

RESEARCH ARTICLE

Sex differences in associations between APOE ε2 and longitudinal cognitive decline

Madeline E. Wood^{1,2} | Lisa Y. Xiong^{1,3} | Yuen Yan Wong^{1,3} | Rachel F. Buckley^{4,5,6} |
 Walter Swardfager^{1,3} | Mario Masellis^{1,7} | Andrew S. P. Lim^{1,7} | Emma Nichols⁸ |
 Renaud La Joie⁹ | Kaitlin B. Casaletto⁹ | Raj G. Kumar¹⁰ |
 Kristen Dams-O'Connor^{10,11} | Priya Palta¹² | Kristen M. George¹³ |
 Claudia L. Satizabal^{14,15} | Lisa L. Barnes¹⁶ | Julie A. Schneider¹⁶ |
 Alexa Pichette Binet¹⁷ | Sylvia Villeneuve^{18,19,20} | Judy Pa²¹ | Adam M. Brickman²² |
 Sandra E. Black^{1,7} | Jennifer S. Rabin^{1,2,7,23} | for the ADNI and Prevent-AD Research
 Groups

¹Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, Ontario, Canada

²Rehabilitation Sciences Institute, University of Toronto, Toronto, Ontario, Canada

³Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada

⁴Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

⁵Florey Institute, University of Melbourne, Parkville, Victoria, Australia

⁶Melbourne School of Psychological Sciences, University of Melbourne, Parkville, Victoria, Australia

⁷Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

⁸Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

⁹Memory and Aging Center, Department of Neurology, Weill Institute for Neurosciences, University of California, San Francisco, California, USA

¹⁰Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, New York, New York, USA

¹¹Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

¹²Departments of Medicine and Epidemiology, Columbia University Irving Medical Center, New York, New York, USA

¹³Department of Public Health Sciences, University of California Davis School of Medicine, Davis, California, USA

¹⁴Department of Population Health Science and Biggs Institute for Alzheimer's and Neurodegenerative Diseases, UT Health San Antonio, San Antonio, Texas, USA

¹⁵Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA

¹⁶Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, USA

¹⁷Clinical Memory Research Unit, Faculty of Medicine, Lund University, Lund, Sweden

¹⁸Centre for Studies on Prevention of Alzheimer's Disease (StoP-AD), Douglas Mental Health University Institute, Centre for Studies on the Prevention of Alzheimer's Disease (StoP-AD), Montreal, Quebec, Canada

¹⁹Department of Psychiatry, McGill University, Montreal, Quebec, Canada

²⁰McConnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, Quebec, Canada

²¹Mark and Mary Stevens Neuroimaging and Informatics Institute, Department of Neurology, University of Southern California, Los Angeles, California, USA

²²Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, New York, USA

²³Harquail Centre for Neuromodulation, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2023 The Authors. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

Correspondence

Jennifer Rabin, Sunnybrook Health Sciences Centre, Room M6-178, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada.
Email: jennifer.rabin@sri.utoronto.ca

Funding information

Harquail Centre for Neuromodulation; Dr. Sandra Black Centre for Brain Resilience & Recovery; Canadian Institutes of Health Research, Grant/Award Numbers: 173253, 438475

Abstract

INTRODUCTION: We examined whether sex modifies the association between APOE $\epsilon 2$ and cognitive decline in two independent samples.

METHODS: We used observational data from cognitively unimpaired non-Hispanic White (NHW) and non-Hispanic Black (NHB) adults. Linear mixed models examined interactive associations of APOE genotype ($\epsilon 2$ or $\epsilon 4$ carrier vs. $\epsilon 3/\epsilon 3$) and sex on cognitive decline in NHW and NHB participants separately.

RESULTS: In both Sample 1 ($N = 9766$) and Sample 2 ($N = 915$), sex modified the association between APOE $\epsilon 2$ and cognitive decline in NHW participants. Specifically, relative to APOE $\epsilon 3/\epsilon 3$, APOE $\epsilon 2$ protected against cognitive decline in men but not women. Among APOE $\epsilon 2$ carriers, men had slower decline than women. Among APOE $\epsilon 3/\epsilon 3$ carriers, cognitive trajectories did not differ between sexes. There were no sex-specific associations of APOE $\epsilon 2$ with cognition in NHB participants ($N = 2010$).

DISCUSSION: In NHW adults, APOE $\epsilon 2$ may protect men but not women against cognitive decline.

KEYWORDS

Alzheimer's disease, APOE, cognitive decline, race/ethnicity, sex differences

Highlights

- We studied sex-specific apolipoprotein E (APOE) $\epsilon 2$ effects on cognitive decline.
- In non-Hispanic White (NHW) adults, APOE $\epsilon 2$ selectively protects men against decline.
- Among men, APOE $\epsilon 2$ was more protective than APOE $\epsilon 3/\epsilon 3$.
- In women, APOE $\epsilon 2$ was no more protective than APOE $\epsilon 3/\epsilon 3$.
- Among APOE $\epsilon 2$ carriers, men had slower decline than women.
- There were no sex-specific APOE $\epsilon 2$ effects in non-Hispanic Black (NHB) adults.

1 | BACKGROUND

Women have a greater lifetime risk of developing Alzheimer's disease (AD) dementia than men.¹ While some studies observe that women's increased risk is related to longer survival,^{2,3} other studies report that sex/gender disparities exist beyond what can be explained by female longevity alone.⁴ Mounting evidence suggests that biological mechanisms underpin sex differences in AD risk and progression.^{5–10}

The apolipoprotein E (APOE) gene encodes a protein that facilitates lipid transport in the brain.¹¹ APOE $\epsilon 3$ is the most common allele¹² and is neutral in relation to risk for AD dementia.¹¹ APOE $\epsilon 4$ is associated with a higher risk of AD dementia¹³ (mostly in non-Hispanic White [NHW] populations¹⁴), whereas APOE $\epsilon 2$ is associated with a lower risk of AD dementia.¹⁵ Studies suggest that there are sex differences in the effects of APOE $\epsilon 4$ on AD risk, such that women with APOE $\epsilon 4$ are disproportionately vulnerable to cognitive impairment¹⁶ and AD¹⁵ compared to their counterpart men.

Although a less robust literature, APOE $\epsilon 2$ may also have sex-specific effects on AD risk. The few reports on sex-specific effects of APOE

$\epsilon 2$ have been in the context of studies focused on APOE $\epsilon 4$ sex differences. One study found that in men but not women, APOE $\epsilon 2$ was associated with reduced risk of progression from normal cognition to mild cognitive impairment (MCI) or AD dementia.¹⁶ By contrast, a meta-analysis found that in cognitively unimpaired older adults, APOE $\epsilon 2/\epsilon 3$ decreased the risk of AD dementia more strongly in women than in men.¹⁷ That same meta-analysis reported the opposite pattern for APOE $\epsilon 2$ homozygosity ($N < 30/\text{sex}$), such that APOE $\epsilon 2/\epsilon 2$ was protective against AD dementia in men but not in women.¹⁷ Other studies examining sex-specific effects of APOE $\epsilon 2$ on cognition have also yielded mixed results, with some showing greater protection for women and others showing greater protection for men.^{18–20} These studies had small numbers of APOE $\epsilon 2$ carriers, and were cross-sectional in design or had limited longitudinal follow-up.^{18–20}

Allele frequencies can vary widely between populations of different ancestral backgrounds (i.e., population stratification), which can lead to unreliable associations between genetic factors and phenotypic outcomes.^{21–23} There is evidence that APOE $\epsilon 4$ confers differential risk for AD across races. While APOE $\epsilon 4$ is more common among Black

RESEARCH IN CONTEXT

1. **Systematic Review:** We performed a literature search using traditional sources (e.g., PubMed, Google Scholar). The limited number of existing studies examining sex-specific effects of apolipoprotein E (APOE) $\epsilon 2$ on Alzheimer's disease (AD) risk have yielded conflicting results. Studies were limited by small numbers of APOE $\epsilon 2$ carriers and lack of longitudinal follow-up.
2. **Interpretation:** Across two independent samples of non-Hispanic White (NHW) adults, we show that APOE $\epsilon 2$ protects men but not women against cognitive decline. We did not observe sex-specific effects of APOE $\epsilon 2$ in non-Hispanic Black adults. These findings are important for understanding biological contributions to sex differences in AD risk, which is crucial for developing sex-specific AD treatment and prevention strategies.
3. **Future Directions:** Future research should seek to replicate and extend these findings in diverse samples. Clarifying the sex-specific effects of APOE $\epsilon 2$ will advance our understanding of the biological drivers of sex disparities in AD.

(vs. White) populations, the association of APOE $\epsilon 4$ with risk for cognitive decline and AD dementia may be attenuated in Black adults.^{24–26}

In the present study, we carried out an in-depth investigation of sex differences in associations between APOE $\epsilon 2$ and longitudinal cognition. We first examined sex differences using pooled data from cognitively unimpaired adults participating in either the National Alzheimer's Coordinating Center (NACC) or Rush Alzheimer's Disease Center cohort studies (Sample 1). To control for population stratification^{21–23} and potentially differing effects of APOE across racial/ethnic groups,^{24–26} we performed analyses separately in NHW and non-Hispanic Black (NHB) participants. On finding sex-specific effects in NHW participants, we then sought to replicate these findings in an independent sample of participants from Alzheimer's Disease Neuroimaging Initiative (ADNI) and Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease (Prevent-AD) (Sample 2).

2 | METHODS**2.1 | Participants**

Data were obtained from four independent sources: (1) NACC; (2) Rush Alzheimer's Disease Center cohort studies: Religious Orders Study (ROS), Memory Aging Project (MAP), and Minority Aging Research Study (MARS); (3) ADNI; and (4) Prevent-AD. Sample 1 consisted of data from NACC and ROS/MAP/MARS. Sample 2 consisted of data from ADNI and Prevent-AD. Research procedures were approved by the relevant ethics committees and participants provided written

informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies.

Since APOE $\epsilon 2$ protects against cognitive decline,²⁷ we restricted our sample to participants classified as cognitively unimpaired at baseline. This allowed us to maintain a representative proportion of $\epsilon 2$ carriers and to examine early cognitive changes with respect to APOE genotype. We also required that participants were ≥ 50 years old at baseline and had at least one follow-up cognitive assessment. In NACC, cognitively unimpaired is defined as a Clinical Dementia Rating (CDR) global score of 0.²⁸ In ROS/MAP/MARS, cognitively unimpaired is defined as the absence of MCI or dementia.^{29,30} In ADNI and Prevent-AD, cognitively unimpaired is defined according to several criteria, one of which is a CDR global score of 0.^{31,32} In the present study, we only included participants who self-identified as NHW or NHB since these were the largest racial/ethnic groups across data sources. Further details on the sample selection process are described in Figure S1 in the supplemental material.

2.2 | Cognition

All four data sources (i.e., NACC, ROS/MAP/MARS, ADNI, Prevent-AD) assess cognition approximately annually. For each data source, we created a comparable cognitive composite that was weighted toward episodic memory (see supplemental material for specific tests). To calculate the composite, we z-transformed raw test scores using the mean and standard deviation of the baseline study samples, and then computed the average of the standardized scores.

2.3 | Genotype

We used publicly available APOE genotype data to classify participants as $\epsilon 2$, $\epsilon 3/\epsilon 3$, or $\epsilon 4$ carriers. The samples had relatively few APOE $\epsilon 2$ homozygotes ($N = 56$ in NACC; $N = 13$ in ROS/MAP/MARS, $N = 1$ in ADNI, $N = 0$ in Prevent-AD), and therefore participants with one or two copies of $\epsilon 2$ were examined together. APOE $\epsilon 3$ homozygotes were the reference group. APOE $\epsilon 2/\epsilon 4$ carriers were excluded due to the opposing effects of $\epsilon 2$ and $\epsilon 4$ alleles on AD risk.²⁷ All samples met Hardy-Weinberg Equilibrium expectations.³³

2.4 | Statistical analysis

Analyses were conducted in R (v.4.1.2). We used t -tests and χ^2 tests to assess differences in baseline characteristics between men and women as well as across samples. We used linear mixed models to examine the interactive effects of APOE allele ($\epsilon 2$ and $\epsilon 4$ vs. reference $\epsilon 3/\epsilon 3$), sex (reference female), and time (years from baseline) on longitudinal cognition separately in NHW and NHB participants. Where possible sex-specific APOE $\epsilon 2$ effects were observed, we then performed sex- and genotype-stratified analyses. Sex-stratified analyses

examined the two-way interaction between APOE allele and time on cognition, allowing us to compare cognitive trajectories of APOE $\epsilon 2$ versus $\epsilon 3/\epsilon 3$ carriers among men and women separately. Genotype-stratified analyses examined the two-way interaction between sex and time on cognition, allowing us to compare cognitive trajectories of men and women APOE $\epsilon 2$ carriers as well as men and women APOE $\epsilon 3/\epsilon 3$ carriers. All models included random intercepts and slopes. As in a previous study,³⁴ including an additional quadratic term for time (to account for accelerated decline with aging) resulted in better model fit compared to models without this term ($p < .05$). Therefore, all models included this term.

We first examined sex differences in associations between APOE $\epsilon 2$ and cognitive decline in NHW and NHB participants from Sample 1. On observing sex-specific effects in NHW participants, we sought to replicate these effects in an independent sample of NHW participants (Sample 2). In exploratory analyses, we examined whether the sex-specific effects of APOE $\epsilon 2$ on longitudinal cognition were more pronounced at older ages. To do so, we repeated the main analyses after restricting the baseline age according to four cutoff values: age ≥ 65 , ≥ 70 , ≥ 75 , and ≥ 80 years. Finally, to contextualize the sex-specific APOE $\epsilon 2$ findings, we compared them against sex-specific APOE $\epsilon 4$ findings.^{15,16}

2.4.1 | Covariates

In all analyses, we adjusted for data source (i.e., NACC vs. ROS/MAP/MARS or ADNI vs. Prevent-AD), baseline age, years of education, and their interactions with time. To account for practice effects on neuropsychological tests, we included a term for the square root of the number of previous study visits. This method assumes the largest improvement in performance after the first testing session, with diminishing returns on subsequent sessions.³⁵ If this covariate was not significant, it was removed from the models. Because vascular risk factors are associated with cognitive decline,^{36,37} we also adjusted for baseline vascular risk and its interaction with time. Vascular risk was quantified using a summary score³⁸ that includes the presence/absence of up to five conditions (diabetes, hypertension, high cholesterol, stroke, and heart conditions; see supplemental material for details). Finally, to determine whether length of cognitive follow-up impacted the results, we re-ran all models after adjusting for total number of visits. When follow-up visits were explicitly modeled, the estimates for the effects of interest were essentially unchanged. For simplicity, we report the results without including terms for visit number.

3 | RESULTS

3.1 | Demographic characteristics

Table 1 summarizes the demographic characteristics for NHW and NHB participants in Sample 1 and NHW participants in Sample 2

(Tables S1 and S2 summarize demographic data for each data source separately). In Sample 1 (NACC and ROS/MAP/MARS), 9766 NHW and 2010 NHB participants met inclusion criteria. In Sample 2 (ADNI and Prevent-AD), 915 NHW participants met inclusion criteria. With respect to NHW participants, Sample 1 was slightly older than Sample 2 (73.0 vs. 70.1 years), had a higher proportion of women (65.0% vs. 59.1%), a slightly higher proportion of APOE $\epsilon 2$ carriers (12.9% vs. 11.8%), and greater number of study visits (median of 6 vs. 5 visits).

3.2 | Sex-specific associations of APOE $\epsilon 2$ with cognitive decline in NHB participants

In Sample 1, the interaction between sex, APOE $\epsilon 2$, and time on cognitive decline was not significant in NHB participants ($\beta = -0.011$, 95% confidence interval [CI]: -0.153 to 0.131 , $p = .88$; Table S3; Figure 1). The lower-order two-way interaction between sex and APOE $\epsilon 2$ was also not significant ($\beta = 0.056$, 95% CI: -0.188 to 0.301 , $p = .65$; Table S3), suggesting that there are no sex-specific associations of APOE $\epsilon 2$ with longitudinal cognition or with cognition collapsed across all time-points. We next tested the two-way interaction between APOE $\epsilon 2$ (vs. $\epsilon 3/\epsilon 3$) and time on cognitive decline (adjusting for sex). In this analysis, APOE $\epsilon 2$ carriers did not exhibit significantly slower cognitive decline relative to $\epsilon 3/\epsilon 3$ carriers ($\beta = 0.046$, 95% CI: -0.012 to 0.104 , $p = .12$; Table S3; Figure S2). Similar findings were observed in sex-stratified analyses (Table S3). With respect to sex-specific effects of APOE $\epsilon 4$, we observed a non-significant interaction between male sex, APOE $\epsilon 4$, and time in NHB participants ($\beta = 0.103$, 95% CI: -0.017 to 0.223 , $p = .09$; Table S3; Figure S3). Sex- and genotype-stratified analyses showed that women with APOE $\epsilon 4$ exhibited faster cognitive decline relative to both women carrying $\epsilon 3/\epsilon 3$ and men carrying $\epsilon 4$ (Table S3).

3.3 | Sex-specific associations of APOE $\epsilon 2$ with cognitive decline in NHW participants

In NHW participants from Sample 1, there was a significant interaction between sex, APOE $\epsilon 2$, and time (Tables 2 and S4; Figure 2). In sex-stratified analyses, men with APOE $\epsilon 2$ exhibited slower cognitive decline than men with APOE $\epsilon 3/\epsilon 3$ (Tables 2 and S4). By contrast, cognitive trajectories did not differ between women with APOE $\epsilon 2$ versus $\epsilon 3/\epsilon 3$ (Tables 2 and S4). In genotype-stratified analyses, cognitive trajectories differed by sex among APOE $\epsilon 2$ carriers, but not among APOE $\epsilon 3/\epsilon 3$ carriers. Specifically, among APOE $\epsilon 2$ carriers, men exhibited slower decline relative to women, whereas rates of decline were similar between men and women carrying APOE $\epsilon 3/\epsilon 3$ (Tables 2 and S4).

Given the relatively large number of participants in NACC ($N = 7931$, N women = 4980, 62.8%) and ROS/MAP ($N = 1835$, N women = 1364, 74.3%), we examined whether the pattern of results was present in each data source separately. In NACC, there was a significant interaction between male sex, APOE $\epsilon 2$, and time on cognitive decline (Tables 2 and S5; Figures S4 and S5). In ROS/MAP, the same three-way interaction was not significant (Tables 2 and S6; Figures S4

TABLE 1 Baseline demographic and clinical characteristics by racial/ethnic group and cohort.

Non-Hispanic Black participants in Sample 1 (NACC & ROS/MAP/MARS)			
Variables	Total sample (n = 2010)	Women (n = 1583, 78.8%)	Men (n = 427, 21.2%)
Age in years, mean (SD)	71.3 (7.59)	71.4 (7.57)	71.0 (7.67)
Education in years, mean (SD)	14.9 (3.10)	14.9 (3.02)	14.9 (3.41)
APOE ε2 carriers, n (%)	336 (16.7)	263 (16.6)	73 (17.1)
ε2/ε3, n (%)	316 (15.7)	248 (15.7)	68 (15.9)
ε2/ε2, n (%)	20 (1.00)	15 (0.95)	5 (1.17)
APOE ε4 carriers, n (%)	662 (32.9)	506 (32.0)	156 (36.5)
ε3/ε4, n (%)	595 (29.6)	454 (28.7)	141 (33.0)
ε4/ε4, n (%)	67 (3.33)	52 (3.28)	15 (3.51)
APOE ε3/ε3 carriers, n (%)	1012 (50.3)	814 (51.4)	198 (46.4)
Total number of visits, median (SD)	5 (3.96)	6 (4.02)*	5 (3.72)*
ε2 carriers, median (SD)	6 (4.11)	6 (4.20)	6 (3.79)
ε4 carriers, median (SD)	5 (3.70)	5 (3.80)	5 (3.33)
ε3/3 carriers, median (SD)	6 (4.05)	6 (4.07)	5 (3.92)
Vascular risk score (range 0–1), mean (SD)	0.36 (0.21)	0.36 (0.21)	0.36 (0.22)
Non-Hispanic White participants in Sample 1 (NACC & ROS/MAP)			
Variables	Total sample (n = 9766)	Women (n = 6344, 65.0%)	Men (n = 3422, 35.0%)
Age in years, mean (SD)	73.0 (9.00)	73.0 (9.14)	72.9 (8.75)
Education in years, mean (SD)	16.3 (2.83)	16.0 (2.75)*	16.9 (2.90)*
APOE ε2 carriers, n (%)	1260 (12.9)	840 (13.2)	420 (12.3)
ε2/ε3, n (%)	1211 (12.4)	814 (12.8)	397 (11.6)
ε2/ε2, n (%)	49 (0.50)	26 (0.41)	23 (0.67)
APOE ε4 carriers, n (%)	2622 (26.8)	1670 (26.3)	952 (27.8)
ε3/ε4, n (%)	2362 (24.2)	1508 (23.8)	854 (25.0)
ε4/ε4, n (%)	260 (2.66)	162 (2.55)	98 (2.86)
APOE ε3/ε3 carriers, n (%)	5884 (60.2)	3834 (60.4)	2050 (59.9)
Total number of visits, median (SD)	6 (4.41)	6 (4.48)*	5 (4.27)*
ε2 carriers, median (SD)	6 (4.53)	6 (4.49)	6 (4.61)
ε4 carriers, median (SD)	5 (4.18)	6 (4.26)*	5 (4.02)*
ε3/3 carriers, median (SD)	6 (4.48)	6 (4.56)*	5 (4.30)
Vascular risk score (range 0–1), mean (SD)	0.26 (0.21)	0.25 (0.20)*	0.28 (0.21)*
Non-Hispanic White participants in Sample 2 (ADNI & Prevent-AD)			
Variables	Total sample (n = 915)	Women (n = 542, 59.1%)	Men (n = 373, 40.8%)
Age in years, mean (SD)	70.1 (7.35)	68.8 (7.17)*	71.9 (7.24)*
Education in years, mean (SD)	16.2 (2.92)	15.7 (2.96)*	16.9 (2.71)*
APOE ε2 carriers, n (%)	108 (11.8)	55 (10.1)	53 (14.2)
ε2/ε3, n (%)	107 (11.7)	55 (10.1)	52 (13.9)
ε2/ε2, n (%)	1 (0.11)	0 (0)	1 (0.27)
APOE ε4 carriers, n (%)	287 (31.4)	176 (32.5)	111 (29.8)
ε3/ε4, n (%)	263 (28.7)	160 (29.5)	103 (27.6)
ε4/ε4, n (%)	24 (2.62)	16 (2.95)	8 (2.14)
APOE ε3/ε3 carriers, n (%)	520 (56.8)	311 (57.3)	209 (56.0)

(Continues)

TABLE 1 (Continued)

Non-Hispanic White participants in Sample 2 (ADNI & Prevent-AD)			
Variables	Total sample (n = 915)	Women (n = 542, 59.1%)	Men (n = 373, 40.8%)
Total number of visits, median (SD)	5 (2.86)	5 (2.70)	5 (3.07)
ε2 carriers, median (SD)	5 (2.61)	5 (2.25)	5 (2.96)
ε4 carriers, median (SD)	5 (2.70)	5 (2.60)	5 (2.86)
ε3/3 carriers, median (SD)	5 (2.99)	5 (2.83)	5 (3.21)
Vascular risk score (range 0–1), mean (SD)	0.37 (0.19)	0.37 (0.20)	0.37 (0.18)

Abbreviations: ADNI, Alzheimer’s Disease Neuroimaging Initiative; MARS, Minority Aging Research Study; MAP, Memory Aging Project; NACC, National Alzheimer’s Coordinating Center; Prevent-AD, Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease; ROS, Religious Orders Study; SD, standard deviation.

**p* < .05. *P*-values represent results of independent samples *t*-tests and chi-square tests comparing men versus women.

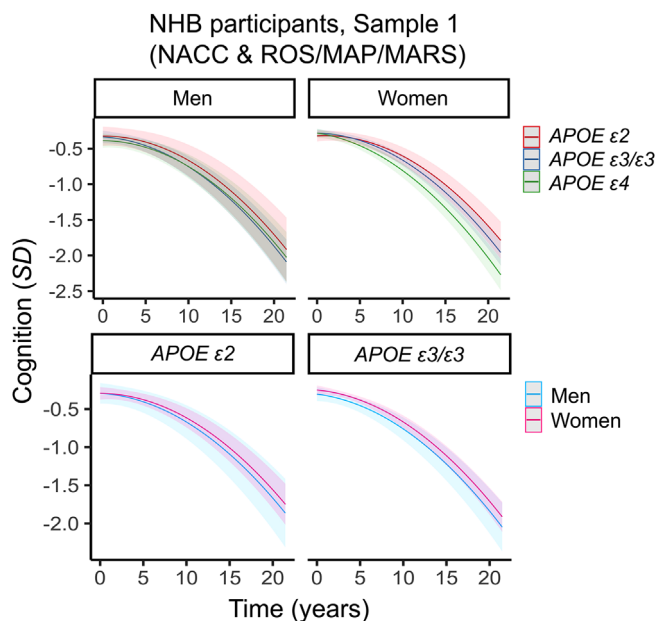


FIGURE 1 Three-way interaction between sex, APOE, and time on cognitive decline in non-Hispanic Black (NHB) participants in Sample 1 (NACC & ROS/MAP/MARS). Plots depict marginal effects, showing change in cognition (standardized score) over time, stratified by sex and genotype (APOE ε4 plot not shown). There were no significant sex differences in associations between APOE ε2 and global cognitive decline. The models are adjusted for covariates. Shaded regions represent 95% confidence intervals.

and S5). However, sex- and genotype-stratified analyses revealed a similar pattern of findings in both data sources (Tables 2, S5, and S6). Sex-stratified analyses showed that men with APOE ε2 had a pattern of slower cognitive decline than men with APOE ε3/ε3, although the interaction was not statistically significant in ROS/MAP ($\beta = 0.149$, 95% CI: -0.022 to 0.319 , $p = .09$; Tables 2 and S6). In both cohorts, women with APOE ε2 did not have slower decline than women carrying APOE ε3/ε3. In genotype-stratified analyses, men with APOE ε2 had significantly slower decline than women with APOE ε2. Similarly, men and women APOE ε3/ε3 carriers did not exhibit different cognitive trajectories.

Next, we sought to replicate the main sex-specific findings in an independent sample of NHW participants from ADNI and Prevent-AD (Sample 2). We again observed a significant interaction between male sex, APOE ε2, and time (Tables 2 and S7; Figure 3), with Sample 2 showing a larger effect than Sample 1 (as demonstrated by a larger standardized beta coefficient). Next, we performed sex-stratified analyses. In men, APOE ε2 carriers had a non-significant pattern of slower decline than ε3/ε3 carriers. While this finding did not reach statistical significance, the effect size was similar to that reported in Sample 1. Surprisingly, women with APOE ε2 had a non-significant pattern of faster decline compared to women with APOE ε3/ε3 (Tables 2 and S7). In genotype-stratified analyses, men with APOE ε2 exhibited significantly slower decline than women with ε2, whereas the rates of decline did not differ between men and women with APOE ε3/ε3 (Tables 2 and S7). The effect sizes in these genotype-stratified analyses were equivalent to or larger than those observed in Sample 1.

In exploratory analyses, we examined whether the sex-specific effect of APOE ε2 on cognitive decline differed across increasing baseline age cutoffs (age ≥ 65 , ≥ 70 , ≥ 75 , and ≥ 80 years). In Sample 1, we observed that the magnitude of the three-way interaction term increased in a positive direction as baseline age increased (Table S8). In Sample 2, we observed a similar increase in magnitude among participants aged 50 through 70 (Table S9). However, the magnitude of the interaction term began to decrease again above the age of 75. This is likely due to the considerably smaller sample sizes at these older ages (Table S9). Together, these findings suggest that male-specific APOE ε2 protection may become more pronounced in older age.

3.4 | Sex-specific associations of APOE ε4 with cognitive decline in NHW participants

To contextualize the APOE ε2 findings in NHW participants in Sample 1 and Sample 2, we sought to replicate previously reported sex differences in associations between APOE ε4 and cognitive decline. In Sample 1, there was a significant interaction between male sex, APOE ε4, and time on cognition in NHW participants ($\beta = 0.064$, 95% CI: 0.007 to 0.120 , $p = .03$; Table S4; Figure 2). Sex-stratified analyses demonstrated

TABLE 2 Sex-specific associations between APOE $\epsilon 2$ (vs. APOE $\epsilon 3/\epsilon 3$) and longitudinal cognition in non-Hispanic White participants.

Analyses	Sample 1 (NACC & ROS/MAP)		NACC		ROS/MAP		Sample 2 (ADNI & Prevent-AD)	
	β (95% CI)	<i>p</i>	β (95% CI)	<i>p</i>	β (95% CI)	<i>p</i>	β (95% CI)	<i>p</i>
Three-way interaction:								
Sex $\times$ APOE $\epsilon 2$ (vs. $\epsilon 3/\epsilon 3$) $\times$ time	0.097 (0.023–0.172)	.01	0.081 (0.010–0.152)	.02	0.127 (–0.069–0.323)	.20	0.195 (0.006–0.385)	.04
Sex-stratified two-way interactions:								
APOE $\epsilon 2$ (vs. $\epsilon 3/\epsilon 3$) $\times$ time in men	0.096 (0.037–0.155)	.001	0.074 (0.020–0.128)	.008	0.149 (–0.022–0.319)	.09	0.093 (–0.056–0.243)	.22
APOE $\epsilon 2$ (vs. $\epsilon 3/\epsilon 3$) $\times$ time in women	–0.001 (–0.044–0.043)	.97	–0.008 (–0.051–0.035)	.71	0.012 (0.089–0.114)	.81	–0.104 (–0.228–0.020)	.10
Genotype-stratified two-way interaction:								
Male sex $\times$ time in APOE $\epsilon 2$ carriers	0.120 (0.051–0.190)	.001	0.095 (0.028–0.161)	.005	0.191 (0.012–0.371)	.04	0.160 (–0.002–0.321)	.05
Male sex $\times$ time in APOE $\epsilon 3/\epsilon 3$ carriers	–0.000 (–0.031–0.030)	.99	–0.005 (–0.033–0.024)	.75	0.038 (–0.044–0.121)	.36	–0.009 (–0.091–0.074)	.84

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; CI: confidence interval; MAP, Memory Aging Project; NACC, National Alzheimer's Coordinating Center; Prevent-AD, Pre-symptomatic Evaluation of Experimental or Novel Treatments for Alzheimer Disease; ROS: Religious Orders Study.

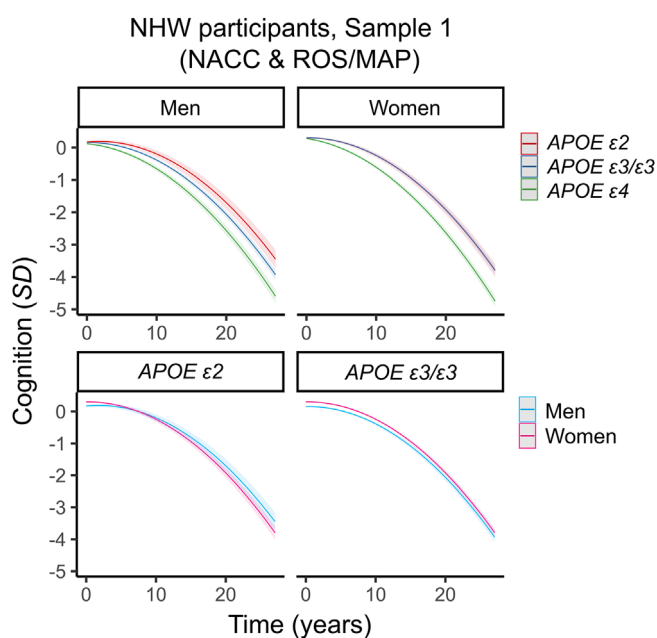


FIGURE 2 Three-way interaction between sex, APOE, and time on cognitive decline in non-Hispanic White (NHW) participants in Sample 1 (NACC & ROS/MAP). Plots depict marginal effects, showing change in cognition (standardized score) over time, stratified by sex and genotype (APOE $\epsilon 4$ plot not shown). In sex-stratified analyses, men carrying APOE $\epsilon 2$ were more protected against decline than men carrying APOE $\epsilon 3/\epsilon 3$. In women, APOE $\epsilon 2$ was no more protective than APOE $\epsilon 3/\epsilon 3$. In genotype-stratified analyses, men carrying APOE $\epsilon 2$ were more protected against decline than women carrying APOE $\epsilon 2$. By contrast, rates of decline did not differ between men and women APOE $\epsilon 3/\epsilon 3$ carriers. The models are adjusted for covariates. Shaded regions represent 95% confidence intervals.

that APOE $\epsilon 4$ (vs. APOE $\epsilon 3/\epsilon 3$) was more strongly associated with cognitive decline in women ($\beta = -0.192$, 95% CI: -0.227 to -0.158 , $p < .001$; Table S4) than men ($\beta = -0.127$, 95% CI: -0.171 to -0.083 , $p < .001$; Table S4). A genotype-stratified analysis showed that men with APOE $\epsilon 4$ declined more slowly than women with APOE $\epsilon 4$ ($\beta = 0.053$, 95% CI: 0.002 to 0.104 , $p = .04$; Table S4; Figure S6). These same findings were not observed in Sample 2, as the interaction between male sex, APOE $\epsilon 4$, and time on longitudinal cognition was not significant ($\beta = 0.041$, 95% CI: -0.095 to 0.177 , $p = .56$; Table S7; Figures 2 and S7).

4 | DISCUSSION

Across two independent samples of cognitively unimpaired NHW participants (Sample 1: NACC and ROS/MAP, Sample 2: ADNI and Prevent-AD), we found that men with APOE $\epsilon 2$ were more protected against cognitive decline compared to both men with APOE $\epsilon 3/\epsilon 3$ and women with APOE $\epsilon 2$. Notably, no sex differences were observed among APOE $\epsilon 3/\epsilon 3$ carriers. Analyses performed separately in NACC and ROS/MAP showed the same pattern of male-specific protection in APOE $\epsilon 2$ carriers. In both Sample 1 and Sample 2, the magnitude of the sex-specific effect of APOE $\epsilon 2$ on cognitive decline was generally more pronounced at older ages when risk for AD is higher.³⁹ The replication of these findings in cognitively unimpaired NHW adults across several data sources provide compelling evidence that APOE $\epsilon 2$ protects men but not women against cognitive decline. In contrast, we observed no sex-specific associations in NHB participants, and APOE $\epsilon 2$ was not significantly associated with attenuated cognitive decline (relative to $\epsilon 3/\epsilon 3$) in men or women.

The biological mechanisms driving the observed sex differences in the NHW participants are unclear. One possibility may relate to

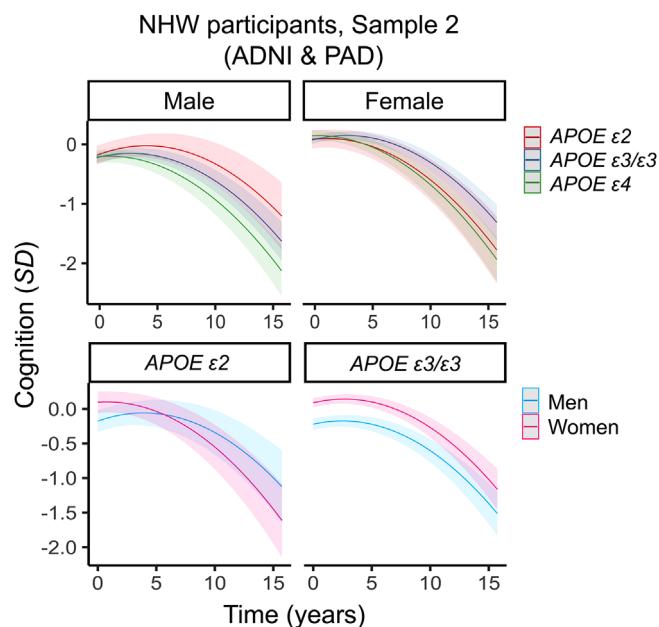


FIGURE 3 Three-way interaction between sex, APOE, and time on cognitive decline in non-Hispanic White (NHW) participants in Sample 2 (ADNI & Prevent-AD). Plots depict marginal effects, showing change in cognition (standardized score) over time, stratified by sex and genotype (APOE $\epsilon 4$ plot not shown). Sex-stratified analyses were not significant. In genotype-stratified analyses, men carrying APOE $\epsilon 2$ were more protected against decline than women carrying APOE $\epsilon 2$, whereas the rates of decline did not differ between men and women carrying APOE $\epsilon 3/\epsilon 3$. The models are adjusted for covariates. Shaded regions represent 95% confidence intervals.

sex hormones, which regulate ApoE protein synthesis.⁴⁰ Estrogen upregulates ApoE synthesis,^{40,41} and like other metabolic and neurological systems,^{42,43} estrogen-mediated APOE processes may become disrupted around menopause when estrogen levels decline. If so, APOE $\epsilon 2$ protection against AD pathology and its downstream cognitive effects may be reduced in postmenopausal women. Additional research is needed to elucidate the biological mechanisms underlying the sex-specific effects of APOE $\epsilon 2$.

The finding of sex-specific associations between APOE $\epsilon 2$ and cognitive decline complements evidence that women (vs. men) carrying APOE $\epsilon 4$ are at disproportionately higher risk for AD.^{15,16,44,45} We replicated this finding in NHW and NHB from Sample 1 (but not Sample 2), observing that women with APOE $\epsilon 4$ had faster rates of cognitive decline than their counterpart men. Interestingly, in NHW participants from Sample 1, the effect size of the three-way interaction of APOE $\epsilon 2$, sex, and time on cognitive decline ($\beta = 0.097$) was greater than that of the equivalent interaction for APOE $\epsilon 4$ ($\beta = 0.064$). This suggests that sex-specific protective effects of APOE $\epsilon 2$ may represent an important yet overlooked contribution to sex disparities in cognitive and AD outcomes.

It is not clear why we did not observe significant associations between APOE $\epsilon 2$ and attenuated cognitive decline in NHB participants of either sex. Previous research demonstrates that pathological drivers of cognitive decline may differ across races.^{46,47} It is possi-

ble that in NHB participants, associations of APOE $\epsilon 2$ with cognition (including potential sex-specific associations) are obscured by more salient predictors of cognitive decline. Alternatively, APOE $\epsilon 2$ protection against AD may be weaker or non-existent in NHB persons. This idea is consistent with previous research in Black persons,^{48,49} and broader evidence that APOE genotypes differentially impact cognition across racial and ethnic groups.^{19,24–26,50}

Despite observing no significant associations of APOE $\epsilon 2$ with attenuated cognitive decline across both sexes in NHB participants, APOE $\epsilon 2$ was more prevalent in NHB compared to NHW participants. This difference aligns with existing reports of racial/ethnic differences in APOE carriage^{19,24,51} and is consistent with broader observations that allele frequencies vary across populations of different ancestral backgrounds.²¹ Future work should seek to further clarify sex-specific APOE effects in diverse cohorts.

In the NHW participants, there were some notable differences in the effect sizes across data sources. Specifically, the effect size of the three-way interaction of APOE $\epsilon 2$, sex, and time was larger in ROS/MAP and Sample 2 (ADNI and Prevent-AD) compared to NACC. Similarly, the effect size of the two-way interaction between APOE $\epsilon 2$ and time in men was larger in ROS/MAP and Sample 2 (ADNI and Prevent-AD) compared to NACC. The reasons for these differences remain unclear but may relate to selection bias. For example, ROS/MAP participants are generally older than NACC participants (mean of 77 vs. 72 years old) and have more follow-up data (median of 10 vs. 5 visits). Given our findings that sex-specific APOE $\epsilon 2$ effects become more salient at older ages, we might expect larger effects in older samples, particularly if they have more follow-up data. Additionally, all participants in Prevent-AD have either a parent or multiple siblings with AD.³² Therefore, the larger effects observed in Sample 2 may suggest that sex-specific APOE effects are more pronounced in a sample enriched with familial AD risk.

The major strength of this study is the replication of sex-specific findings across two independent samples of pooled data (as well as separately in NACC and ROS/MAP). This is particularly notable given different sampling procedures, demographic characteristics, cognitive tests, and follow-up times across the studies. The present study has several limitations. First, study participants are generally well-educated, which may limit the generalizability of our findings. Second, since whole genome sequencing or equivalent data were not available for many study participants, we were unable to adjust our analyses for genetic principal components (to account for possible population admixture). This approach is ideal, as there may be multiple genetic subpopulations in our samples. Third, in Sample 2, there were too few NHB participants ($N = 52$) to perform a replication analysis. It will be important for future research to replicate and extend the present findings to other diverse groups. Fourth, while we verified that the NHW and NHB samples aligned with Hardy-Weinberg Equilibrium expectations, the recorded APOE genotypes may contain miscalls, which may bias effect estimates, particularly in smaller APOE genotype stratified samples. Fifth, a challenge to studying sex differences in AD is that women are more likely than men to survive to older ages.³ When a gene, such as APOE, has pleiotropic effects on risk for mortality and AD,⁵² this survival bias can cause spurious associations. Finally, given

the rarity of APOE ε2 homozygosity, we were unable to investigate sex differences in allelic dose effects.

5 | CONCLUSION

Our results clarify the longstanding view that APOE ε2 protects against AD.^{11,27,50,53,54} Among NHW adults, we found that APOE ε2 protects men but not women against cognitive decline. These findings have important implications for understanding the biological drivers of sex differences in AD risk, which is crucial for developing sex-specific strategies to prevent and treat AD dementia. Large and diverse samples are needed to replicate the present findings and to further clarify the sex-specific effects of APOE ε2 on risk for AD.

ACKNOWLEDGMENTS

M.E.W. receives support from the Canadian Institutes of Health Research (Canada Graduate Scholarships – Master's). L.Y.X. gratefully acknowledges financial support from the Canadian Institutes of Health Research (Doctoral Research Award: Canadian Graduate Scholarships; 202111FBD-476226). R.F.B. is supported by a K99/R00 award from NIA (R00AG061238-03), an Alzheimer's Association Research Fellowship (AARF-20-675646), and philanthropic support. W.S. gratefully acknowledges financial support from the Canadian Institute of Health Research (Team Grant); The Natural Sciences and Engineering Research Council of Canada (RGPIN-2017-06962); the Alzheimer's Association & Brain Canada (AARG501466); Weston Brain Institute & Alzheimer's Research UK, Alzheimer's Association and Michael J. Fox Foundation (BAND3). The work was supported in part through funding from the Canada Research Chairs Program. A.S.P.L. receives support from R01AG071638, R01AG052488 and RF1AG070436. E.N. receives support from T32AG000247. R.L. receives support from K99AG065501. K.B.C. receives support from R01AG072475. C.S. receives support from the Texas Alzheimer's Research and Care Consortium (2020-58-81-CR) and R01 AG059727, UF1 NS125513, and P30 AG066546. L.L.B. receives support from R01AG022018 and P30AG010161/P30AG072975. JAS receives support from P30AG010161/P30AG072975, R01AG015819, R01AG17917, R01AG022018. J.P. receives support from RF1AG054617. J.S.R. receives support from the Harquail Centre for Neuromodulation, the Dr. Sandra Black Centre for Brain Resilience & Recovery, Canadian Institutes of Health Research (173253, 438475), and the Alzheimer's Society of Canada. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADCs: P50 AG005131 (PI James Brewer, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG005136 (PI Thomas Grabowski, MD), P50 AG005138 (PI Mary Sano, PhD), P50 AG005142 (PI Helena Chui, MD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005681 (PI John Morris, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG008051 (PI Thomas Wisniewski, MD), P50 AG008702 (PI Scott Small, MD), P30 AG010124 (PI John Trojanowski, MD, PhD), P30 AG010129 (PI Charles DeCarli, MD), P30 AG010133 (PI Andrew Saykin, PsyD), P30 AG010161 (PI

David Bennett, MD), P30 AG012300 (PI Roger Rosenberg, MD), P30 AG013846 (PI Neil Kowall, MD), P30 AG013854 (PI Robert Vassar, PhD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P30 AG019610 (PI Eric Reiman, MD), P50 AG023501 (PI Bruce Miller, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P30 AG028383 (PI Linda Van Eldik, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), P30 AG035982 (PI Russell Swerdlow, MD), P50 AG047266 (PI Todd Golde, MD, PhD), P50 AG047270 (PI Stephen Strittmatter, MD, PhD), P50 AG047366 (PI Victor Henderson, MD, MS), P30 AG049638 (PI Suzanne Craft, PhD), P30 AG053760 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P20 AG068024 (PI Erik Roberson, MD, PhD), P20 AG068053 (PI Marwan Sabbagh, MD), P20 AG068077 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), and P30 AG072959 (PI James Leverenz, MD). We thank the study participants and staff of the Rush Alzheimer's Disease Center. This work was supported by NIA grants P30 AG010161 (ROS; PI David Bennett, MD), R01AG17917 (MAP; PI David Bennett, MD), and R01AG22018 (MARS; PI Lisa Barnes, PhD).

CONFLICT OF INTEREST STATEMENT

A.S.P.L. sat on a paid advisory board for Eisai within the past 12 months. L.L.B. was named Deputy Editor of Alzheimer's & Dementia in 2023. J.A.S. serves on the Scientific Advisory Boards for AVID radio-pharmaceuticals (subsidiary of Lilly), Alnylam Pharmaceuticals, Apellis Pharmaceuticals, Takeda Pharmaceuticals, and the National Hockey League. M.E.W., L.Y.X., Y.Y.W., R.F.B., W.S., M.M., E.N., R.L.J., K.B.C., R.G.K., K.D.O.C., P.P., K.M.G., C.L.S., A.P.B., S.V., J.P., A.M.B., S.E.B., and J.S.R. have no conflicts of interests to disclose. Author disclosures are available in the [supporting information](#).

REFERENCES

- Chêne G, Beiser A, Au R, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement J Alzheimers Assoc*. 2015;11(3):310-320. doi:[10.1016/j.jalz.2013.10.005](#)
- Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. *Neurology*. 1997;49(6):1498-1504. doi:[10.1212/wnl.49.6.1498](#)
- Shaw C, Hayes-Larson E, Glymour MM, et al. Evaluation of selective survival and sex/gender differences in dementia incidence using a simulation model. *JAMA Netw Open*. 2021;4(3):e211001. doi:[10.1001/jamanetworkopen.2021.1001](#)
- Nebel RA, Aggarwal NT, Barnes LL, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. *Alzheimers Dement*. 2018;14(9):1171-1183. doi:[10.1016/j.jalz.2018.04.008](#)
- Buckley RF, Mormino EC, Amariglio RE, et al. Sex, amyloid, and APOEε4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. *Alzheimers Dement J Alzheimers Assoc*. 2018;14(9):1193-1203. doi:[10.1016/j.jalz.2018.04.010](#)
- Edwards L, La Joie R, Iaccarino L, et al. Multimodal neuroimaging of sex differences in cognitively impaired patients on the Alzheimer's continuum: greater tau-PET retention in females. *Neurobiol Aging*. 2021;105:86-98. doi:[10.1016/j.neurobiolaging.2021.04.003](#)
- Liesinger AM, Graff-Radford NR, Duara R, et al. Sex and age interact to determine clinicopathologic differences in Alzheimer's disease.

- Acta Neuropathol (Berl)*. 2018;136(6):873-885. doi:[10.1007/s00401-018-1908-x](https://doi.org/10.1007/s00401-018-1908-x)
8. Oveisgharan S, Arvanitakis Z, Yu L, Farfel J, Schneider JA, Bennett DA. Sex differences in Alzheimer's disease and common neuropathologies of aging. *Acta Neuropathol (Berl)*. 2018;136(6):887-900. doi:[10.1007/s00401-018-1920-1](https://doi.org/10.1007/s00401-018-1920-1)
9. Palta P, Rippon B, Tahmi M, et al. Sex differences in in vivo tau neuropathology in a multiethnic sample of late middle-aged adults. *Neurobiol Aging*. 2021;103:109-116. doi:[10.1016/j.neurobiolaging.2021.03.007](https://doi.org/10.1016/j.neurobiolaging.2021.03.007)
10. Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: a think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimers Dement*. 2016;12(11):1186-1196. doi:[10.1016/j.jalz.2016.08.004](https://doi.org/10.1016/j.jalz.2016.08.004)
11. Liu CC, Kaneiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms, and therapy. *Nat Rev Neurol*. 2013;9(2):106-118. doi:[10.1038/nrneurol.2012.263](https://doi.org/10.1038/nrneurol.2012.263)
12. Singh PP, Singh M, Mastana SS. APOE distribution in world populations with new data from India and the UK. *Ann Hum Biol*. 2006;33(3):279-308. doi:[10.1080/03014460600594513](https://doi.org/10.1080/03014460600594513)
13. 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. doi:[10.1038/ng1934](https://doi.org/10.1038/ng1934)
14. Rubin L, Ingram LA, Resciniti NV, et al. Genetic Risk Factors for Alzheimer's disease in racial/ethnic minority populations in the U.S.: a scoping review. *Front Public Health*. 2021;9:784958. doi:[10.3389/fpubh.2021.784958](https://doi.org/10.3389/fpubh.2021.784958)
15. Farrer LA. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA*. 1997;278(16):1349-1356. doi:[10.1001/jama.278.16.1349](https://doi.org/10.1001/jama.278.16.1349)
16. Altmann A, Tian L, Henderson VW, Greicius MD. Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease: sex and APOE -Related AD Risk. *Ann Neurol*. 2014;75(4):563-573. doi:[10.1002/ana.24135](https://doi.org/10.1002/ana.24135)
17. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer's disease. *JAMA Neurol*. 2017;74(10):1178-1189. doi:[10.1001/jamaneurol.2017.2188](https://doi.org/10.1001/jamaneurol.2017.2188)
18. Lamonja-Vicente N, Dacosta-Aguayo R, López-Olóriz J, et al. Sex-specific protective effects of APOE ε2 on cognitive performance. *J Gerontol Ser A*. 2021;76(1):41-49. doi:[10.1093/gerona/glaa247](https://doi.org/10.1093/gerona/glaa247)
19. Beydoun MA, Weiss J, Beydoun HA, et al. Race, APOE genotypes, and cognitive decline among middle-aged urban adults. *Alzheimers Res Ther*. 2021;13(1):120. doi:[10.1186/s13195-021-00855-y](https://doi.org/10.1186/s13195-021-00855-y)
20. Qiu C, Kivipelto M, Agüero-Torres H, Winblad B, Fratiglioni L. Risk and protective effects of the APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *J Neurol Neurosurg Psychiatry*. 2004;75(6):828-833. doi:[10.1136/jnnp.2003.021493](https://doi.org/10.1136/jnnp.2003.021493)
21. Hellwege J, Keaton J, Giri A, Gao X, Velez Edwards DR, Edwards TL. Population stratification in genetic association studies. *Curr Protoc Hum Genet*. 2017;95:1.22.1-1.22.23. doi:[10.1002/cphg.48](https://doi.org/10.1002/cphg.48)
22. Cardon LR, Palmer LJ. Population stratification and spurious allelic association. *Lancet Lond Engl*. 2003;361(9357):598-604. doi:[10.1016/S0140-6736\(03\)12520-2](https://doi.org/10.1016/S0140-6736(03)12520-2)
23. Liu XQ, Paterson AD, John EM, Knight JA. The role of self-defined race/ethnicity in population structure control. *Ann Hum Genet*. 2006;70(Pt 4):496-505. doi:[10.1111/j.1469-1809.2005.00255.x](https://doi.org/10.1111/j.1469-1809.2005.00255.x)
24. Qin W, Li W, Wang Q, et al. Race-related association between APOE genotype and Alzheimer's disease: a systematic review and meta-analysis. *J Alzheimers Dis*. 2021;83(2):897-906. doi:[10.3233/JAD-210549](https://doi.org/10.3233/JAD-210549)
25. Weuve J, Barnes LL, Mendes de Leon CF, et al. Cognitive aging in Black and White Americans: cognition, cognitive decline, and incidence of Alzheimer disease dementia. *Epidemiol Camb Mass*. 2018;29(1):151-159. doi:[10.1097/EDE.0000000000000747](https://doi.org/10.1097/EDE.0000000000000747)
26. Griswold AJ, Celis K, Bussies PL, et al. Increased APOE ε4 expression is associated with the difference in Alzheimer's disease risk from diverse ancestral backgrounds. *Alzheimers Dement*. 2021;17(7):1179-1188. doi:[10.1002/alz.12287](https://doi.org/10.1002/alz.12287)
27. 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. doi:[10.1016/j.neubiorev.2013.10.010](https://doi.org/10.1016/j.neubiorev.2013.10.010)
28. National Alzheimer's Coordinating Center. NACC Uniform Data Set initial visit packet version 3.0. Published online 2015.
29. Bennett DA, Schneider JA, Aggarwal NT, et al. Decision rules guiding the clinical diagnosis of Alzheimer's disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. *Neuroepidemiology*. 2006;27(3):169-176. doi:[10.1159/000096129](https://doi.org/10.1159/000096129)
30. Bennett DA, Wilson RS, Schneider JA, et al. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002;59(2):198-205. doi:[10.1212/wnl.59.2.198](https://doi.org/10.1212/wnl.59.2.198)
31. Petersen RC, Aisen PS, Beckett LA, et al>
32. Tremblay-Mercier J, Madjar C, Das S, et al. Open science datasets from PREVENT-AD, a longitudinal cohort of pre-symptomatic Alzheimer's disease. *NeuroImage Clin*. 2021;31:102733. doi:[10.1016/j.nicl.2021.102733](https://doi.org/10.1016/j.nicl.2021.102733)
33. Namipashaki A, Razaghi-Moghadam Z, Ansari-Pour N. The essentiality of reporting Hardy-Weinberg Equilibrium calculations in population-based genetic association studies. *Cell J*. 2015;17(2):187-192. doi:[10.22074/cellj.2016.3711](https://doi.org/10.22074/cellj.2016.3711)
34. Buckley RF, Scott MR, Jacobs HIL, et al. Sex mediates relationships between regional tau pathology and cognitive decline. *Ann Neurol*. 2020;88(5):921-932. doi:[10.1002/ana.25878](https://doi.org/10.1002/ana.25878)
35. Vivot A, Power MC, Glymour MM, et al. Jump, hop, or skip: modeling practice effects in studies of determinants of cognitive change in older adults. *Am J Epidemiol*. 2016;183(4):302-314. doi:[10.1093/aje/kww212](https://doi.org/10.1093/aje/kww212)
36. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for health-care professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42(9):2672-2713. doi:[10.1161/STR.0b013e3182299496](https://doi.org/10.1161/STR.0b013e3182299496)
37. Rabin JS, Schultz AP, Hedden T, et al. Interactive associations of vascular risk and β-amyloid burden with cognitive decline in clinically normal elderly individuals: findings from the Harvard Aging Brain Study. *JAMA Neurol*. 2018;75(9):1124-1131. doi:[10.1001/jamaneurol.2018.1123](https://doi.org/10.1001/jamaneurol.2018.1123)
38. Rabin JS, Nichols E, La Joie R, et al. Cerebral amyloid angiopathy interacts with neuritic amyloid plaques to promote tau and cognitive decline. *Brain*. 2022;145(8):2823-2833. doi:[10.1093/brain/awac178](https://doi.org/10.1093/brain/awac178)
39. 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. doi:[10.1016/j.jsbmb.2016.03.012](https://doi.org/10.1016/j.jsbmb.2016.03.012)
40. Gamache J, Yun Y, Chiba-Falek O. Sex-dependent effect of APOE on Alzheimer's disease and other age-related neurodegenerative disorders. *Dis Model Mech*. 2020;13(8):dmm045211. doi:[10.1242/dmm.045211](https://doi.org/10.1242/dmm.045211)
41. Ratnakumar A, Zimmerman SE, Jordan BA, Mar JC. Estrogen activates Alzheimer's disease genes. *Alzheimers Dement Transl Res Clin Interv*. 2019;5:906-917. doi:[10.1016/j.trci.2019.09.004](https://doi.org/10.1016/j.trci.2019.09.004)
42. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol*. 2015;11(7):393-405. doi:[10.1038/nrendo.2015.82](https://doi.org/10.1038/nrendo.2015.82)
43. Mosconi L, Berti V, Quinn C, et al. Sex differences in Alzheimer risk. *Neurology*. 2017;89(13):1382-1390. doi:[10.1212/WNL.0000000000004425](https://doi.org/10.1212/WNL.0000000000004425)
44. Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of Apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurol*. 2018;75(8):989-998. doi:[10.1001/jamaneurol.2018.0821](https://doi.org/10.1001/jamaneurol.2018.0821)

45. Fleisher A, Grundman M, Jr JackCR, et al. Sex, Apolipoprotein E ϵ 4 status, and hippocampal volume in Mild Cognitive Impairment. *Arch Neurol*. 2005;62(6):953-957. doi:[10.1001/archneur.62.6.953](https://doi.org/10.1001/archneur.62.6.953)
46. Barnes LL, Leurgans S, Aggarwal NT, et al. Mixed pathology is more likely in black than white decedents with Alzheimer dementia. *Neurology*. 2015;85(6):528-534. doi:[10.1212/WNL.0000000000001834](https://doi.org/10.1212/WNL.0000000000001834)
47. Morris JC, Schindler SE, McCue LM, et al. Assessment of racial disparities in biomarkers for Alzheimer disease. *JAMA Neurol*. 2019;76(3):264-273. doi:[10.1001/jamaneurol.2018.4249](https://doi.org/10.1001/jamaneurol.2018.4249)
48. Deters KD, Napolioni V, Sperling RA, et al. Amyloid PET imaging in self-identified non-Hispanic Black participants of the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) Study. *Neurology*. 2021;96(11):e1491-e1500. doi:[10.1212/WNL.00000000000011599](https://doi.org/10.1212/WNL.00000000000011599)
49. Blue EE, Horimoto ARVR, Mukherjee S, Wijsman EM, Thornton TA. Local ancestry at APOE modifies Alzheimer's disease risk in Caribbean Hispanics. *Alzheimers Dement J Alzheimers Assoc*. 2019;15(12):1524-1532. doi:[10.1016/j.jalz.2019.07.016](https://doi.org/10.1016/j.jalz.2019.07.016)
50. Blair CK, Folsom AR, Knopman DS, et al. APOE genotype and cognitive decline in a middle-aged cohort. *Neurology*. 2005;64(2):268-276. doi:[10.1212/01.WNL.0000149643.91367.8A](https://doi.org/10.1212/01.WNL.0000149643.91367.8A)
51. Rajan KB, Barnes LL, Wilson RS, Weuve J, McAninch EA, Evans DA. Apolipoprotein E genotypes, age, race, and cognitive decline in a population sample. *J Am Geriatr Soc*. 2019;67(4):734-740. doi:[10.1111/jgs.15727](https://doi.org/10.1111/jgs.15727)
52. Eissman JM, Dumitrescu L, Mahoney ER, et al. Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease. *Brain J Neurol*. 2022;145(7):2541-2554. doi:[10.1093/brain/awac177](https://doi.org/10.1093/brain/awac177)
53. Martins C a R, Oulhaj A, de Jager CA, Williams JH. APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. *Neurology*. 2005;65(12):1888-1893. doi:[10.1212/01.wnl.0000188871.74093.12](https://doi.org/10.1212/01.wnl.0000188871.74093.12)
54. Wilson RS. The apolipoprotein E epsilon2 allele and decline in episodic memory. *J Neurol Neurosurg Psychiatry*. 2002;73(6):672-677. doi:[10.1136/jnnp.73.6.672](https://doi.org/10.1136/jnnp.73.6.672)

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wood ME, Xiong LY, Wong YY, et al. Sex differences in associations between APOE ϵ 2 and longitudinal cognitive decline. *Alzheimer's Dement*. 2023;1-11. <https://doi.org/10.1002/alz.13036>