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RESEARCH ARTICLE

APOE and Alzheimer's disease and related dementias risk among 12,221 Hispanics/Latinos

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Abstract

BACKGROUND: Effect of apolipoprotein E (*APOE*) on Alzheimer's disease and related dementias (ADRD) risk is heterogeneous across populations, with scarce data on Hispanics/Latinos.

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METHODS: *APOE* genotype was studied in 12,221 Hispanics/Latinos (per cohort and via metanalysis): Caribbean-Hispanics, Mexicans, Mexican-Americans, and Peruvians/Bolivians. A subsample had longitudinal assessment and plasma p-tau. We tested the modifying effects of global and local ancestries. Results were replicated in an independent Peruvian cohort and brain samples.

RESULTS: *APOE* ε4 effect was strongest in Peruvians/Bolivians (odds ratio [OR] = 6.13, 95% confidence interval [CI] = 2.71–13.83), followed by Mexicans (OR = 4.31, 95% CI = 1.58–11.74), Mexican-Americans (OR = 3.06, 95% CI = 2.04–4.59), and Caribbean-Hispanics (OR = 2.22, 95% CI = 1.99–2.48). Meta-analyses showed OR = 2.32 (95% CI = 2.09–2.57) and OR = 0.81 (95% CI = 0.68–0.97) for the ε4 and ε2 allele, respectively. The *APOE* ε4 effect was replicated independently in Peruvians (OR = 5.06, 95% CI = 2.48–10.70). ε4 carriers displayed higher ADRD conversions and p-tau levels. Global and local ancestries did not modify ADRD risk, and they were associated with Braak stage.

DISCUSSION: *APOE* shows a heterogeneous effect on ADRD risk in our Hispanics/Latinos sample, the largest to date.

KEYWORDS
admixture, ADRD, *APOE*, health disparities, Hispanic/Latino population

Highlights

- The apolipoprotein E (*APOE*) ε4 effect is stronger in Peruvians/Bolivians than in other Hispanic/Latino groups.
- The strong *APOE* effect size in Peruvians and Bolivians was replicated in a second independent Peruvian cohort.
- Meta-analysis for ε4 and ε2 confirmed a significant association with Alzheimer's disease and related dementias (ADRD).
- Global and local ancestry do not modify the association between *APOE* genotype and ADRD.

1 | BACKGROUND

Alzheimer's disease (AD), responsible for 60%–80% of cases of dementia worldwide,[1,2] represents a major health challenge with significant social and economic consequences.

More than 80 genetic loci have been associated with AD[3]; however, the apolipoprotein E (*APOE*) ε4 allele remains the strongest genetic risk factor. Although prevalence estimates of AD are higher among ethnic populations such as non-Hispanic Blacks and Hispanics compared to non-Hispanic Whites,[4] research has shown that the impact of *APOE* genotype differs significantly across ethnoracial groups.[5] These large differences in *APOE* ε4 effects are likely to depend on both global genetic ancestry and local genetic ancestry, as well as gene—environment interactions.[6,7] The strongest association between AD and *APOE* ε4 has been observed in East Asians[8] followed by non-Hispanic Whites.[9] Studies addressing the relationship between *APOE* and AD risk in non-White populations have shown that the *APOE* effect is considerably weaker in African descent and Caribbean-Hispanic populations.[9,10]

Local ancestry analyses can provide insight into the ancestral origin of the genetic information surrounding *APOE*, which may differ from the global average ancestry assessed across an individual's entire genome,[5] and therefore may help to explain the observed heterogeneity in the *APOE* association with AD risk.

Using a neuropathological sample of 400 admixed Brazilians, Naslavsky et al.[11] showed that *APOE* and its association with AD neuropathology was highly influenced by ancestry. The association between *APOE* ε4 risk and risk of AD was attenuated in individuals of African American ancestry compared to those of European ancestry. *APOE* local ancestry analysis also shows that previously identified protective variant located 2 Mb from *APOE* reduces the AD risk effect of *APOE* ε4 homozygotes by ≈75% in populations of African descent.[12] Follow-up analyses confirmed that the minimum shared haplotype containing the protective variant was found exclusively in populations with

African ancestry.[13] Griswold et al.[14] showed that among patients with AD, African American *APOE* ε4 carriers with surrounding African local genomic ancestry expressed significantly less *APOE* than non-Hispanic White carriers with European local ancestry. These differences in *APOE* ε4 expression may contribute to the differences in AD and may lead to therapeutic interventions. Rajabli et al.[15,16] also argued that rather than non-genetic ethnic, or environmental factors, the difference in *APOE* AD risk between African American and European populations was due to ancestral genomic background surrounding the *APOE* locus.

Conflictive results have been reported for Hispanics/Latinos in the literature. Blue et al.[17] reported that ancestry-specific genetic variation encompassing the *APOE* locus was the reason for the weaker *APOE* ε4 effect in Caribbean–Hispanics when compared to non-Hispanic White populations. Previous studies have shown that in Mexican Americans, the *APOE* ε4 allele is less common and confers less risk for AD than in non-Hispanic Whitess.[18,19] The Hispanic Community Health Study/Study of Latinos (HCHS/SOL), comprising >4000 participants of diverse ancestral backgrounds, reported a heterogeneous effect of *APOE* across groups, with a protective effect associated with Native American ancestry and a strong effect size for the ε4 allele in Cubans (interestingly, the Cuban population have the lowest proportion of Native American ancestry).[20] On the contrary, a small pilot study[21] showed that the effect of the ε4 allele on AD risk in Peruvians (a population with the highest Native American ancestry among all Hispanic/Latino groups) is significantly higher (OR >5) than in other Hispanic/Latino populations.

In this study, we investigated the association between *APOE* genotype and Alzheimer's disease and related dementias (ADRD) risk in four different Hispanic/Latino populations: Caribbean Hispanics, Mexican Americans, Mexicans, and Peruvians/Bolivians. Second, we investigated whether genetic ancestry modified the *APOE* effect on disease risk.

RESEARCH IN CONTEXT

Systematic Review: We reviewed the literature focusing on studies investigating the risk associated with apolipoprotein E (*APOE*) genotypes and the risk of Alzheimer's disease and related dementias (ADRD). Although extensive literature is available for European-descended groups, data on Hispanics/Latinos are scarce, and usually different populations (e.g., Mexicans, Caribbean Hispanics, etc.) are conflated into one group.

Interpretation: A total of 12,221 participants were included in this study. The strength of the association between apolipoprotein E (*APOE*) ε4 and Alzheimer's disease and related dementias (ADRD) decreased as Native American ancestry decreased, that is, it was found higher in Peruvians/Bolivians followed by Mexicans, Mexican Americans, and finally Caribbean Hispanics. *APOE* ε2 was confirmed to be protective toward ADRD risk. Local ancestry did not modify the association between ADRD and *APOE* genotype. All findings were validated using subsamples with well-established AD endophenotypes (plasma phosphorylated tau (p-tau)181 and p-tau217, and Braak staging).

Future Directions: This study provides a robust estimate for the role of *APOE* in determining ADRD risk in Hispanic/Latino populations and amends previous investigations with conflictive findings. Further investigations are needed to understand the higher effect of *APOE* isoforms in Native American–predominant populations.

2 | METHODS

2.1 | Study populations

Individual studies (Table 1) were approved by the institutional review boards at the respective universities and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from all participants. Within each of the study cohorts, the identity of the participants was self-reported, that is, participants were asked to identify with predefined ethnic/racial categories.

2.1.1 | Washington Heights Inwood Aging project (WHICAP)

A detailed description of the WHICAP cohort has been provided previously. Briefly, WHICAP[9,22] is an ongoing Northern Manhattan-based community-based study of randomly selected elderly individuals from three ethnic groups: non-Hispanic Whites, Caribbean Hispanics, and African Americans. Analyses were restricted to Caribbean Hispanic participants (n = 2124). Clinical dementia status (cognitively healthy and ADRD participants) at the last evaluation was determined using the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA).[23] A subset of samples (n = 366) had blood AD biomarker phosphorylated tau (p-tau), generated using Single Molecule Array.

2.1.2 | Estudio Familiar de Influencia Genética en Alzheimer (EFIGA)

EFIGA is a longitudinal family-based study recruiting families with at least two living relatives with dementia history as well as unrelated sporadic AD cases and healthy controls. Clinical diagnosis of AD was based on the NINCDS–ADRDA criteria.[23] The sample for the current analyses consisted of 6648 participants.

2.1.3 | 10/66 Puerto Rico

The 10/66 PR is part of the large 10/66 consortium (it refers to the 66% of people with dementia residing in developing countries). The study recruits individuals aged 65 years or older in several countries focused

TABLE 1 Characteristics of the cohorts.

	Caribbean Hispanics			Mexican Americans		Mexicans	Peruvians Bolivians	
	WHICAP	EFIGA	10/66 PR	HABS-HD	TARCC	Mex-Cog	GAPP	Total
N	2124	6648	1368	493	414	823	351	12,221
% Female	1480 (70)	4407 (66)	924 (67)	319 (65)	264 (64)	477 (58)	241 (67)	8112 (66)
Age, mean ± SD	79 ± 7	73 ± 9	76 ± 8	67 ± 6	69 ± 7	69 ± 8	72 ± 8	74 ± 9
Education, mean ± SD	7 ± 5	7 ± 5	4 ± 4	9 ± 5	10 ± 5	6 ± 5	10 ± 6	6 ± 5
APOE ε4 non-carriers, *N* (%)	1594 (75)	3965 (60)	1060 (77)	409 (83)	310 (75)	676 (81)	294 (84)	8308 (68)
APOE ε4/, N* (%)	491 (23)	2281 (34)	282 (21)	77 (16)	98 (24)	138 (17)	52 (15)	3419 (28)
APOE ε4/ε4, N (%)	39 (2)	402 (6)	26 (2)	7 (1)	6 (1)	9 (1)	5 (1)	494 (4)
APOE ε2/, N* (%)	304 (14)	763 (11)	126 (9)	31 (6)	31 (7)	45 (5)	11 (3)	1311 (11)
ADRD, *N* (%)	643 (30)	3391 (51)	137 (10)	61 (12)	108 (26)	254 (31)	108 (31)	3602 (29)
European, %avg	58	53	68	47	53	35	19	53
Native, %avg	10	7	14	48	42	61	79	17
African, %avg	33	40	17	5	5	4	2	30

mainly on lower-income economies.[24] The diagnosis of dementia was assigned according to 10/66 protocol and subsequently harmonized[25] by the Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium (ADSP-PHC). The sample for the current analyses consisted of 1368 participants.

2.1.4 | The Health & Aging Brain among Latino Elders (HABLE)/Health and Aging Brain Study (HABS-HD)

HABLE/HABS-HD is an ongoing, longitudinal, single-site community-based project to understand health disparities in mild cognitive impairment (MCI) and AD among elderly Mexican Americans in Texas (United States). Detailed descriptions of the cohort and methodologies have been reported previously.[26] Clinical dementia diagnoses were based on consensus panel–based analysis of informant or self-report of daily function, Clinical Dementia Rating (CDR), and neuropsychological results. The analyses sample consisted of 493 subjects. A subset of HABS-HD samples ($n = 534$) had the available blood AD biomarker p-tau181. The Biotinylated-AT270 assay was used as the capture antibody for anti-p-tau181 and SULFO-TAG-Ru-4G10-E2 as the detector antibody for anti-tau monoclonal antibody.

2.1.5 | Texas Alzheimer's Research and Care Consortium (TARCC)

TARCC is an ethnically diverse, longitudinal, multi-site study recruiting participants older than 55 years of age and older, at dementia clinics from five Texas academic medical institutions. Each participant underwent a standardized annual examination, which included medical evaluation, neuropsychological testing, and blood draw. Detailed descriptions can be found elsewhere.[27,28] Clinical dementia diagnoses were based on consensus panel-based analysis of informant or self-report of daily function, CDR, and neuropsychological results. A total of 493 participants were included in the analysis.

2.1.6 | The Mexican Health and Aging Study (MHAS)—Cognitive Aging Ancillary Study in Mexico (Mex-Cog)

The Mexican Health and Aging Study (MHAS) is a prospective study designed to evaluate the impact of disease on the health, function, and mortality of adults 50 years and older in both urban and rural areas of Mexico. Detailed descriptions can be found in previous publications.[29] For this study, we used a sub-sample of the MHAS cohort ($N = 823$) known as "Cognitive Aging Ancillary Study in Mexico" (Mex-Cog), an in-depth cognitive protocol.[30] Due to the lack of a formal AD diagnosis, we implemented a surrogate diagnosis approach, leveraging the extensive cognitive data and implementing a model-based clustering method (R package *VarSelLCM*[31]). Briefly, the analyses used the entire MexCog cohort ($N = 2042$ individuals) and seven cognitive domains to derive a diagnostic algorithm using a clustering approach. Three resulting clusters were considered as surrogates for cognitively healthy participants, ADRD cases, and MCI. Detailed information can be found in the Supplementary File and Figures S1 and S2.

2.1.7 | Genetics of Alzheimer's Disease in Peruvian Populations (GAPP) study

The GAPP study is an ongoing prospective cohort of unrelated AD cases, MCI (according to the NINCDS-ADRDA[23]), and cognitively healthy controls in Peru and Bolivia. Participants were recruited at four

sites (Arequipa, Puno, Lima, and La Paz) if they were older than 60-years of age, self-reported as Quechuas, Aymaras, or Mestizos, and had an identified informant. A total of 351 subjects were included in the analysis. A subset of samples (n = 347) had available blood AD biomarker p-tau217 generated using Simoa technology on the Quanterix HD-X platform, which we used to further validate the main findings obtained with clinical diagnosis.

2.1.8 | Peruvian Alzheimer's Disease Initiative (PeADI)

To replicate the observations from GAPP—the smallest of the cohorts included in this project—we obtained data from an independent study of Peruvians for AD, the PeADI cohort, already described elsewhere.[21] Briefly, PeADI comprises unrelated cases and controls ascertained from the Instituto Nacional de Ciencias Neurologicas in Lima, Peru, following NINCDS–ADRDA criteria.[23] It is important to note that this cohort is independent of GAPP, confirmed by analyses of GWAS data (see Section 2.3). A total of 190 subjects were included in the analysis.

2.1.9 | New York Brain Bank (NYBB) brain autopsy cohort

To validate our findings from local ancestry at the *APOE* locus and its association with ADRD risk, we included 44 brain samples obtained from the New York Brain Bank (NYBB) at Columbia University. Age, sex, ethnic group (Hispanic/Latino), neuropathological diagnoses, and Braak staging data were provided by the NYBB. A detailed description of the cohorts can be found elsewhere.[32]

2.2 | *APOE* genotyping

For the Mex-Cog and GAPP samples, DNA was extracted from participants' blood. The genotypes at *APOE* single nucleotide polymorphisms (SNPs) rs7412 and rs429358 for blood-derived samples were imputed using the TOPMed imputation server[33] (https://imputation.biodatacatalyst.nhlbi.nih.gov/#!). The combination of genotypes at rs429358 and rs7412 was used to define the three main *APOE* alleles (ε4, ε3, and ε2). Ambiguous ε2ε4/ε1ε3 genotypes were coded as ε2/ε4, since the frequency of ε1 allele is very rare. We used the ε3/ε3 genotype as a reference genotype. In WHICAP, EFIGA, 10/66 PR, TARCC, and HABS-HD cohorts, participant's blood samples underwent direct genotyping of *APOE*.

2.3 | Genetic association analyses

Analyses were restricted to participants 60 years of age and older. Genotypes at the *APOE* locus were coded using an allelic dosage model: (1) no ε4 or ε2 alleles, (2) one ε4 or ε2 alleles (heterozygous individuals), and (3) two copies of ε4 or ε2 alleles (homozygous individuals). The association between *APOE* dosage and ADRD was assessed using generalized mixed models in R[34] (*glmer* package), adjusted for sex, age, education (fixed effects), study (EFIGA vs WHICAP vs 10/66 PR; HABS-HD vs TARCC), and relatedness (modeled as random effects to account for pedigree structure [EFIGA] or cryptic relatedness). To maximize the sample size and statistical power, association analyses in Caribbean Hispanic and Mexican Americans cohorts were conducted by combining the available cohorts, that is, WHICAP+EFIGA+10/66 PR and HABS-HD+TARCC, respectively. This approach allowed us to effectively analyze strata with limited sample size such as homozygous *APOE* ε4 carriers versus non-carriers and carriers of the *APOE* ε2 allele, relatively rare in most populations. A second generalized mixed model considered a random effect factor when merging all four subpopulations (Peruvians/Bolivians, Mexicans, Mexicans Americans, and Caribbean Hispanics). Stratified models (sex-stratified; global ancestry-stratified) were performed in all combined studies to maximize statistical power. Study cohorts were combined via a meta-analysis approach using the *metafor* package in R.[34] To investigate potential relatedness between Peruvians from GAPP and from PeADI, we employed the software King[35] (–kinship function) applied on genomewide genotype QCed data: individuals with $K > 0.0442$ were excluded from the PeADI study.

2.4 | Global and local ancestry estimation

Global ancestry (GA) proportions, Native American (NAA), European (EUR), and African (AFR), were estimated with ADMIXTURE (v1.3.0) software[36] using the Human Genome Diversity Project (HGDP) as the reference panel as detailed in our previous publications.[37] Each study's genotyping array underwent standard quality control already described in previous publications for EFIGA, WHICAP, 10/66 PR,[38,39] and GAPP.[40] Individuals with sex discrepancies and low genotype call rates (<95%) were excluded. Additional exclusion criteria included SNPs with high genotype missing rates (>95%), minimum allele frequencies <1%, and deviations from Hardy-Weinberg equilibrium ($p \leq 10^{-6}$). As described previously,[37] local ancestry (LA) within the *APOE* region (±500 kb) was inferred by employing the Efficient-Local Ancestry Inference (ELAI) software (v0.99)[41] to estimate locus-specific haplotypes derived for EUR, AFR, and NAA original founder populations. ELAI exploits a two-layer hidden Markov model by estimating cluster-switch rates, which enhances estimation of recombination hotspots. Individuals who reported ancestral switches within the *APOE* region (e.g., switch from NAA to EUR) or where ELAI could not estimate with enough certainty the LA, were excluded from the analyses.

We tested any potential modifying effect of LA_{NAA} or LA_{AFR} on the association between *APOE* and ADRD "main approach"):

$$ADRD \sim SEX + AGE + EDUCATION + GA - AFR + LA_{AFR} + APOE - \varepsilon 4 + \mathbf{APOE}\text{-}\varepsilon 4 * \mathbf{LA}_{AFR} + (1\backslash STUDY) + (1\backslash FID)$$

$$ADRD \sim SEX + AGE + EDUCATION + GA - NAA + LA_{NAA} + APOE - \varepsilon 4 + \mathbf{APOE}\text{-}\varepsilon 4 * \mathbf{LA}_{NAA} + (1\backslash STUDY) + (1\backslash FID)$$

where LA indicates local ancestry, GA is global ancestry, and FID is the sample cluster. We also carried out a secondary model ("conservative approach") by restricting the sample to homozygous-LA samples only, that is, samples exhibiting NAA/NAA or EUR/EUR or AFR/AFR ancestry at the *APOE* locus. This approach allowed us to focus on the relationship between one specific local ancestry, *APOE* genotype, and ADRD, avoiding complex relationships between mixed local ancestry, *APOE*, and risk of ADRD (e.g., individuals showing NAA/AFR local ancestry).

2.5 | Replication cohorts

To validate our results, we used an independent Peruvian cohort (PeADI cohort) along with NYBB brain samples (described in Sections 2.1.8 and 2.1.9). We applied the same statistical approach used for testing the association between *APOE* and ADRD across the other studies (see Section 2.3). For NYBB, we employed an ordinal logistic regression to estimate the modifying effect of LA at the *APOE* locus (i.e., NAA and AFR, holding EUR as the reference) on the association between Braak stage and *APOE*:

$$Braak_{[0-6]} \sim sex + ageatdeath + LA_{NAA} + APOE-\varepsilon4 + APOE-\varepsilon4 * LA_{NAA}$$
$$Braak_{[0-6]} \sim sex + ageatdeath + LA_{AFR} + APOE-\varepsilon4 + APOE-\varepsilon4 * LA_{AFR}$$

2.6 | Survival analyses

In the WHICAP+EFIGA cohort, mixed-effects Cox models were used to examine the effect of *APOE* on progression to ADRD. We estimated the hazard ratio (HR), and its 95% confidence interval (CI) for survival while controlling for family relatedness employing the *coxme* R package. Significance alpha levels were set at $p = 0.05$. The R package *adjustedCurves* was used to plot adjusted survival curves with its CIs. Analyses were restricted to participants at least 60 years of age at baseline and diagnosed as incident ADRD or dementia-free at the last visit. All statistical models were adjusted for sex, age at baseline, and education.

3 | RESULTS

3.1 | Cohorts' description

Characteristics of the study's participants are summarized in Table 1. Peruvians/Bolivians from GAPP, Mexican Americans from TARCC, and EFIGA families were specifically recruited based on ADRD diagnosis, which is reflected in their higher frequency of affected participants (31%, 26%, and 51%, respectively) when compared to HABS-HD, which is a community-based study (12%). The prevalence of ADRD in Caribbean Hispanic participants from WHICAP was 30%. The diagnostic categories in Mex-Cog were assigned using the two extremes of our statistical clustering as surrogates for cognitively healthy and ADRD cases (31%). Detailed results for Mex-Cog can be found in the Supporting Information. *APOE* ε4 frequencies ranged from 15% to 34% for heterozygous carriers and from 1% to 6% for homozygous carriers. The genetic ancestral composition was significantly different across cohorts (Figures 1 and S3). Peruvians/Bolivians and Mexicans showed a predominant NAA ancestry (averages of 79% and 61%, respectively), whereas Caribbean Hispanics from EFIGA+WHICAP appeared to have a major contribution of European (~56%) and African (~35%) ancestry. The Mexican Americans from HABS-HD+TARCC exhibited similar proportions of both European (≈50%) and NAA ancestry (≈50%). Figure 1 shows the distribution of the four Hispanic/Latino populations according to their principal component analyses and ancestry proportions.

3.2 | Association between *APOE* ε4/ε2 and ADRD

We observed a significant association between *APOE* ε4 allele dosage and ADRD across the cohorts (Tables 2 and S1 for the extensive regression outputs, including predictors and covariates coefficients and CIs). The genetic effect of at least one copy of the ε4 allele on disease risk was higher in Peruvians/Bolivians (odds ratio [OR] = 6.13, 95% CI = 2.71–13.83) compared to Mexicans (OR = 4.31, 95% CI = 1.58–11.74), Mexican Americans (OR = 3.06, 95% CI = 2.04–4.59), or Caribbean Hispanics (OR = 2.22, 95% CI = 1.99–2.48). We observed a protective effect for the *APOE* ε2 allele on ADRD risk (although not statistically significant) in WHICAP+EFIGA+10/66 PR (OR = 0.84, 95% CI = 0.70–1.02), TARCC+HABS-HD (OR = 0.50, 95% CI = 0.19–1.31), Mex-Cog (OR = 0.34, 95% CI = 0.10–1.14), and GAPP (OR = 0.62, 95% CI = 0.08–4.70).

Consistently, the joint analysis encompassing all samples showed a significant association between ADRD and *APOE* ε4 allele (ε4 heterozygous: OR = 2.30, 95% CI = 2.07–2.56; ε4 homozygous: OR = 7.67, 95% CI = 6.06–9.71) or the *APOE* ε2 allele (OR = 0.81, 95% CI = 0.68–0.97, $p = 0.024$).

3.3 | Stratified analyses

When stratified by GA, samples with predominantly NAA ancestry and *APOE* ε4 heterozygous carriers showed a significant association between *APOE* ε4 allele and ADRD, (OR = 3.90, 95% CI = 2.31–6.57). Results restricted to predominant European GA are shown in Table S2, where the ε4 allele risk on AD was also found significant (OR = 3.02, 95% CI = 2.62–3.47). Association between the ε4 allele and ADRD in the men's strata (OR = 2.20, 95% CI = 1.85–2.62) was found significant yet weaker than in women (OR = 2.84, 95% CI = 2.51–3.22). Consistently, interaction analyses showed a significant sex**APOE* ε4 result (OR = 1.26, 95% CI = 1.02–1.55, $p = 0.03$; Table S3).

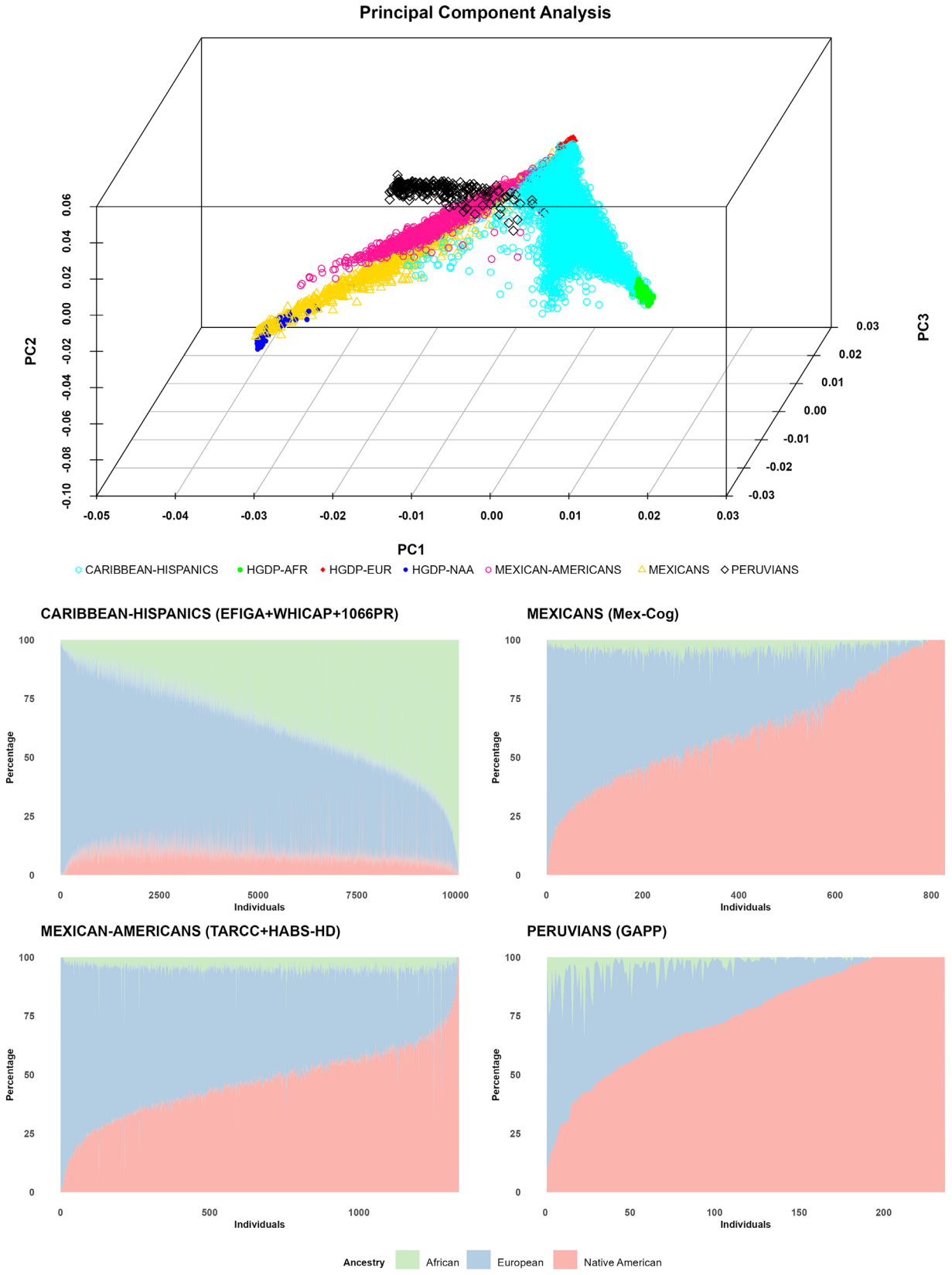

FIGURE 1 Principal component analyses for the four Hispanic/Latino cohorts, along with three reference populations from the Human Genome Diversity Project (European [HGDP-EUR], African [HGDP-AFR], Native American [HGDP-NAA]). The three-dimensional axes represent the three principal components (PCs) used to plot genetic ancestry proportions. The colors of each point (each point represents an individual) correspond to the different cohorts, including the reference population panels (light blue = Africans from the Human Genome Diversity Project; green = Europeans from the Human Genome Diversity Project; red = Native Americans from the Human Genome Diversity Project; dark blue = Caribbean Hispanics; fuchsia = Mexican Americans; yellow = Mexicans; black = Peruvians).

TABLE 2 Results of the association between the ε4 and ε2 alleles and ADRD across cohorts.

Cohort	*N*	*APOE*[a]	OR	95% CI	*p*
HISPANICS/LATINOS merged sample	12,221	ε4	2.66	2.39–2.95	<**0.001**
		ε4/*	2.30	2.07–2.56	<**0.001**
		ε4/ε4	7.67	6.06–9.71	<**0.001**
	8308[c]	ε2	0.81	0.68–0.97	**0.024**
Individual cohorts					
CARIBBEAN HISPANICS *(WHICAP+EFIGA+10/66 PR)*	10,140	ε4	2.22	1.99–2.48	<**0.001**
		ε4/*	1.93	1.72–2.16	<**0.001**
		ε4/ε4	5.90	4.64–7.49	<**0.001**
	6619[c]	ε2	0.84	0.70–1.02	0.070
MEXICAN AMERICANS *(TARCC+HABS-HD)*	907	ε4[b]	3.06	2.04–4.59	<**0.001**
	719[c]	ε2	0.50	0.19–1.31	0.158
MEXICANS *(Mex-Cog)*	823	ε4[b]	4.31	1.58–11.74	**0.004**
	676[c]	ε2	0.34	0.10–1.14	0.080
PERUVIANS/BOLIVIANS *(GAPP)*	351	ε4[b]	6.13	2.71–13.83	<**0.001**
	294[c]	ε2	0.62	0.08–4.70	0.640

Note: The *p*-values considered as significant have been marked as bold.
[a]ε4 or ε2 corresponds to presence of at least one copy of the ε4 allele; ε4/ε4 corresponds to carriers of two copies of the ε4 allele; ε4/* corresponds to carries of one single copy of the ε4 allele.
[b]In GAPP, Mex-Cog and HABS-HD+TARCC cohorts, due to the small number of ε4/ε4, the 95% confidence intervals were not computed because of its low reliability.
[c]ε2 effect computed on ε4 non-carriers only.

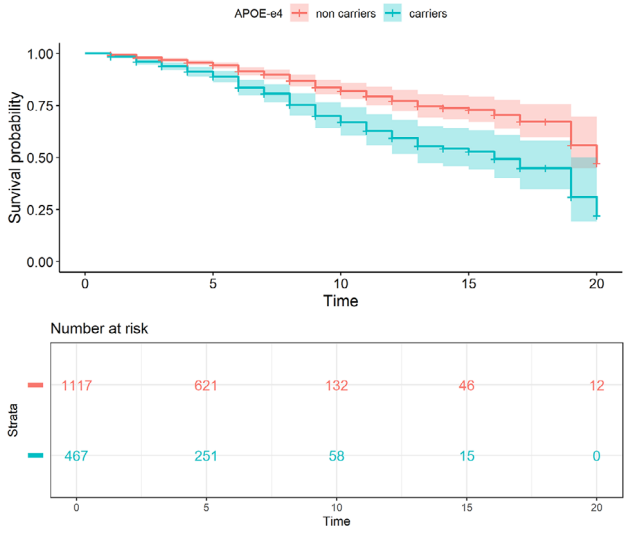

FIGURE 2 Mixed-effects Cox model in WHICAP+EFIGA. *APOE* ε4 carriers versus non-carriers are plotted over the follow-up time.

3.4 | Survival analyses

Results from mixed-effects Cox models in Caribbean Hispanics (WHICAP+EFIGA, *N* = 1.584; incidence cases *N* = 248; median years of follow-up = 5 [interquartile range (IQR) = 5]) showed statistically significant differences in the number of conversions between ε4 allele carriers versus non-carriers (HR = 3.65, 95% CI = 1.62–8.23 for homozygous ε4 carriers). Figure 2 plots survival curves for ε4 carriers versus non-carriers, whereas Figure S4 displays ε4 dosage curves; full results can be found in Table S4.

3.5 | *APOE* and ADRD association meta-analysis across cohorts

We conducted a fixed-effect and random-effect meta-analysis across cohorts. The overall effect size for the ε4 allele was estimated to be 2.32 (95% CI = 2.09–2.57, $p < 0.001$, fixed effect). For the *ε2* allele, the meta-analysis estimated an OR = 0.81 (95% CI = 0.68–0.97, $p = 0.023$, fixed effect). Forest plots for the *APOE* ε4 and ε2 alleles are shown in Figure 3.

3.6 | Plasma ADRD biomarkers association analyses

Across cohorts, the *APOE* ε4 allele was associated with higher plasma levels of p-tau181 or p-tau217 biomarkers (concentrations were $\log_{10}$ transformed and standardized). The results can be found in Table S5.

3.7 | *APOE* local ancestry analyses

In HABS-HD+TARCC, GAPP, and Mex-Cog, NAA, EUR, and AFR local ancestry background at the *APOE* region was not associated with clinical ADRD, and it did not modify the association between *APOE* and ADRD (Table S6). This result applied to both main and conservative

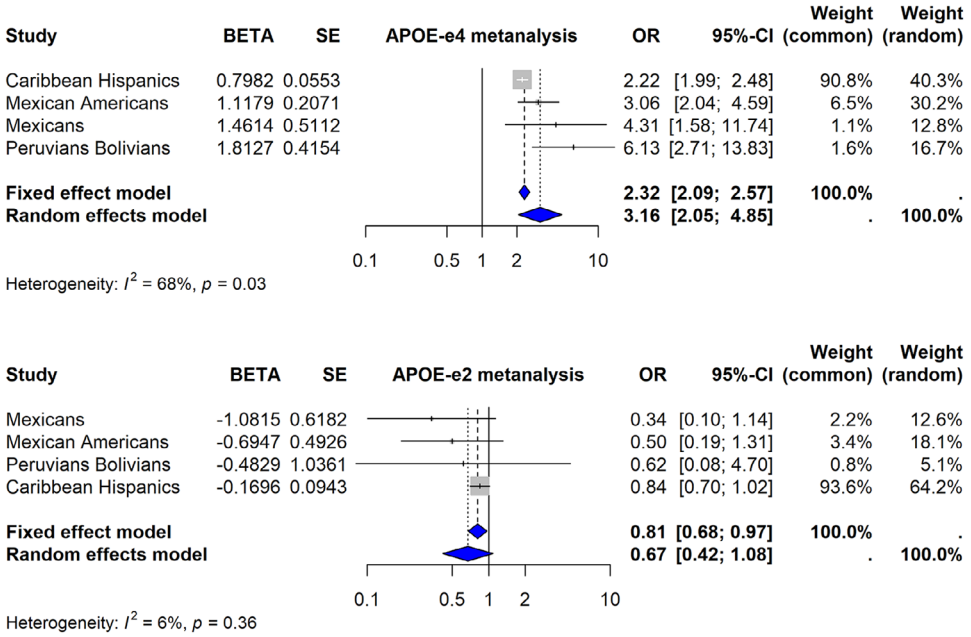

FIGURE 3 Meta-analysis and forest plot for ε4 (upper panel) and ε2 (lower panel) alleles. The plot details the beta coefficients (BETAs), standard errors (SEs), odd ratios (ORs), 95% confidence intervals (CIs), and the individual study weights according to their contributions to the pooled estimates. The horizontal lines represent the study's 95% CIs, with each end of the line representing the boundaries of the CI. A black dot represents the point estimate of the study, and it also provides a visual representation of the size of the study (the largest dot corresponds to a larger sample size). The dotted vertical lines are drawn at the value of the overall common effect. The diamond below the studies represents the overall pooled effect.

approaches. A mosaic plot representing the LA frequencies at the *APOE* region is shown in Figure S5.

3.8 | Replication analyses

Only one PeADI subject was found to be related to a GAPP participant (kinship >0.0442) and therefore excluded from analyses. The PeADI cohort exhibits on average 63% NAA, 32% EUR, and 4% AFR ancestry; we observed a robust significant association between at least one copy of the ε4 allele and ADRD (OR = 5.06, 95% CI = 2.48–10.70).

In the NYBB sample, we did not find a significant modifying effect of local ancestry at the *APOE* region on the association between *APOE* and Braak staging (*APOE* ε4*LA_{NAA}: proportional OR = 2.13 [0.16–30.63]; *APOE* ε4*LA_{AFR}: proportional OR = 2.29 [0.18–33.35]).

4 | DISCUSSION

APOE ε4 allele continues to be the strongest and most replicated ADRD genetic risk factor in the non-Hispanic White population. However, in populations with admixed genetic backgrounds, the risk conferred by the different *APOE* isoforms is heterogeneous. Genetic studies examining the association between ADRD risk and *APOE* in African Americans and Caribbean Hispanics showed that the risk is attenuated, especially when the ancestral background around the *APOE* locus is from the African haplotypes.[15,17] Our results showed that the *APOE* ε4 allele confers a heterogenous risk for ADRD across Hispanic/Latino populations but none of our cohort replicated the effect of local ancestral background around the *APOE* region in determining ADRD risk, as previously reported by less-powered studies.

The strongest association for the ε4 allele was observed in Peruvians/Bolivians; the latter show on average 79% NAA ancestral background, the highest proportion when compared to other Hispanic/Latino groups. Indeed, we obtained data from an independent Peruvian cohort (which already reported an exceptionally high effect size for AD risk[21]). We confirmed the strong association signal from ε4 carriers, replicating the findings from GAPP. This observation is also consistent with the strong association between the *APOE* ε4 allele and ADRD observed in our Mexican sample, which ranked second in terms of NAA proportions. Weaker effect sizes were observed in Mexican Americans and Caribbean Hispanics, the latter showing the smallest effect size overall. Of interest, indigenous populations from the American continents descend from an Ancient East Asian lineage, and the *APOE* ε4 effect on AD is known to be strikingly higher in East Asians compared to non-Hispanic Whites or African-descent populations.[42]

The effect of the *ε4* allele was further corroborated by plasma AD biomarker analyses. Despite the heterogeneity of the platforms employed, all cohorts showed a significant increase in plasma levels of p-tau181 or p-tau217 among *APOE* ε4 carriers. This confirmatory analysis is crucial because it addresses one of the study's main limitations, that is, relying solely on ADRD clinical diagnosis as the primary analysis's outcome.

The relationship between NAA and ADRD's risk, mediated or not by *APOE*, will require further studies to be fully understood. Global ancestry or local ancestry does not explain the ε4 allele increasing effect sizes as NAA becomes more prominent. Nevertheless, several publications have confirmed the role of NAA in determining ADRD risk.[43,44] Despite limited power, they suggested a protective effect on AD (not confirmed in our study). This effect could be driven by loci not yet identified, acting independently or as modifiers. Nevertheless, our data suggest that the ε4 allele, when present, overshadows other loci and consequently increases the ADRD risk. The lack of association between local ancestry at the *APOE* locus and diseased risk is further confirmed by our secondary analysis in brain samples.

It is important to note that we confirmed the protective effect of the *APOE* ε2 allele on the ADRD risk. Studies have reported extensively on the neuroprotective effect of the ε2 variant, reducing the risk of ADRD, Lewy body dementia, and cardiovascular diseases.[45,46] In both the joint and the meta-analysis approaches, we estimated an ≈23% reduced risk of developing ADRD per ε2 allele copy. These results reinforced and validated the robustness of our data, including the surrogate diagnosis used in Mexicans via the clustering approach (in which the ε2 allele showed a trend of association with lesser ADRD risk). Finally, we also confirmed that women carrying at least one *APOE* ε4 allele are disproportionately affected by ADRD, compared to their male counterparts.[47]

A recent publication encompassing 68,756 individuals from four different ethnic groups[5] reported a decreasing effect for the *APOE* ε4 allele from East Asians to Whites, non-Hispanic Blacks, and ultimately Hispanics. Specifically, they found striking lower effect sizes for both ε4 (OR = 1.90 [1.70–2.13] vs OR = 2.66 [2.39–2.95] in our study) and ε2 (OR = 0.90 [0.74–1.10] vs OR = 0.81 [0.68–0.97] in our study). It is notable that we found a protective effect on trends in both Caribbean Hispanics and Mexicans. In addition to the obvious methodological differences, the reason for the targeted underestimation of the *APOE* estimate in the Hispanic group could be explained by a simplification commonly adopted in genetic studies, that is, clumping individuals with significantly different ethnic backgrounds into a single group, that is, "Hispanic/Latino." In fact, "Hispanic" or "Latino" are extremely vague umbrella terms, since there is great heterogeneity in terms of the genetic admixture and environmental factors of the individuals considered under such denomination. Our work attempted to address this limitation by acknowledging the complexity of these populations and providing granular estimates within each Hispanic/Latino group.

Our study has some limitations. First, the potential heterogeneity across cohorts is introduced by the different measures of cognitive status or clinical diagnosis. However, results were validated using plasma p-tau181/p-tau217 biomarkers and a large brain biobank. Moreover, several large genetic studies routinely include "ADRD cases" based on questionnaires (e.g., family history[48]) rather than a formal clinical diagnosis, a much less accurate approach. Second, we cannot exclude the possibility that ADRD risk from *APOE* may be mediated or modified by race-confounded features such as socioeconomic status, depression, and cardiovascular disease. These effects may differ across the cohorts, potentially altering our findings. Third, our cohorts range from national samples representing urban and rural areas (e.g., Mex-Cog), to the small sample-sized case–control cohort (e.g., GAPP). Although this heterogeneity might limit the generalizability of our results, our study has assembled the largest sample of Hispanics/Latinos to date, providing a unique contribution to a deeper understanding of ADRD genetics in non-White diverse populations. Future work should aim to reproduce our findings with larger, and more representative, diverse samples. Different genetic architectures among ethnic groups may influence how genetic factors contribute to ADRD risk. Extending genetic studies to include more diverse admixed populations, and more specifically those with Native American backgrounds, will be critical for gaining further insight into ADRD pathogenesis.

AUTHOR CONTRIBUTIONS

Sandra Barral, Richard Mayeux, and Giuseppe Tosto conceptualized, drafted, and edited the article. Richard Mayeux, Dolly Reyes-Dumeyer, Robert C. Barber, Sid O'Bryant, Lawrence S. Honig, Rebeca Wong, Nilton Custodio, and Giuseppe Tosto contributed to the acquisition of data. Sandra Barral, Zikun Yang, Basilio Cieza, A.L., Y.M., Adam M. Brickman, Silvia Mejia Arango, Alejandra Michaels Obregon, Rafael Samper-Ternent, Nilton Custodio, Richard Mayeux, Marcio Soto-Añari, and Giuseppe Tosto contributed to the data analysis. Giuseppe Tosto and Zikun Yang contributed to preparing the figures.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

Applications for data sharing by qualified investigators can be made on the National Institute onf Aging Genetics of Alzheimer's Disase Data Storage Site (NIAGADS website (https://www.niagads.org/). Data sharing requests will be subject to the limitations specified in data transfer agreements between each study site and the individual research centers.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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