ORIGINAL CONTRIBUTION

Apolipoprotein E Polymorphism and Alzheimer Disease

The Indo-US Cross-National Dementia Study

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Background: The *APOE*E4* allele of the gene for apolipoprotein E (*APOE*) has been reported as a risk factor for Alzheimer disease (AD) to varying degrees in different ethnic groups.

Objective: To compare *APOE*E4*-AD epidemiological associations in India and the United States in a cross-national epidemiological study.

Design: Case-control design within 2 cohort studies, using standardized cognitive screening and clinical evaluation to identify AD and other dementias and polymerase chain reaction to identify *APOE* genotyping.

Participants: Rural community samples, aged 55 years or older (n=4450) in Ballabgarh, India, and 70 years or older (n=886) in the Monongahela Valley region of southwestern Pennsylvania.

Main Outcome Measures: Criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for probable and possible AD and Clinical Dementia Rating (CDR) scale for dementia staging.

Results: Frequency of *APOE*E4* was significantly lower ($P<.001$) in Ballabgarh vs the Monongahela Valley (0.07 vs 0.11). Frequency of probable or possible AD, with CDR of at least 1.0, in the Indian vs US samples, was as follows: aged 55 to 69 years, 0.1% (Indian sample only); aged 70 to 79 years, 0.7% vs 3.1%; aged 80 years or older, 4.0% vs 15.7%. Among those aged 70 years or older, adjusted odds ratios (95% confidence interval) for AD among carriers of *APOE*E4* vs noncarriers were 3.4 (1.2-9.3) and 2.3 (1.3-4.0) in the Indian and US samples, respectively, and not significantly different between cohorts ($P=.20$).

Conclusion: This first report of *APOE*E4* and AD from the Indian subcontinent shows very low prevalence of AD in Ballabgarh, India, but association of *APOE*E4* with AD at similar strength in Indian and US samples.

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DEMENTIA AFFECTS 5% to 10% of individuals aged 65 years or older in Europe and North America at any given time. Alzheimer disease (AD) is the most frequent cause of dementia.[1] Of the many putative genetic risk factors for AD, only the gene for apolipoprotein E (*APOE*) has thus far been shown to be associated with both early- and late-onset AD of sporadic and familial varieties.[2-4] The **E4* allele of the *APOE* gene has been consistently shown to be associated with AD in many studies of white populations, whereas the **E2* allele has in some studies appeared to be protective against AD.[4] Findings appear similar in a Chinese population[5] but, based on a number of studies in African, African American, and Hispanic populations, the evidence of an *APOE*-AD association is mixed.[6-8] Thus, there may be interactions between *APOE* and racial or ethnic group as well as environmental factors that might modify the increased risk of AD conferred by the *APOE*E4* allele in different populations.[7] To our knowledge, there are no previous reports from the Indian subcontinent, of which the population represents approximately one sixth that of the world.[9]

Under a National Institute on Ageing–sponsored program of cross-national investigations,[10] the Indo-US Cross-National Dementia Epidemiology Study was funded as a collaborative venture between the University of Pittsburgh, Pittsburgh, Pa, and the Centre for Ageing Research in India (CARI), New Delhi. The study was designed to compare the prevalence, incidence, risk factors, and outcome of AD and other

SUBJECTS AND METHODS

MONONGAHELA VALLEY STUDY SITE

The mid-Monongahela Valley is a largely rural postindustrial area in southwestern Pennsylvania. An age-stratified (65-74 years and 75 years or older) random sample of community-dwelling adults listed in the local voter registration lists was drawn for an epidemiological project named the Monongahela Valley Independent Elders Survey (MoVIES). The MoVIES cohort at baseline consisted of 1422 randomly sampled and 259 volunteer community-dwelling elderly who met the same entry criteria, recruited and characterized from April 1, 1987, through October 20, 1989.[12,13] The cohort has since been observed through approximately biennial data collection waves. At each wave, participants undergo cognitive screening, on the basis of which they are classified as cognitively impaired, cognitively declined from previous waves, or cognitively intact, based on operational criteria. At each wave, those designated as cognitively impaired or declined and a random sample of unimpaired controls selected during the baseline wave undergo a standardized clinical evaluation consisting of history, general physical examination, detailed neurological and mental status examinations, laboratory investigations, and review of medical records. This evaluation followed the assessment protocols of the University of Pittsburgh Alzheimer's Disease Research Center and the Consortium to Establish a Registry for Alzheimer's Disease,[14] modified for use in the field. It culminates in a consensus diagnosis intended to establish the presence or absence of a dementia syndrome according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* (*DSM-III-R*),[15] the stage of dementia according to the Clinical Dementia Rating (CDR) scale,[16] and probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group.[17] Further details of the MoVIES cohort, sampling and screening criteria, and diagnostic assessment methods have been reported previously.[12,13,18-20]

When the *APOE* gene was first reported as a risk factor for AD in 1993,[2,3] the MoVIES cohort was in its third biennial data collection wave. From January 26, 1994, through October 23, 1997, blood specimens for *APOE* genotyping were collected from surviving members of the MoVIES cohort, who by that time were all older than 70 years. Of the 1681 subjects in the original (1987-1989) MoVIES cohort, 886 white individuals who were still alive and participating in the study and had not moved to nursing homes underwent blood sample draws for genotyping. The likely survival bias in the genotyped subsample of the MoVIES cohort precludes its use for prevalence estimation but does not affect its usefulness for case-control and other risk and protective factor studies.

Blood samples were collected by venipuncture (88%) or by finger- or earlobe-stick (12%). The DNA was isolated with the use of a commercially available kit (QIAmp kit; QIAGEN Inc, Chatsworth, Calif). The *APOE* genotyping was performed by means of a polymerase chain reaction protocol as described previously.[21]

BALLABGARH STUDY SITE

Ballabgarh is a rural agricultural area in the state of Haryana in northern India. The initial phase of the study was devoted to developing appropriate assessment tools for the Hindi-speaking Ballabgarh elderly population, approximately three quarters of whom were totally illiterate. The development of the cognitive screening battery,[22,23] the functional ability scale,[24] and the clinical diagnostic protocol[25] used in our study and designed to maximize comparability to the MoVIES study have been described in detail elsewhere.

After instrument development, the entire population aged 55 years or older in the 28 villages in the Ballabgarh study area was recruited and surveyed from December 4, 1995, through December 9, 1997. Recruitment for the present study was extended to all adults aged 55 years or older, rather than 65, because of the relatively short life expectancy (62.1 years at birth) of individuals in this area.[26] Demographic data collected included age confirmation (reported previously[25]), education (years of formal schooling), and literacy (ability to write a sentence and read the local

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dementias between the rural communities of Ballabgarh in northern India and the Monongahela Valley region in southwestern Pennsylvania.

The prevalence of AD and other dementias among the elderly in Ballabgarh was recently reported to be the lowest thus far reported in the world,[11] suggesting that different risk and protective factors might be operating in this Indian community than in other populations. We herein report and compare the relationship between AD and the *APOE* polymorphism in large, community-based samples of the elderly populations of Ballabgarh and the Monongahela Valley, to answer the following 3 primary research questions: (1) Is the frequency of the *APOE*E4* allele different between study cohorts from both populations? (2) Is the *APOE*E4* allele associated with AD in both cohorts? (3) If so, is the strength of the association similar in the two cohorts?

RESULTS

DEMOGRAPHICS

As of the reference dates, the MoVIES cohort (n=886) had a mean age of 79.3 (4.8) years, with a median of 78.7 years; 61.1% were aged 70 to 79 years, and 38.9% were aged 80 years or older. Women constituted 64.2% of the sample. For education, 38.3% did not graduate from high school, 36.0% were high school graduates, and 25.7% had more than a high school education.

In the Ballabgarh cohort (n=4450), the mean age was 67.1 (7.2) years, with a median of 65.7 years as of the reference dates; 72.0% were aged 55 to 69 years, 21.8% were aged 70 to 79 years, and 6.2% were aged 80 years or older. Women constituted 48.0% of the sample. Although 73.9% had no formal schooling, 1.6% of unschooled individuals had some literacy as defined ear-

newspaper). Using methods and criteria closely following those in the MoVIES project, all participants underwent cognitive screening. Those whose scores fell below operational criteria for cognitive impairment and a random sample of unimpaired controls were selected for detailed clinical evaluation. The standardized clinical evaluation protocol, also following that of the MoVIES project, culminated in a *DSM-III-R* diagnosis of dementia syndrome, a diagnosis of probable or possible AD according to NINCDS-ADRDA criteria, and a CDR rating of the stage of dementia. Further descriptions of the cohort and of screening and diagnostic methods are found in previous reports.[11,22-25]

Blood sample draws for *APOE* genotyping were performed during the prevalence (baseline) phase. Of the 5126 subjects originally recruited in this cohort, 4450 individuals (86.8% of the cohort) provided finger-stick blood samples. The DNA was isolated with the use of the blood kits described above, and *APOE* genotyping was performed by means of polymerase chain reaction analysis. Reliability was established between both laboratories by blind genotyping in the Indian laboratory of a sample of specimens provided from the US laboratory, and by blind reading in the US laboratory of a sample of gel photographs prepared in the Indian laboratory. Government of India regulations prohibit the export of human specimens to overseas laboratories for research.

At both study sites, informed consent was obtained after full explanation of the nature of the study procedures, all of which were performed according to protocols approved by the University of Pittsburgh Institutional Review Board. For the Ballabgarh site, approval was also obtained from the Human Volunteers Protection Committee of CARI.

STATISTICAL ANALYSES

Means (SDs) and medians were calculated for age in both cohorts. The Monongahela Valley cohort was classified into groups aged 70 to 79 years and 80 years or older, and the Ballabgarh cohort was classified into groups aged 55 to 69 years, 70 to 79 years, and 80 years or older. Cross-national comparisons used only the groups aged 70 to 79 years and 80 years or older. Proportions of each cohort by sex and education or literacy level were calculated.

Gene counting was used to calculate *APOE* allele frequencies in each cohort. In each cohort, adherence to Hardy-Weinberg expectation was tested by means of χ^2 goodness-of-fit tests. Within each cohort, *APOE* allele frequencies were calculated by and compared among the age groups to determine whether *APOE*E4* frequency decreased with age. The χ^2 tests were used to compare frequencies of each allele between cohorts.

Within each cohort, the proportion of subjects by CDR stage and with diagnosis of probable or possible AD were calculated for the entire cohort and by age group as of the reference date (date of blood sample draw for genotyping). As with any cross-sectional study, it was recognized that dementia would develop subsequently in some individuals classified as nondemented for the purpose of the current analyses.

A case-control design, with cases and controls identified as of the reference date, was used to examine cross-sectional relationships of *APOE* genotype with all dementias and with AD in both cohorts. Logistic regression was used to calculate the odds ratios (ORs) and the associated 95% confidence intervals (CIs) for a diagnosis of AD in *APOE*E4* carriers (subjects with at least one copy of the *APOE*E4* allele) compared with noncarriers. Logistic regression models were also fit to look for associations of *APOE*E4* with all dementias combined (ie, including non-AD dementias). Four different logistic regression models were fit for each cohort, with outcome variables being probable or possible AD with CDR of at least 1.0, probable or possible AD with CDR of at least 0.5, all dementia with CDR of at least 1.0, and all dementia with CDR of at least 0.5. Models restricted to probable or possible AD excluded subjects with other dementias; models restricted to subjects with CDR of at least 1.0 treated subjects with CDR of 0.5 as not demented. The ORs were adjusted for age (continuous variable) and education (MoVIES cohort, high school graduates vs subjects with less than high school) or literacy (Ballabgarh cohort, literate vs illiterate subjects.) The logarithms of the ORs for AD in both cohorts were then compared using a z test.[27] Similar logistic regression models were fit to calculate ORs and CIs for AD among *APOE*E2* carriers compared with noncarriers in each cohort. Models were also fit to MoVIES data, adjusting for random or volunteer status.[13]

lier. For the present analyses, we classified the Ballabgarh cohort according to literacy (rather than education) as 26.5% literate and 73.5% illiterate.

Frequencies of *APOE* alleles in both cohorts are presented in **Table 1**.

In the MoVIES cohort, the frequencies of the *APOE*E2*, *APOE*E3*, and *APOE*E4* alleles were 0.07, 0.82, and 0.11, respectively; the genotype distributions were in Hardy-Weinberg equilibrium ($P=.76$). Of 186 *APOE*E4* carriers, 11 were **E4/*E4* homozygous. The *APOE*E4* frequencies in both age groups (Table 1) were not significantly different ($P=.48$).

In the Ballabgarh cohort, the frequencies of the *APOE*E2*, *APOE*E3*, and *APOE*E4* alleles were 0.04, 0.89, and 0.07, respectively. Of 632 *APOE*E4* carriers, 22 were **E4/*E4* homozygous. The distribution of *APOE* genotypes in the Ballabgarh cohort deviated from Hardy-Weinberg equilibrium (χ^2_3 was 9.12 compared with the critical value of 7.81; $P=.03$). Since equilibrium may not hold for the population after the age of reproduction, this deviation in our older population might have been the result of selective survival. Further, rapid declines in infant and child mortality in recent decades may have rendered the population unstable with regard to *APOE* frequencies.

The *APOE*E4* frequency in the 3 age groups (Table 1) showed no trend with age in Ballabgarh. The frequencies of *APOE*E2* and *APOE*E4* alleles in the population aged 70 years or older were significantly lower in the Ballabgarh than in the MoVIES cohort ($P<.001$ by χ^2).

FREQUENCY OF AD AND OTHER DEMENTIAS

In the MoVIES cohort, 132 subjects (14.9%) had any or all dementia according to *DSM-III-R* and a CDR stage of at least 0.5 as of the reference date. Of those with any

Table 1. Frequencies of Dementia, AD, and *APOE* Alleles*

Age, y	No. of Subjects	No. (%) of Subjects: Overall Dementia, CDR Stage 0.5	Overall Dementia, CDR Stage ≥1.0	Probable or Possible AD, CDR Stage 0.5	Probable or Possible AD, CDR Stage ≥1.0	*APOE* Allele Frequencies *E2	*E3	*E4
Ballabgarh, India, cohort								
55-69	3203	3 (0.09)	8 (0.2)	3 (0.09)	3 (0.09)	0.04	0.88	0.08
70-79	971	2 (0.2)	9 (0.9)	2 (0.2)	7 (0.7)	0.03	0.90	0.06
≥80	276	2 (0.7)	12 (4.3)	2 (0.7)	11 (4.0)	0.04	0.88	0.08
Total	**4450**	**7** (0.2)	**29** (0.7)	**7** (0.2)	**21** (0.5)	0.04	0.89	0.07
Monongahela Valley, Pa, cohort								
70-79	541	19 (3.5)	19 (3.5)	16 (3.0)	17 (3.1)	0.07	0.81	0.12
≥80	345	38 (11.0)	56 (16.2)	28 (8.1)	54 (15.7)	0.06	0.83	0.10
Total	**886**	**57** (6.4)	**75** (8.5)	**44** (5.0)	**71** (8.0)	0.07	0.82	0.11

*AD indicates Alzheimer disease; APOE, gene for apolipoprotein E; and CDR, Clinical Dementia Rating. Cohorts are described in the "Subjects and Methods" section.

dementia, 115 (87.1%) had probable or possible AD according to NINCDS-ADRDA criteria. Restricting the analyses to subjects with CDR stage of at least 1.0, 75 subjects (8.5%) had any dementia, 71 (94.7%) of whom had probable or possible AD.

In the Ballabgarh cohort, 36 (0.8%) had any dementia according to *DSM-III-R* and a CDR stage of at least 0.5. Of the demented, 28 (77.8%) had probable or possible AD according to NINCDS-ADRDA criteria. Among those with CDR stage of at least 1.0, there were 29 (0.7%) subjects with any dementia, 21 (72.4%) of whom had probable or possible AD. Further breakdown of these diagnosis and stage categories in both samples by age groups is shown in Table 1, and by genotype in **Table 2**.

Table 2. Frequencies of *APOE* Genotype by Diagnosis of Dementia and Probable or Possible AD*

APOE Genotype	Monongahela Valley, Pa, Cohort: Total Sample	All Dementias	AD	Ballabgarh, India, Cohort: Total Sample	All Dementias	AD
*E2/*E2	2	1	1	13	0	0
*E2/*E3	103	14	10	290	1	1
*E3/*E3	595	84	72	3515	25	19
*E3/*E4	159	31	30	577	9	7
*E2/*E4	16	1	1	33	0	0
*E4/*E4	11	1	1	22	1	1
Total	**886**	**132**	**115**	**4450**	**36**	**28**

*Abbreviations are given in the footnote to Table 1. Cohorts are described in the "Subjects and Methods" section of the text.

ASSOCIATIONS BETWEEN AD AND *APOE* GENOTYPES

Adjusted ORs used to estimate cross-sectional associations between *APOE* genotypes, and AD and dementia in both cohorts are shown in **Table 3**.

*APOE*E4* ALLELE

After adjustment for age and education (in the MoVIES cohort), and for age and literacy (in the Ballabgarh cohort), the OR (with 95% CI) for probable or possible AD with CDR stage of at least 1.0, in *APOE*E4* carriers compared with noncarriers, was 2.26 (1.29-3.95) in the MoVIES cohort and 3.35 (1.20-9.39) in the Ballabgarh cohort aged 70 years or older. Odds ratios for all dementias and for CDR of at least 0.5 in both cohorts, including the entire Ballabgarh cohort (all age groups), are shown in Table 3. In the MoVIES data, controlling for selection (random vs volunteer) status by including it as an independent variable in the models barely changed the ORs or CIs.

Since the MoVIES subjects undergoing genotyping were all aged 70 years or older, we restricted cross-national comparisons across Indian and US cohorts to subjects in the category aged 70 years or older. The ORs reported for AD with CDR of at least 1.0 were not significantly different across cohorts ($P=.25$), to the extent that a difference could be detected with available power. Essentially, the *APOE*E4* allele was associated with AD at similar strength in both cohorts.

*APOE*E2* ALLELE

After adjustment for age and education (in the Monongahela Valley), and for age and literacy (in Ballabgarh), the OR for probable or possible AD with CDR stage of at least 1.0, given the presence of at least 1 *APOE*E2* allele, was calculated for both cohorts. No significant association was found between *APOE*E2* and AD as all CIs included 1, most likely because of lack of power.

All models had adequate fit by Hosmer-Lemeshow goodness-of-fit test.[28]

COMMENT

The frequencies of AD and the *APOE*E4* allele were higher among those who underwent genotyping within our US sample than in our Indian sample. The *APOE*E4* carrier status and the presence of probable or

Table 3. Associations Among *APOEE4*, All Dementias, and AD***

Cohort, Age	No. of Subjects	CDR Stage ≥0.5			CDR Stage ≥1.0		
		No. of Cases	Odds Ratio (95% CI)†	*P*	No. of Cases	Odds Ratio (95% CI)†	*P*
Ballabgarh, India, aged ≥55 y							
Probable or possible AD‡	4442	28	2.63 (1.12-6.15)	.03	21	2.62 (0.98-7.01)	.05
All dementias	4450	36	2.44 (1.15-5.18)	.02	29	2.39 (1.04-5.52)	.04
Ballabgarh, aged ≥70 y							
Probable or possible AD‡	1244	22	3.15 (1.23-8.10)	.02	18	3.35 (1.20-9.39)	.02
All dementias	1247	25	3.15 (1.30-7.61)	.01	21	3.31 (1.28-8.58)	.01
Monongahela Valley, Pa, aged ≥70 y							
Probable or possible AD‡	869	115	1.70 (1.05-2.76)	.03	71	2.26 (1.29-3.95)	.004
All dementias	886	132	1.48 (0.93-2.38)	.10	75	2.10 (1.21-3.63)	.008

**CI indicates confidence interval. Other abbreviations are given in the footnote to Table 1. Cohorts are described in the "Subjects and Methods" section.*
†Multiple logistic regression models were adjusted for age and educational level in the Monongahela Valley data and for age and literacy in the Ballabgarh data.
‡By criteria from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for clinical diagnosis; other dementias were excluded from this model (hence smaller sample).

possible AD were positively associated in both cohorts. In each cohort, the elevated risk was about 2- to 3-fold, ie, the ORs were lower than those reported from the highly selected populations of Alzheimer's Disease Centers and similar referral centers.[21,29,30] The ORs in our cohorts were within the range reported from other community-based studies of white populations in East Boston[31] and Rotterdam,[32] which included mild dementias, although lower than those from Framingham,[33] which included only moderate to severe dementias. No associations were found between *APOE*E2* and AD or overall dementia in either cohort. The effects of *APOE* on AD appear similar in both our cohorts. Hence, differences between them in the prevalence of AD may be attributed at least partly to the lower frequency of *APOE*E4* in the Indian cohort, which itself may be a function of survival. Life expectancy at birth for individuals in India is 62.1 years, as compared with 76.1 years among US white individuals; remaining life expectancy at 70 years of age in India is 10.6 years, compared with 14.0 years among US white individuals, according to the the 1991 census of India[22] and the 1990 US census.[34] Within the limited age range of both our elderly cohorts, we did not find a decreasing trend for *APOE*E4* allele frequencies with age. However, a negative association between age and *APOE*E4* has been noted by some previous studies,[35-37] suggesting selective survival.

Previous studies of *APOE* polymorphism in individuals from India or of Indian ancestry have reported *APOE*E4* allele frequencies of 0.101,[38] 0.127,[39] 0.127,[40] and 0.103 (M. Ilyas Kamboh, PhD, and A. Ramesh, PhD, unpublished data, 1990), which appear marginally higher than the frequency of 0.07 in Ballabgarh inhabitants aged 55 years or older. None of the previous studies provided the age distributions of their populations, which appeared to represent small convenience (eg, blood bank) samples rather than defined representative communities. None of the previous reports included diagnostic information on AD or other diseases. Although ours is the largest Indian sample from which *APOE* allele frequencies have been reported, it is not representative of the population of India as a whole.

On the basis of a multicenter meta-analysis, Farrer et al[7] recently concluded that the *APOE*E4* allele "represents a major risk factor for AD in all ethnic groups studied, across all ages between 40 and 90 years, and in both men and women." Studies included in the meta-analysis were of ethnic groups described as Caucasian, African American, Hispanic, and Japanese. Our US study population was white, a term often used interchangeably with *Caucasian*. However, our nonwhite Asian Indian population would also have to be classified as Caucasian, as natives of India and western Asia are described as forming "a Caucasoid cluster when compared with Asians from further north and east."[41] Previous genetic studies have suggested that linguistic (ie, ethnic) differences account for much of the genetic diversity of present-day Indian populations[42,43]; the ethnically diverse population of India is politically divided into linguistic states. Our study was conducted in Haryana, a northern Indian state whose inhabitants speak an Indo-European language (the Haryanvi dialect of Hindi). A study of Indians in 2 adjacent states, where the Punjabi and Hindi languages are spoken, demonstrated Caucasoid genetic features in addition to at least 1 marker suggesting ancient East Asian lineage.[42] Thus, there is likely to be genetic admixture even in our Indian study population, which is probably more ethnically homogeneous than our Monongahela Valley study population of mixed European ancestry. Cross-ethnic comparisons can reveal important environmental differences (including, eg, cultural, geographic, socioeconomic, or dietary factors) that may be relevant to disease and that may interact with genetic risk. However, the genetic basis of conventional racial and ethnic distinctions per se is far from clear.[43] Given the recent proliferation in reports of genetic studies from unique national, geographic, linguistic, racial, and ethnic groups, caution is warranted in comparing genetic data between studies that use different or overlapping ethnic classifications.

Our study had some limitations. The current report excluded the 17 African American subjects in our US genotyped cohort because of their small numbers. In both cohorts, the category of all dementias was

largely composed of probable or possible AD; we had too few cases of non-AD dementias to allow separate analyses of their relationship with *APOE*. As with most community-based studies, both cohorts included too few **E4/*E4* homozygotes to allow the exploration of dose-dependent risk of AD conferred by *APOE*E4*. Although the US cohort at its inception was representative of its base population, some natural attrition had occurred during the 6 years of follow-up before genotyping was performed. Although our clinical and genetic measures were comparable across the Indian and US cohorts, the two cohorts are very different from each other in a variety of cultural and environmental aspects that cannot easily be compared. Despite these differences, the cohorts revealed similar strength of association between *APOE*E4* and AD; thus, the difference in disease occurrence between both study populations cannot be explained by differential risk, or modification of risk, with respect to the *APOE* polymorphism. As alternative explanations, differences in additional genetic risk and protective factors, survival effects, or environmental factors are promising directions for future research.

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