JAMA Neurology | Original Investigation

Apolipoprotein E Genotype and Sex Risk Factors for Alzheimer Disease

A Meta-analysis

Scott C. Neu, PhD; Judy Pa, PhD; Walter Kukull, PhD; Duane Beekly, BS; Amanda Kuzma, MS; Prabhakaran Gangadharan, MS; Li-San Wang, PhD; Klaus Romero, MD; Stephen P. Arneric, PhD; Alberto Redolfi, PhD; Daniele Orlandi, MsC; Giovanni B. Frisoni, MD; Rhoda Au, PhD; Sherral Devine, PhD; Sanford Auerbach, MD; Ana Espinosa, PhD; Mercè Boada, MD, PhD; Agustín Ruiz, MD, PhD; Sterling C. Johnson, PhD; Rebecca Koscik, PhD; Jiun-Jie Wang, PhD; Wen-Chuin Hsu, MD; Yao-Liang Chen, MD; Arthur W. Toga, PhD

Editorial page 1167

Author Audio Interview

Supplemental content

IMPORTANCE It is unclear whether female carriers of the apolipoprotein E (APOE) ε4 allele are at greater risk of developing Alzheimer disease (AD) than men, and the sex-dependent association of mild cognitive impairment (MCI) and APOE has not been established.

OBJECTIVE To determine how sex and APOE genotype affect the risks for developing MCI and AD.

DATA SOURCES Twenty-seven independent research studies in the Global Alzheimer's Association Interactive Network with data on nearly 58 000 participants.

STUDY SELECTION Non-Hispanic white individuals with clinical diagnostic and APOE genotype data.

DATA EXTRACTION AND SYNTHESIS Homogeneous data sets were pooled in case-control analyses, and logistic regression models were used to compute risks.

MAIN OUTCOMES AND MEASURES Age-adjusted odds ratios (ORs) and 95% confidence intervals for developing MCI and AD were calculated for men and women across APOE genotypes.

RESULTS Participants were men and women between ages 55 and 85 years. Across data sets most participants were white, and for many participants, racial/ethnic information was either not collected or not known. Men (OR, 3.09; 95% CI, 2.79-3.42) and women (OR, 3.31; CI, 3.03-3.61) with the APOE ε3/ε4 genotype from ages 55 to 85 years did not show a difference in AD risk; however, women had an increased risk compared with men between the ages of 65 and 75 years (women, OR, 4.37; 95% CI, 3.82-5.00; men, OR, 3.14; 95% CI, 2.68-3.67; *P* = .002). Men with APOE ε3/ε4 had an increased risk of AD compared with men with APOE ε3/ε3. The APOE ε2/ε3 genotype conferred a protective effect on women (OR, 0.51; 95% CI, 0.43-0.61) decreasing their risk of AD more (*P* value = .01) than men (OR, 0.71; 95% CI, 0.60-0.85). There was no difference between men with APOE ε3/ε4 (OR, 1.55; 95% CI, 1.36-1.76) and women (OR, 1.60; 95% CI, 1.43-1.81) in their risk of developing MCI between the ages of 55 and 85 years, but women had an increased risk between 55 and 70 years (women, OR, 1.43; 95% CI, 1.19-1.73; men, OR, 1.07; 95% CI, 0.87-1.30; *P* = .05). There were no significant differences between men and women in their risks for converting from MCI to AD between the ages of 55 and 85 years. Individuals with APOE ε4/ε4 showed increased risks vs individuals with ε3/ε4, but no significant differences between men and women with ε4/ε4 were seen.

CONCLUSIONS AND RELEVANCE Contrary to long-standing views, men and women with the APOE ε3/ε4 genotype have nearly the same odds of developing AD from age 55 to 85 years, but women have an increased risk at younger ages.

JAMA Neurol. 2017;74(10):1178-1189. doi:10.1001/jamaneurol.2017.2188

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Arthur W. Toga, PhD, Laboratory of Neuro Imaging, Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, 2025 Zonal Ave, Los Angeles, CA 90033 (toga@loni.usc.edu).

For nearly 20 years, the prevalent view has been that women who carry copies of the ε4 allele of the apolipoprotein E (*APOE*) gene have a greater risk of developing Alzheimer disease (AD) than men with the same number of copies.[1] The ε4 allele is the main genetic risk factor for late-onset Alzheimer disease (AD),[2] and sex-based differences in AD risk have important implications for treatment trials, diagnostics, and therapeutics.[3] Additionally, the sex-dependent relationship between APOE and mild cognitive impairment (MCI), which is often a transitional phase from cognitively normal (NL) aging to dementia,[4] is unclear. Studies are in general agreement that the APOE ε4 allele is a risk factor for developing MCI,[5-11] but there is controversy as to whether it increases[10,12-14] or does not increase[9,11,15,16] the risks of transitioning from MCI to AD or dementia. The 3 most common alleles of the *APOE* gene are ε2, ε3, and ε4; whereas carrying the ε4 allele increases one's risk of developing AD, the ε2 allele conversely has a putative protective effect that is associated with longevity and a lower AD risk.[17]

Studies of participants with a family history of late-onset AD have reported that women with 1 copy of ε4 have a greater risk than male heterozygote ε4 carriers, who in turn have about the same risk as male ε3 homozygotes.[18,19] This sex dependence was also found in first-degree (parents and siblings) relatives of individuals with AD,[20,21] and in the meta-analysis of Farrer et al,[1] which aggregated data from 40 independent research studies. Among studies of residents in city suburbs and communities, there is general agreement that elderly female ε4 carriers have an increased risk of AD, dementia, and cognitive decline vs male ε4 carriers.[22-25] However, when participants are randomly recruited from hospitals, retirement homes, and aging consortiums, most studies have found no sex-specific difference between men and women in the risks of AD and dementia associated with the APOE ε4 allele.[26-29] The sex-dependent role of APOE ε4 in the risks of developing MCI and in MCI conversions to AD has been recently investigated,[3,30] and there is evidence that women are at greater risk than men.

Methods

We collected data sets from 27 independent research studies totaling nearly 58 000 participants. Information was collected on each participant's APOE genotype, sex, race, ethnicity, diagnosis (NL, MCI, or AD), and age at diagnosis. From these data sets we included only white participants who were mostly non-Hispanic. The Global Alzheimer's Association Interactive Network receives coded information and does not distribute data.

Global Alzheimer's Association Interactive Network Data Sets

Prospective participants for this meta-analysis were identified using resources[31] from the Global Alzheimer's Association Interactive Network.[32,33] As shown in **Table 1**,[34-58] we used multiple data sets from 12 research institutions in the Global Alzheimer's Association Interactive Network, with 2 institutions (National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site and Coalition Against Major Diseases) managing data from several independent studies. Details of the data sets obtained through the Global Alzheimer's Association Interactive Network are given in the eAppendix in the Supplement.

We did not receive information about clinical diagnoses for all participants, and in some cases the ages of elderly participants were truncated downward to 90 years to protect their identities. We excluded patients with missing information and/or 90-year truncated ages from all data sets. In many data sets, birth dates were rounded to the nearest year as an extra measure to protect patient confidentiality. We excluded data from participants in the National Alzheimer's Coordinating Center (NACC) data set who were also known to have participated in the Alzheimer's Disease Neuroimaging Initiative Study; however, the full extent of the participant overlap between NACC and the Alzheimer's Disease Neuroimaging Initiative has not currently been established but is estimated to be at most 3%. Across data sets, most participants were white, and for many participants, racial/ethnic information was either not collected or not known. Owing to insufficient numbers of other races/ethnicities, we only included white participants (along with participants from the Fundació ACE and Australian Imaging, Biomarker and Lifestyle Flagship Study of Ageing data sets) with non-Hispanic or unknown ethnicities. Through our correspondences with data set providers, we estimate that Hispanic participants make up no more than 5% of all white participants with unknown ethnicities. After applying exclusion criteria, these data sets were representative of non-Hispanic white individuals in North America and Europe.

The descriptions of the clinical diagnoses we received were unstandardized[33] and the levels of detail varied across different data sets according to how each disease was defined (eg, mild or moderate AD) and how it was recorded (eg, AD associated with cerebrovascular disease). We worked directly with each data set provider to translate each set of diagnoses into our 3 general preplanned diagnoses: NL, MCI, and AD. In addition, we excluded all patients with a clinical history of stroke, cerebrovascular disease, Lewy bodies, amyloid precursor protein or presenilin gene mutations, or comorbidity with any other known neurological disease. All subtypes of MCI (eg, amnestic and nonamnestic) were combined into a single MCI diagnosis.

Key Points

Question Are female carriers of the apolipoprotein E ε4 allele at greater risk of developing Alzheimer disease than men?

Findings In this meta-analysis of 27 independent research studies with 58 000 participants, women and men with 1 copy of apolipoprotein E ε4 did not show a difference in risk of Alzheimer disease from age 55 to 85 years. However, these women were at increased risk vs men between ages 65 and 75 years.

Meaning Sex-specific treatments for cognitive decline and Alzheimer disease may need to be initiated a younger age, especially in those who carry an apolipoprotein E ε4 allele.

Table 1. Characteristics of APOE Data Sets From the Global Alzheimer's Association Interactive Network

Data Set	Name	No. of Participants	Diagnosis	Race/Country, No. (%)	Ethnicity, No. (%)	Ascertainment
ACE	Fundació ACE[34]	1243	MCI, AD	99 Spain; 1 other races	100 Unknown ethnicity	Mostly residents of Barcelona, Spain
ADNI	Alzheimer's Disease Neuroimaging Initiative[35]	2065	NL, MCI, AD	1911 (93) White 98 (5) Black 56 (2) Other races	1988 (96) Non-Hispanic 63 (3) Hispanic 14 (1) Unknown ethnicity	59 Acquisition sites across United States and Canada
AIBL	The Australian Imaging, Biomarkers and Lifestyle Flagship Study of Aging[36]	834	NL, MCI, AD	834 (100) Australia	834 (100) Unknown ethnicity	2 Acquisition centers in Australia
ARWIBO	Alzheimer Disease Repository Without Borders[37,38]	1201	NL, MCI, AD	1201 (100) White	1201 (100) Non-Hispanic	Mostly residents of Brescia, Italy
CAMD	Coalition Against Major Diseases[39]	2382	MCI, AD	2173 (91) White 130 (5) Asian 60 (3) Black 19 (1) Other races	1367 (58) Non-Hispanic 863 (36) Unknown ethnicity 152 (6) Hispanic	NA
1009	Clinical Trial 1009	162	AD	161 (99) White 1 (1) Other races	162 (100) Unknown ethnicity	Canada and several European countries
1056	Clinical Trial 1056	493	AD	454 (92) White 35 (7) Asian 4 (1) Black	471 (95) Non-Hispanic 17 (3) Hispanic 5 (2) Unknown ethnicity	Several countries
1057	Clinical Trial 1057	500	AD	442 (88) White 46 (9) Asian 12 (3) Other races	403 (81) Non-Hispanic 97 (19) Hispanic	Europe, Japan, and Argentina
1058	Clinical Trial 1058	166	AD	127 (76) White 36 (22) Asian 3 (2) Other races	149 (90) Non-Hispanic 17 (10) Hispanic	Several countries
1105	Clinical Trial 1105	266	NA	260 (98) White 4 (1.5) Black 2 (0.5) Other races	266 (100) Unknown ethnicity	United States, Canada, Europe, South Africa
1132	Clinical Trial 1132	286	MCI	267 (93) White 14 (5) Black 5 (2) Other races	286 (100) Unknown ethnicity	Multiple US states
1136	Clinical Trial 1136	141	AD	141 (100) White	141 (100) Unknown ethnicity	Scandinavia
1142	Clinical Trial 1142	368	AD	321 (87) White 33 (9) Black 8 (2) Asian 6 (2) Other races	344 (93) Non-Hispanic 21 (6) Hispanic 3 (1) Unknown ethnicity	Multiple US states
EDSD	European Diffusion Tensor Imaging Study in Dementia[40]	196	NL, MCI, AD	196 (100) White	196 (100) Non-Hispanic	9 Memory assessment clinics in 4 European countries
FHS	Framingham Heart Study[41]	5402	NL, MCI, AD	5391 (99) White 11 (1) Other races	5390 (99) Non-Hispanic 12 (1) Hispanic	Residents of Framingham, Massachusetts
LMRR	Laboratory of Magnetic Resonance Research	113	NL, MCI, AD	113 (100) Asian	113 (100) Non-Hispanic	Residents of Taiwan
NACC	National Alzheimer's Coordinating Center[42]	23 999	NL, MCI, AD	19 906 (83) White 2503 (10) Black 1081 (5) Other races 509 (2) Asian	22 246 (92) Non-Hispanic 1652 (7) Hispanic 101 (1) Unknown ethnicity	34 Centers in United States

(continued)

Table 1. Characteristics of APOE Data Sets From the Global Alzheimer's Association Interactive Network (continued)

Data Set	Name	No. of Participants	Diagnosis	Race/Country, No. (%)	Ethnicity, No. (%)	Ascertainment
NIAGADS	National Institute on Aging Genetics of Alzheimer Disease Data Storage Site[43]	18 869	NL, AD	17 203 (91) White 1392 (8) Other races 274 (1) Black	9675 (51) Unknown ethnicity 8588 (46) Non-Hispanic 606 (3) Hispanic	
UPitt	University of Pittsburgh study[44]	2436	NL, AD	2194 (90) White 242 (10) Other races	2436 (100) Unknown ethnicity	Recruited patients from 1 center at University of Pittsburgh
TGEN2	Translational Genomics Research Institute study[45-47]	1599	AD	1027 (64) White 572 (36) Other races	1599 (100) Unknown ethnicity	Brain donors and healthy controls with first-degree relative with AD
ROS/MAP	Religious Orders Study/Rush Memory and Aging Project[48-51]	1571	AD	1570 (99.9) White 1 (0.1) Black	1562 (99) Non-Hispanic 9 (1) Hispanic	40 Religious groups from 12 states in mid-west United States/40 retirement communities in northeastern Illinois
WashU	Washington University study	670	NL, AD	670 (100) White	670 (100) Unknown ethnicity	
MIRAGE	Multi Institutional Research of Alzheimer Genetic Epidemiology study[52]	1245	NL, AD	1165 (94) White 80 (6) Other races	1245 (100) Unknown ethnicity	17 Clinical centers in the United States, Canada, Germany, and Greece
NIA-LOAD	National Institute on Aging LOAD Family Study[53]	5220	NL, AD	4449 (85) White 498 (10) Other races 273 (5) Black	4594 (88) Non-Hispanic 597 (11) Hispanic 29 (1) Unknown ethnicity	Recruited families with 2 or more AD siblings
ACT	Adult Changes in Thought[54]	2432	NL, AD	2432 (100) White	2432 (100) Non-Hispanic	Random patients from a Seattle HMO
UMVUMSSM	University of Miami, Vanderbilt University, Mount Sinai School of Medicine study[55]	1632	NL, AD	1632 (100) White	1632 (100) Unknown ethnicity	
MAYO GWAS	Mayo Clinic GWAS study[56]	2064	NL, AD	2064 (100) White	2064 (100) Unknown ethnicity	3 Mayo Clinics in the United States
PharmaCog (E-ADNI)	Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development[57]	143	MCI	143 (100) White	143 (100) Non-Hispanic	9 Memory assessment clinics in 4 European countries
WRAP	Wisconsin Registry for Alzheimer Prevention[58]	1532	NL, MCI	1396 (91) White 118 (8) Black 18 (1) Other races	1497 (98) Non-Hispanic 35 (2) Hispanic	Persons with or without parental history of sporadic AD recruited throughout Wisconsin
Total	NA	57 979	NA	NA	NA	NA

Abbreviations: AD, Alzheimer disease; APOE, apolipoprotein E; GWAS, genome-wide association study; HMO, health maintenance organization; LOAD, late-onset Alzheimer disease; MCI, mild cognitive impairment; NA, not applicable; NL, normal cognitive.

For longitudinal data sets (eg, NACC and Framingham Heart Study) that had multiple diagnoses per participant, we assigned each participant a single diagnosis. Each participant without a history of MCI or AD was assigned an NL diagnosis, each participant with a history of MCI and no history of AD was assigned an MCI diagnosis, and each participant with a history of AD and no history of MCI was assigned an AD diagnosis. Participants with a history of both MCI and AD were randomly assigned either an MCI or AD diagnosis. We used the latest examination age for the diagnosis age of participants with NL and the earliest recorded age of MCI or AD for participants with MCI and AD, respectively. With the exception of the FHS data set, no participants were followed up more than 10 years; therefore, our NL diagnosis ages were not significantly skewed toward very old ages. We used these diagnosis assignments to form 3 case-control study groups containing 22 AD-NL, 10 MCI-NL, and 7 AD-MCI data sets.

Statistical Analysis

Meta-analyses of the case-control study groups were conducted using the Mantel-Haenszel fixed-effects method to calculate odds ratios for each sex and APOE genotype, using the APOE ε3/ε3 genotype as the referent. We imputed missing NL data in the ACE, Coalition Against Major Diseases, Translational Genomics Research Institute series 2, and Religious Orders Study and Rush Memory and Aging Project data sets using available NL participant data as follows. The Mann-Whitney *U* test was used to compare the age distributions of participants with normal cognition from each research study, and dissimilar NL participant data was excluded. In particular, we excluded the Alzheimer's Disease Repository Without Borders and Wisconsin Registry for Alzheimer's Prevention data sets because the median age of their participants with NL was relatively young (mid-50s to mid-60s) and that of the Adult Changes in Thought data set was comparatively older (lower 80s). Variations in the total numbers of ε2, ε3, and ε4 alleles of participants with NL were then compared using the χ^2 test of homogeneity to exclude correspondingly heterogeneous data sets. The resultant NL participant data contained men (χ^2 of homogeneity = 0.84) and women (χ^2 of homogeneity = 0.90), with NL diagnoses from the Alzheimer's Disease Neuroimaging Initiative, Australian Imaging, Biomarker and Lifestyle Flagship Study of Aging, NACC, and Washington University, St Louis, data sets, respectively. The participants with NL used for imputation were in Hardy-Weinberg equilibrium (men: $\chi^2 = 3.0$; $P = .39$; women: $\chi^2 = 1.2$; $P = .75$), their ages were normally distributed (men, mean [SD], 73.5 [7.0] years; women, mean [SD], 74.6 [7.1] years), and their APOE genotype frequencies were consistent with those reported for the general population of the United States.[59] Forest plots of the log odds ratios (ORs) for the APOE ε3/ε4 genotype by sex are shown in eFigures 1-3 in the Supplement. Separate meta-analyses were also performed in 3 age ranges (55-65 years, 65-75 years, and 75-85 years).

The meta-analyses were repeated after removing ascertainment-biased studies from the case-control study groups. Community-based studies (ACE, Alzheimer's Disease Repository Without Borders, and Framingham Heart Study) that recruited participants in localized geographic regions and disease-biased studies (National Institute on Aging Late-Onset Alzheimer's Disease Family Study and TGEN2) that recruited participants with family histories of AD were excluded. The Religious Orders Study and Rush Memory and Aging Project were also excluded because we did not have enough information to definitively remove participants with comorbidities from its data set.

Data from each ascertainment-adjusted case-control study group were then pooled together, and logistic regression was used to calculate ORs for each sex and APOE genotype (**Table 2**). For each sex, a continuous age variable and 5 indicator variables (values of 1 or zero) representing the 5 APOE genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε4, and ε4/ε4) were used, with the APOE ε3/ε3 genotype as the referent. We also conducted another pooled analysis where we added a sex indicator variable and 5 additional covariates that were products of the sex variable with each APOE genotype variable to test for sex interactions. The age-dependent curves shown in **Figure 1** were derived by adding several quadratic covariate products to the logistic regression that were created by combining APOE genotype, sex, and age. Because the NACC data set was predominantly larger (48% to 85%) than other data sets in the pooled analysis, we separated it from the pooled data and repeated the analyses without it and exclusively with it. Results of all these analyses are listed in the eMethods and eTables 1-3 in the Supplement for the APOE ε3/ε4 genotype.

Statistical analyses were performed in R, version 3.3.1, using the metafor meta-analysis package, version 1.9-9, along with the glm generalized linear model function (R Programming).[60] Mathematica,[61] version 10.0, was used for curve fitting and plotting. The *P* value level of significance was .05, and *P* values were 2-sided.

Results

From an aggregation of 27 independent research studies with a total of 57 979 participants (Table 1), meta-analyses were performed on 31 340 non-Hispanic white individuals, with clinical diagnoses between ages 55 and 85 years in 3 case-control analyses (**Figure 2**). After excluding ascertainment-biased studies, the data in each analysis were pooled, and ORs for each sex and APOE genotype (Table 2) were calculated. In all case-control analyses, between-study heterogeneity was reduced after the removal of ascertainment-biased study data. However, *P* values from the Tarone[62] test of heterogeneity (Table 2) still detected significant study heterogeneity in the female APOE ε3/ε4 data (OR, 3.31; 95% CI, 3.03-3.61; $P = .03$) and in the APOE ε4/ε4 data (men, OR, 11.7; 95% CI, 9.24-14.7; $P = .02$; women, OR, 9.67; 95% CI, 8.07-11.6; $P < .001$) of the AD-NL analysis. On further investigation (eTable 1 in the Supplement), we found that the heterogeneity in the female APOE ε3/ε4 data was localized to ages 75 to 85 years (OR, 3.28; 95% CI, 2.92-3.68; $P = .003$). This determination was supported after comparing the ORs in that age range from analyses without the NACC data set (OR, 2.67; 95% CI, 2.23-3.21) and with the NACC data set exclusively (OR, 4.12; 95% CI, 3.41-4.98).

Table 2. Age-Adjusted Odds Ratios of Developing AD and MCI for Men and Women Across APOE Genotypes Between the Ages of 55 and 85 Years

APOE Genotype	Sex	Controls, No.	Cases, No.	Odds Ratio (95% CI)	*P* Value	*P* Value for Tarone
AD-NL						
NL[a]	NA	9279	NA	NA	NA	NA
AD[b]	NA	NA	10 485	NA	NA	NA
ε3/ε3	Male	2184	1642	1 [Reference]	NA	NA
	Female	3284	1936	1 [Reference]	NA	NA
ε2/ε2	Male	23	6	0.34 (0.14-0.84)	.02	.24
	Female	23	9	0.69 (0.32-1.51)	.35	.12
ε2/ε3	Male	415	222	0.71 (0.60-0.85)	<.001	.35
	Female	646	199	0.51 (0.43-0.61)	<.001	.07
ε2/ε4	Male	74	115	2.07 (1.54-2.79)	<.001	.82
	Female	129	173	2.28 (1.80-2.88)	<.001	.02
ε3/ε4	Male	867	2002	3.09 (2.79-3.42)	<.001	.53
	Female	1390	2639	3.31 (3.03-3.61)	<.001	.03
ε4/ε4	Male	86	733	11.7 (9.24-14.7)	<.001	.02
	Female	158	809	9.67 (8.07-11.6)	<.001	<.001
MCI-NL						
NL[c]	NA	6471	NA	NA	NA	NA
MCI[d]	NA	NA	5077	NA	NA	NA
ε3/ε3	Male	1407	1378	1 [Reference]	NA	NA
	Female	2329	1092	1 [Reference]	NA	NA
ε2/ε2	Male	12	8	0.68 (0.28-1.68)	.41	>.99
	Female	17	7	0.87 (0.36-2.11)	.76	.91
ε2/ε3	Male	257	247	0.99 (0.82-1.19)	.89	.44
	Female	457	172	0.78 (0.65-0.95)	.01	.46
ε2/ε4	Male	48	74	1.61 (1.11-2.34)	.01	.81
	Female	100	69	1.54 (1.12-2.11)	.007	.008
ε3/ε4	Male	595	893	1.55 (1.36-1.76)	<.001	.26
	Female	1068	777	1.60 (1.43-1.81)	<.001	.66
ε4/ε4	Male	55	187	3.60 (2.64-4.91)	<.001	.56
	Female	126	173	3.25 (2.55-4.15)	<.001	.22
AD-MCI						
MCI[e]	NA	4496	NA	NA	NA	NA
AD[f]	NA	NA	5228	NA	NA	NA
ε3/ε3	Male	1235	892	1 [Reference]	NA	NA
	Female	948	821	1 [Reference]	NA	NA
ε2/ε2	Male	8	2	0.36 (0.08-1.69)	.19	.92
	Female	7	5	0.83 (0.26-2.63)	.75	.98
ε2/ε3	Male	220	122	0.77 (0.61-0.97)	.03	.19
	Female	148	85	0.66 (0.49-0.87)	.004	.93
ε2/ε4	Male	66	63	1.33 (0.93-1.90)	.12	.83
	Female	57	84	1.69 (1.19-2.39)	.003	.38
ε3/ε4	Male	798	1098	1.90 (1.68-2.15)	<.001	.86
	Female	680	1234	2.11 (1.84-2.40)	<.001	.46
ε4/ε4	Male	175	426	3.45 (2.83-4.20)	<.001	.13
	Female	154	396	3.14 (2.54-3.87)	<.001	.77

Abbreviations: AD, Alzheimer disease; APOE, Apolipoprotein E; MCI, mild cognitive impairment; NA, not applicable; NL, normal cognition.

[a] Male and female mean (SD) age, 73.4 (6.4) years and 72.7 (6.7) years, respectively.

[b] Male and female mean (SD) age, 73.6 (7.1) years and 73.7 (7.1) years, respectively.

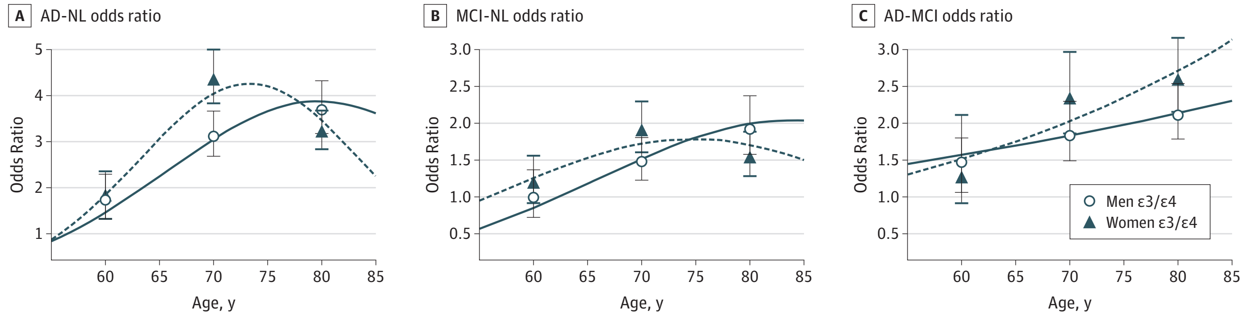
[c] Male and female mean (SD) age, 72.6 (7.2) years and 71.5 (7.5) years, respectively.

[d] Male and female mean (SD) age, 73.1 (7.2) years and 72.6 (7.5) years, respectively.

[e] Male and female mean (SD) age, 73.6 (7.0) years and 73.2 (7.3) years, respectively.

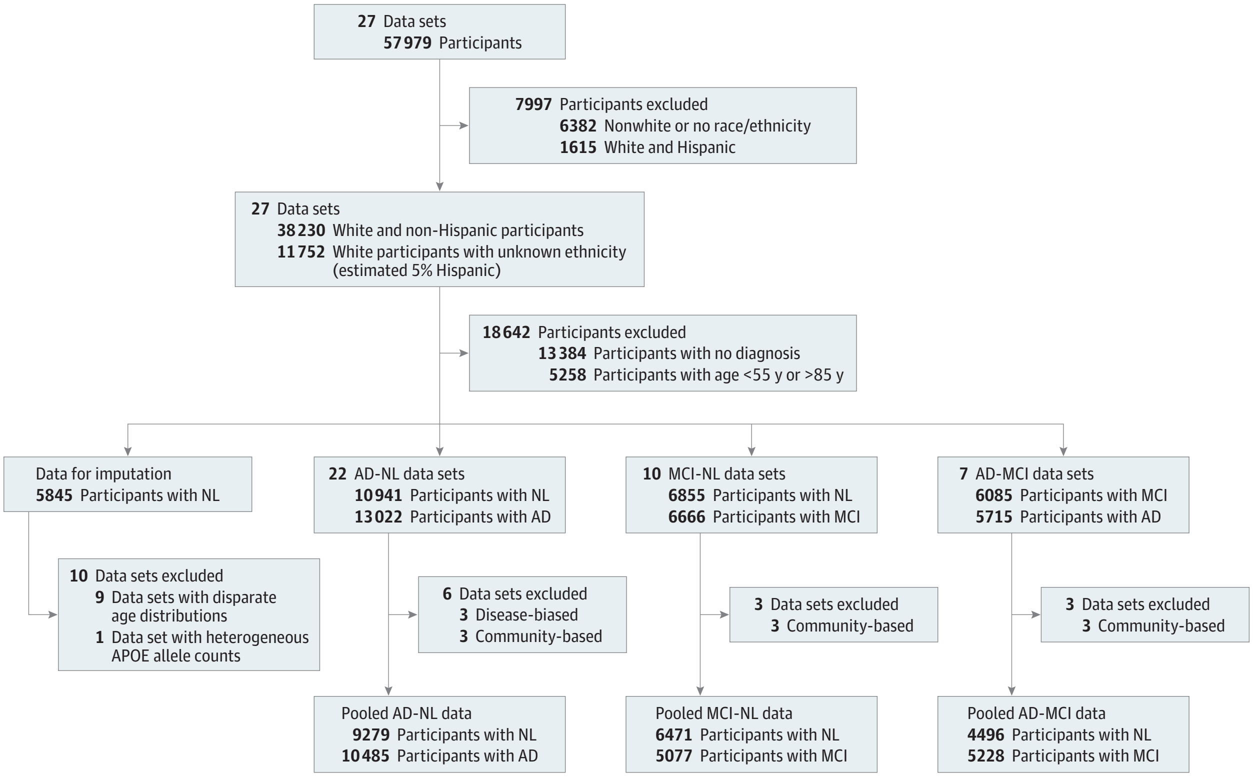
[f] Male and female mean (SD) age, 74.0 (7.5) years and 73.8 (7.7) years, respectively.

Figure 1. Alzheimer Disease (AD) and Mild Cognitive Impairment (MCI) Odds Ratios for Men and Women With APOE ε3/ε4 Genotypes Between the Ages of 55 and 85 Years



Alzheimer disease and MCI risk factors were calculated for men and women between ages 55 and 85 years for each APOE genotype. Age-adjusted odds ratios are listed in Table 2 and shown in Figure 1 as a function of age for the APOE ε3/ε4 genotype. All male odds ratios were calculated relative to men with ε3/ε3, and all female odds ratios relative to women with ε3/ε3. Three conversion cases were considered: (1) developing AD from a cognitively normal (NL) status, (2) developing MCI from an NL status, and (3) transitioning from MCI to AD. Each conversion is labeled AD-NL, MCI-NL, and AD-MCI, respectively, in Table 2 and Figure 1.

Figure 2. PRISMA Flowchart



AD indicates Alzheimer disease; MCI, mild cognitive impairment; NL, normal cognition.

Otherwise, between the ages of 55 and 85 years, the 95% confidence intervals of the ORs calculated from pooled data without the NACC data set overlapped the confidence intervals of the ORs calculated using the NACC data set alone.

As shown in Table 2, men and women with the APOE ε3/ε4 genotype had the same risks of developing AD (men, OR, 3.09; 95% CI, 2.79-3.42; women, OR, 3.31; 95% CI, 3.03-3.61; *P* = .47) between the ages of 55 and 85 years. Men with APOE ε3/ε4 had an increased risk of AD compared with men with ε3/ε3 (*P* < .001). The APOE ε2/ε3 genotype decreased the risk of AD more for women than for men (women, OR, 0.51; 95% CI, 0.43-0.61; men, OR, 0.71; 95% CI, 0.60-0.85; *P* = .01). Men and women with the APOE ε3/ε4 genotype had the same risks of developing MCI between ages 55 and 85 years (men, OR, 1.55; 95% CI, 1.36-1.76; women, OR, 1.60; 95% CI, 1.43-1.81; *P* value = .82).

Odds ratio curves for men and women with the APOE ε3/ε4 genotype are shown in Figure 1 between age 55 and 85 years. The ORs calculated from the pooled data analyses in 3 age ranges (55-65 years, 65-75 years, and 75-85 years) are plotted for each sex, with error bars indicating their 95% confidence intervals. As shown in Figure 1A between ages 65 and 75 years, women with APOE ε3/ε4 had an increased risk of AD compared with men with ε3/ε4 (women, OR, 4.37; 95% CI, 3.82-5.00; men, OR, 3.14; 95% CI, 2.68-3.67; *P* = .002). In Figure 1B, the OR curves suggested that women with APOE ε3/ε4 were at higher risk for developing MCI than men between ages 55 and 70 years, which was confirmed in a separate analysis in that age range (women, OR, 1.43; 95% CI, 1.19-1.73; men, OR, 1.07; 95% CI, 0.87-1.30; *P* = .05). No significant risk differences between men and women for MCI to AD transitions were found in Figure 1C, but the OR curves parallel a previous study that found that APOE ε4 increased the risk of transitioning from MCI to AD between the ages of 70 to 85 years, but not between the ages of 55 to 69 years.[16]

Discussion

When examining the entire age span from 55 to 85 years, men and women with the APOE ε3/ε4 genotype had nearly the same odds of developing MCI and AD, both in comparisons between data sets and in data set aggregation. Notably, women had an increased risk of MCI between ages 55 and 70 years and an increased risk of AD between ages 65 and 75 years. These results are consistent with a previous study that found a significant association between APOE ε4 and cognitive decline between ages 70 and 80 years in women only[24] and with another study that found that episodic memory was more impaired in women with APOE ε3/ε4 than in men with ε3/ε4 between ages 70 and 74 years.[25] Mechanisms that underlie these sex differences may be linked to physiologic changes associated with menopause and estrogen loss that begins at a mean age of 51 years[63] just prior to our risk groups. Studies in animals and humans have reported an interaction between APOE ε4, menopause, and cognitive decline (for a review, see Riedel et al[64]). Furthermore, other evidence suggests that carrying 1 copy of APOE ε4 shifts the age at onset in women, but not in men.[18] Collectively, our findings, along with previous work, warrant further investigation into a likely complex set of risk factors with consideration of sex-specific treatments for cognitive decline and AD. For example, if women are at increased risk for AD at younger ages, it is plausible that treatments for women may need to be initiated earlier, especially in those who carry an APOE ε4 allele. Both men and women with APOE ε3/ε4 had an increased risk of AD compared with men and women with ε3/ε3, respectively. The APOE ε2/ε3 genotype conferred more of a protective effect on women, decreasing their risk of AD more than men. No significant sex-dependent differences were found for transitioning between MCI and AD. Our ORs for developing MCI are consistent with other studies.[6,65]

After adjusting for NL participant differences between AD studies by replacing participants with NL with the data set we used for imputation, there was significant variation of AD risk between data sets; the male and female ε3/ε4 ORs were near 1 for the ACE data set and nearly 7 for the National Institute on Aging Late-Onset Alzheimer's Disease Family Study data set. In retrospect, high ORs were not remarkable for the National Institute on Aging Late-Onset Alzheimer's Disease Family Study, which recruited families with 2 or more affected siblings with AD because family history of AD is an AD risk factor and the probability of carrying a genetic mutation in a recognized AD gene increases with the number of first-degree relatives affected with AD.[66] The lowest ORs tended to be associated with community-based studies (eg, ACE, ARWIBO, and FHS) that ascertained participants from geographically specific cities and suburbs. As shown in eFigure 4 in the Supplement, most data points clustered around the NACC data point; these studies primarily recruited random participants who were unrelated to each other.

These results are notably different from those of Farrer et al,[1] who found that the relative odds of women with ε3/ε4 compared with men with ε3/ε4 for developing AD were about 1.5, and that men with ε3/ε3 and ε3/ε4 had the same AD risks when participants were ascertained from clinics/hospitals and autopsies/brain banks (n = 6305). Many of the participants in their meta-analysis had family histories of AD, they noted differences with population-based studies, and they aggregated participants with early-onset AD. Inclusion of the latter participants could help explain why their AD ORs curves for individuals with ε3/ε4 reached their maxima around ages 60 to 65 years, as opposed to ours, which reached their maxima around ages 73 to 80 years. These results are in closer agreement with studies that have found ε3/ε4 carriers to have a mean age at clinical onset of 76 years, and the risk for developing late-onset AD to occur primarily between ages 60 and 79 years.[26] We note that between the ages of 65 to 75 years, the ORs of women and men with APOE ε3/ε4 differed by a factor of about 1.5, which is consistent with the results of Farrer et al[1] across all ages. Our result that the APOE ε2/ε3 genotype decreased the risk of AD more for women than for men is the opposite of what they found; this is likely owing to the fact that our analysis (n = 1482) used more than 3 times the number of participants than they used (n = 447).

In agreement with previous studies,[1,67] we found that individuals with 2 copies of the APOE ε4 allele were at greater risk for developing AD than individuals with only 1 copy. No significant differences between men and women with ε4/ε4 were seen in their risks for developing AD, which is consistent with the results reported by Farrer et al.[1] Apolipoprotein ε4 homozygotes also had increased risks compared with ε4 heterozygotes for MCI and for transitioning from MCI to AD.

Ascertainment biases are known to modify the true effects of APOE on the risks of developing AD, and they may have played a role in the variations we found between data sets. Men have higher rates of cardiovascular disease and stroke than women, so men who live to old age may be healthier than women of the same age and therefore have lesser risks of developing AD.[68,69] On average, women live longer than men, which makes it difficult to locate older men with AD in sufficient numbers to study. There may be increased study participation rates among individuals with a family history of AD,[70] which is an established risk factor for developing AD.[71-73] Population-based studies can oversample participants from families in areas where widows outnumber widowers.[23] Nonresponders are generally burdened with higher rates of illness than responders to surveys, and they require extra effort to participate.[74] Biases may occur when recruitment and dropout occur continuously throughout studies,[29] or when individuals do not consent to or are not available for genotyping. A notable example of ascertainment bias occurred in a study that compared participants sampled from a research clinic with participants recruited through a health maintenance organization; they found that the research-based cohort contained younger participants, more severe AD cases, and a higher APOE ε4 allele frequency.[75]

Limitations

Variability in the methods used to define AD and MCI across data sets could have affected our results. We relied on the expertise of each data set provider to translate their diagnostic definitions into our general AD and MCI diagnoses independently of other data set providers. Although it would have been preferable to use MCI subtypes (eg, amnestic and nonamnestic), that level of diagnostic detail was mostly unavailable. We could not adjust for known AD risk factors, such as the number of years of education and family history of AD/dementia, because in many data sets that information was not provided. Nor could we account for sex-dependent differences owing to factors such as cigarette smoking, hormonal changes with age, and alcohol use.[76] As previously mentioned, in some data sets the birth dates of participants were rounded to the nearest year, and that limited the accuracy in determining the onset ages of AD and MCI. Finally, we were not able to fully exclude all Hispanic participants from our meta-analysis because in many cases information about race/ethnicity was not collected. Although we believe the percentage of Hispanic participants to be less than 5%, this could have affected our results because the odds of developing AD is different among Hispanic individuals than in white individuals.[1] Considering these limitations, our results should not be generalized beyond white non-Hispanic individuals in North America and Europe. Taken together, limited information on risk factors were not modeled in our analysis owing to our large pooled cohort approach. Of particular note, lifestyle factors, such as lower educational attainment and vascular risk factors, are well-documented contributors to Alzheimer risk[77] and could have influenced our findings.

Conclusions

In this meta-analysis of 27 independent research studies with 58 000 participants, women and men with 1 copy of APOE ε4 did not show a difference in risk of Alzheimer disease across the lifespan of 55 to 85 years. However, these women were at increased risk vs men between ages 65 and 75 years.

ARTICLE INFORMATION

Accepted for Publication: May 10, 2017.

Published Online: August 28, 2017. doi:10.1001/jamaneurol.2017.2188

Author Affiliations: Laboratory of Neuro Imaging, Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Los Angeles (Neu, Pa, Toga); National Alzheimer's Coordinating Center, University of Washington, Seattle (Kukull, Beekly); Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia (Kuzma, Gangadharan, L.-S. Wang); Coalition Against Major Disease, Critical Path Institute, Tucson, Arizona (Romero, Arneric); IRCCS Fatebenefratelli, The National Centre for Alzheimer's Disease, Brescia, Italy (Redolfi, Orlandi, Frisoni); University Hospitals and University of Geneva, Geneva, Switzerland (Frisoni); Department of Anatomy and Neurobiology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts (Au); Department Neurology and Epidemiology, Boston University Schools of Medicine and Public Health, Boston, Massachusetts (Au); Framingham Heart Study, Boston University Schools of Medicine and Public Health, Boston, Massachusetts (Au); Department of Neurology, Framingham Heart Study, Boston University School of Medicine, Boston, Massachusetts (Devine, Auerbach); Research Center and Memory Clinic, Fundació ACE, Institut Català de Neurociències Aplicades, Barcelona, Spain (Espinosa, Boada, Ruiz); University of Wisconsin School of Medicine and Public Health, Madison (Johnson, Koscik); Department of Medical Imaging and Radiological Sciences, Chang Gung University, Taoyuan City, Taiwan (J.-J. Wang); Neuroscience Research Center, Chang Gung Memorial Hospital at Linkou, Taoyuan City, Taiwan (J.-J. Wang); Department of Neurology, Chang Gung Memorial Hospital at Linkou, Taoyuan City, Taiwan (Hsu); Dementia Center, Chang Gung Memorial Hospital at Linkou, Taoyuan City, Taiwan (Hsu); Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital at Linkou, Taoyuan City, Taiwan (Chen); Department of Medical Imaging and Intervention, Keelung Branch, Chang Gung Memorial Hospital, Keelung City, Taiwan (Chen).

Author Contributions: Dr Neu had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.
Concept and design: Neu, Pa, Romero, Toga.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Neu, Gangadharan, Romero, Hsu, Chen, Toga.
Critical revision of the manuscript for important intellectual content: Neu, Pa, Kukull, Beekly, Kuzma, L. Wang, Romero, Arneric, Redolfi, Orlandi, Frisoni, Au, Devine, Auerbach, Espinosa, Boada, Ruiz, Johnson, Koscik, J. Wang, Toga.
Statistical analysis: Neu, Pa, Romero, J. Wang, Toga.
Obtained funding: Au, Toga.
Administrative, technical, or material support: Pa, Kukull, Beekly, Kuzma, L. Wang, Arneric, Redolfi, Orlandi, Au, Devine, Auerbach, Boada, Ruiz, Johnson, Koscik, J. Wang, Chen, Toga.
Supervision: Romero, Frisoni, Devine, Espinosa, Boada, Toga.

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the Global Alzheimer's Association Interactive Network initiative of the Alzheimer's Association (GAAIN-14-244631) and National Institutes of Health grants U54-EB020406 and P41-EB015922. Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (National Institutes of Health grant U01 AG024904) and Department of Defense Alzheimer's Disease Neuroimaging Initiative (Department of Defense award W81XWH-12-2-0012). The Alzheimer's Disease Neuroimaging Initiative is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc; Biogen; Bristol- Myers Squibb Company; CereSpir Inc; Cogstate; Eisai Inc; Elan Pharmaceuticals Inc; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech Inc; Fujirebio; GE Healthcare; IXICO Ltd; Janssen Alzheimer Immunotherapy Research and Development LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck and Co Inc; Meso Scale Diagnostics LLC; NeuroRx Research; Neuro-track Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc; Piramal Imaging; Servier; Takeda Pharmaceutical Company;

and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health. The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. Alzheimer's Disease Neuroimaging Initiative data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Data used in the preparation of this article were obtained from the Australian Imaging Biomarkers and Lifestyle (ABIL) flagship study of aging funded by the Commonwealth Scientific and Industrial Research Organization which was made available at the ADNI database. The AIBL researchers are listed at http://www.aibl.csiro.au. The National Alzheimer Coordinating Center database is funded by grant U01 AG016976 from the National Institute of Aging. National Alzheimer Coordinating Center data are contributed by the National Institute of Aging–funded Alzheimer's Disease Cooperative Studies: P30 AG019610 (Principal Investigator [PI], Eric Reiman, MD), P30 AG013846 (PI, Neil Kowall, MD), P50 AG008702 (PI, Scott Small, MD), P50 AG025688 (PI, Allan Levey, MD, PhD), P50 AG047266 (PI, Todd Golde, MD, PhD), P30 AG010133 (PI, Andrew Saykin, PsyD), P50 AG005146 (PI, Marilyn Albert, PhD), P50 AG005134 (PI, Bradley Hyman, MD, PhD), P50 AG016574 (PI, Ronald Petersen, MD, PhD), P50 AG005138 (PI, Mary Sano, PhD), P30 AG008051 (PI, Steven Ferris, PhD), P30 AG013854 (PI, M. Marsel Mesulam, MD), P30 AG008017 (PI, Jeffrey Kaye, MD), P30 AG010161 (PI, David Bennett, MD), P50 AG047366 (PI, Victor Henderson, MD, MS), P30 AG010129 (PI, Charles DeCarli, MD), P50 AG016573 (PI, Frank LaFerla, PhD), P50 AG016570 (PI, Marie-Francoise Chesselet, MD, PhD), P50 AG005131 (PI, Douglas Galasko, MD), P50 AG023501 (PI, Bruce Miller, MD), P30 AG035982 (PI, Russell Swerdlow, MD), P30 AG028383 (PI, Linda Van Eldik, PhD), P30 AG010124 (PI, John Trojanowski, MD, PhD), P50 AG005133 (PI, Oscar Lopez, MD), P50 AG005142 (PI, Helena Chui, MD), P30 AG012300 (PI, Roger Rosenberg, MD), P50 AG005136 (PI, Thomas Montine, MD, PhD), P50 AG033514 (PI, Sanjay Asthana, MD, FRCP), P50 AG005681 (PI, John Morris, MD), and P50 AG047270 (PI, Stephen Strittmatter, MD, PhD). Data for this study were prepared, archived, and distributed by grant U24-AG041689-01 from the National Institute on Aging Alzheimer's Disease Data Storage Site at the University of Pennsylvania, funded by the National Institute on Aging. The Alzheimer's Disease Genetics Consortium supported the collection of samples used in this study through National Institutes of Aging grants U01AG032984 and RC2AG036528. Samples from the National Cell Repository for Alzheimer's Disease, which receives government support under cooperative agreement grant U24 AG21886 awarded by the National Institutes of Aging, were used in this study.
The studies included were supported by grants U01 AG006781, U01 HG004610, U01 HG006375, and U01 HG008657 for ACT; P30AG10161 and R01AG15819 for ROS, R01AG17917 for MAP; U24 AG026395, U24 AG026390, and R01AG041797 for NIA-LOAD; R01AG09029 and R01AG025259 for MIRAGE; R01 AG032990, U01 AG046139, R01 NS080820, RF1 AG051504 and P50 AG016574 for Mayo; R01 AG027944, R01 AG028786, R01 AG019085, the Alzheimer's Association (IIRG09133827), and the BrightFocus Foundation (A2011048) for University of Miami, P50 AG005138, P01 AG002219 for Mount Sinai School of Medicine, R01 AG019085 for Vanderbilt University; P50 AG005681, P01 AG03991, P01 AG026276 for Washington University St. Louis; P50 AG005133, AG030653, AG041718, AG07562, AG02365 for University of Pittsburgh. The TGen series was also funded by National Institutes of Aging grant AG041232, The Banner Alzheimer's Foundation, The Johnnie B. Byrd Sr Alzheimer's Institute, the Medical Research Council, and the state of Arizona and also includes samples from the following sites: Newcastle Brain Tissue Resource (funding via the Medical Research Council, local NHS trusts and Newcastle University), MRC London Brain Bank for Neurodegenerative Diseases (funding via the Medical Research Council),South West Dementia Brain Bank (funding via numerous sources including the Higher Education Funding Council for England, Alzheimer's Research Trust, BRACE as well as North Bristol National Health Services Trust Research and Innovation Department, The Netherlands Brain Bank (funding via numerous sources including Stichting MS Research, Brain Net Europe, Hersenstichting Nederland Breinbrekend Werk, International Parkinson Fonds, and Internationale Stiching Alzheimer Onderzoek), Institut de Neuropatologia, Servei Anatomia Patologica, and Universitat de Barcelona. Data used in preparation of this article were obtained from the Coalition Against Major Diseases database. A complete listing of Coalition Against Major Diseases members can be found at http://c-path.org/programs/camd/. Funding of the Coalition Against Major Diseases database is made possible by membership dues and by grant 1U18FD005320 from the US Food and Drug Administration's Critical Path Public Private Partnerships Grant Program. ARWIBO, EDSD, and PharmaCOG (alias E-ADNI) data used in the preparation of this article were obtained from NeuGRID4You initiative (http://www.neugrid4you.eu) funded by grant 283562 from the European Commission under grant agreement. Data used in this study were supported by the Framingham Heart Study's National Heart, Lung, and Blood Institute contract (N01-HC-25195), by grants R01-AG016495, R01-AG008122, R01-AG033040 from the National Institute on Aging, and by grant R01-NS017950 from the National Institute of Neurological Disorders and Stroke. Fundació ACE collaborates with the Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, and is one of the participating centers of the Dementia Genetics Spanish Consortium. Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas is an Instituto de Salud Carlos III ISCIII Project. Dr Ruiz is supported by grant PI13/02434 from Acción Estratégica en Salud, Instituto de Salud Carlos III (ISCIII), Ministerio de Economía y Competitividad, Spain. Genetic Research project at Fundació ACE is funded by Fundación Bancaria La Caixa (Barcelona, Spain), GRIFOLS SA and intramural funds. Data used in this study were supported by the National Institutes of Health grant R01-AG027161. Dr Wang received support from Health Ageing Research Center, ChangGung University, and Center for Advanced Molecular Imaging and Translation, Chang Gung Memorial Hospital, Linkou. This work was supported by grants UL1TR001855 and UL1TR000130 from the National Center for Advancing Translational Science of the US National Institutes of Health.

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

REFERENCES

1. Farrer LA, Cupples LA, Haines JL, et al; APOE and Alzheimer Disease Meta Analysis Consortium. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA*. 1997;278(16):1349-1356.

2. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy [published correction appears in *Nat Rev Neurol*. 2013. doi:10.1038/nmeurol.2013.32]. *Nat Rev Neurol*. 2013;9(2):106-118.

3. Ungar L, Altmann A, Greicius MD. Apolipoprotein E, gender, and Alzheimer's disease: an overlooked, but potent and promising interaction. *Brain Imaging Behav*. 2014;8(2):262-273.

4. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med*. 2014;275(3):214-228.

5. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol*. 2003;60(10):1394-1399.

6. Tervo S, Kivipelto M, Hänninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. *Dement Geriatr Cogn Disord*. 2004;17(3):196-203.

7. Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. *Neurology*. 2006;66(6):828-832.

8. Boyle PA, Buchman AS, Wilson RS, Kelly JF, Bennett DA. The APOE ε4 allele is associated with incident mild cognitive impairment among community-dwelling older persons. *Neuroepidemiology*. 2010;34(1):43-49.

9. Barabash A, Marcos A, Ancín I, et al. APOE, ACT and CHRNA7 genes in the conversion from amnestic mild cognitive impairment to Alzheimer's disease. *Neurobiol Aging*. 2009;30(8):1254-1264.

10. Xu WL, Caracciolo B, Wang HX, Santoni G, Winblad B, Fratiglioni L. Accelerated progression from mild cognitive impairment to dementia among APOE ε4ε4 carriers. *J Alzheimers Dis*. 2013;33(2):507-515.

11. Brainerd CJ, Reyna VF, Petersen RC, et al. The apolipoprotein E genotype predicts longitudinal transitions to mild cognitive impairment but not to Alzheimer's dementia: findings from a nationally representative study. *Neuropsychology*. 2013;27(1):86-94.

12. Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *JAMA*. 1995;273(16):1274-1278.

13. Samaranch L, Cervantes S, Barabash A, et al. The effect of MAPT H1 and APOE ε4 on transition from mild cognitive impairment to dementia. *J Alzheimers Dis*. 2010;22(4):1065-1071.

14. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Berry-Kravis E, Bennett DA. The apolipoprotein E ϵ4 allele and incident Alzheimer's disease in persons with mild cognitive impairment. *Neurocase*. 2005;11(1):3-7.

15. DeCarli C, Mungas D, Harvey D, et al. Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. *Neurology*. 2004;63(2):220-227.

16. Devanand DP, Pelton GH, Zamora D, et al. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with mild cognitive impairment. *Arch Neurol*. 2005;62(6):975-980.

17. Suri S, Heise V, Trachtenberg AJ, Mackay CE. The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE ε2. *Neurosci Biobehav Rev*. 2013;37(10 Pt 2):2878-2886.

18. Payami H, Montee KR, Kaye JA, et al. Alzheimer's disease, apolipoprotein E4, and gender. *JAMA*. 1994;271(17):1316-1317.

19. Payami H, Zareparsi S, Montee KR, et al. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: a possible clue to the higher incidence of Alzheimer disease in women. *Am J Hum Genet*. 1996;58(4):803-811.

20. Farrer LA, Cupples LA, van Duijn CM, et al. Apolipoprotein E genotype in patients with Alzheimer's disease: implications for the risk of dementia among relatives. *Ann Neurol*. 1995;38(5):797-808.

21. Martinez M, Campion D, Brice A, et al. Apolipoprotein E ϵ4 allele and familial aggregation of Alzheimer disease. *Arch Neurol*. 1998;55(6):810-816.

22. Breitner JC, Wyse BW, Anthony JC, et al. APOE-ε4 count predicts age when prevalence of AD increases, then declines: the Cache County Study. *Neurology*. 1999;53(2):321-331.

23. Molero AE, Pino-Ramírez G, Maestre GE. Modulation by age and gender of risk for Alzheimer's disease and vascular dementia associated with the apolipoprotein E-ε4 allele in Latin Americans: findings from the Maracaibo Aging Study. *Neurosci Lett*. 2001;307(1):5-8.

24. Mortensen EL, Høgh P. A gender difference in the association between APOE genotype and age-related cognitive decline. *Neurology*. 2001;57(1):89-95.

25. Lehmann DJ, Refsum H, Nurk E, et al. Apolipoprotein E ε4 and impaired episodic memory in community-dwelling elderly people: a marked sex difference. The Hordaland Health Study. *J Neurol Neurosurg Psychiatry*. 2006;77(8):902-908.

26. Bickeböller H, Campion D, Brice A, et al. Apolipoprotein E and Alzheimer disease: genotype-specific risks by age and sex. *Am J Hum Genet*. 1997;60(2):439-446.

27. Combarros O, Leno C, Oterino A, et al. Gender effect on apolipoprotein E ε4 allele-associated risk for sporadic Alzheimer's disease. *Acta Neurol Scand*. 1998;97(1):68-71.

28. Slooter AJ, 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(7):964-968.

29. Beydoun MA, Boueiz A, Abougergi MS, et al. Sex differences in the association of the apolipoprotein E epsilon 4 allele with incidence of dementia, cognitive impairment, and decline. *Neurobiol Aging*. 2012;33(4):720-731.e4.

30. Altmann A, Tian L, Henderson VW, Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75(4):563-573.

31. The Global Alzheimer's Association Interactive Network. http://www.gaain.org. Accessed May 7, 2017.

32. Neu SC, Crawford KL, Toga AW. Sharing data in the global alzheimer's association interactive network. *Neuroimage*. 2016;124(Pt B):1168-1174.

33. Toga AW, Neu SC, Bhatt P, Crawford KL, Ashish N. The Global Alzheimer's Association Interactive Network. *Alzheimers Dement*. 2016;12(1):49-54.

34. Boada M, Tárraga L, Hernández I, et al; Fundació ACE Alzheimer Research Center and Memory Clinic. Design of a comprehensive Alzheimer's disease clinic and research center in Spain to meet critical patient and family needs. *Alzheimers Dement*. 2014;10(3):409-415.

35. Weiner MW, Aisen PS, Jack CR Jr, et al; Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's disease neuroimaging initiative: progress report and future plans. *Alzheimers Dement*. 2010;6(3):202-11.e7.

36. Ellis KA, Bush AI, Darby D, et al; AIBL Research Group. The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *Int Psychogeriatr*. 2009;21(4):672-687.

37. Frisoni GB, Prestia A, Zanetti O, et al. Markers of Alzheimer's disease in a population attending a memory clinic. *Alzheimers Dement*. 2009;5(4):307-317.

38. Galluzzi S, Testa C, Boccardi M, et al. The Italian Brain Normative Archive of structural MR scans: norms for medial temporal atrophy and white matter lesions. *Aging Clin Exp Res*. 2009;21(4-5):266-276.

39. Neville J, Kopko S, Broadbent S, et al; Coalition Against Major Diseases. Development of a unified clinical trial database for Alzheimer's disease. *Alzheimers Dement*. 2015;11(10):1212-1221.

40. Teipel SJ, Wegrzyn M, Meindl T, et al; EDSD study group. Anatomical MRI and DTI in the diagnosis of Alzheimer's disease: a European multicenter study. *J Alzheimers Dis*. 2012;31(s3)(suppl 3):S33-S47.

41. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. *Ann N Y Acad Sci*. 1963;107(2):539-556.

42. Beekly DL, Ramos EM, Lee WW, et al; NIA Alzheimer's Disease Centers. The National Alzheimer's Coordinating Center (NACC) database: the uniform data set. *Alzheimer Dis Assoc Disord*. 2007;21(3):249-258.

43. Partch AB, Laufer D, Valladares O, et al. Nia genetics of Alzheimer's disease data storage site (NIAGADS): 2015 update. *Alzheimers Dement*. 2015;11(7):362.

44. Kamboh MI, Minster RL, Demirci FY, et al. Association of CLU and PICALM variants with Alzheimer's disease. *Neurobiol Aging*. 2012;33(3):518-521.

45. Reiman EM, Webster JA, Myers AJ, et al. GAB2 alleles modify Alzheimer's risk in APOE epsilon4 carriers. *Neuron*. 2007;54(5):713-720.

46. Caselli RJ, Reiman EM, Locke DE, et al. Cognitive domain decline in healthy apolipoprotein E ε4 homozygotes before the diagnosis of mild cognitive impairment. *Arch Neurol*. 2007;64(9):1306-1311.

47. Webster JA, Gibbs JR, Clarke J, et al; NACC-Neuropathology Group. Genetic control of human brain transcript expression in Alzheimer disease. *Am J Hum Genet*. 2009;84(4):445-458.

48. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002;59(2):198-205.

49. Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. *Neurology*. 2005;64(5):834-841.

50. Bennett DA, Schneider JA, Buchman AS, Mendes de Leon C, Bienias JL, Wilson RS. The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology*. 2005;25(4):163-175.

51. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69(24):2197-2204.

52. Green RC, Cupples LA, Go R, et al; MIRAGE Study Group. Risk of dementia among white and African American relatives of patients with Alzheimer disease. *JAMA*. 2002;287(3):329-336.

53. Lee JH, Cheng R, Graff-Radford N, Foroud T, Mayeux R; National Institute on Aging Late-Onset Alzheimer's Disease Family Study Group. Analyses of the national institute on aging late-onset alzheimer's disease family study: implication of additional loci. *Arch Neurol*. 2008;65(11):1518-1526.

54. Kukull WA, Higdon R, Bowen JD, et al. Dementia and Alzheimer disease incidence: a prospective cohort study. *Arch Neurol*. 2002;59(11):1737-1746.

55. Beecham GW, Martin ER, Li YJ, et al. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am J Hum Genet*. 2009;84(1):35-43.

56. Carrasquillo MM, Zou F, Pankratz VS, et al. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. *Nat Genet*. 2009;41(2):192-198.

57. Galluzzi S, Marizzoni M, Babiloni C, et al; PharmaCog Consortium. Clinical and biomarker profiling of prodromal Alzheimer's disease in workpackage 5 of the Innovative Medicines

Initiative PharmaCog project: a 'European ADNI study'. *J Intern Med*. 2016;279(6):576-591.

58. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. *J Geriatr Psychiatry Neurol*. 2005;18(4):245-249.

59. Raber J, Huang Y, Ashford JW. ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol Aging*. 2004;25(5):641-650.

60. The R project for statistical computing. http://www.r-project.org. Accessed May 8, 2017.

61. Wolfram Mathematica. http://www.wolfram.com/mathematica. Accessed May 8, 2017.

62. Tarone RE. On heterogeneity tests based on efficient scores. *Biometrika*. 1985;72(1):91-95.

63. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas*. 1992;14(2):103-115.

64. Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: triad of risk of Alzheimer's disease. *J Steroid Biochem Mol Biol*. 2016;160:134-147.

65. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, Verhey FR, Visser PJ. Predictive value of APOE-ε4 allele for progression from MCI to AD-type dementia: a meta-analysis. *J Neurol Neurosurg Psychiatry*. 2011;82(10):1149-1156.

66. Loy CT, Schofield PR, Turner AM, Kwok JB. Genetics of dementia. *Lancet*. 2014;383(9919):828-840.

67. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet*. 2007;39(1):17-23.

68. Chêne G, Beiser A, Au R, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement*. 2015;11(3):310-320.

69. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. *Stroke*. 2009;40(4):1082-1090.

70. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? *Am J Epidemiol*. 2001;153(2):132-136.

71. Fratiglioni L, Ahlbom A, Viitanen M, Winblad B. Risk factors for late-onset Alzheimer's disease: a population-based, case-control study. *Ann Neurol*. 1993;33(3):258-266.

72. Mayeux R, Sano M, Chen J, Tatemichi T, Stern Y. Risk of dementia in first-degree relatives of patients with Alzheimer's disease and related disorders. *Arch Neurol*. 1991;48(3):269-273.

73. Lautenschlager NT, Cupples LA, Rao VS, et al. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? *Neurology*. 1996;46(3):641-650.

74. Norton MC, Breitner JC, Welsh KA, Wyse BW. Characteristics of nonresponders in a community survey of the elderly. *J Am Geriatr Soc*. 1994;42(12):1252-1256.

75. Tsuang D, Kukull W, Sheppard L, et al. Impact of sample selection on APOE epsilon 4 allele frequency: a comparison of two Alzheimer's disease samples. *J Am Geriatr Soc*. 1996;44(6):704-707.

76. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol*. 2014;6:37-48.

77. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10(9):819-828.