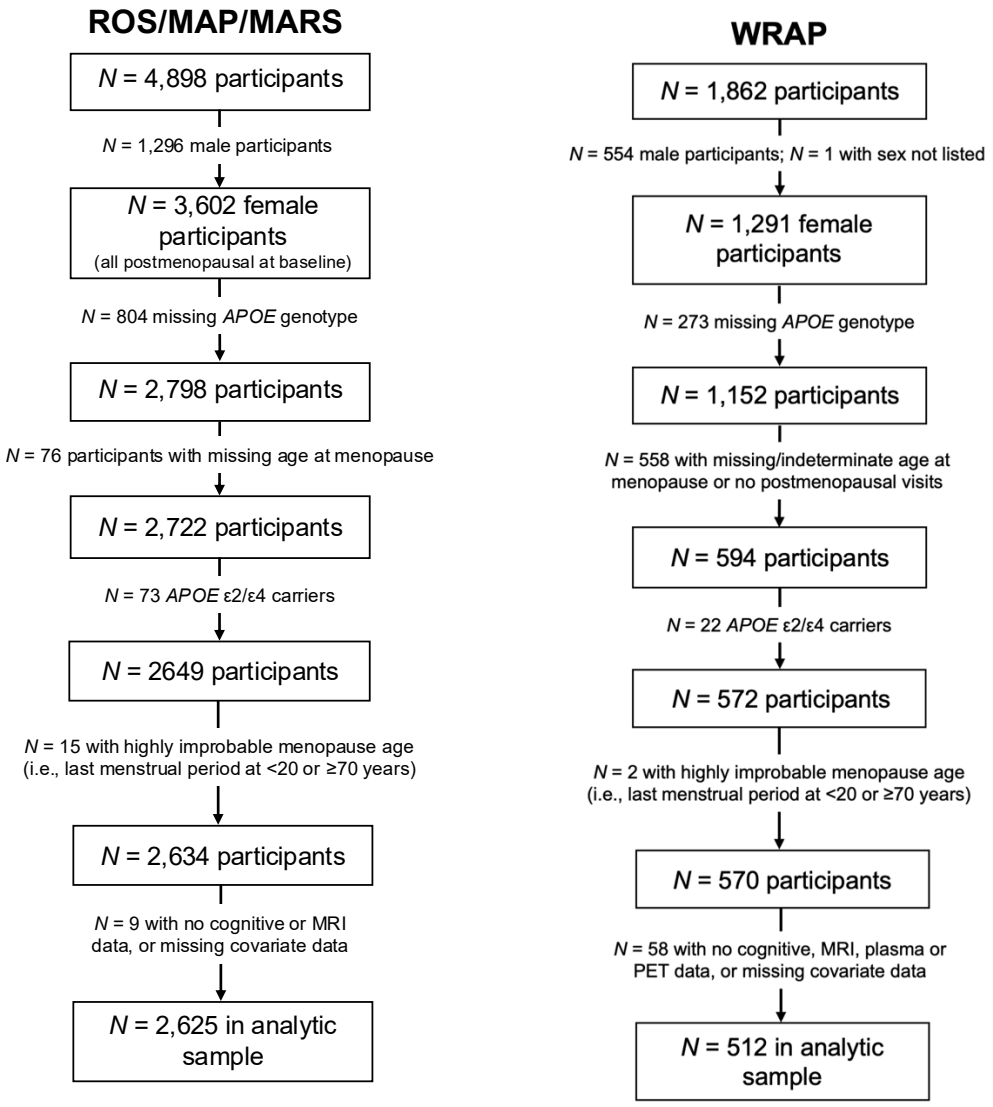
Supplemental Online Material

eMethods.

eFigure 1. Flow charts depicting sample selection in each data source.



eTable1. Demographic characteristics of male participants.

	Dataset 1: ROS/MAP/MARS *N* = 982	**Dataset 2: WRAP** *N* = 415
Age at baseline, mean (*SD*)	77.6 (7.54)	55.4 (6.98)
Years of education, mean (*SD*)	16.6 (4.06)	16.4 (2.99)
Study, *N* (%)		
ROS	367 (37.4)	-
MAP	466 (47.5)	-
MARS	149 (15.2)	-
Race, *N* (%)		
White	800 (81.5)	367 (88.4)
Black or African American	173 (17.6)	43 (10.4)
American Indian or Alaska Native	1 (0.1)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)
Asian	1 (0.1)	2 (0.5)
Unknown	7 (0.7)	3 (0.7)
APOE, *N* (%)		
ε2/ε2	8 (0.8)	0 (0)
ε2/ε3	138 (14.1)	37 (8.9)
ε3/ε3	597 (60.8)	236 (56.9)
ε3/ε4	222 (22.6)	134 (32.3)
ε4/ε4	17 (1.7)	8 (1.9)
Cognitive diagnosis at study entry (%)		
No cognitive impairment	640 (65.2)	404 (97.3)
MCI	270 (27.5)	8 (1.9)
Dementia	72 (7.33)	2 (0.5)
BMI, mean (*SD*)	27.5 (4.39)	29.4 (5.09)
Ever smoked, *N* (%)	483 (49.4)	166 (40.6)
Total follow-up, mean (*SD*) years	8.27 (6.31)	4.5 (2.17)
Number of longitudinal cognitive visits, median (IQR)	7 (4, 12)	5 (3, 5)
Number of longitudinal MRI visits, median (IQR)	2 (1, 4)	-
Number of longitudinal plasma visits, median (IQR)	-	3 (2, 4)
Aβ-PET positivity, *N* (%)	-	32 (20.5)
Sample sizes for each outcome (*N*)		
Memory	982	399
MRI	136	142
Plasma p-tau217	-	385
Aβ-PET	-	156 (154 PiB, 2 NAV)

eTable2. Demographic characteristics of White and Black participants.

	Dataset 1: ROS/MAP/MARS			Dataset 2: WRAP		
	White *N* = 1,972	Black *N* = 633	P value	White *N* = 456	Black *N* = 50	P value
Age at baseline, mean (*SD*)	78.7 (7.62)	73.4 (6.76)	<.001	60.0 (5.44)	62.9 (5.87)	<.001
Years of education, mean (*SD*)	16.0 (3.57)	14.9 (3.38)	<.001	16.0 (2.77)	15.5 (2.55)	.21
Study, *N* (%)						
ROS	807 (40.9)	65 (10.3)				
MAP	1,972 (59.1)	73 (11.5)				
MARS	0 (0.0)	495 (78.2)	<.001	-	-	-
APOE, *N* (%)						
ε2/ε2	11 (0.6)	5 (0.8)		3 (0.7)	1 (2.0)	
ε2/ε3	257 (13.0)	80 (12.6)		34 (7.5)	4 (8.0)	
ε3/ε3	1,261 (63.9)	341 (53.9)		237 (52.0)	22 (44.0)	
ε3/ε4	406 (20.6)	178 (28.1)		159 (34.9)	21 (42.0)	
ε4/ε4	37 (1.9)	29 (4.6)	<.001	23 (5.0)	2 (4.0)	.67
Age at menopause, mean (*SD*)	48.2 (6.79)	45.6 (8.45)	<.001	50.6 (5.69)	45.4 (9.17)	<.001
Surgical menopause, *N* (%)	610 (30.9)	338 (53.4)	<.001	9 (2.0)	5 (10.0)	.005
History of hormone therapy, *N* (%)	776 (39.4)	176 (27.8)	<.001	240 (52.6)	15 (30.0)	.004
Cognitive diagnosis at study entry (%)						
No cognitive impairment	1,448 (73.4)	464 (73.3)		447 (98.0)	49 (98.0)	
MCI	446 (22.6)	155 (24.5)		9 (2.0)	1(2.0)	
Dementia	78 (4.0)	14 (2.2)	.11	0 (0.0)	0 (0.0)	>.99
BMI, mean (*SD*)	27.2 (5.48)	30.2 (6.44)	<.001	28.6 (6.61)	35.1 (8.14)	<.001
Ever smoked, *N* (%)	518 (26.3)	269 (42.5)	<.001	182 (40.2)	27 (54.0)	.08
Total follow-up, mean (*SD*) years	9.11 (6.15)	9.73 (6.27)	.03	5.37 (3.36)	4.01 (2.91)	.01
Number of longitudinal cognitive visits, median (IQR)	8 (5, 12)	8 (5, 12)	.18	3 (2, 5)	2 (1, 3)	<.001
Number of longitudinal MRI visits, median (IQR)	2 (1, 4)	2 (1, 4)	.15	-	-	-
Number of longitudinal plasma visits, median (IQR)	-	-	-	3 (2, 4)	2 (1, 2)	<.001

eTable3. Results of post hoc analyses repeating models stratified by race.

Analyses	**ROS/MAP/MARS**		**WRAP**	
Model	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Memory ~ *APOE ε4* * age at menopause * time + covariates				
White participants: *APOE ε4* * age at menopause * time	0.082 (0.012, 0.152)	.02	0.071 (-0.015, 0.157)	.10
Black participants*: APOE ε4* * age at menopause * time	0.155 (0.049, 0.261)	.004	0.311 (-0.142, 0.763)	.18
Cortical thickness ~ *APOE ε4* * age at menopause * time + covariates				
White participants: *APOE ε4* * age at menopause * time	-0.006 (-0.110, 0.099)	.92	-	-
Black participants: *APOE ε4* * age at menopause * time	0.155 (0.051, 0.260)	.004	-	-
Brain volume ~ *APOE ε4* * age at menopause + covariates				
White participants: *APOE ε4* * age at menopause	-	-	0.230 (-0.058, 0.517)	.12
Black participants: *APOE ε4* * age at menopause	-	-	-	-
Plasma p-tau217 ~ *APOE ε4* * age at menopause * time + covariates				
White participants: *APOE ε4* * age at menopause * time	-	-	-0.051 (-0.112, 0.011)	.11
Black participants: *APOE ε4* * age at menopause * time	-	-	-0.219 (-0.573, 0.135)	.22
Aβ-PET ~ *APOE ε4* * age at menopause + covariates				
White participants: *APOE ε4* * age at menopause	-	-	-0.141 (-0.263, -0.018)	.02
Black participants: *APOE ε4* * age at menopause	-	-	-	-

eTable4. Results of post hoc analyses evaluating dose effects of *APOE ε4* alleles.

Analyses	**ROS/MAP/MARS**		**WRAP**	
Model	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Memory ~ *APOE ε4* dose * age at menopause * time + covariates				
APOE ε3/ε4 * age at menopause * time	0.059 (0.002, 0.117)	.04	0.109 (0.024, 0.195)	.01
APOE ε4/ε4 * age at menopause * time	0.086 (-0.086, 0.258)	.33	-0.05 (-0.268, 0.162)	.63
Cortical thickness ~ *APOE ε4* dose * age at menopause * time + covariates				
APOE ε3/ε4 * age at menopause * time	0.071 (-0.000, 0.143)	.05	-	-
APOE ε4/ε4 * age at menopause * time	0.142 (-0.116, 0.400)	.28	-	-
Brain volume ~ *APOE ε4* dose * age at menopause + covariates				
APOE ε3/ε4 * age at menopause	-	-	0.325 (0.085, 0.566)	.008
APOE ε4/ε4 * age at menopause	-	-	-0.206 (-0.803, 0.391)	.50
Plasma p-tau217 ~ *APOE ε4* dose * age at menopause * time + covariates				
APOE ε3/ε4 * age at menopause * time	-	-	-0.046 (-0.109, 0.017)	.15
APOE ε4/ε4 * age at menopause * time	-	-	-0.150 (-0.307, 0.007)	.06
Aβ-PET ~ *APOE ε4* dose * age at menopause + covariates				
APOE ε3/ε4 * age at menopause	-	-	-0.109 (-0.234, 0.017)	.09
APOE ε4/ε4 * age at menopause	-	-	-0.074 (-0.337, 0.190)	.58

eTable5. Results of sensitivity analyses repeating models additionally adjusting for BMI and smoking history.

Analyses	**ROS/MAP/MARS**		**WRAP**	
Model	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Memory ~ *APOE ε4* * age at menopause * time + covariates				
APOE ε4 * age at menopause * time	0.065 (0.008, 0.122)	.03	0.092 (0.008, 0.176)	.03
Cortical thickness ~ *APOE ε4* * age at menopause * time + covariates				
APOE ε4 * age at menopause * time	0.068 (-0.004, 0.140)	.06	-	-
Brain volume ~ *APOE ε4* * age at menopause + covariates				
APOE ε4 * age at menopause	-	-	0.231 (-0.004, 0.466)	.05
Plasma p-tau217 ~ *APOE ε4* * age at menopause * time + covariates				
APOE ε4 * age at menopause * time	-	-	-0.063 (-0.124, -0.001)	.05
Aβ-PET ~ *APOE ε4* * age at menopause + covariates				
APOE ε4 * age at menopause	-	-	-0.162 (-0.272, -0.052)	.004

eTable6. Results of sensitivity analyses using an *ε3/ε3* reference group.

Analyses	**ROS/MAP/MARS**		**WRAP**	
Model	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Memory ~ *APOE* genotype * age at menopause * time + covariates				
APOE ε4 * age at menopause * time	0.060 (0.002, 0.117)	.04	0.076 (-0.014, 0.166)	.10
APOE ε2 * age at menopause * time	-0.027 (-0.102, 0.049)	.49	-0.045 (-0.160, 0.070)	.44
Cortical thickness ~ *APOE* genotype * age at menopause * time + covariates				
APOE ε4 * age at menopause * time	0.075 (0.003, 0.146)	.04	-	-
APOE ε2 * age at menopause * time	0.036 (-0.083, 0.155)	.56	-	-
Brain volume ~ *APOE* genotype * age at menopause + covariates				
APOE ε4 * age at menopause	-	-	0.206 (-0.047, 0.459)	.11
APOE ε2 * age at menopause	-	-	-0.185 (-0.566, 0.196)	.34
Plasma p-tau217 ~ *APOE* genotype * age at menopause * time + covariates				
APOE ε4 * age at menopause * time	-	-	-0.071 (-0.136, -0.006)	.03
APOE ε2 * age at menopause * time	-	-	-0.048 (-0.139, 0.043)	.30
Aβ-PET ~ *APOE* genotype * age at menopause + covariates				
APOE ε4 * age at menopause	-	-	-0.155 (-0.277, -0.033)	.01
APOE ε2 * age at menopause	-	-	-0.049 (-0.230, 0.132)	.59