4 and *APOE* *2 dosage**															
APOE *2 dosage	1	-	-	1,233	0.71 [0.59, 0.86]	**3.79E-04**	1,193	0.71 [0.58, 0.86]	**4.45E-04**	923	0.73 [0.58, 0.90]	**4.39E-03**	492	0.68 [0.49, 0.94]	**0.022**
APOE *33	6	Ref.	-	2,714	Ref.	-	2,613	Ref.	-	2,041	Ref.	-	1,119	Ref.	-
APOE *4 dosage	1	-	-	2,683	2.44 [2.19, 2.71]	**9.33E-61**	2,593	2.38 [2.13, 2.65]	**5.77E-56**	2,028	2.34 [2.06, 2.65]	**9.97E-41**	1,031	2.09 [1.73, 2.52]	**1.06E-14**
***APOE* genotype**															
APOE *22	1	-	-	60	0.70 [0.33, 1.47]	0.34	58	0.74 [0.35, 1.58]	0.44	46	0.87 [0.38, 1.97]	0.74	31	0.85 [0.30, 2.46]	0.77
APOE *23	1	-	-	874	0.68 [0.56, 0.84]	**3.41E-04**	847	0.68 [0.55, 0.83]	**2.82E-04**	644	0.67 [0.53, 0.86]	**1.75E-03**	329	0.60 [0.41, 0.89]	**9.99E-03**
APOE *33	6	Ref.	-	2,714	Ref.	-	2,613	Ref.	-	2,041	Ref.	-	1,119	Ref.	-
APOE *24	1	-	-	299	1.66 [1.26, 2.19]	**3.01E-04**	288	1.57 [1.18, 2.09]	**1.76E-03**	233	1.84 [1.35, 2.52]	**1.32E-04**	132	1.48 [0.94, 2.32]	0.088
APOE *34	1	-	-	2,016	2.20 [1.92, 2.53]	**5.23E-29**	1,946	2.12 [1.84, 2.44]	**1.25E-25**	1,529	2.10 [1.79, 2.47]	**2.21E-19**	780	1.89 [1.48, 2.40]	**2.74E-07**
APOE *44	0	-	-	368	6.92 [5.33, 8.98]	**7.25E-48**	359	6.69 [5.14, 8.71]	**1.80E-45**	266	6.42 [4.73, 8.70]	**5.37E-33**	119	5.17 [3.28, 8.16]	**1.72E-12**

Note (when considering significant associations only) there was a pattern for increasing global European, or decreasing global African, ancestry to associate with increased effect estimates for *APOE**4 (orange-shaded cells). Compared to eTable14, the global African ancestry proportion >90% was added since sample sizes were permissive to do so and we believed it was of interest to better assess the role of global African ancestry on *APOE* genotype associations with AD risk.

eTable 16. Sensitivity Case-Control Regression Analyses Mirroring Table 1, Considering Stratifications Across Global Population Ancestry Proportion Greater Than 75%

	Global Population Ancestry Proportion >75%									Race/ethnicity effect		
	European (EUR)			African (AFR)			Amerindian (AMR)			EUR vs. AFR	EUR vs. AMR	EUR vs. AFR
Group/Model	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	No. carriers	OR (95% CI)	P-value	P-value	P-value	P-value
***APOE* across race/ethnicity**												
***APOE* *4 and *APOE* *2 dosage**												
APOE *2 dosage	3,782	0.55 [0.51, 0.60]	**3.45E-39**	1,083	0.77 [0.62, 0.94]	**0.012**	44	0.48 [0.15, 1.59]	0.23	**4.00E-03**	0.83	0.45
APOE *33	17,383	Ref.	-	2,355	Ref.	-	447	Ref.	-	-	-	-
APOE *4 dosage	13,866	3.45 [3.29, 3.62]	**<1.0E-300**	2,287	2.29 [2.04, 2.58]	**1.12E-42**	133	2.02 [1.32, 3.10]	**1.12E-03**	**3.13E-10**	**0.014**	0.58
***APOE* genotype**												
APOE *22	135	0.40 [0.26, 0.62]	**3.94E-05**	54	1.14 [0.56, 2.34]	0.72	1	0.00 [0.00, Inf]	0.99	**0.015**	0.99	0.99
APOE *23	2,906	0.54 [0.49, 0.59]	**4.64E-37**	765	0.69 [0.55, 0.88]	**2.10E-03**	40	0.50 [0.15, 1.68]	0.26	**0.048**	0.90	0.60
APOE *33	17,383	Ref.	-	2,355	Ref.	-	447	Ref.	-	-	-	-
APOE *24	741	2.22 [1.89, 2.60]	**1.13E-22**	264	1.78 [1.32, 2.40]	**1.78E-04**	3	0.00 [0.00, Inf]	0.99	**0.203**	0.99	0.99
APOE *34	10,867	3.43 [3.25, 3.63]	**<1.0E-300**	1,727	2.10 [1.80, 2.45]	**5.85E-21**	121	2.15 [1.31, 3.51]	**2.36E-03**	**4.11E-09**	0.063	0.93
APOE *44	2,258	12.84 [11.15, 14.80]	**3.00E-273**	296	5.92 [4.45, 7.88]	**3.03E-34**	9	3.05 [0.71, 13.05]	0.13	**1.96E-06**	0.054	0.38

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