Supplementary Online Content

Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. *JAMA Neurol*. Published online August 28, 2017. doi:10.1001/jamaneurol.2017.2188

eAppendix 1. Data Set Descriptions
eFigure 1. Forest Plots of the Log Odds Ratios of Developing Alzheimer's Disease for Men and Women with the APOE ε3/ε4 Genotype from 22 Independent Studies from Ages 55 to 85
eFigure 2. Forest Plots of the Log Odds Ratios of Developing Mild Cognitive Impairment for Men and Women with the APOE ε3/ε4 Genotype from 10 Independent Studies from Ages 55 to 85
eFigure 3. Forest Plots of the Log Odds Ratios for Transitioning from Mild Cognitive Impairment to Alzheimer's Disease for Men and Women with the APOE ε3/ε4 Genotype from 7 Independent Studies from Ages 55 to 85
eFigure 4. Age-adjusted odds ratios of developing Alzheimer's disease for men and women with the APOE ε3/ε4 genotype from 22 independent studies.
eMethods.
eTable 1. Odds Ratios and Heterogeneity Tests for Developing Alzheimer's Disease for Men and Women with the APOE ε3/ε4 Genotype in Three Age Ranges
eTable 2. Odds Ratios and Heterogeneity Tests for Developing Mild Cognitive Impairment for Men and Women with the APOE ε3/ε4 Genotype in Three Age Ranges
eTable 3. Odds Ratios for Transitioning from Mild Cognitive Impairment to Alzheimer's Disease for Men and Women with the APOE ε3/ε4 Genotype in Three Age Ranges
eTable 4. Data used in eFigure 4.

This supplementary material has been provided by the authors to give readers additional information about their work.

eList 1. Data Set Descriptions

Fundació ACE: A private organization[1] dedicated to the diagnosis, treatment, research, and support for people with dementia, especially focusing on people suffering from Alzheimer's Disease and their relatives and caregivers. There were 19,720 individuals evaluated and diagnosed between 1996 and 2015. Of these, 9,948 had AD, 6,181 had MCI, and 3,394 had no cognitive impairment. APOE genotyping was available in 3,300 subjects.

Alzheimer's Disease Neuroimaging Initiative: ADNI[2] was launched in 2003 as a public-private partnership; its primary goal has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early Alzheimer's disease. ADNI has 59 acquisition sites located across the United States and Canada. Through its 3 phases, it has targeted participants with AD, different stages of MCI, and normal controls.

Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing: AIBL[3] seeks to discover which biomarkers, cognitive characteristics, and health and lifestyle factors determine the development of AD. AIBL collects data at two centers in Australia; one at Perth in Western Australia and one in Melbourne, Victoria. AIBL follows ADNI protocols and has enrolled participants with AD, MCI, and healthy controls.

Alzheimer's Disease Repository Without Borders: ARWIBO[4,5] is a cross-sectional data set including data from more than 2,700 patients enrolled in Brescia, Italy and nearby areas. The database contains clinical information and MRI images weighted in T1 and T2 as well as PET scans of healthy elderly controls, individuals with mild cognitive impairment (MCI), and patients with Alzheimer's disease.

Coalition Against Major Diseases: CAMD[6] is a public-private partnership aimed at creating new tools and methods that can be applied to increase the efficiency of the development process of new treatments for Alzheimer's disease (AD) and related neurodegenerative disorders with impaired cognition and function. CAMD has developed an online repository for clinical trial data obtained in globally executed randomized controlled AD clinical studies. Because they do not share information about the masked therapeutic candidates, we refer to each of their data sets by its CAMD index: 1009, 1056, 1057, 1058, 1105, 1132, 1136, and 1142.

European Diffusion Tensor Imaging Study in Dementia: EDSD[7] is a framework of nine European centers: Amsterdam (Netherlands), Brescia (Italy), Dublin (Ireland), Frankfurt (Germany), Freiburg (Germany), Milano (Italy), Mainz (Germany), Munich (Germany), and Rostock (Germany). It is a cross-sectional multicenter study characterized by 471 Diffusion Tensor Imaging (DTI) and 471 structural MRI (MPRAGE) scans and clinical variables coming from patients with Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI) and Healthy Elderly Subjects.

Framingham Heart Study: FHS[8,9,10] was begun in 1948 to explore risk factors for and consequences of cardiovascular disease in a longitudinal population-based cohort. At entry, 5209 residents of Framingham, Massachusetts who were 28 to 62 years of age were enrolled. FHS consists of 6 different groups representing original participants, their offspring and spouses, a third generation, and two smaller ethnic minority cohorts.

Laboratory of Magnetic Resonance Research: LMRR supports research in Taiwan that utilizes imaging modalities in humans and animals. The team uses MRI for the studies of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. In dementia studies, more than 200 subjects have been followed longitudinally.

National Alzheimer's Coordinating Center: NACC[11] was established by the National Institute on Aging/NIH in 1999 to facilitate collaborative research. Using data collected from the 34 NIA-funded Alzheimer's Disease Centers (ADCs) across the United States, NACC has developed and maintains a large relational database of standardized clinical and neuropathological research data.

National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site: NIAGADS[12] is a national genetics data repository that facilitates access of genotypic data to qualified investigators for the study of the genetics of late-onset Alzheimer's Disease. NIAGADS houses 38 different data sets that are made available to qualified investigators in the scientific community for secondary analysis in accordance with standards established by the National Institute on Aging. We received APOE data from the following data sets are managed by NIAGADS:

- UPitt (NG00026): The University of Pittsburgh dataset[13] contains 1,271 Caucasian AD cases (of which 277 were autopsy-confirmed) recruited by the University of Pittsburgh Alzheimer's Disease Research Center, and 841 Caucasian, cognitively normal elders ages 60 and older (2 were autopsy-confirmed).
- TGEN2 (NG00028): This data set[14,15,16] contains 864 clinically- and neuropathologically-characterized brain donors, and 493 cognitively normal elders without dementia or significant AD pathology. Samples were obtained from twenty-one different National Institute on Aging-supported AD Center brain banks and from the Miami Brain Bank. Additional individual samples from other brain banks in the United States, United Kingdom, and the Netherlands were also obtained in the same manner.
- ROS/MAP (NG00029): Religious Orders Study[17,18] and Rush Memory and Aging Project[19,20] are two community-based cohort studies. The ROS has been on-going since 1993, with a rolling admission. Through July of 2010, 1,139 older nuns, priests, and brothers from across the United States initially free of dementia who agreed to annual clinical evaluation and brain donation at the time of death completed their baseline evaluation. The MAP has been on-going since 1997, also with a rolling admission. Through July of 2010, 1,356 older persons from across northeastern Illinois initially free of dementia who agreed to annual clinical evaluation and organ donation at the time of death completed their baseline evaluation.

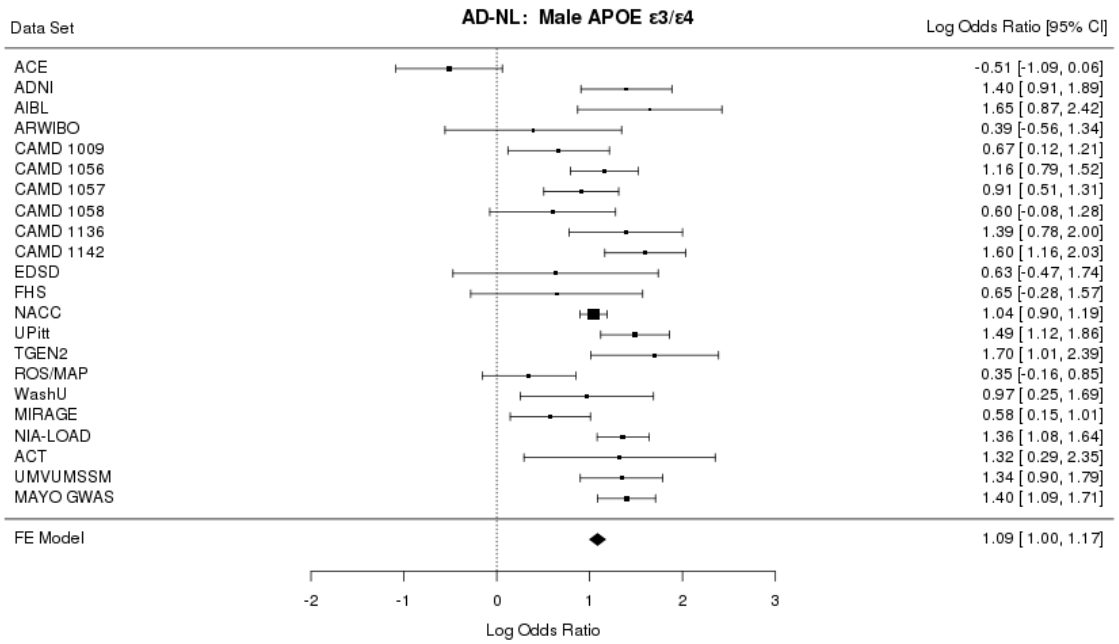
- WashU (NG00030): A European American LOAD case-control dataset consisting of 339 cases and 187 healthy elderly controls. Participants were recruited as part of a longitudinal study of healthy aging and dementia.
- MIRAGE (NG00031): The Multi Institutional Research of Alzheimer Genetic Epidemiology study[21] is a family-based genetic epidemiological study of AD that enrolled AD cases and unaffected sibling controls at 17 clinical centers in the United States, Canada, Germany, and Greece, and contributed 1,262 subjects (509 AD cases and 753 cognitively normal elders). Although information on family history of dementia among first-degree relatives (parents, siblings, children) was collected, it was not available for our analysis.
- NIA-LOAD (NG00032): The National Institute on Aging LOAD Family Study[22] recruited families with two or more affected siblings with LOAD and unrelated cognitively normal elders similar in age and ethnic background. A total of 1,819 cases and 1,969 cognitively normal elders from 1,802 families were recruited and one case per family was selected after determining the individual with the strictest diagnosis. The controls included only those samples that were neurologically evaluated to be normal and were not related to a study participant.
- ACT (NG00034): The Adult Changes in Thought[23] cohort is an urban and suburban elderly population from a stable HMO that includes 2,581 cognitively intact subjects over age 65 and 811 subjects who were enrolled using the same methods except oversampling clinics with more minorities. New subjects are contacted, screened and enrolled to keep 2000 active at-risk person-years accruing in each calendar year for an enrollment of 4,146 participants.
- UMVUMSSM (NG00042): The Miami and Medical School of Mount Sinai GWAS data set[24] contains 1,186 cases and 1,135 controls ascertained through the Collaborative Alzheimer's Project (CAP) comprising the University of Miami (UM), Vanderbilt University (VU) and Mount Sinai School of Medicine (MSSM).
- MAYO GWAS (NG00043): All subjects[25] in the Mayo clinical case-control series were diagnosed by a neurologist at the Mayo Clinic in Jacksonville, Florida (JS series) or Rochester, Minnesota, (RS series). In the autopsy confirmed series (AUT), all brains came from a brain bank at the Mayo Clinic in Jacksonville, FL.

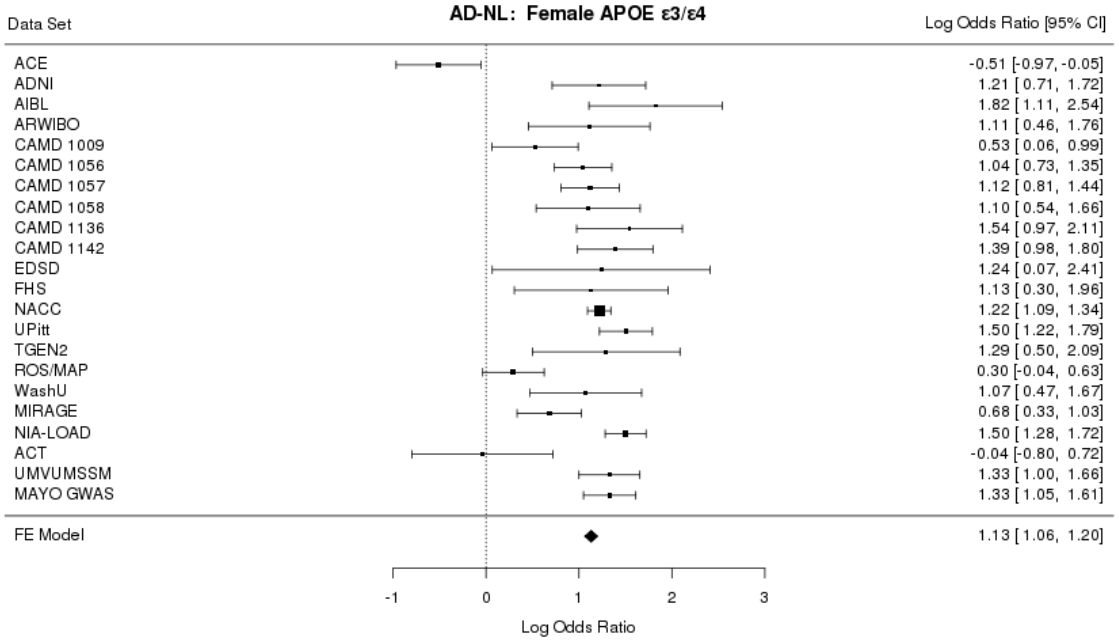
Prediction of cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development: PharmaCog[26] (alias E-ADNI) is an industry-academic European project aimed at identifying biomarkers sensitive to symptomatic and disease modifying effects of drugs for Alzheimer's disease. Nine clinical sites participated in this study across Italy (Brescia, Verona, and Genoa), Spain (Barcelona), France (Marseille, Lille, and Toulouse) and Germany (Leipzig and Essen). 147 MCI patients have been studied along 7 time points (i.e.: BSL, T06, T12, T18, T24, T30 and T36) collecting multimodal image scans (MPRAGE, T2*, FLAIR, DTI, rsfMRI), clinical variables, and biospecimens.

Wisconsin Registry for Alzheimer's Prevention: WRAP[27] is a longitudinal cohort study involving middle-aged adult children with parents with Alzheimer's disease. The main goal of WRAP is to understand the factors (biological, medical, environmental, and lifestyle choices) that increase a person's risk of developing Alzheimer's disease. WRAP

is an observational study that is tracking the characteristics and habits of two important groups of volunteers: people who have one or both parents with Alzheimer's disease (the family history group), and people whose parents lived to old age with no signs of Alzheimer's disease or other serious memory problems (the control group).

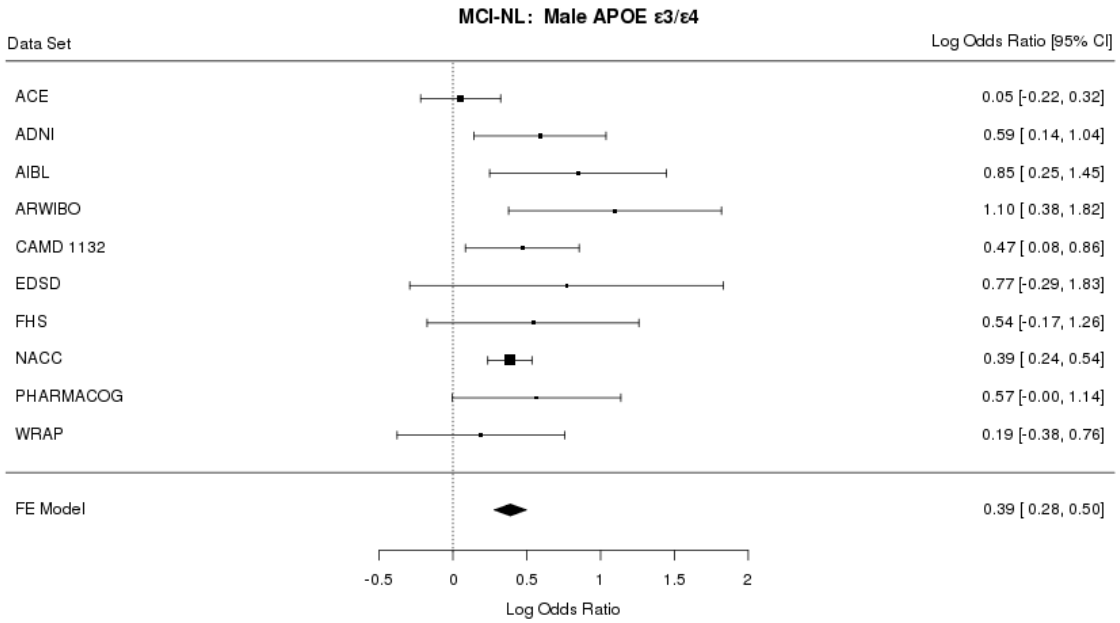
eFigure 1. Forest Plots of the Log Odds Ratios of Developing Alzheimer's Disease for Men and Women with the APOE ε 3/ ε 4 Genotype from 22 Independent Studies from Ages 55 to 85

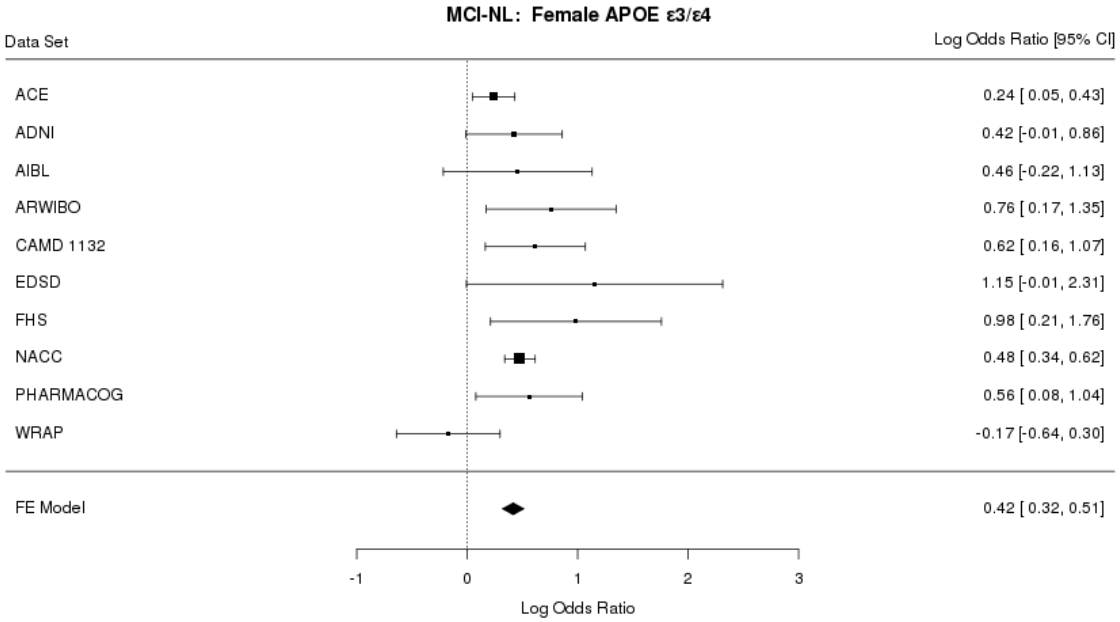




Abbreviations: AD=Alzheimer's disease; APOE=Apolipoprotein E; CI=confidence interval; FE=fixed effects; NL=normal cognition

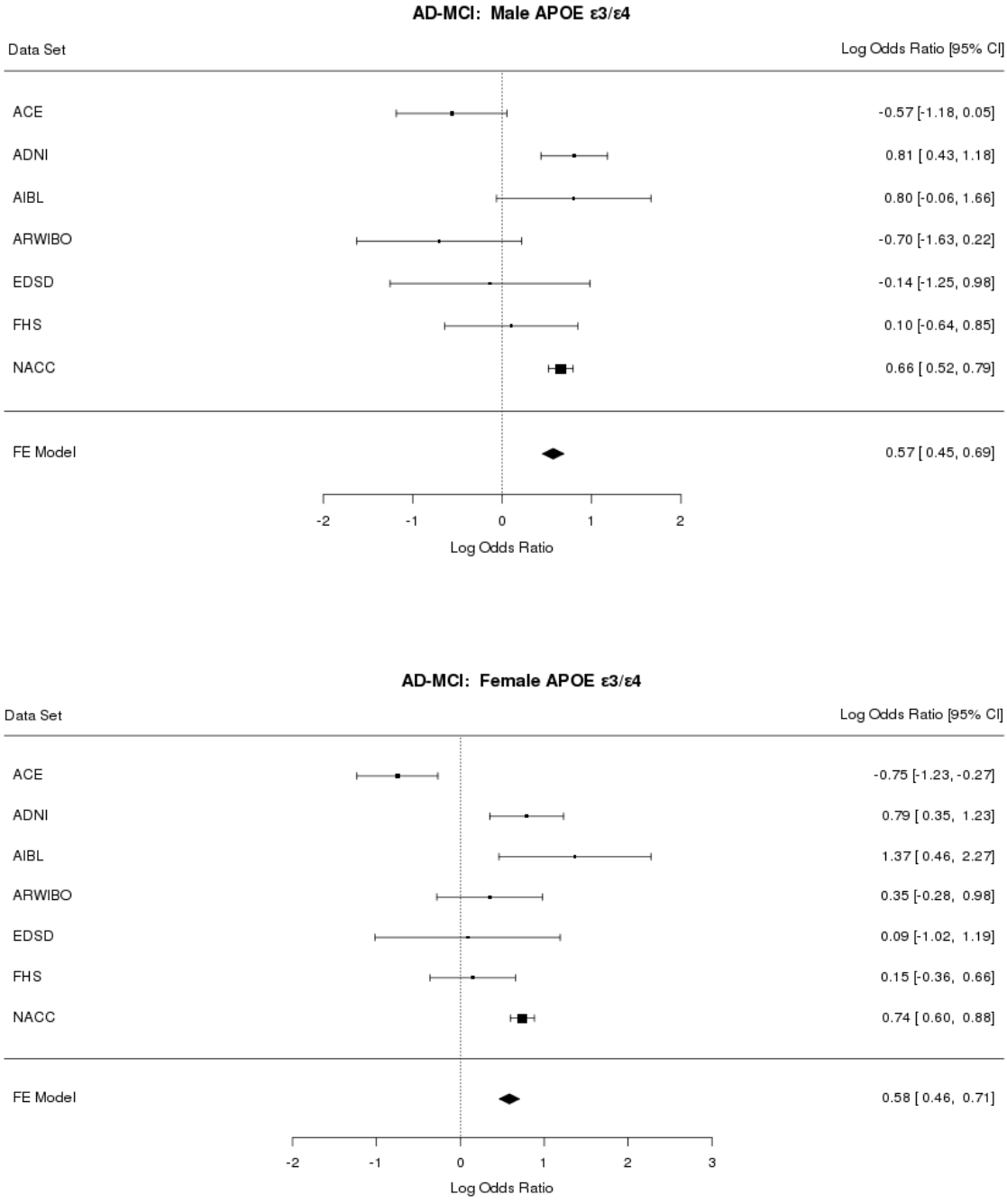
eFigure 2. Forest Plots of the Odds Ratios of Developing Mild Cognitive Impairment for Men and Women with the APOE ε 3/ ε 4 Genotype from 10 Independent Studies from Ages 55 to 85





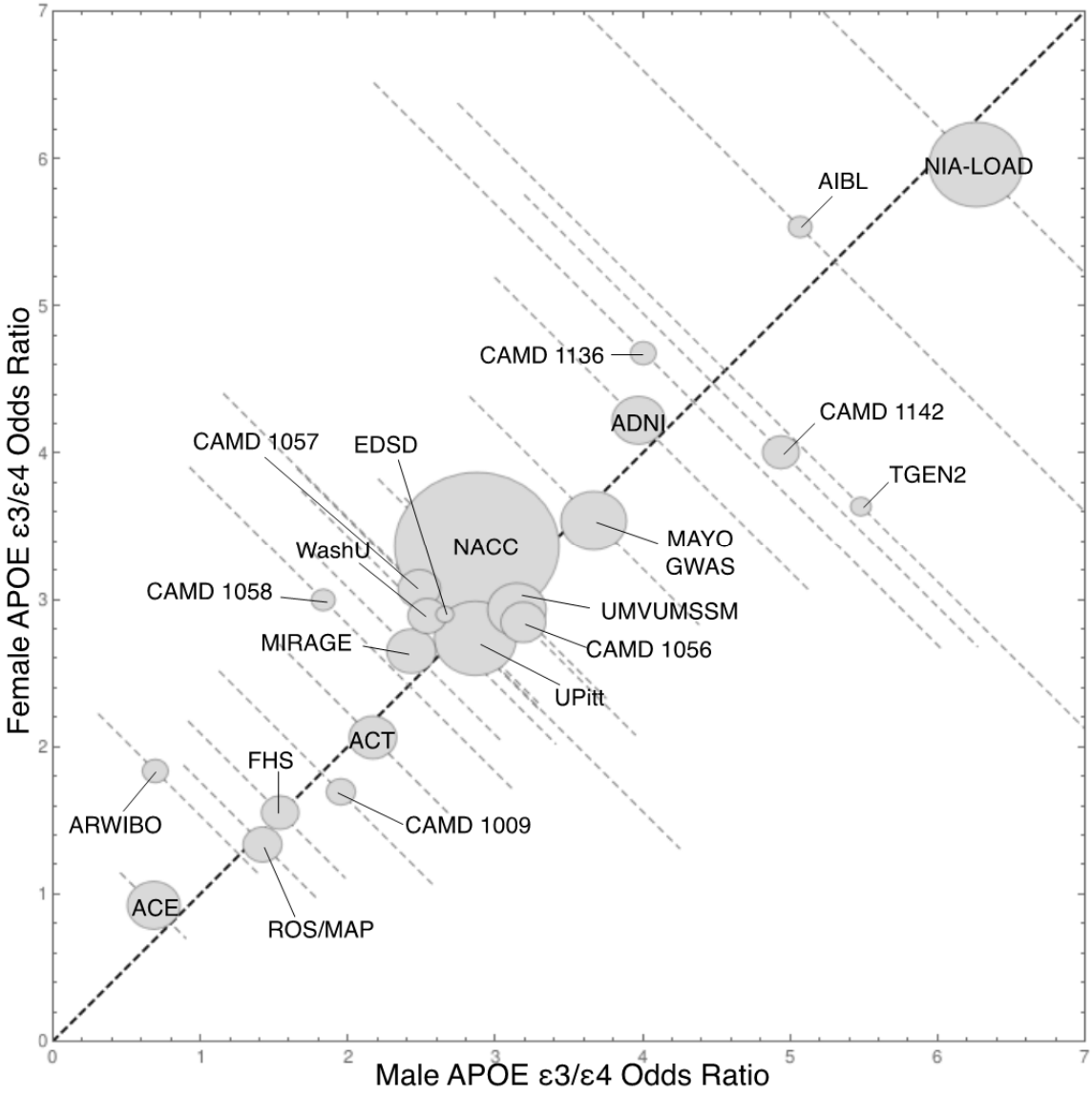
Abbreviations: APOE=Apolipoprotein E; CI=confidence interval; FE=fixed effects; MCI=mild cognitive impairment; NL=normal cognition

eFigure 3. Forest Plots of the Odds Ratios for Transitioning from Mild Cognitive Impairment to Alzheimer's Disease for Men and Women with the APOE ε 3/ ε 4 Genotype from 7 Independent Studies from Ages 55 to 85



Abbreviations: AD=Alzheimer's disease; APOE=Apolipoprotein E; CI=confidence interval; FE=fixed effects; MCI=mild cognitive impairment

eFigure 4. Age-adjusted odds ratios of developing Alzheimer's disease for men and women with the APOE ε 3/ ε 4 genotype from 22 independent studies.



Each data point shows the relative relationship of Alzheimer's disease risk between men and women from each data set; higher risks are associated with larger odds ratio values. The area of each data point is proportional to the total number of male and female Alzheimer's disease cases in each data set. The dashed line delineates where the Alzheimer's disease risks for men and women are the same. Confidence intervals (95%) were used to draw error bars perpendicular to the dashed line for some data points.

eMethods.

Sub-Analyses Referenced in eTables 1 – 3

1. Fixed-effects meta-analysis using Mantel-Haenszel method
    a. R (version 3.3.1) using the "metafor" meta-analysis package (version 1.9-9)
2. Fixed-effects meta-analysis using Mantel-Haenszel method excluding community-based (ACE, ARWIBO, FHS) and disease-biased (NIA-LOAD, TGEN2, ROS/MAP) data sets
    a. R (version 3.3.1) using the "metafor" meta-analysis package (version 1.9-9) function rma.mh(measure="OR")
3. Logistic regression of pooled data using a continuous age variable and five indicator (values of one or zero) variables representing the five APOE genotypes (ε 2/ ε 2, ε 2/ ε 3, ε 2/ ε 4, ε 3/ ε 4, and ε 4/ ε 4) with the APOE ε 3/ ε 3 genotype as the referent
    a. R (version 3.3.1) using the generalized linear model function glm(dx ~ age + n22 + n23 + n24 + n34 + n44, family=binomial)
4. Sub-analysis #3 with NACC data only
    a. R (version 3.3.1) using the generalized linear model function glm(dx ~ age + n22 + n23 + n24 + n34 + n44, family=binomial)
5. Sub-analysis #3 with NACC data excluded
    a. R (version 3.3.1) using the generalized linear model function glm(dx ~ age + n22 + n23 + n24 + n34 + n44, family=binomial)

eTable 1. Odds Ratios and Heterogeneity Tests for Developing Alzheimer's Disease for Men and Women with the APOE ε 3/ ε 4 Genotype in Three Age Ranges

AD-NL APOE ε 3/ ε 4:

Age Range	Sex	Sub-Analysis*	ε 3/ ε 4 Cases/ Controls	ε 3/ ε 3 Cases/ Controls	Odds Ratio (95% CI)	Odds Ratio P Value	Tarone's χ^2	Tarone's P Value
55 to 65 y	Male	#1			1.75 (1.40 to 2.19)	P<.001	18.5	0.62
		#2			1.71 (1.34 to 2.19)	P<.001	8.07	0.92
		#3	256/128	257/226	1.74 (1.32 to 2.30)	P<.001		
		#4	123/78	142/149	1.62 (1.12 to 2.34)	P<.001		
		#5	133/50	115/77	1.74 (1.12 to 2.69)	0.01		
	Female	#1			1.95 (1.61 to 2.36)	P<.001	28.1	0.11
		#2			1.75 (1.43 to 2.16)	P<.001	11.3	0.73
		#3	334/244	308/423	1.89 (1.51 to 2.35)	P<.001		
		#4	143/156	158/293	1.69 (1.25 to 2.28)	P<.001		
		#5	191/88	150/130	1.96	P<.00		

					(1.38 to 2.78)	1		
65 to 75 y	Male	#1			3.05 (2.67 to 3.47)	P<.001	38.8	0.01
		#2			3.05 (2.64 to 3.53)	P<.001	20.5	0.15
		#3	776/417	581/979	3.14 (2.68 to 3.67)	P<.001		
		#4	295/203	229/423	2.68 (2.11 to 3.41)	P<.001		
		#5	481/214	352/556	3.55 (2.88 to 4.38)	P<.001		
	Female	#1			4.26 (3.80 to 4.77)	P<.001	55.2	P<.001
		#2			4.36 (3.83 to 4.96)	P<.001	21.5	0.12
		#3	1122/659	616/1570	4.37 (3.82 to 5.00)	P<.001		
		#4	367/352	168/740	4.60 (3.68 to 5.75)	P<.001		
		#5	755/307	448/830	4.58 (3.84 to 5.46)	P<.001		
75 to 85 y	Male	#1			3.46 (3.05 to	P<.001	55.3	P<.001

					3.91)			
		#2			3.81 (3.31 to 4.38)	P<.001	17.1	0.31
		#3	1042/341	857/1025	3.71 (3.18 to 4.32)	P<.001		
		#4	532/159	429/478	3.76 (3.02 to 4.69)	P<.001		
		#5	510/182	428/547	3.61 (2.92 to 4.46)	P<.001		
	Female	#1			2.96 (2.68 to 3.28)	P<.001	93.4	P<.001
		#2			3.28 (2.92 to 3.68)	P<.001	34.6	0.003
		#3	1288/530	1085/1377	3.22 (2.83 to 3.67)	P<.001		
		#4	598/270	424/746	4.12 (3.41 to 4.98)	P<.001		
		#5	690/260	661/631	2.67 (2.23 to 3.21)	P<.001		

Abbreviations: AD=Alzheimer's disease; CI=confidence interval; NL=normal cognition; y=years

*See eMethods in this Supplement

eTable 2. Odds Ratios and Heterogeneity Tests for Developing Mild Cognitive Impairment for Men and Women with the APOE ε 3/ ε 4 Genotype in Three Age Ranges

MCI-NL APOE ε 3/ ε 4:

Age Range	Sex	Sub-Analysis*	ε 3/ ε 4 Cases/ Controls	ε 3/ ε 3 Cases/ Controls	Odds Ratio (95% CI)	Odds Ratio P Value	Tarone's χ^2	Tarone's P Value
55 to 65 y	Male	#1			1.08 (0.83 to 1.42)	0.55	9.05	0.43
		#2			1.07 (0.80 to 1.43)	0.65	5.14	0.53
		#3	118/120	203/205	0.99 (0.72 to 1.37)	0.96		
		#4	74/78	136/149	1.04 (0.70 to 1.55)	0.83		
		#5	44/42	67/56	0.88 (0.50 to 1.53)	0.04		
	Female	#1			1.12 (0.87 to 1.45)	0.36	5.38	0.80
		#2			1.16 (0.88 to 1.53)	0.29	5.00	0.54
		#3	135/262	194/439	1.19 (0.91 to 1.56)	0.20		
		#4	72/156	112/293	1.21 (0.85 to 1.73)	0.28		
		#5	63/106	82/146	1.13	0.57		

					(0.74 to 1.72)			
65 to 75 y	Male	#1			1.43 (1.22 to 1.69)	P<.001	12.5	0.19
		#2			1.45 (1.20 to 1.75)	P<.001	5.67	0.46
		#3	383/278	542/585	1.49 (1.23 to 1.80)	P<.001		
		#4	260/203	375/423	1.44 (1.15 to 1.82)	0.002		
		#5	123/75	167/162	1.59 (1.11 to 2.28)	P<.001		
	Female	#1			1.89 (1.62 to 2.20)	P<.001	15.1	0.09
		#2			1.86 (1.56 to 2.22)	P<.001	8.48	0.20
		#3	354/479	391/1017	1.92 (1.60 to 2.30)	P<.001		
		#4	252/352	265/740	2.00 (1.61 to 2.48)	P<.001		
		#5	102/127	126/277	1.74 (1.24 to 2.43)	0.001		
75 to 85 y	Male	#1			1.80 (1.52 to	P<.001	20.4	0.02

					2.12)			
		#2			1.98 (1.63 to 2.40)	P<.001	12.7	0.05
		#3	401/198	641/618	1.95 (1.60 to 2.40)	P<.001		
		#4	286/159	495/478	1.74 (1.38 to 2.19)	P<.001		
		#5	115/39	146/140	2.83 (1.84 to 4.35)	P<.001		
	Female	#1			1.45 (1.25 to 1.68)	P<.001	7.78	0.56
		#2			1.53 (1.27 to 1.84)	P<.001	3.37	0.76
		#3	293/328	516/874	1.55 (1.28 to 1.88)	P<.001		
		#4	223/270	399/746	1.58 (1.27 to 1.96)	P<.001		
		#5	70/58	117/128	1.37 (0.89 to 2.12)	0.13		

Abbreviations: CI=confidence interval; MCI=mild cognitive impairment; NL=normal cognition; y=years

*See eMethods in this Supplement

eTable 3. Odds Ratios for Transitioning from Mild Cognitive Impairment to Alzheimer's Disease for Men and Women with the APOE ε 3/ ε 4 Genotype in Three Age Ranges

AD-MCI APOE ε 3/ ε 4:

Age Range	Sex	Sub-Analysis*	ε 3/ ε 4 Cases/ Controls	ε 3/ ε 3 Cases/ Controls	Odds Ratio (95% CI)	Odds Ratio P Value	Tarone's χ^2	Tarone's P Value
55 to 65 y	Male	#1			1.39 (0.99 to 1.95)	0.06	8.61	0.20
		#2			1.53 (1.08 to 2.18)	0.02	1.38	0.71
		#3	134/94	153/157	1.49 (1.05 to 2.11)	0.03		
		#4	123/74	142/136	1.61 (1.11 to 2.35)	0.01		
		#5	11/20	11/21	1.06 (0.37 to 2.99)	0.43		
	Female	#1			1.31 (0.94 to 1.83)	0.11	6.86	0.23
		#2			1.28 (0.90 to 1.81)	0.16	3.95	0.27
		#3	152/99	174/144	1.28 (0.91 to 1.80)	0.15		
		#4	143/72	158/112	1.43 (0.98 to 2.09)	0.06		
		#5	9/27	16/32	0.63	0.30		

					(0.24 to 1.68)			
65 to 75 y	Male	#1			1.73 (1.41 to 2.12)	P<.001	8.94	0.18
		#2			1.87 (1.51 to 2.31)	P<.001	1.96	0.58
		#3	343/336	261/473	1.85 (1.49 to 2.29)	P<.001		
		#4	295/260	229/375	1.86 (1.47 to 2.35)	P<.001		
		#5	48/76	32/98	1.98 (1.15 to 3.40)	P<.001		
	Female	#1			1.92 (1.56 to 2.37)	P<.001	26.4	P<.001
		#2			2.45 (1.94 to 3.09)	P<.001	4.75	0.19
		#3	429/313	184/323	2.35 (1.86 to 2.96)	P<.001		
		#4	367/252	168/265	2.25 (1.75 to 2.90)	P<.001		
		#5	62/61	16/58	3.44 (1.77 to 6.69)	P<.001		
75 to 85 y	Male	#1			1.93 (1.64 to	P<.001	20.2	0.003

					2.28)			
		#2			2.17 (1.82 to 2.59)	P<.001	2.79	0.42
		#3	621/370	480/605	2.12 (1.78 to 2.53)	P<.001		
		#4	532/286	429/495	2.15 (1.77 to 2.61)	P<.001		
		#5	89/84	51/110	2.30 (1.47 to 3.60)	P<.001		
	Female	#1			2.04 (1.72 to 2.41)	P<.001	36.0	P<.001
		#2			2.52 (2.08 to 3.05)	P<.001	2.08	0.56
		#3	655/269	463/482	2.59 (2.14 to 3.14)	P<.001		
		#4	598/223	424/399	2.58 (2.09 to 3.17)	P<.001		
		#5	57/46	39/83	2.75 (1.58 to 4.78)	0.006		

Abbreviations: AD=Alzheimer's disease; CI=confidence interval; MCI=mild cognitive impairment; y=years

*See eMethods in this Supplement

eTable 4. Data used in eFigure 4.

Data Set	Male Odds Ratio (95% CI)	Female Odds Ratio (95% CI)	Number of Cases
ACE	0.68 (0.46 to 1.00)	0.92 (0.70 to 1.22)	418
ADNI	3.97 (3.00 to 5.24)	4.22 (3.07 to 5.81)	419
AIBL	5.07 (2.53 to 10.17)	5.53 (2.95 to 10.35)	85
ARWIBO	0.70 (0.31 to 1.54)	1.83 (1.12 to 3.01)	101
CAMD			
1009	1.95 (1.13 to 3.36)	1.69 (1.07 to 2.70)	129
1056	3.19 (2.21 to 4.59)	2.84 (2.08 to 3.87)	300
1057	2.48 (1.66 to 3.71)	3.07 (2.24 to 4.20)	270
1058	1.83 (0.93 to 3.59)	3.00 (1.72 to 5.25)	86
1136	4.01 (2.18 to 7.39)	4.68 (2.65 to 8.26)	100
1142	4.94 (3.20 to 7.64)	4.01 (2.68 to 6.02)	202
EDSD	2.66 (1.16 to 6.05)	2.90 (1.31 to 6.41)	48
FHS	1.54 (0.91 to 2.59)	1.55 (1.11 to 2.17)	210
NACC	2.88 (2.52 to 3.29)	3.36 (2.99 to 3.78)	4021
NIAGADS			
UPitt	2.86 (2.27 to 3.60)	2.73 (2.30 to 3.25)	1008
TGEN2	5.48 (2.75 to 10.89)	3.64 (1.65 to 8.06)	65
ROS/MAP	1.42 (0.86 to 2.34)	1.34 (0.96 to 1.87)	227
WashU	2.54 (1.69 to 3.82)	2.89 (2.01 to 4.13)	225
MIRAGE	2.43 (1.71 to 3.46)	2.65 (2.02 to 3.49)	359
NIA-LOAD	6.26 (4.98 to 7.87)	5.96 (5.04 to 7.05)	1318
ACT	2.17 (1.54 to 3.07)	2.06 (1.54 to 2.75)	338
UMVUMSSM	3.15 (2.31 to 4.31)	2.93 (2.33 to 3.69)	513
MAYO GWAS	3.67 (2.83 to 4.76)	3.54 (2.83 to 4.44)	644

Abbreviations: CI, confidence interval

eReferences:

[1] Boada M, Tárraga L, Hernández I, Valero S, Alegret M, Ruiz A, Lopez OL, Becker JT, Center FA, Clinic M. Design of a comprehensive Alzheimer's disease clinic and research center in Spain to meet critical patient and family needs. Alzheimer's & Dementia. 2014 May 31;10(3):409-15.

[2] Weiner MW, Aisen PS, Jack CR, Jagust WJ, Trojanowski JQ, Shaw L, Saykin AJ, Morris JC, Cairns N, Beckett LA, Toga A. The Alzheimer's disease neuroimaging initiative: progress report and future plans. Alzheimer's & Dementia. 2010 May 31;6(3):202-11.

[3] Ellis KA, Bush AI, Darby D, De Fazio D, Foster J, Hudson P, Lautenschlager NT, Lenzo N, Martins RN, Maruff P, Masters C. 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. International Psychogeriatrics. 2009 Aug 1;21(04):672-87.

[4] Frisoni GB, Prestia A, Zanetti O, Galluzzi S, Romano M, Cotelli M, Gennarelli M, Binetti G, Bocchio L, Paghera B, Amicucci G, Bonetti M, Benussi L, Ghidoni R, Geroldi C. Markers of Alzheimer's disease in a population attending a memory clinic. Alzheimers Dement. 2009 Jul;5(4):307-17.

[5] Galluzzi S, Testa C, Boccardi M, Bresciani L, Benussi L, Ghidoni R, Beltramello A, Bonetti M, Bono G, Falini A, Magnani G, Minonzio G, Piovan E, Binetti G, Frisoni GB. The Italian Brain Normative Archive of structural MR scans: norms for medial temporal atrophy and white matter lesions. Aging Clin Exp Res. 2009 Aug-Oct;21(4-5):266-76.

[6] Neville J, Kopko S, Broadbent S, Avilés E, Stafford R, Solinsky CM, Bain LJ, Cisneroz M, Romero K, Stephenson D. Development of a unified clinical trial database for Alzheimer's disease. Alzheimer's & Dementia. 2015 Oct 31;11(10):1212-21.

[7] Teipel SJ, Wegrzyn M, Meindl T, Frisoni G, Bokde AL, Fellgiebel A, Filippi M, Hampel H, Klöppel S, Hauenstein K, Ewers M. Anatomical MRI and DTI in the diagnosis of Alzheimer's disease: a European multicenter study. Journal of Alzheimer's Disease. 2012 Jan 1;31(s3).

[8] Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. Annals of the New York Academy of Sciences. 1963 May 1;107(2):539-56.

[9] Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham offspring study. Design and preliminary data. Preventive medicine. 1975 Dec 31;4(4):518-25.

[10] Splansky, G.L., Corey, D., Yang, Q., Atwood, L.D., Cupples, L.A., Benjamin, E.J., D'Agostino, R.B., Fox, C.S., Larson, M.G., Murabito, J.M. and O'Donnell, C.J., 2007. The third generation cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *American journal of epidemiology*, *165*(11), pp.1328-1335.

[11] Beekly DL, Ramos EM, Lee WW, Deitrich WD, Jacka ME, Wu J, Hubbard JL, Koepsell TD, Morris JC, Kukull WA. The National Alzheimer's Coordinating Center (NACC) database: the uniform data set. Alzheimer Disease & Associated Disorders. 2007 Jul 1;21(3):249-58.

[12] Partch AB, Laufer D, Valladares O, Iodice J, Greenfest-Allen E, Childress DM, Malamon J, Gangadharan P, Arnold SE, Stoeckert CJ, Schellenberg GD. Nia genetics of Alzheimer's disease

data storage site (NIAGADS): 2015 update. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2015 Jan 7;11(7):P362.

13 Kamboh MI, Minster RL, Demirci FY, Ganguli M, DeKosky ST, Lopez OL, Barmada MM. Association of CLU and PICALM variants with Alzheimer's disease. Neurobiology of aging. 2012 Mar 31;33(3):518-21.

14 Reiman EM, Webster JA, Myers AJ, Hardy J, Dunckley T, Zismann VL, Joshipura KD, Pearson JV, Hu-Lince D, Huentelman MJ, Craig DW. GAB2 alleles modify Alzheimer's risk in APOE ε4 carriers. Neuron. 2007 Jun 7;54(5):713-20.

15 Caselli RJ, Reiman EM, Locke DE, Hutton ML, Hentz JG, Hoffman-Snyder C, Woodruff BK, Alexander GE, Osborne D. Cognitive domain decline in healthy apolipoprotein E ε4 homozygotes before the diagnosis of mild cognitive impairment. Archives of neurology. 2007 Sep 1;64(9):1306-11.

16 Webster JA, Gibbs JR, Clarke J, Ray M, Zhang W, Holmans P, Rohrer K, Zhao A, Marlowe L, Kaleem M, McCorquodale DS. Genetic control of human brain transcript expression in Alzheimer disease. The American Journal of Human Genetics. 2009 Apr 10;84(4):445-58.

17 Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J. Natural history of mild cognitive impairment in older persons. Neurology. 2002 Jul 23;59(2):198-205.

18 Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS. Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions. Neurology. 2005 Mar 8;64(5):834-41.

19 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 Oct 28;25(4):163-75.

20 Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007 Dec 11;69(24):2197-204.

21 Green RC, Cupples LA, Go R, Benke KS, Edeki T, Griffith PA, Williams M, Hipps Y, Graff-Radford N, Bachman D, Farrer LA. Risk of dementia among white and African American relatives of patients with Alzheimer disease. Jama. 2002 Jan 16;287(3):329-36.

22 Lee JH, Cheng R, Graff-Radford N, Foroud T, Mayeux R. Analyses of the national institute on aging late-onset alzheimer's disease family study: implication of additional loci. Archives of neurology. 2008 Nov 10;65(11):1518-26.

23 Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, van Belle G, Jolley L, Larson EB. Dementia and Alzheimer disease incidence: a prospective cohort study. Archives of neurology. 2002 Nov 1;59(11):1737-46.

[24] Beecham GW, Martin ER, Li YJ, Slifer MA, Gilbert JR, Haines JL, Pericak-Vance MA. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. The American Journal of Human Genetics. 2009 Jan 9;84(1):35-43.

[25] Carrasquillo MM, Zou F, Pankratz VS, Wilcox SL, Ma L, Walker LP, Younkin SG, Younkin CS, Younkin LH, Bisceglio GD, Ertekin-Taner N. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease. Nature genetics. 2009 Feb 1;41(2):192-8.

[26] Galluzzi S, Marizzoni M, Babiloni C, Albani D, Antelmi L, Bagnoli C, Bartres-Faz D, Cordone S, Didic M, Farotti L, Fiedler U, Forloni G, Girtler N, Hensch T, Jovicich J, Leeuwis A, Marra C, Molinuevo JL, Nobili F, Pariente J, Parnetti L, Payoux P, Del Percio C, Ranjeva JP, Rolandi , Rossini PM, Schönknecht P, Soricelli A, Tsolaki M, Visser PJ, Wiltfang J, Richardson JC, Bordet R, Blin O, Frisoni GB; 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 Jun;279(6):576-91.

[27] 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. Journal of geriatric psychiatry and neurology. 2005 Dec 1;18(4):245-9.