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Apolipoprotein E (*APOE*) genotype, dementia, and memory performance among Caribbean Hispanic versus US populations

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Abstract

Introduction: Apolipoprotein E (*APOE*) is considered the major susceptibility gene for developing Alzheimer's disease. However, the strength of this risk factor is not well established across diverse Hispanic populations.

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AUTHOR CONTRIBUTIONS

Jorge Llibre-Guerra and Jing Li had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jorge J. Llibre-Guerra, Juan J. Llibre Rodriguez, William H. Dow. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Jorge J. Llibre-Guerra, Jing Li. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Jing Li, Yuting Qian. Obtained funding: William H. Dow. Project administration: Mao-Mei Liu. Study supervision: Juan de Jesús Llibre Rodriguez, Ivonne Z. Jiménez Velázquez, Daisy Acosta, Aquiles Salas, William H. Dow.

CONFLICTS OF INTEREST

The authors report no disclosures relevant to this manuscript.

SUPPORTING INFORMATION

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

Methods: We investigated the associations among *APOE* genotype, dementia prevalence, and memory performance (immediate and delayed recall scores) in Caribbean Hispanics (CH), African Americans (AA), Hispanic Americans (HA) and non-Hispanic White Americans (NHW). Multivariable logistic regressions and negative binomial regressions were used to examine these associations by subsample.

Results: Our final dataset included 13,516 participants (5198 men, 8318 women) across all subsamples, with a mean age of 74.8 years. Prevalence of *APOE ε*4 allele was similar in CHs, HAs, and NHWs (21.8%–25.4%), but was substantially higher in AAs (33.6%; $P < 0.001$). *APOE ε*4 carriers had higher dementia prevalence across all groups.

Discussion: *APOE ε*4 *was* similarly associated with increased relative risk of dementia and lower memory performance in all subsamples.

Keywords

admixture; Alzheimer's disease; apolipoprotein E; Blacks; cognitive performance; dementia; Hispanics/Latinos; Non-Hispanic Whites

1 | INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia[1] and has emerged as a significant societal issue and a global priority.[2] Risk of AD is influenced by both genetic and environmental factors. Genetic factors include pathogenic variants in the *amyloid precursor protein*(*APP*), *presenilin 1* (*PSEN1*), and *presenilin 2* (*PSEN2*) genes leading to dominantly inherited AD (DIAD)[3,4] and susceptibility loci in (not deterministic) genes that increase the risk of developing disease.[5,6] Apolipoprotein E (*APOE*) is considered the major susceptibility gene for developing AD; possession of the *ε*4 allele leads to a significant increase in an individual's risk of developing AD.[7,8] However, disease prevalence varies according to ancestry; for example, compared to non-Hispanic Whites (NHWs) and Asian populations, the association between *APOE ε*4 and AD has been found in several studies to be weaker or inconsistent among African[9,10] and Hispanic populations,[11,12] suggesting gene by environment, and/or gene by gene interactions.[13] Furthermore, within Hispanic populations, the interaction between *APOE ε*4 and disease has been found to vary.[11,14-17]

The reasons for these disparities in NHWs, African American (AAs), Hispanic Americans (HAs), and among Hispanic subgroups are still poorly understood and highly controversial. Observed diferences may be the result of gene by environment interactions,[18,19] given large heterogeneity between these groups. In addition, the widely varying admixture across subgroups may also play an important role, given the unique admixtures across Amerindian, African, and European continental ancestries.[20,21] Furthermore, the differential effect of *APOE ε*4 across populations may be confounded by unique characteristics in previous highly selective cohorts, which have often been used instead of population-based studies. Few studies of Hispanics have cross-population comparisons on the frequency and effect of *APOE* on dementia prevalence and cognitive performance.

To address these gaps in the literature, we used population-based data from the 10/66 Dementia Research Group (10/66) and the US Health and Retirement Study (HRS) to

examine associations between *APOE* genotype, dementia, and memory performance in Caribbean Hispanics (CA) and US older adults by race/ethnicity (AA, HA, and NHW). We also examined the extent to which these associations may be mediated by admixture proportions on a subsample of these populations with admixture information.

2 | METHODS

2.1 | Data and study population

The primary analyses in this study used community-dwelling participants aged 65 years and over enrolled in the 10/66 study and in the HRS study.

2.1.1 | 10/66 data—We use the baseline prevalence wave of the 10/66 study, which was a population-based sample of adults aged 65 years and over in urban areas in Cuba (Havana and Matanzas), Dominican Republic (Santo Domingo), Puerto Rico (San Juan), and Venezuela (Caracas). Participants received an assessment lasting 3 hours, including participant interview, physical examination, cognitive assessment, blood draw, and informant interview.[22] Written informed consent was obtained from all participants and their study partners. Local institutional review boards, and the King's College London Research Ethics Committee approved this project. The full protocol for the 10/66 population-based surveys is available in an open-access publication.[22,23]

2.1.2 | HRS data—We used US data from the HRS, a biennial longitudinal panel study that has surveyed a representative sample of approximately 20,000 adults over the age of 50 in the United States since 1992.[24] The HRS collects rich data on cognition, demographics, socioeconomic characteristics, and health. *APOE* and other genetic data were available for a subset of HRS respondents in 2008 from whom saliva was collected.

2.1.3 | Study sample—We included all 10/66 respondents in the baseline surveys, conducted between 2003 and 2008, in Cuba, Dominican Republic, Puerto Rico, and Venezuela for whom *APOE* genotype was available (genotype data were not available to us for other 10/66 Latin American surveys). In primary analyses, we pooled respondents across the four 10/66 sites to increase statistical power. For comparability across samples, we included all HRS respondents in the 2008 wave who were aged 65 and older; had non-missing *APOE* genotype; and were either HA, AA, or NHW.

2.2 | Measures

Participants were evaluated using the 10/66 and HRS protocols, which generate information on dementia diagnosis, physical health, demographics, non-communicable disease risk factors, disability, and socioeconomic status, among others.[22] Assessments relevant to the current analyses are described in detail below.

2.2.1 | 10/66 dementia status—Dementia was diagnosed using the cross-culturally validated 10/66 dementia diagnosis algorithm, for which strong concurrent and predictive validity has been demonstrated.[25,26] Dementia diagnosis was established following: (1) a structured clinical interview; (2) a cognitive test battery including (a) the Community

Screening Instrument for Dementia (CSI-D),[27] (b) a verbal fluency task, and (c) the modified Consortium to Establish a Registry for Alzheimer's Disease 10 word list learning task with delayed recall;[28] and (3) an informant interview (CSI-D)[27] for evidence of cognitive and functional decline. This dementia measure has been previously used[29] for cross-national comparisons to the Langa-Weir dementia measure in the US HRS.

2.2.2 | HRS dementia status—We assigned dementia status among HRS respondents using the validated Langa-Weir method.[30] The Langa-Weir method relies on an individual's Modified Telephone Interview for Cognitive Status (TICS-M) score, which ranges from 0 to 27 and is based on the following components: an immediate and delayed 10-noun free recall test, a serial 7 subtraction test, and a backward count from 20 test. A respondent was classified as having dementia if their TICS-M score was below 7. The method uses an analogous algorithm that relies on proxy responses for respondents who could not answer the survey for themselves.[31] We used the Langa-Weir method, as alternative algorithms[32,33] explicitly incorporated education or race/ethnicity in calculating dementia probability, whereas we aimed to make comparisons in dementia and its determinants across race/ethnicity subgroups.

2.2.3 | Memory performance—Memory performance is among the cognitive measures best harmonized across the 10/66 and HRS assessments. To complement the analysis of dementia status, we study the *APOE* relationship with memory performance. Specifically, both the 10/66 and HRS include a 10 word list learning task with delayed recall.[28] We used the scores from the 10 word list learning immediate, and from the delayed recall, as the two dependent variables to study memory performance.

2.2.4 | *APOE* genotype—Our key independent variable of interest was *APOE* genotype. In the primary analysis, we used an indicator for whether the respondent carried any *APOE* $\varepsilon 4$ allele, as well as an indicator for the carriage of *APOE* $\varepsilon 2$. In secondary analysis, we examined the full *APOE* genotype including six indicators for all combinations of the *APOE* alleles ($\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$).

2.2.5 | Covariates—Age was ascertained using documented age, or an event calendar as provided by participant or informant report. Educational attainment was measured differently between 10/66 and the HRS, due in part to contextual differences across regions, following the approach of prior research.[29] For 10/66 respondents, we categorized educational attainment as (1) not completing primary school, (2) completed primary school, or (3) secondary school or above. For HRS respondents, we categorized educational attainment as (1) no high school degree, (2) high school degree or equivalent, or (3) some college or above. Ethnicity in the HRS was ascertained using self-report by participant or informant as follows: NHW, AA, and HA. Self-reported ethnicity is not available in 10/66 data; for ease of description we refer to all as "Caribbean Hispanic" (CH).

Biochemical analysis: DNA was extracted, quantitated, and archived for Cuba at the National Centre for Medical Genetics in Havana; for Venezuela at the immunogenetics section of the Instituto Venezolano de Investigaciones Cientificas; and for Dominican Republic and Puerto Rico at KBioscience, UK. In Cuba and Venezuela, *APOE*

ε4 genotype was determined using Hhal digestion of amplified products. For the Dominican Republic and Puerto Rico we applied a method based on the observation that *APOE* ε2, ε3, and ε4 alleles differ in amino acid sequence at C112R, single nucleotide polymorphism (SNP) rs429358 and R158C, SNP rs7412. Admixture data were available only in a Caribbean subsample (Cuba and Dominican Republic). Genetic admixture was determine by using 60 SNPs, which has been shown to be sufficient to estimate three-way individual admixture proportions with a standard error less than 0.1.[14,34,35] Genotyping was performed by KBiosciences (http://kbioscience.co.uk), using the KAS-Par chemistry allele specific polymerase chain reaction SNP genotyping system (http://www.kbioscience.co.uk/genotyping/genotyping_chemistry.htm). The ADMIXMAP program[36,37] (http://homepages.ed.ac.uk/pmckeigu/admixmap/) generated posterior means of individual admixture from ancestry informative marker data.

In the HRS, saliva samples were collected from HRS participants beginning in 2006. HRS respondents were genotyped using the Illumina HumanOnmi2.5 array and the Illumina HumanExome-12v1 array.

2.3 | Statistical analysis

Descriptive statistics were calculated for all variables. For continuous variables, these included means and standard deviations. For categorical variables, these included counts and proportions in each category. First, we described the *APOE* genotype distribution and allele frequency by sample and race/ethnicity. We then examined associations between carriage of any *APOE* ε4 allele versus none, and outcome variables (dementia prevalence and immediate and delayed recall scores) with crude and adjusted prevalence ratios (PR). Associations were estimated separately by race/ethnicity (HA, AA, and NHW) among the HRS sample and pooled across the 10/66 sites (CH). All adjusted analyses controlled for age, sex, and level of education.

We conducted several secondary analyses. First, to assess the representativeness of the subset of HRS respondents with genetic data, we compared the sociodemographic and cognitive variables between subsamples of HRS respondents with and without genetic data. We also examined associations between specific *APOE* genotypes and dementia prevalence by sample. We further focused on a subsample with ancestry data in both 10/66 and HRS to examine whether admixture mediates the associations among *APOE* genotype, dementia, and cognitive performance; this also allows us to test the extent to which the *APOE* relationships with our outcome variables would be different when controlling for ancestry. Only a subset of respondents in the Cuba and Dominican Republic sample had complete ancestry data, whereas all our HRS sample had data on the first 10 principal components. We first reported the frequency of *APOE* genotype by categories of African and Native American ancestry proportions (> 60%, 30%–60%, < 30%) in the combined Cuba and Dominican Republic subsample. We then examined whether ancestry mediates the effect of *APOE* ε4 on cognitive performance or dementia in a series of multivariable regression analyses analogous to our main regressions; these regressions controlled for African and Native American ancestry for Dominican Republic and Cuba subsamples, and indicators for the 10 principal components by race/ethnicity for the HRS sample.

All analyses were performed using Stata 17 MP (College Station, TX). All *P*-values were from two-sided tests and results were deemed statistically significant at $P < 0.05$. The study protocol was reviewed and approved by the institutional review boards of University of California, Berkeley and Weill Cornell Medical College.

3 | RESULTS

3.1 | Sample characteristics

Our final dataset included 13,516 participants (5198 men, 8318 women), with a mean age of 74.8 years. Summary statistics including sample size, sex, age, education, cognitive performance, and distribution of the *APOE* alleles by ethnicity are shown in Table 1. Mean age 74.8 (±7.1) was similar across all cohorts. Levels of education were higher in NHWs, with 45.6% completing college or above, compared to 29.0% in AA, 16.6% in HAs, and 36.7% in CHs who completed secondary schooling and above. In the HRS sample the prevalence of dementia was 3.1% in NHWs, 10.6% in HAs, and 12.5% in AAs. The low dementia prevalence particularly in the HRS NHW group could be partially due to selection into genetic data collection. We showed that HRS respondents by ethnicity with and without genetic information were broadly similar in demographic characteristics, except that those with genetic information were slightly younger and better educated than their counterparts (Table S1 in supporting information). However, Table S1 also shows that HRS participants with dementia were substantially less likely to have genetic information in the data; nevertheless, these data have been widely used for genetic analyses; thus, we proceed while noting this caveat. In the 10/66 sample, prevalence of dementia was 9.5% (6.9% in Venezuela, 10.6% in Cuba, 11.7% in Puerto Rico, and 11.8% in Dominican Republic). The cognitive healthy cohort included 7182 in the US-HRS (AA = 795, NHW = 5874, HA = 513) and 5383 in the Caribbean cohort. Summary statistics of the Caribbean cohort by country/island are shown in Table S2 in supporting information.

3.2 | *APOE* genotype and allele distributions by ethnic group

APOE $\varepsilon 4$ allele frequencies were similar in NHWs, HAs, and CHs, but $\varepsilon 4$ frequency was substantially higher in AAs ($P < 0.001$; Table 1). Further stratification among the Caribbean sample show frequencies of *APOE* $\varepsilon 4$ by country (Table S2). In Cuba, 413 (16.5%) had one or more $\varepsilon 4$ alleles, in Dominican Republic 336 (32.2%), in Venezuela 200 (21.3%), in Puerto Rico 347 (23.8%). Genetic ancestry was available in Dominican Republic and Cuba. Mean African admixture was higher in Dominican Republic relative to Cuba (52% vs. 18%, $P < 0.001$). Pooling Dominican Republic and Cuba we found that mean African admixture increased from 50% among those with no $\varepsilon 4$ alleles to 55% with one and 56% for those with two $\varepsilon 4$ alleles ($P = 0.016$).

3.3 | *APOE* genotype, dementia prevalence, and cognitive performance

Dementia prevalence by *APOE* genotypes is shown in Table 2. Further stratification among the Caribbean sample is shown in Table S3 in supporting information. Across all ethnic groups, *APOE* $\varepsilon 4$ carriers had higher dementia prevalence. Figure 1 shows dementia prevalence and 10-word list delayed recall scores separately for those with and without *APOE* $\varepsilon 4$ for each of our sample (CH sample and the US-HRS sample by ethnicity),

stratified by age group (65–74, 75–84, 85 and above). Differences in dementia prevalence by carriage of *APOE* ε4 were most pronounced among the oldest age group (85 and above); they visually appeared smaller in magnitude among AAs compared to other groups, though the wide confidence intervals in this group make it impossible to reject magnitudes similar to those of other race/ethnic groups. Those with *APOE* ε4 generally had lower 10-word list delayed recall scores than those without *APOE* ε4 across ethnic groups and age categories.

Table 3 shows the adjusted associations between the *APOE* alleles and cognitive outcomes across all groups. Carriage of one or more *APOE* ε4 alleles was independently associated with increased prevalence of dementia, with prevalence ratios significant for CHs (1.92, 95% confidence interval [CI] 1.62, 2.22) and NHWs (1.83, 95% CI 1.26, 2.40). They were positive though non-significant for HAs (1.64, 95% 0.81, 2.47) and AAs (1.26, 95% CI 0.81, 1.71), which could be due to smaller sample sizes. Carriage of *APOE* ε4 was consistently associated with incident rate ratios (IRRs) less than one for both immediate and delayed recall scores, though they were non-significant for HAs for both outcomes. There was no evidence of a protective effect of ε2/ε2 or ε2/ε3 genotypes across all dependent variables and ethnic groups, although the confidence intervals were wide enough to prevent rejecting reasonably side protective effects. Overall, results across groups were similar with overlapping 95% CIs for all estimates. Analogous regressions examining the associations between the full *APOE* genotype and dementia prevalence show similar results (Table S4 in supporting information).

3.4 | Admixture, *APOE* genotype, and dementia prevalence.

Genetic ancestry was available in Cuban (n = 585) and Dominican Republic (n = 1055) subsamples. We examined the effect of admixture on dementia prevalence and cognitive performance and whether admixture mediates the effect of *APOE* ε4 on dementia prevalence and cognitive performance. African admixture was not associated with increased risk for dementia or overall cognitive performance in the Caribbean subsample. Associations between *APOE* ε4 carriage and cognitive outcomes were very similar before and after controlling for admixture variables across all subsamples (Table S6 in supporting information).

4 | DISCUSSION

In the present study we contribute to a growing body of research examining the extent to which associations among *APOE* genotype, dementia prevalence, and cognitive performance may be heterogeneous across different ethno-racial groups and/or contexts. In these population-based samples of CHs, HAs, AAs, and NHWs, we found that carriage of one or more *APOE* ε4 alleles was associated with prevalent dementia and lower memory performance, and furthermore that these associations were of similar magnitudes across racial and ethnic groups. This is despite varying admixtures and life course environments. In addition, we found no evidence that admixture mediates the associations between *APOE* genotype and cognitive outcomes across racial and ethnic groups.

The association between *APOE* genotype and risk of AD is well established in White populations; however, a number of studies have suggested a weaker or inconsistent

association between ε4 and AD in AAs.[38-40] Similarly, previous studies investigating the association of *APOE* ε4 and AD in HAs have found inconsistent results. Due to the high heterogeneity in Hispanic populations (e.g., admixture, diet, environment, vascular risk factors), it is possible that genetic susceptibility related to the *APOE* ε4 allele is inconsistently expressed, varying according to population origin. Nevertheless, in our study we found no significant differences in the effect of *APOE* ε4 across ethnic cohorts.

Furthermore, we note that previous studies have shown that associations between ε4 and AD have been substantially larger when estimated in clinic-based samples versus community-based populations (odds ratio [OR] = 8.6 vs. 2.8, respectively).[41] Our associations are smaller still. Among factors that may explain this is our use of a relative elderly cohort. Prior evidence suggests that the association between ε4 and dementia is stronger in younger age groups;[42,43] for example, a similar study in the Framingham cohort suggests a low AD positive predictive value of ε4 in older population-based cohorts.[44] Furthermore, older population cohorts are more subject to mortality bias, particularly for ε4 homozygotes, due to cardiovascular disease, in which *APOE* ε4 is known to play a role.[45,46]

In relation to the associations between *APOE* ε4 and memory performance, previous studies have found that ε4 is associated with lower cognitive performance and faster decline on episodic memory.[47] Our results provide further confirmation of this association, with notably similar magnitudes across diverse US and CH samples.

Regarding genetic admixture and *APOE* ε4 associations with dementia, our study is not consistent with prior research showing that they may vary according to admixture.[48,49] However, we cannot reject that the similar associations found in our different samples are due to offsetting factors. Further research is needed to understand this relationship in diverse populations, including the role of education, access to health care, socioeconomic status, and other environmental factors that may make ancestry factors difficult to interpret. In particular, education level and quality of education may explain differences in dementia prevalence across populations.[29,50,51]

The present study is not without limitations, and several aspects of our research need to be kept in mind when interpreting these results. First, the classification procedure for assigning dementia status and cognitive assessment differed in the HRS and 10/66, which could influence the comparability of our risk estimations between dementia and *APOE* status. Previous studies have shown that cross-cohort administration, scoring, and procedural differences are frequent and may impact data interpretation.[52] Importantly, our dementia outcome did not involve neuroimaging, disease-specific biomarker measures, or trained dementia specialist assessment, therefore etiological diagnosis (e.g., AD dementia, vascular dementia, Lewy body dementia) was not available. The use of dementia as a broad category may reduce our power to detect specific interactions between *APOE* genotype and dementia etiology. Second, ethnic minority samples included in the HRS were relatively small; thus, these results must be interpreted cautiously. Third, the subset of HRS respondents for whom genetic data were available may produce different associations than had genetic data been available in the full HRS sample, though we attempted to account for this by controlling for sex, age, and education in all adjusted analyses. Fourth, genetic ancestry was only available

for a random subsample of the 10/66; thus, analyses controlling for ancestry were only possible in this subsample of the CHs. Future studies will be needed to better understand the role of *APOE* and admixture in affecting cognitive performance and the development of dementia. Latino populations, a uniquely admixed group, may provide the ideal environment to estimate such interactions.

Despite these limitations, the present study includes a large population-based sample with a high response rate, which alleviates concerns of possible confounders related to highly selective cohorts derived from memory-based clinics and minimizes selection bias. In addition, only a limited number of *APOE ε*4 and dementia research studies have included Hispanic populations, which are typically included as monolithic without taking into consideration the diversity of the Hispanic community. Our study included a diverse ethnic representation including CHs, AAs, NHWs, and Hispanics living in the United States.

Future studies in larger and more diverse data sets are needed to develop a better understanding of the role of *APOE* in the development of dementia in Latinos, and evaluate the complex relationships among ancestry, *APOE,* dementia, and environmental risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ROLE OF THE FUNDER/SPONSOR

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Brayne C, Miller B, Robinson L, et al. Dementia and aging populations—A global priority for contextualized research and health policy. PLOS Med. 2017;14:e1002275. 10.1371/journal.pmed.1002275 [PubMed: 28350794]
2. Prince M, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M, World Alzheimer Report 2016 improving healthcare for people living with dementia. Coverage, Quality and costs now and in the future 2016:1–140.
3. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012;367:795–804. 10.1056/NEJMoa1202753 [PubMed: 22784036]

4. Llibre-Guerra JJ, Li Y, Allegri RF, et al. Dominantly inherited Alzheimer's disease in Latin America: genetic heterogeneity and clinical phenotypes. Alzheimer's Dement 2020:alz.12227. 10.1002/alz.12227
5. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet. 2019;51:414–430. 10.1038/s41588-019-0358-2 [PubMed: 30820047]
6. Van Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet Med. 2016;18:421–430. 10.1038/gim.2015.117 [PubMed: 26312828]
7. Farrer LA. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease. Jama. 1997;278:1349. 10.1001/jama.1997.03550160069041 [PubMed: 9343467]
8. Emrani S, Arain HA, DeMarshall C, Nuriel T. APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer's disease: a systematic review. Alzheimers Res Ther. 2020;12:141. 10.1186/s13195-020-00712-4 [PubMed: 33148345]
9. Hendrie HC, Murrell J, Baiyewu O, et al. APOE *ε*4 and the risk for Alzheimer's disease and cognitive decline in African Americans and Yoruba. Int Psychogeriatrics. 2014;26:977–985. 10.1017/S1041610214000167
10. Gureje O, Ogunniyi A, Baiyewu O, et al. APOE epsilon4 is not associated with Alzheimer's disease in elderly Nigerians. Ann Neurol. 2006;59:182–185. 10.1002/ana.20694 [PubMed: 16278853]
11. Llibre-Guerra JJ, Li Y, Allen IE, et al. Race, genetic admixture, and cognitive performance in the cuban population. Journals Gerontol Ser A. 2021. 10.1093/gerona/glab063
12. Granot-hershkovitz E, Daviglus M, Tarraf W, et al. 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. 2020:1–9. 10.1002/alz.12205
13. Hendrie HC, Murrell J, Gao S, Unverzagt FW, Ogunniyi A, Hall KS. International studies in dementia with particular emphasis on populations of African origin. Alzheimer Dis Assoc Disord. 2011;20:S42–6. 10.1097/00002093-200607001-00005
14. Teruel BM, Rodríguez JJL, McKeigue P, et al. Interactions between genetic admixture, ethnic identity, APOE genotype and dementia prevalence in an admixed Cuban sample; a cross-sectional population survey and nested case-control study. BMC Med Genet. 2011;12:43. 10.1186/1471-2350-12-43 [PubMed: 21435264]
15. Rajabli F, Feliciano BE, Celis K, et al. Ancestral origin of ApoE *ε*4 Alzheimer's disease risk in Puerto Rican and African American populations. PLoS Genet. 2018;14:e1007791. 10.1371/journal.pgen.1007791 [PubMed: 30517106]
16. O'Bryant SE, Johnson L, Balldin V, et al. Characterization of Mexican Americans with Mild Cognitive Impairment and Alzheimer's Disease. J Alzheimer's. Dis 2012;33:373–379. 10.3233/JAD-2012-121420
17. Haan MN, Mungas DM, Gonzalez HM, Ortiz TA, Acharya A, Jagust WJ. Prevalence of dementia in older Latinos: the influence of type 2 diabetes mellitus, stroke and genetic factors. J Am Geriatr Soc. 2003;51:169–177. 10.1046/j.1532-5415.2003.51054.x [PubMed: 12558712]
18. Chin AL, Negash S, Hamilton R. Diversity and disparity in dementia: the impact of ethnoracial differences in Alzheimer disease. Alzheimer Dis Assoc Disord. 2011;25:187–195. 10.1097/WAD.0b013e318211c6c9 [PubMed: 21399486]
19. González HM, Tarraf W, Jian X, et al. Apolipoprotein E genotypes among diverse middle-aged and older Latinos: study of Latinos-Investigation of Neurocognitive Aging results (HCHS/SOL). Sci Reports. 2018;8:1–6. 10.1038/s41598-018-35573-3.812018
20. Homburger JR, Moreno-Estrada A, Gignoux CR, et al. Genomic Insights into the Ancestry and Demographic History of South America. PLoS Genet. 2015;11:e1005602. 10.1371/journal.pgen.1005602 [PubMed: 26636962]
21. Moreno-Estrada A, Gravel S, Zakharia F, et al. Reconstructing the population genetic history of the Caribbean. PLoS Genet. 2013;9:e1003925. 10.1371/journal.pgen.1003925 [PubMed: 24244192]

22. Prince M, Ferri CP, Acosta D, et al. The protocols for the 10/66 dementia research group population-based research programme. BMC Public Health. 2007;7:165. 10.1186/1471-2458-7-165 [PubMed: 17659078]

23. Prina AM, Acosta D, Acostas I, et al. Cohort Profile: the 10/66 study. Int J Epidemiol. 2016;46:dyw056. 10.1093/ije/dyw056

24. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). Int J Epidemiol. 2014;43:576–585. 10.1093/IJE/DYU067 [PubMed: 24671021]

25. Prince M, Acosta D, Chiu H, Scazufca M, Varghese M. Dementia diagnosis in developing countries: a cross-cultural validation study. Lancet. 2003;03:12772–12779. 10.1016/S0140-6736

26. Prince MJ, De Rodriguez JL, Noriega L, et al. The 10/66 Dementia Research Group's fully operationalised DSM-IV dementia computerized diagnostic algorithm, compared with the 10/66 dementia algorithm and a clinician diagnosis: a population validation study. BMC Public Health. 2008. 10.1186/1471-2458-8-219

27. Hall KS, Hendrie HC, Rodgers DD, et al. The development of a dementia screening interview in two distinct languages. Int J Methods Psychiatry. 1993.

28. Sosa AL, Albanese E, Prince M, et al. Population normative data for the 10/66 Dementia Research Group cognitive test battery from Latin America, India and China: a cross-sectional survey. BMC Neurol. 2009;9:48. 10.1186/1471-2377-9-48 [PubMed: 19709405]

29. Li J, Llibre-Guerra JJ, Harrati A, et al. Associations between education and dementia in the Caribbean and the United States: an international comparison. Alzheimer's Dement Transl Res Clin Interv. 2021;7. 10.1002/TRC2.12204

30. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of Cognition using surveys and neuropsychological assessment: the health and retirement study and the aging, demographics, and memory study. J Gerontol Ser B. 2011;66B:i162–71. 10.1093/GERONB/GBR048

31. AF J A short form of the informant questionnaire on cognitive decline in the elderly (IQCODE): development and cross-validation. Psychol Med. 1994;24:145–153. 10.1017/S003329170002691X [PubMed: 8208879]

32. Gianattasio KZ, Wu Q, Glymour MM, Power MC. Comparison of methods for algorithmic classification of dementia status in the health and Retirement Study. Epidemiology. 2019;30:291–302. 10.1097/EDE.0000000000000945 [PubMed: 30461528]

33. Gianattasio KZ, Ciarleglio A, Power MC. Development of algorithmic dementia ascertainment for racial/ethnic disparities research in the US Health and Retirement Study. Epidemiology. 2020;31:126–133. 10.1097/EDE.0000000000001101 [PubMed: 31567393]

34. Smith MW, Patterson N, Lautenberger JA, et al. A high-density admixture map for disease gene discovery in African Americans. Am J Hum Genet. 2004. 10.1086/420856

35. Smith MW, Lautenberger JA, Shin HD, et al. Markers for mapping by admixture linkage disequilibrium in African American and hispanic populations. Am J Hum Genet. 2001. 10.1086/323922

36. Hoggart CJ, Shriver MD, Kittles RA, Clayton DG, McKeigue PM. Design and analysis of admixture mapping studies. Am J Hum Genet. 2004. 10.1086/420855

37. Shriner D. Overview of admixture mapping n.d. 10.1002/0471142905.hg0123s76

38. Maestre G, Ottman R, Stern Y, et al. Apolipoprotein E and Alzheimer's disease: ethnic variation in genotypic risks. Ann Neurol. 1995;37:254–259. 10.1002/ana.410370217 [PubMed: 7847867]

39. Tang MX, Maestre G, Tsai WY, et al. Effect of age, ethnicity, and head injury on the Association between APOE Genotypes and Alzheimer's Disease. Ann N Y Acad Sci. 1996;802:6–15. 10.1111/J.1749-6632.1996.TB32593.X [PubMed: 8993479]

40. Sahota A, Yang M, Gao S, et al. Apolipoprotein E—associated risk for Alzheimer's disease in the African-American population is genotype dependent. Ann Neurol. 1997;42:659–661. 10.1002/ANA.410420418 [PubMed: 9382479]

41. Gianattasio KZ, Bennett EE, Wei J, et al. Generalizability of findings from a clinical sample to a community-based sample: a comparison of ADNI and ARIC. Alzheimer's Dement. 2021;17:1265–1276. 10.1002/ALZ.12293 [PubMed: 33527720]

42. Slooter AJC, Cruts M, Kalmijn S, et al. Risk estimates of dementia by apolipoprotein e genotypes from a population-based incidence study: the Rotterdam Study. Arch Neurol. 1998;55:964–968. 10.1001/ARCHNEUR.55.7.964 [PubMed: 9678314]
43. van der Lee SJ, Wolters FJ, Ikram MK, et al. The effect of APOE and other common genetic variants on the onset of Alzheimer's disease and dementia: a community-based cohort study. Lancet Neurol. 2018;17:434–444. 10.1016/S1474-4422(18)30053-X [PubMed: 29555425]
44. Myers RH, Schaefer EJ, Wilson PWF, et al. Apolipoprotein E epsilon4 association with dementia in a population-based study: the Framingham study. Neurology. 1996;46:673–677. 10.1212/WNL.46.3.673 [PubMed: 8618665]
45. Heffernan AL, Chidgey C, Peng P, Masters CL, Roberts BR. The Neurobiology and Age-Related Prevalence of the ε4 Allele of Apolipoprotein E in Alzheimer's Disease Cohorts. J Mol Neurosci. 2016;60:316–324. 10.1007/S12031-016-0804-X [PubMed: 27498201]
46. Wolters FJ, Yang Q, Biggs ML, et al. The impact of APOE genotype on survival: results of 38537 participants from six population-based cohorts (E2-CHARGE). PLoS One. 2019;14:e0219668. 10.1371/JOURNAL.PONE.0219668 [PubMed: 31356640]
47. Barnes LL, Arvanitakis Z, Yu L, Kelly J, De Jager PL, Bennett DA. Apolipoprotein E and change in episodic memory in blacks and whites. Neuroepidemiology. 2013;40:211–219. 10.1159/000342778 [PubMed: 23364031]
48. Blue EE, Horimoto ARVR, Mukherjee S, Wijsman EM, Thornton TA. Local ancestry at APOE modifies Alzheimer's disease risk in Caribbean Hispanics. Alzheimers Dement. 2019;15:1524–1532. 10.1016/j.jalz.2019.07.016 [PubMed: 31606368]
49. Hohman TJ, Cooke-Bailey JN, Reitz C, et al. Global and local ancestry in African-Americans: implications for Alzheimer's disease risk. Alzheimers Dement. 2016;12:233–243. 10.1016/j.jalz.2015.02.012 [PubMed: 26092349]
50. Gross AL, Mungas DM, Crane PK, et al. Effects of education and race on cognitive decline: an integrative study of generalizability versus study-specific results. Psychol Aging. 2015;30:863–880. 10.1037/pag0000032 [PubMed: 26523693]
51. Manly JJ, Schupf N, Tang M-X, Stern Y. Cognitive decline and literacy among ethnically diverse elders. J Geriatr Psychiatry Neurol. 2005;18:213–217. 10.1177/0891988705281868 [PubMed: 16306242]
52. Briceño EM, Gross AL, Giordani BJ, et al. Pre-Statistical considerations for harmonization of cognitive instruments: harmonization of ARIC, CARDIA, CHS, FHS, MESA, and NOMAS. J Alzheimer's Dis. 2021;83:1803–1813. 10.3233/JAD-210459 [PubMed: 34459397]

RESEARCH IN CONTEXT

Systematic Review:

A literature review was completed using traditional sources and databases. Several studies suggest that in populations of West African ancestry, and Hispanics, the association of apolipoprotein E (*APOE*) ε4 genotype and Alzheimer's disease (AD) is weaker. However, these studies have been rare in Latin American population-based samples.

Interpretation:

We found similar associations between *APOE* ε4 genotype, dementia prevalence, and memory performance across diverse populations of Caribbean Hispanics and US ethnic groups. These associations remained similar after we controlled for admixture proportions.

Future Directions:

Future studies are needed to better understand the interaction between admixture and *APOE* genotype in modifying risk for dementia and AD, especially in highly admixed populations. Latin American populations, where many populations have three-way admixture (European, African, and Native American) might be ideal to further explore such interactions.

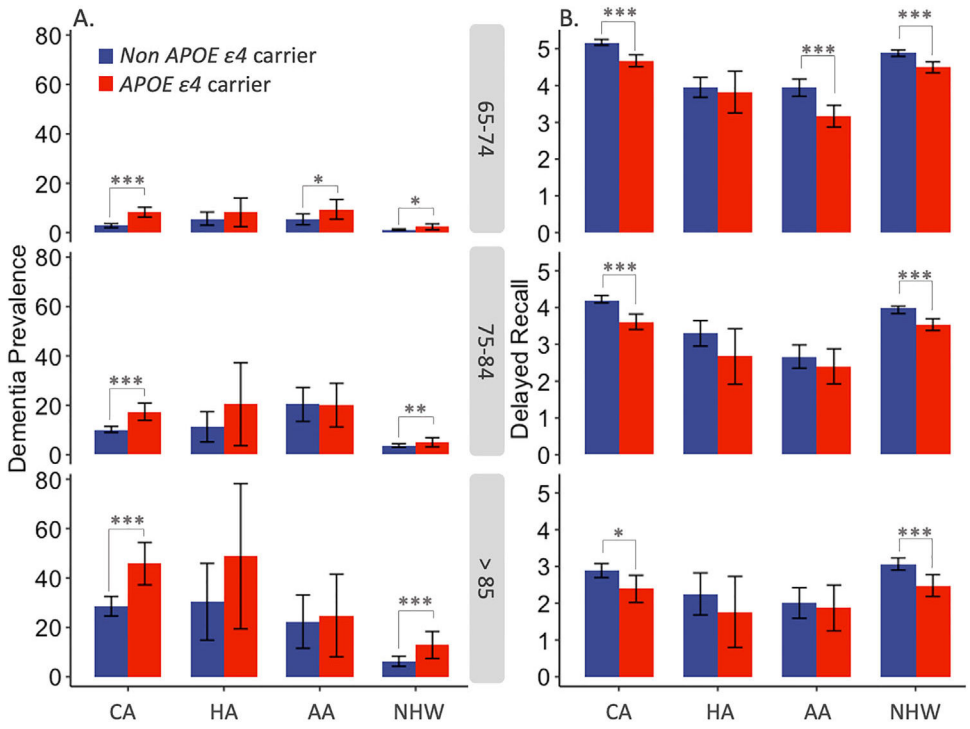

FIGURE 1.

Dementia prevalence and 10-word delayed recall scores by ethnic group and age category.

Notes: Bars in Panel A show dementia prevalence with 95% confidence intervals. Panel B shows mean number of 10-word delayed recall with 95% confidence intervals. CA, Caribbean Hispanic; HA, Hispanic Americans; AA, African American;NHW, Non-Hispanic White. Red color indicates APOE $\varepsilon 4$ carriers (4/$\varepsilon 4$, 3/$\varepsilon 4$, $\varepsilon 2$/$\varepsilon 4$), Blue color indicates non APOE $\varepsilon 4$ carriers ($\varepsilon 2$/$\varepsilon 2$, $\varepsilon 2$/$\varepsilon 3$, $\varepsilon 3$/$\varepsilon 3$) *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

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TABLE 1

Summary statistics of study sample

		United States		
	Caribbean Hispanics N = 5947	**Hispanic Americans N = 576**	**African Americans N = 917**	**Non-Hispanic White Americans N = 6070**
Demographics				
Female n (%)	3959 (66.6)	341 (55.6)	575 (62.4)	3440 (56.8)
Age mean (SD)	74.8 (7.1)	73.0 (6.7)	73.8 (6.9)	74.9 (7.4)
Education				
Less than high school (US)/less than primary school (Carib) n(%)	1935 (32.5)	386 (67.6)	417 (45.0)	1210 (19.2)
High-school graduate (US)/completing primary school (Carib) n (%)	1830 (30.8)	104 (15.8)	244 (26.0)	2159 (35.3)
Some college and above (US)/Secondary schooling and above (Carib) n (%)	2182 (36.7)	86 (16.6)	256 (29.0)	2701 (45.6)
***APOE* genotype**				
Number of *APOE* ε4 alleles n (%)				
0 n (%)	4651 (78.2)	445 (77.1)	605 (66.4)	4525 (74.6)
1 n (%)	1192 (20.0)	126 (22.4)	280 (30.7)	1447 (23.9)
2 n (%)	104 (1.7)	5 (0.6)	32 (2.9)	98 (1.5)
Any ε4 allele	1296 (21.8)	131 (22.9)	312 (33.6)	1545 (25.4)
Cognitive status				
Dementia n (%)	564 (9.5)	63 (10.6)	122 (12.5)	196 (3.1)
Immediate recall, mean (SD)	4.8 (1.6)	4.6 (1.7)	4.6 (1.7)	5.3 (1.6)
Delayed recall, mean (SD)	4.5 (2.2)	3.6 (2.0)	3.2 (2.0)	4.2 (2.0)

[a] Summary statistics for the Caribbean Hispanics sample are unweighted.

[b] Total number of observations and number of observations in each cell of categories for US subsamples are unweighted. Percentages for categorical variables and means and standard deviations for continuous variables for US subsamples are weighted using person-level analytic weights available in the Health and Retirement Study. All *P*-values for differences across groups were significant at 0.1%.

Abbreviations: *APOE,* apolipoprotein E; SD, standard deviation.

TABLE 2

Dementia prevalence by number of *APOE ε4* alleles and race/ethnicity

Number of *APOE* alleles	Dementia prevalence n/N (%)			
	Caribbean Hispanics[a]	Hispanic Americans[b]	Blacks/African Americans[b]	Non-Hispanic White Americans[b]
0	372/4651 (8.0)	44/445 (8.9)	73/605 (11.7)	123/4525 (2.6)
1	171/1192 (14.3)	N/A[c]	45/280 (14.6)	65/1447 (4.1)
2	21/104 (20.2)	N/A[c]	4/32 (10.8)	8/98 (9.4)
1 or 2	192/1296 (14.8)	19/131 (16.1)	49/312 (14.2)	73/1545 (4.4)

[a]Dementia prevalence and number of observations with dementia in each cell for Caribbean Hispanics subsamples are unweighted.

[b]Number of observations with dementia is in each cell for US subsamples are unweighted. Dementia prevalence for US subsamples are weighted using person-level analyticweights available in the Health and Retirement Study.

[c]Numbers censored due to small cell size.

Abbreviation: *APOE,* apolipoprotein E.

TABLE 3

Associations between *APOE* allele and cognitive function

	Caribbean Hispanics[c] N = 5947	Hispanic Americans[d] N = 576	Blacks/African Americans[d] N = 917	Non-Hispanic White Americans[d] N = 6070
Panel A: Dementia status [a]				
Any *ε*4	1.92 [1.62–2.22]	1.64 [0.81–2.47]	1.26 [0.81–1.71]	1.83 [1.26–2.40]
Any *ε*2	0.87 [0.65–1.09]	0.82 [0.07–1.56]	1.26 [0.78–1.74]	1.01 [0.60–1.42]
Panel B: Immediate recall [b]				
Any *ε*4	0.94 [0.92–0.96]	0.95 [0.88–1.03]	0.96 [0.92–1.01]	0.95 [0.93–0.96]
Any *ε*2	1.00 [0.98–1.03]	1.04 [0.94–1.16]	0.98 [0.93–1.03]	1.00 [0.98–1.02]
Panel C: Delayed recall [b]				
Any *ε*4	0.90 [0.87–0.93]	0.91 [0.81–1.03]	0.84 [0.76–0.93]	0.91 [0.88–0.93]
Any *ε*2	1.00 [0.96–1.04]	1.10 [0.96–1.25]	0.98 [0.88–1.09]	1.01 [0.98–1.05]

[a] Coefficients reported in Panel A are prevalence ratios (PRs) estimated from logistic regressions with dementia status as the dependent variable. PRs are interpreted as the ratios of estimated dementia prevalence between those with a particular *APOE* allele (e.g., *ε*4) to those without the allele in each sample. Ninety-five percent confidence intervals of the PRs are in brackets. All regressions adjusted for age, age squared, sex, and education.

[b] Coefficients reported in Panels B and C are incidence rate ratios (IRRs) estimated from Poisson regressions with number of correct words recalled in 10-word immediate recall (Panel B) and 10-word delayed recall (Panel C) as the dependent variable. IRRs are interpreted as the ratios of expected number of words recalled between those with a particular *APOE* allele to those without the allele in each sample. Ninety-five percent confidence intervals of the IRRs are in brackets. All regressions adjusted for age, age squared, sex, and education.

[c] Country indicators were additionally adjusted for the Caribbean Hispanics sample.

[d] Prevalence ratios, incidence rate ratios, and their confidence intervals for US samples are from weighted regressions using person-level analytic weights. Number of observations for each sample is unweighted.

Abbreviation: *APOE,* apolipoprotein E.