

FEATURED ARTICLE

APOE alleles' association with cognitive function differs across Hispanic/Latino groups and genetic ancestry in the study of Latinos-investigation of neurocognitive aging (HCHS/SOL)

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Abstract

Introduction: Apolipoprotein E (APOE) alleles are associated with cognitive decline, mild cognitive impairment (MCI), and Alzheimer's disease in Whites, but have weaker and inconsistent effects reported in Latinos. We hypothesized that this heterogeneity is due to ancestry-specific genetic effects.

Methods: We investigated the associations of the APOE alleles with significant cognitive decline and MCI in 4183 Latinos, stratified by six Latino backgrounds, and explored whether the proportion of continental genetic ancestry (European, African, and Amerindian) modifies these associations.

Results: APOE ε4 was associated with an increased risk of significant cognitive decline (odds ratio [OR] = 1.15, *P*-value = 0.03), with the strongest association in Cubans

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(OR = 1.46, P -value = 0.007). *APOE*- ϵ 2 was associated with decreased risk of MCI (OR = 0.37, P -value = 0.04) in Puerto Ricans. Amerindian genetic ancestry was found to protect from the risk conferred by *APOE* ϵ 4 on significant cognitive decline.

Discussion: Results suggest that *APOE* alleles' effects on cognitive outcomes differ across six Latino backgrounds and are modified by continental genetic ancestry.

KEYWORDS

admixture, Alzheimer's disease, ancestry, apolipoprotein E, cognitive decline, genetic epidemiology, Hispanics/Latinos, mild cognitive impairment

1 | BACKGROUND

Cognitive decline, mild cognitive impairment (MCI), and Alzheimer's disease and related dementias (ADRD) are a growing worldwide epidemic and one of the leading causes of death in the elderly population.¹ MCI is a prodromal cognitive impairment state preceding the more serious cognitive dysfunction characteristic of dementia. It can involve problems with memory, language, thinking, and judgment that are greater than normal age-related changes.^{2,3} Cognitive decline is a normal process of aging; however, in ADRD patients it begins many years before dementia is diagnosed and accelerates during the course of the disease.³ Self-reported cognitive decline has lately been introduced to the field, to extend ADRD risk diagnosis to an earlier stage before MCI.⁴ Hispanics/Latinos (Latinos henceforth) are the fastest-growing ethnic group in the United States,⁵ and suffer from higher rates of ADRD, compared to Whites.^{6,7}

The apolipoprotein E (*APOE*) ϵ 4 allele is the strongest known genetic risk factor for ADRD,⁸ and it has also been linked to more rapid cognitive aging, such as increased cognitive decline and MCI.⁹⁻¹¹ The *APOE* gene exists as three polymorphic alleles ϵ 2, ϵ 3, and ϵ 4 which are determined by two single nucleotide polymorphisms (SNPs: rs429358 and rs7412), that substitute amino acids in the protein, resulting in functional changes. In general, *APOE* ϵ 4 confers increased risk for cognitive decline, MCI, and ADRD compared to the more common *APOE* ϵ 3, whereas the *APOE* ϵ 2 is considered neuroprotective.¹² However, most of these findings are based on studies of individuals of European ancestry. Several population-based studies have shown ancestry heterogeneity of the *APOE* ϵ 4ADRD association.¹³⁻¹⁵ By comparing haplotype ϵ 4/ ϵ 4 to haplotype ϵ 3/ ϵ 3, Farrer et al.⁸ reported strong effects in Japanese (odds ratio [OR] = 33.1), and Whites (OR = 12.5), and weaker effects among African Americans (OR = 5.7) and Latinos (OR = 2.2). Other studies investigating the association of *APOE* ϵ 4 with MCI and

dementia in Latinos have produced inconsistent results.¹⁶⁻²⁰ A study of Mexican Americans indicated that haplotype ϵ 4/ ϵ 4, compared to haplotype ϵ 3/ ϵ 3, was associated with lower cognitive scores and higher dementia, though not significant (risk ratio [RR] = 2.04, confidence interval [CI] = 0.88-4.72).¹⁶ Similarly, two other studies suggested that the *APOE* ϵ 4 allele is both less common and confers less risk for MCI or ADRD in Mexican Latinos compared to Whites.^{17,18} However, another study in Caribbean Latinos (ie, Dominicans and Puerto Ricans) showed that late-onset familial Alzheimer's disease (AD) is strongly associated with *APOE* ϵ 4, with the *APOE* ϵ 4 allele more likely to be transmitted among affected individuals than unaffected relatives.¹⁹ These inconsistent results may be due, in part, to small sample sizes, different study designs and samples, and definitions of cognitive outcome,²⁰ as well as to the heterogeneity of the Latino groups in which the studies were conducted.

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a population-based longitudinal cohort study of 16,415 U.S. Hispanic/Latino adults that enrolled participants from Cuban, Central American, Dominican, Mexican, Puerto Rican, and South American backgrounds.^{21,22} Previous characterization of the genetic diversity in the HCHS/SOL cohort has shown that Latino individuals have admixed genomes consisting of three predominant continental ancestries: Amerindian, European, and African with varying proportions among and within each background group.²³ Furthermore, it was shown that the *APOE* alleles have different distributions among the six Latino background groups,²⁰ consistent with different *APOE* allele frequencies among the ancestral populations.

Previous association analysis of the *APOE* alleles with MCI in the HCHS/SOL ancillary Study of Latinos-Investigation of Neurocognitive Aging (SOL-INCA) did not detect significant associations.²⁴ We hypothesized that there are differential association effects of the *APOE* alleles in the six Latino background groups on

significant cognitive decline and MCI, which could potentially explain the inconsistent reported literature results of the association of *APOE* alleles with cognitive function, MCI, and dementia in Latinos. To address this, we tested the association of *APOE* alleles with significant cognitive decline and MCI and stratified the analyses by the six Latino background groups. Next, we hypothesized that differences in proportions of continental ancestries in the six Latino background groups will explain the heterogeneous *APOE* alleles' effects on significant cognitive decline and MCI. The purpose of this study was to determine whether genetic ancestry modifies the effect of *APOE* alleles on the significant cognitive decline and MCI by testing interaction effects between the three Latino continental ancestries and the *APOE* alleles.

2 | METHODS

2.1 | Study population

The HCHS/SOL is a multisite, prospective cohort study of diverse Latinos enrolled at four field centers (Bronx, New York; Chicago, Illinois; Miami, Florida; and San Diego, California). The sampling design details have been previously described.^{21,22} A total of 16,415 self-identified Hispanic/Latino adults, 18 to 74 years old, were enrolled at HCHS/SOL baseline visit 1 (2008–2011). Anthropometry, biospecimens, and health information about risk/protective factors were collected. The baseline cognitive battery included four tests: Six-Item Screener (SIS; mental status);²⁵ Brief-Spanish English Verbal Learning Test (B-SEVLT; verbal episodic learning and memory);²⁶ Word Fluency;²⁷ and Digit Symbol Substitution test (DSS; processing speed, executive function). HCHS/SOL visit 2 occurred between 2014 and 2017 with an abbreviated protocol. SOL-INCA is an HCHS/SOL ancillary study that occurred at visit 2, and included the oversampled middle-aged and older participants (50 years and older) who were administered the visit 1 cognitive battery, plus additional complementing cognitive tests to determine self-reported measures of cognitive decline (Everyday Cognition-12 [E-Cog12])²⁸ and functional status (Instrumental Activities of Daily Living Scale [IADL]), among other cognitive tests.²⁹ Overall, 6377 participants were re-examined in SOL-INCA after an average of 7 years since their visit 1 cognitive assessment. Of the 6377 participants, 2127 were excluded from analyses (1688 did not consent for genetic data, 420 failed *APOE* genotyping, 67 had missing cognitive outcomes, and 19 had missing covariates), totaling an analytic sample of 4183 individuals (mean age = 62.1 years and 52.5% were women). All participants in this analysis signed informed consent in their preferred language (Spanish/English) to use their genetic and non-genetic data. The study was reviewed and approved by the institutional review boards at all collaborating institutions.

2.2 | Cognitive outcomes

We analyzed two binary cognitive variables that were previously constructed³⁰ based on cognitive tests and self-report: significant

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources. Several publications have shown weak and inconsistent results for the association of the apolipoprotein E (*APOE*) alleles with cognitive decline, mild cognitive impairment (MCI), and Alzheimer's disease-related dementias in Latinos, despite higher rates of these disorders compared to non-Latino Whites. Publications are appropriately cited.
2. Interpretation: Our findings suggest a differential association between the *APOE* ϵ 2 and *APOE* ϵ 4 alleles and risk for significant cognitive decline and MCI in the six Latino groups defined by country of origin. We also found that Amerindian genetic ancestry protects from the risk conferred by *APOE* ϵ 4 on significant cognitive decline. Inconsistent estimated associations in Latinos may be due to different admixture patterns of continental ancestry across Latino groups.
3. Future directions: Future studies are needed to (a) identify enriched Amerindian genetic variants interacting with the *APOE* ϵ 4 allele, and the mechanism of interactions and (b) develop genetic measures for predicting significant cognitive decline and MCI in admixed individuals, potentially taking into account proportion ancestry or specific genetic variants.

cognitive decline, and MCI. Cognitive decline measures the cognitive decline between HCHS/SOL visit 1 and the SOL-INCA exam, based on a latent factor model taking into account cognitive test scores. Individuals were classified as meeting significant cognitive decline criteria if they had a change in global cognitive performance between the two exams that exceeded -0.055 standard deviation (SD) yearly.³⁰

Individuals were classified as MCI according to National Institute on Aging-Alzheimer's Association if they fit the following three criteria:³¹ (1) a cognitive test score below -1 SD based on SOL-INCA robust internal norms, (2) significant cognitive decline (described above), and (3) self-reported cognitive decline based on the E-Cog12.²⁸ Also, individuals that had both a cognitive deficit < -2 SD in any neurocognitive test at the SOL-INCA exam and more than minimal cognitive impairment in the IADL scale, were classified as MCI. Additional information about the SOL-INCA cognitive assessment approach is provided in detail in Appendix 1 of a previous publication.³⁰

2.3 | Genetic data

Genotyping, quality control, and continental ancestry inference were previously described.^{23,32} In brief, genotyping was performed using Illumina custom array and genome-wide imputation was

conducted with the 1000 Genome Project reference panel.³² Principal components (PCs) were estimated using PC-Relate³³ and continental-ancestry proportions were calculated using ADMIXTURE software.^{23,34} “Genetic analysis groups” were constructed based on a combination of self-identified Hispanic/Latino background and genetic similarity, and are classified as Cuban, Dominican, and Puerto Rican (Caribbean groups); and Mexican, Central American, and South American (Mainland groups).²³ APOE genotyping was performed using commercial TaqMan assays previously described.²⁰ APOE variants were in Hardy-Weinberg equilibrium ($P > 0.05$).

2.4 | Statistical analysis

We provided descriptive statistics to characterize the demographic and cognitive outcomes and APOE allele distributions in the full analytic dataset and by background groups. We tested the associations between APOE $\epsilon 2$ and $\epsilon 4$ alleles with cognitive outcomes in the same model (APOE $\epsilon 3$ used as the reference allele) using a complex survey design from the R “survey” package,³⁵ with a “quasipoisson” family for binary traits. This method accounts for the stratification, clustering, and probability weighting in HCHS/SOL to allow correct generalizations to the target population of U.S. Latinos. Models were adjusted for age, sex, education, center, first five genetic PCs, and “genetic analysis groups.” We tested both an additive and a dominant inheritance mode of the APOE alleles. For a given APOE allele, additive inheritance mode counts the number of the alleles for each individual (0, 1, or 2); dominant mode 1 if an individual had at least one allele, 0 otherwise. Carriers of both alleles ie, APOE $\epsilon 2/\epsilon 4$ were included in the model by giving a value 1 for the APOE $\epsilon 2$ variable and a value of 1 for the APOE $\epsilon 4$ variable (for both modes of inheritance).

Further association analyses of APOE $\epsilon 4$ and $\epsilon 2$ alleles with cognitive outcomes were done separately for each of the six genetic analysis groups and the significance of the results was evaluated through 10,000 permutations for each group, to protect from potential high type 1 error due to the low proportion of APOE variants. Effect modification by genetic analysis groups was tested by including multiplicative interaction terms of these groups with the APOE alleles followed by a Cochran's Q heterogeneity test accounting for correlations between effect estimates. Continental-ancestry proportion interaction with APOE alleles effects was tested separately for each of the three ancestries (European, African, and Amerindian), by including the continental-ancestry proportion variable together with a multiplicative interaction term of ancestry with the APOE allele (analytic dataset $n = 3618$).²³

Power calculation analysis for the two cognitive outcomes (cognitive decline and MCI) was calculated using population risk allele frequencies.³⁶ For APOE $\epsilon 4$ association with cognitive decline, the effect size was estimated based on the Cuban group and for APOE $\epsilon 4$ association with MCI, the effect size was estimated based on the Puerto Rican group, because these groups showed significant effects. This calculation did not account for age distribution in the background groups.

3 | RESULTS

Table 1 presents summary statistics of the SOL-INCA analytic sample used in this article, including sample size, distribution of sex, age, education, measures of cognitive function, distribution of the APOE alleles, and genetic proportion ancestries by genetic background groups. Overall, our dataset included 4183 participants (1568 men; 2615 women), with a mean age of 62.1 years. Figure S1 in supporting information illustrates the overlap between the two dichotomous cognitive outcomes. Thirty percent of the population was classified with significant cognitive decline ($n = 1250$); of these, one third were also classified as MCI ($n = 430$). Twelve more participants have solely MCI.

The distribution of the APOE alleles in our SOL-INCA analytic sample by genetic background groups demonstrates the differential distribution, similar to the results published by González et al.²⁰ Overall, APOE $\epsilon 3$ is the most frequent allele in all Latino background groups, while $\epsilon 4$ and $\epsilon 2$ are relatively rare. Table 2 summarizes the associations between the APOE alleles and cognitive outcomes in the SOL-INCA population based on an additive inheritance model. The OR for cognitive decline with one APOE $\epsilon 4$ allele, compared to individuals without APOE $\epsilon 4$ allele, was 1.15 (95% CI [1.01;1.32], P -value = 0.03); restriction to older subsets of the SOL-INCA population resulted in stronger association (ORs = 1.15-1.31; Table S1 in supporting information). However, no significant associations were obtained between APOE $\epsilon 4$ allele and MCI, and between APOE $\epsilon 2$ allele and both cognitive outcomes in the total SOL-INCA analytic sample.

We further stratified and explored the association of the APOE alleles with cognitive outcomes in the six background groups: Cuban, Dominican, Mexican, Puerto-Rican, South-American, and Central-American, summarized in Table 3 (additive model). The association between the APOE $\epsilon 4$ allele with cognitive decline remained significant only for Cubans showing a stronger effect compared to the effect in the total population (OR = 1.46, 95% CI [1.13;1.88], P -value = 0.007). Additionally, stratification to Latino background groups also revealed a new nominally significant protective association between the APOE $\epsilon 2$ allele and MCI in the Puerto Rican group (OR = 0.37, 95% CI [0.16;0.84], P -value = 0.04). Heterogeneity tests for differences between the background group association tests were not significant.

Tables S2 and S3 in supporting information present similar associations between APOE alleles and cognitive outcomes in the SOL-INCA analytic sample, based on a dominant inheritance mode. Power analysis for the cognitive traits is presented in Table S4 in supporting information. Power for the APOE allele associations with cognitive functions is substantially different among the six Latino backgrounds (ranges: MCI 0.34–1.00, cognitive decline 0.26–0.88).

Proportion ancestry interaction with APOE alleles' effects on cognitive outcomes is presented in Table 4. A significant interaction effect was found between Amerindian ancestry and APOE $\epsilon 4$ on cognitive decline (OR = 0.47, 95% CI [0.24;0.93], P -value = 0.04), such that protection from the risk of cognitive decline in APOE $\epsilon 4$ carriers was associated with higher Amerindian proportion ancestry (Figure 1).

TABLE 1 Demographics, neurocognitive, and genetic characteristics of SOL-INCA by genetic background groups

		Cuban	Dominican	Mexican	Puerto Rican	South American	Central American	Overall
N		875	424	1411	734	313	417	4183
Sex (%)	Female	490 (48.1)	300 (60.5)	902 (53.1)	447 (50.9)	192 (56)	277 (58.4)	2,615 (52.5)
Age in years	Mean (SD)	62.6 (8.58)	61.65 (8.19)	61.7 (7.57)	62.9 (8.12)	61.96 (8.13)	61.35 (7.39)	62.08 (8.18)
Age (%)								
	50–59	342 (31.6)	192 (40.9)	642 (45.7)	281 (35.2)	139 (39.3)	182 (42.4)	1782 (38.4)
	60–69	364 (32.3)	162 (37.3)	547 (35.5)	306 (35.6)	123 (35.7)	184 (39.6)	1690 (35)
	70+	169 (36.1)	70 (21.8)	222 (18.8)	147 (29.2)	51 (25.1)	51 (18)	711 (26.6)
Education (%)								
	< 12	208 (24)	191 (43)	686 (46.1)	305 (42.1)	65 (18.3)	162 (39.5)	1622 (36)
	12	226 (24.5)	84 (20.1)	283 (21.4)	164 (20.7)	64 (18.2)	83 (17.8)	906 (21.7)
	> 12	441 (51.6)	149 (36.9)	442 (32.5)	265 (37.3)	184 (63.5)	172 (42.7)	1655 (42.3)
Neurocognitive traits (%)								
	Significant cognitive decline	232 (27.9)	140 (32)	436 (32.5)	241 (37.4)	87 (27.4)	113 (28.6)	1250 (31.2)
	MCI	85 (11.1)	47 (11.8)	148 (10.6)	87 (13.4)	28 (8.3)	46 (12.3)	442 (11.3)
APOE genotype (%)								
	ε2/ε2	2 (0.1)	4 (1)	4 (0.2)	2 (0.3)	0 (0)	1 (0)	14 (0.3)
	ε2/ε3	96 (10)	56 (13.8)	70 (4.1)	60 (8.2)	20 (4.9)	27 (6.5)	330 (7.8)
	ε2/ε4	14 (1.2)	14 (4)	7 (0.8)	11 (1.3)	2 (0.7)	3 (0.9)	51 (1.3)
	ε3/ε3	570 (66.3)	231 (56)	1059 (76.2)	490 (68.1)	235 (78.4)	303 (72.3)	2893 (69.5)
	ε3/ε4	178 (20.6)	107 (22.6)	253 (17.2)	163 (21.3)	46 (13.4)	75 (18.1)	824 (19.4)
	ε4/ε4	15 (1.7)	12 (2.5)	18 (1.5)	8 (0.9)	10 (2.6)	8 (2.2)	71 (1.7)
APOE allele (%)								
	ε2	114 (0.06)	78 (0.10)	85 (0.03)	75 (0.05)	22 (0.03)	32 (0.04)	409 (0.05)
	ε3	1414 (0.82)	625 (0.74)	2441 (0.87)	1203 (0.83)	536 (0.88)	708 (0.85)	6940 (0.83)
	ε4	222 (0.13)	145 (0.16)	296 (0.11)	190 (0.12)	68 (0.10)	94 (0.12)	1017 (0.12)
Proportion genetic ancestry (mean [SD])								
	N	780	358	1194	641	272	364	3618
	African	0.16 (0.20)	0.46 (0.16)	0.04 (0.02)	0.22 (0.13)	0.07 (0.08)	0.10 (0.06)	0.16 (0.18)
	European	0.80 (0.21)	0.48 (0.15)	0.46 (0.20)	0.65 (0.12)	0.50 (0.22)	0.46 (0.15)	0.60 (0.24)
	Amerindian	0.05 (0.04)	0.06 (0.02)	0.49 (0.20)	0.13 (0.03)	0.43 (0.23)	0.44 (0.15)	0.24 (0.24)

Note: (%) based on the sampling weights and complex survey design.

Abbreviations: APOE, apolipoprotein E; MCI, mild cognitive impairment; SD, standard deviation; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging.

Additional analyses of continuous cognitive decline are reported in Appendix 1 and show similar results to the significant cognitive decline outcome.

4 | DISCUSSION

We performed an association study of APOE alleles and cognitive outcomes in a large cohort of diverse middle-aged and older Latinos. Our main result showed an association between the APOE ε4

allele and the risk of significant cognitive decline. In the stratified analysis, this result remained significant only for Cubans. We also found an association between APOE ε2 and decreased risk of MCI only in Puerto Ricans, suggesting differential effects of the APOE alleles on cognitive function in the Latino background groups. We further discovered that an increased proportion of genetic Amerindian ancestry was associated with a protective effect from the risk of APOE ε4 on significant cognitive decline, compatible with the known low proportion of Amerindian ancestry in the Cuban background group.²³

TABLE 2 APOE alleles association with neurocognitive function in the SOL-INCA (additive inheritance mode)

Trait	APOE allele	OR [95% CI]	P-value
Significant cognitive decline	2	1.04 [0.85;1.29]	6.85E-01
	4	1.15 [1.01;1.32]	3.35E-02
MCI	2	0.78 [0.51;1.17]	2.30E-01
	4	0.94 [0.72;1.22]	6.19E-01

Notes: Models adjusted for sex, age, education, center, genetic background groups, and first five PCs. APOE ε3 used as the reference allele. Effect sizes and SEs were estimated based on the complex survey design method and were used to ORs and 95% CIs. OR values larger than 1 represent decreased neurocognitive function

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; MCI, mild cognitive impairment; OR, odds ratio; PC, principal component; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging; SE, standard error.

We infer that ancestry-specific genetic variants may explain the differential effects of APOE alleles in the six Latino backgrounds.

The association of APOE ε4 allele with significant cognitive decline (OR = 1.15) is compatible with previous results presenting a relatively weaker association between APOE ε4 allele and ADRD in the Latino population compared to Whites (OR = 2.2).⁸ The difference in effect sizes may be due to the difference in the tested phenotypes, significant cognitive decline versus ADRD. Cognitive decline modeling differs substantially between studies, thus a comparison of effect sizes of APOE alleles on significant cognitive decline is not feasible.³⁷ In the analysis stratified by “genetic analysis groups,” we anticipated some relationship between APOE ε4 and significant cognitive decline specifically among Cubans because they have higher degrees of European ancestry.²³ Cubans in our analytic dataset are also older (a risk factor for cognitive decline) and more educated (a protective factor for cognitive decline) compared to the other Latino backgrounds; however, our models controlled for age and education. A previous study conducted in Cubans from Cuba also reported an association between APOE ε4 and incident of dementia with a stronger effect in middle-aged adults (<70 years) compared to older adults (>70 years).³⁸

The non-significant results for the APOE ε4 allele association with significant cognitive decline in the five other Latino backgrounds are consistent with their lower percentage of European ancestry.²³ This could also result from the predominantly middle-aged SOL-INCA population (mean age 62.1 years), a population not fully presenting with significant cognitive decline, whereas most epidemiological studies on APOE and cognitive decline outcomes are conducted in individuals ≥65 years. This claim is supported by analysis restricted to older subsets of the population resulting in a stronger association between APOE ε4 allele and significant cognitive decline in the older subsets (Table S1). Alternatively, it may result from limited statistical power eg, power = 0.26 for the South American group for the cognitive decline trait (Table S4), or it could present a true differential effect size of APOE ε4 on significant cognitive decline in the different Latino backgrounds. The latter hypothesis is supported by the fact that the statistical power

TABLE 3 APOE alleles association with neurocognitive function in the SOL-INCA by background groups (additive inheritance mode)

Trait	APOE allele	Cuban (n = 875)		Dominican (n = 424)		Mexican (n = 1411)		Puerto Rican (n = 734)		South American (n = 313)		Central American (n = 417)	
		OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value
Significant cognitive decline	2	1.20 [0.80;1.80]	3.96E-01	0.98 [0.62;1.55]	9.46E-01	1.03 [0.69;1.54]	8.79E-01	1.06 [0.69;1.62]	7.95E-01	1.93 [1.03;3.62]	7.17E-02	0.65 [0.30;1.38]	3.07E-01
	4	1.46 [1.13;1.88]	7.00E-03	0.95 [0.70;1.30]	7.69E-01	1.05 [0.77;1.43]	7.69E-01	1.04 [0.84;1.29]	7.31E-01	0.91 [0.55;1.50]	7.39E-01	1.05 [0.76;1.46]	7.71E-01
MCI	2	0.98 [0.49;1.96]	9.54E-01	1.05 [0.40;2.72]	9.33E-01	0.54 [0.23;1.29]	2.19E-01	0.37 [0.16;0.84]	4.41E-02	0.74 [0.14;3.87]	7.85E-01	0.34 [0.05;2.19]	3.23E-01
	4	0.80 [0.42;1.53]	5.26E-01	0.98 [0.55;1.72]	9.43E-01	0.90 [0.58;1.38]	6.64E-01	1.04 [0.65;1.67]	8.64E-01	0.83 [0.39;1.76]	6.90E-01	1.08 [0.58;2.01]	8.34E-01

Notes: Models adjusted for sex, age, education, center, and first five PCs. Effect sizes and SEs were estimated based on the complex survey design method, and were used to compute ORs and 95% CIs. APOE ε3 used as the reference allele. OR values larger than 1 represent decreased neurocognitive function. P-values were estimated based on 10,000 permutations for each genetic background group. Heterogeneity P-values were not significant.

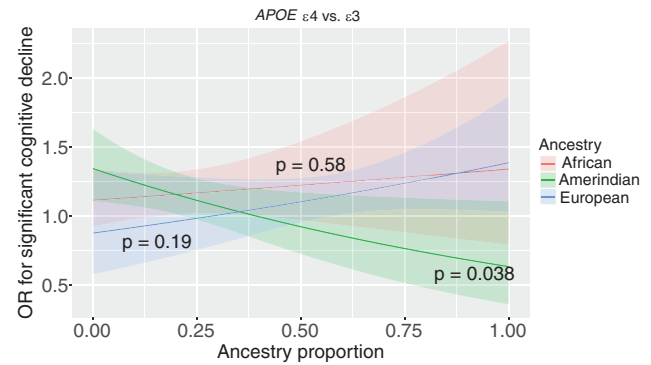
Abbreviations: APOE, apolipoprotein E; CI, confidence interval; MCI, mild cognitive impairment; OR, odds ratio; PC, principal component; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging; SE, standard error.

TABLE 4 The interaction effect of proportion ancestry and APOE alleles on neurocognitive function in the SOL-INCA (additive inheritance mode)

Trait	APOE allele	Europe			Africa			Amerindian					
		Interaction		APOE allele	Interaction		APOE allele	Interaction		APOE allele			
		OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value				
Significant cognitive decline	2	1.76 [0.70;4.40]	2.41E-01	0.77 [0.42;1.40]	4.06E-01	0.60 [0.22;1.61]	3.22E-01	1.23 [0.90;1.67]	2.03E-01	1.14 [0.32;4.05]	8.43E-01	1.08 [0.79;1.46]	6.48E-01
	4	1.58 [0.82;3.06]	1.90E-01	0.88 [0.58;1.33]	5.47E-01	1.20 [0.64;2.28]	5.77E-01	1.11 [0.93;1.34]	2.63E-01	0.47 [0.24;0.93]	3.83E-02	1.34 [1.11;1.63]	3.70E-03
MCI	2	0.47 [0.05;4.71]	5.50E-01	1.20 [0.30;4.83]	8.12E-01	4.63 [0.66;32.36]	1.57E-01	0.49 [0.24;1.01]	6.84E-02	0.03 [0.00;1.38]	1.07E-01	1.16 [0.60;2.25]	6.70E-01
	4	1.37 [0.38;4.92]	6.59E-01	0.81 [0.36;1.85]	6.39E-01	0.76 [0.16;3.68]	7.50E-01	1.05 [0.72;1.52]	8.26E-01	1.01 [0.34;3.01]	9.92E-01	0.99 [0.66;1.50]	9.72E-01

Notes: Models adjusted for sex, age, education, center, and first five PCs. Effect sizes and SEs were estimated based on the complex survey design method and were used to compute ORs and 95% CIs. APOE ϵ 3 used as the reference allele. Interaction P-values were estimated based on 10,000 permutations for each ancestry separately. OR values larger than 1 represent decreased neurocognitive function.

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; MCI, mild cognitive impairment; OR, odds ratio; PC, principal component; SOL-INCA, Study of Latinos-Investigation of Neurocognitive Aging.

**FIGURE 1** Interaction of proportion continental ancestry with apolipoprotein E (APOE) ϵ 4 allele effects on significant cognitive decline. Interaction P-values were estimated based on 10,000 permutations for each ancestry separately

for the Mexican group for the association of APOE ϵ 4 with cognitive decline status is 0.88, yet not significant. Three previous studies focusing on Mexican-origin Latinos also showed the non-significant result with a relatively weak effect of APOE ϵ 4 allele on dementia, MCI, or AD.^{16–18}

Unique to this study, continental-ancestry proportion, which captures genetic variation across the genomes, further revealed that an increased proportion of genetic Amerindian ancestry was associated with a protective effect from the risk of APOE ϵ 4 on significant cognitive decline. This result is also compatible with the APOE ϵ 4 significant risk effect we found in Latino Cubans, which were shown to have the lowest proportion of Amerindian ancestry among all Latino background groups (Table 1). By using all three ancestries of the admixed Latino population we could infer the protective effect of the Amerindian ancestry, rather than the European or African ancestries being harmful (if there were only two studied ancestries, we could not distinguish between the protective effect of one and the risk effect of the other). This result is inconsistent with a recent report in Peruvians (78 AD cases and 128 controls) suggesting that Amerindian local ancestry in the APOE region is contributing to a strong risk for AD in APOE ϵ 4 carriers.³⁹ Two other studies in Caribbean Hispanics suggest a protective effect of the African local ancestry in the APOE region from the risk of APO ϵ 4 on AD.^{40,41} Therefore, we also studied whether local ancestry at the APOE region modifies the effects of APOE on significant cognitive decline (results not shown). While the Amerindian local ancestry association was protective, it was not statistically significant (P -value >0.2). It is a topic of future research to perform a more comprehensive analysis of local ancestry at an expanded region around the APOE gene and potentially genome-wide, and search for specific genetic variants explaining the observed interaction of global Amerindian genetic ancestry with APOE ϵ 4 in its effect on significant cognitive decline.

Our study also highlights a protective association between APOE ϵ 2 and MCI solely in the Puerto Rican background group (Table 3), compatible with the known neuroprotective effect of APOE ϵ 2.⁸ The direction of this effect was similarly protective in several other Latino

background groups; however, they were not significant, despite high power estimations especially for the Cuban and Mexican background groups (Table S4). APOE $\epsilon 2$ is relatively rare and its effect on cognitive function is less studied compared to APOE $\epsilon 4$,⁴² specifically in the Latino population. A meta-analysis based predominantly on the Chinese population suggests that APOE $\epsilon 2/\epsilon 3$ genotype provides slight protection for MCI.⁴³

We did not observe the expected risk effects of the APOE $\epsilon 4$ alleles with MCI. This could be explained by our middle-aged SOL-INCA population, not fully presenting MCI. While both significant cognitive decline and MCI are markers for ADRD, our results might indicate that significant cognitive decline, which appears in an earlier stage before MCI, is an important risk marker for ADRD in this SOL-INCA dataset.⁴⁴

This is the first study to examine Latino genetic diversity in the context of significant cognitive decline and MCI that used both background groups and continental genetic ancestry proportions, which is a major step forward in the field of cognitive aging and ADRD precision medicine. Second, this cohort is composed of Latino middle-aged and older adults, thus there is less significant survival bias compared to studies of older adults. However, this dataset does not include biomarkers such as advanced imaging or fluid biomarkers, which could have validated the significant cognitive decline and MCI status. Also, we note that significant cognitive decline measure is not a clinical phenotype. To address this limitation, we report a similar analysis of APOE alleles with continuous cognitive decline (Appendix 1), and the results are similar to the results of significant cognitive decline. Because we examined six different Latino background groups, Winner's curse bias might also explain our significant result in the stratified analyses. Overall, our differential association results in the Latino background groups may suggest a true differential genetic association between APOE alleles and cognitive outcomes related to admixed genomes. However, they could alternatively represent the lifestyle and environmental factors differing between the Latino ancestries, such as smoking, nutrition, alcohol consumption, physical activity, sleep phenotypes, air pollution, and metal exposure, that may also interact with APOE alleles and cognitive function risk.⁴⁵ Further analysis in SOL-INCA and other samples with older Latino populations, accounting for environmental characteristics, may further delineate the associations between the APOE alleles and cognitive outcomes.

Overall, our study, together with other studies focusing on the Latino population, may lead to a better understanding of the role of APOE in the development of ADRD in Latinos and potentially in American Indians by extension thus advancing the development of personalized risk prediction and strategies to address Latinos' health disparities in neurodegenerative aging and disorders.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

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

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