Population-specific effects of APOE in NACC

Introduction

In their 1997 study published in JAMA, Farrer and colleagues investigated the association between APOE genotype and Alzheimer's disease (AD), and how age, sex, and ethnicity may influence this association. The study found that the APOE e4 allele was associated with an increased risk of AD in Caucasian subjects, while the e2 allele was associated with a reduced risk. Interestingly, the association between APOE e4 and AD was weaker in African Americans and Hispanics compared to Caucasians, but stronger in Japanese participants (Table 1; Figure 1).

The participants in the study were enrolled from various sources, including community/population-based studies, clinic/hospital-based studies, and autopsy/brain bank-based studies. The case patients were diagnosed with definite or probable AD, while the controls were free of neurodegenerative and neuropsychiatric illnesses. Participants with ADAD mutations or co-morbid pathology were excluded from the study. Logistic regression models were used to assess the influence of APOE, sex, and age on the odds of developing AD. Age at onset of AD among cases and age at last visit among controls were used as the age variable.

While the study reported population differences in the effect of APOE genotype on the risk of AD, no statistical analysis was conducted to formally test this. Here we used Fishzer's Z score method (eq 1; Zhou et al 2019) to compare the reported beta coefficients and standard errors between each population to determine if they were statistically different from each other (Figure 1). This method allowed for a more rigorous analysis of the population differences in the APOE-AD association reported in the study. Additionaly, we sought to replicate the oringal findings using the National Alzheimer's Disease Co-ordinatings Uniform Dataset.

$$z = (\beta 1 - \beta 2)/sqrt(SE1^2 + SE^2) \quad (1)$$

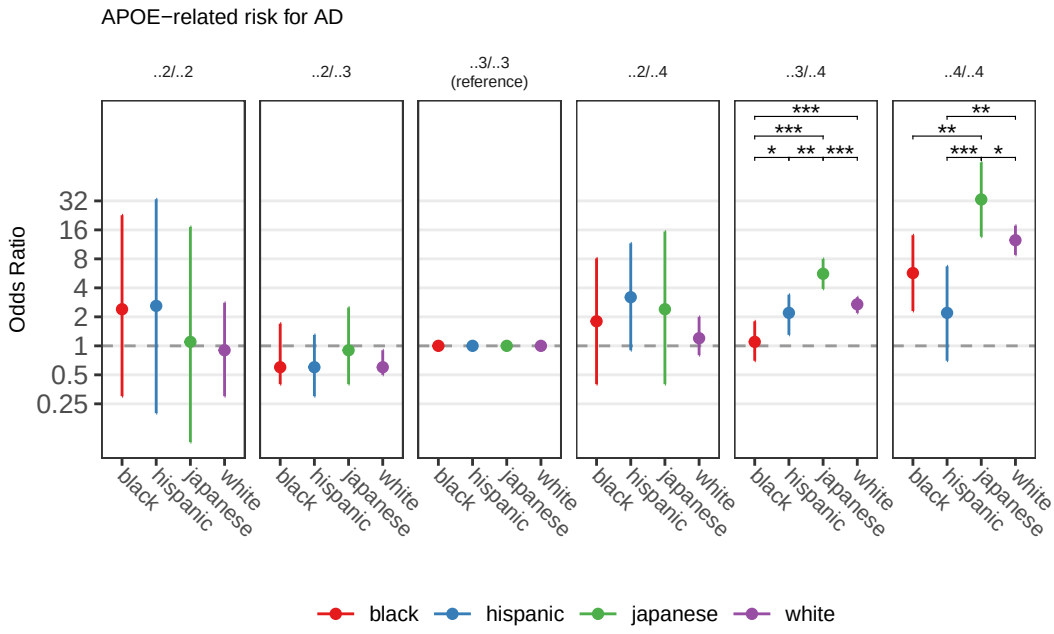
Table 1: Affect of APOE genotype on AD risk r

	White, n = 4858	Black, n = 474

apoe	Case Frq	Ctrl Frq	N	Effect	Case Frq	Ctrl Frq	N	Effect
3/ 3 (reference)	36.4	60.9	2683	1	36.2	50.4	206	1
2/ 2	0.2	0.8	36	0.9 (0.3, 2.8)	1.7	0.8	6	2.4 (0.3, 22.7)
2/ 3	4.8	12.7	568	0.6 (0.5, 0.9)	9.8	12.9	54	0.6 (0.4, 1.7)
2/ 4	2.6	2.6	152	1.2 (0.8, 2)	2.1	2.1	10	1.8 (0.4, 8.1)
3/ 4	41.1	21.3	1226	2.7 (2.2, 3.2)	37.9	31.8	164	1.1 (0.7, 1.8)
4/ 4	14.8	1.8	193	12.5 (8.8, 17.7)	12.3	2.1	34	5.7 (2.3, 14.1)

Using the Fisher's z score method, we observed population-based differences in the effect of the e4 homozygous genotype on the risk of developing AD. Specifically, we found that Japansese carriers of the e4/e4 allele had a higher risk of developing AD compared to African Americans, Hispanics, and White populations. In contrast, the e4/e4 allele was associated with a lower risk of developing AD in Hispanic populations compared to White populations.

Moreover, the e3/e4 allele was found to be associated with increased odds of developing AD in Japanese populations compared to White, Black, and Hispanic populations. In contrast, the e3/e4 allele was associated with a lower risk of developing AD in Black populations compared to Hispanic and White populations.



NACC UDS

We conducted a replication study of the findings reported in Farrer et al 1997, using data from the National Alzheimer's Coordinating Center's Uniform Dataset (NACC UDS). The dataset included 43780 participants at last visit, including participants reported as NLW (n = 32,321), Black (n = 5,470), Latinx (n = 2,308), Asian (n = 1,173), or other (n = 2,508) race/ethnicity.

Participants who met any of the following exclusion criteria were not included in the analysis:

- Age < 55: 1739
- American Indian or Alaska Native, Multiracial, uknown: 2382
- Dominantly inherited AD mutation: 112
- Dominantly inherited FTD mutation: 179
- Cognitive impairment not due to MCI: 1584
- Primary diagnosis is not ADRD:3694
- Missing APOE genotype:19719
- Missing age of onset: 1241

Table 2: Table 1 NACC Cohort Characteristics

Characteristic	**N**	**NHW**, N = 15,950	**Asian**, N = 571	**Black**, N = 2,197	**Hispanic**, N = 923
SEX	19,641				
Male		7,298 (46%)	231 (40%)	581 (26%)	313 (34%)
Female		8,652 (54%)	340 (60%)	1,616 (74%)	610 (66%)
NACCAGE	19,641	77 (10)	75 (10)	76 (9)	76 (9)
aoo	19,641	73 (10)	71 (9)	74 (9)	72 (9)
apoe_geno	19,641				
e3/e3		7,894 (49%)	346 (61%)	892 (41%)	550 (60%)
e2+		1,371 (8.6%)	64 (11%)	272 (12%)	47 (5.1%)
e2/e4		376 (2.4%)	8 (1.4%)	109 (5.0%)	6 (0.7%)
e3/e4		5,135 (32%)	130 (23%)	755 (34%)	283 (31%)
e4/e4		1,174 (7.4%)	23 (4.0%)	169 (7.7%)	37 (4.0%)
EDUC	19,641	16.48 (7.26)	17.77 (12.92)	14.62 (6.06)	13.07 (8.54)
CDRSUM	19,641	4.7 (5.9)	3.6 (4.9)	3.3 (5.2)	4.6 (5.9)
NACCUDSD	19,641				
CU		6,604 (41%)	263 (46%)	1,208 (55%)	384 (42%)
MCI		2,009 (13%)	92 (16%)	292 (13%)	155 (17%)
ADRD		7,337 (46%)	216 (38%)	697 (32%)	384 (42%)
NACCETPR	19,641				
AD		7,271 (46%)	238 (42%)	835 (38%)	458 (50%)
LBD		692 (4.3%)	14 (2.5%)	31 (1.4%)	22 (2.4%)

Characteristic N	**NHW**, N = 15,950	**Asian**, N = 571	**Black**, N = 2,197	**Hispanic**, N = 923
FTLD	1,014 (6.4%)	24 (4.2%)	14 (0.6%)	20 (2.2%)
VCID	369 (2.3%)	32 (5.6%)	109 (5.0%)	39 (4.2%)
CU	6,604 (41%)	263 (46%)	1,208 (55%)	384 (42%)

Stratified models

Logistic regression models were used to examine the effect of APOE genotype on ADRD, stratified by reported race/ethnicity and adjusted for age and sex. In addition to examining the association between APOE genotype and ADRD in different racial/ethnic groups, we used Fisher's z score method to formally test whether the effect sizes of APOE on ADRD differed across racial/ethnic groups. We compared the reported beta coefficients and standard errors for APOE in each racial/ethnic group to determine if they were statistically different from each other. Age at onset of ADRD among cases and age at last visit among controls was used as the age variable. The following outcomes were examined:

- Cognitivly impaired (MCI and dementia) due ADRD vs controls
- Dementia due to ADRD vs controls
- Cognitivly impaired (MCI and AD) due AD vs controls
- Dementia due to AD vs controls

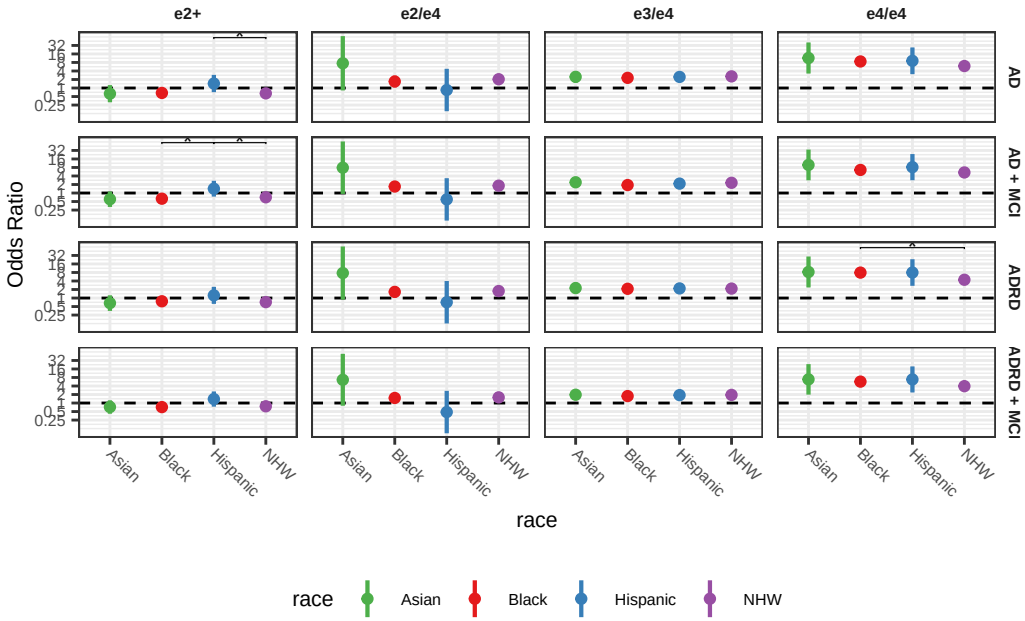
In our analysis of the NACC UDS dataset, we found significant associations between APOE genotype and risk of Alzheimer's disease across different racial and ethnic populations. Specifically, we observed that the e3/e4 allele was consistently associated with increased risk of AD across all four populations studied. The e2/e4 allele, on the other hand, was found to be associated with increased risk in all populations except for Hispanics. Finally, we observed that carriers of the e2+ allele had a lower risk of AD only in non-Hispanic White and Black populations.

	term	effect	p.value
ADRD + MCI			
NHW	e2+	0.77 (0.68, 0.86)	1.53×10^{-5}
NHW	e2/e4	1.6 (1.3, 2)	3.50×10^{-5}
NHW	e3/e4	1.9 (1.8, 2.1)	6.12×10^{-65}
NHW	e4/e4	3.9 (3.3, 4.7)	2.02×10^{-57}
Asian	e2+	0.72 (0.42, 1.2)	0.246
Asian	e2/e4	6.6 (0.8, 55)	0.079
Asian	e3/e4	2 (1.3, 3)	0.002
Asian	e4/e4	6.9 (2, 24)	0.002
Black	e2+	0.72 (0.54, 0.97)	0.029

Black	e2/e4	1.5 (1, 2.3)	0.045
Black	e3/e4	1.8 (1.4, 2.1)	2.32×10^{-8}
Black	e4/e4	5.7 (3.8, 8.5)	1.08×10^{-17}
Hispanic	e2+	1.4 (0.75, 2.6)	0.304
Hispanic	e2/e4	0.48 (0.085, 2.7)	0.404
Hispanic	e3/e4	1.9 (1.4, 2.6)	3.49×10^{-5}
Hispanic	e4/e4	6.8 (2.4, 20)	3.89×10^{-4}
ADRD			
NHW	e2+	0.72 (0.63, 0.82)	1.55×10^{-6}
NHW	e2/e4	1.8 (1.4, 2.2)	1.43×10^{-6}
NHW	e3/e4	2.2 (2, 2.3)	4.35×10^{-77}
NHW	e4/e4	4.4 (3.7, 5.3)	3.23×10^{-64}
Asian	e2+	0.66 (0.35, 1.2)	0.203
Asian	e2/e4	7.6 (0.88, 67)	0.066
Asian	e3/e4	2.3 (1.4, 3.5)	4.64×10^{-4}
Asian	e4/e4	8.3 (2.4, 29)	9.76×10^{-4}
Black	e2+	0.77 (0.54, 1.1)	0.134
Black	e2/e4	1.6 (1, 2.6)	0.032
Black	e3/e4	2.1 (1.7, 2.7)	5.30×10^{-11}
Black	e4/e4	7.9 (5.2, 12)	2.27×10^{-22}
Hispanic	e2+	1.2 (0.62, 2.5)	0.539
Hispanic	e2/e4	0.71 (0.13, 4)	0.697
Hispanic	e3/e4	2.2 (1.6, 3)	2.40×10^{-6}
Hispanic	e4/e4	8 (2.7, 24)	1.72×10^{-4}
AD + MCI			
NHW	e2+	0.71 (0.62, 0.81)	3.83×10^{-7}
NHW	e2/e4	1.8 (1.5, 2.3)	2.04×10^{-7}
NHW	e3/e4	2.3 (2.1, 2.5)	1.71×10^{-93}
NHW	e4/e4	5.3 (4.5, 6.3)	1.38×10^{-82}
Asian	e2+	0.6 (0.32, 1.1)	0.116
Asian	e2/e4	7.9 (0.93, 66)	0.058
Asian	e3/e4	2.4 (1.5, 3.7)	1.18×10^{-4}
Asian	e4/e4	9.8 (2.8, 34)	3.38×10^{-4}
Hispanic	e2+	1.4 (0.75, 2.7)	0.284
Hispanic	e2/e4	0.6 (0.11, 3.3)	0.556
Hispanic	e3/e4	2.1 (1.6, 2.9)	1.74×10^{-6}
Hispanic	e4/e4	8.2 (2.8, 24)	1.06×10^{-4}
Black	e2+	0.63 (0.45, 0.88)	0.006
Black	e2/e4	1.7 (1.1, 2.6)	0.013
Black	e3/e4	1.9 (1.5, 2.4)	1.32×10^{-9}

Black	e4/e4	6.5 (4.4, 9.8)	1.62×10^{-19}
AD			
NHW	e2+	0.65 (0.56, 0.76)	3.50×10^{-8}
NHW	e2/e4	2 (1.6, 2.6)	3.83×10^{-9}
NHW	e3/e4	2.6 (2.4, 2.8)	1.30×10^{-106}
NHW	e4/e4	6 (5, 7.1)	4.58×10^{-90}
Asian	e2+	0.63 (0.31, 1.3)	0.197
Asian	e2/e4	7.5 (0.82, 68)	0.074
Asian	e3/e4	2.5 (1.5, 4)	1.80×10^{-4}
Asian	e4/e4	12 (3.2, 41)	1.55×10^{-4}
Black	e2+	0.67 (0.46, 0.98)	0.040
Black	e2/e4	1.7 (1.1, 2.7)	0.029
Black	e3/e4	2.3 (1.8, 2.9)	3.84×10^{-12}
Black	e4/e4	8.7 (5.7, 13)	3.27×10^{-23}
Hispanic	e2+	1.4 (0.71, 2.9)	0.309
Hispanic	e2/e4	0.85 (0.15, 4.8)	0.854
Hispanic	e3/e4	2.5 (1.8, 3.4)	1.12×10^{-7}
Hispanic	e4/e4	9.2 (3.1, 27)	6.58×10^{-5}

There was limited evidence of population-specific effects of APOE geneotype on AD risk was observed in the NACC UDS. The e2+ allele was associated with lower risk in NHW and Black populations in comparison to Hispanics, while the e4/e4 allele was associated with higher risk in Black populations compared to NHW.


e2+
e2/e4
e3/e4
e4/e4
AD
AD + MCI
ADRD
ADRD + MCI
Odds Ratio
32
16
8
4
2
1
0.5
0.25
Asian
Black
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race
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NHW