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RESEARCH ARTICLE

Sex variation in the relationship between *APOE ε4*, cognitive decline, and dementia

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Abstract

INTRODUCTION: We examine if the relationship between apolipoprotein E (*APOE*) ε4 and cognitive decline and dementia onset differs by sex in non-Hispanic White and Black respondents from the Health and Retirement Study.

METHODS: We used race-stratified linear mixed models to estimate cognitive decline and Cox proportional hazards models to estimate time to dementia onset. Sex differences were estimated using interaction terms.

RESULTS: *APOE* ε4 was associated with cognitive decline ($b = -0.4$) and dementia onset (hazard ratio [HR] = 1.48) in White adults, and cognitive decline ($b = -0.5$) in Black adults. The relationship between *APOE* ε4 and cognitive decline or dementia onset did not differ by sex in either group.

DISCUSSION: Our findings question a key hypothesis in the field—that female *APOE* ε4 carriers experience faster cognitive decline and earlier dementia onset than their male counterparts—and highlight the importance of using probability samples to reduce survivor and participation bias commonly found in genetics research.

KEYWORDS
APOE, cognition, dementia, non-Hispanic Black, non-Hispanic White, sex, United States

Highlights

- White apolipoprotein E ε4 allele (*APOE* ε4) carriers had faster cognitive decline and earlier dementia onset.
- Black *APOE* ε4 carriers had faster cognitive decline.
- These patterns did not vary by sex for either Black or White adults.

1 | BACKGROUND

The apolipoprotein E ε4 allele (*APOE* ε4) is a well-established genetic risk factor for late-onset Alzheimer's disease (AD)[1–4] associated with a 3- to 15-fold increase in AD risk.[5,6] *APOE* ε4 is also associated with preclinical signs of dementia, including poorer cognitive performance and faster cognitive decline.[7,8]

Clinical and community-based studies have identified sex differences in the strength of *APOE* ε4 for clinical and pathological AD and cognitive decline,[5,9–14] with several reporting that female *APOE* ε4 carriers transition to clinical AD at higher rates and experience faster cognitive decline than their male counterparts.[9,11–14] This pattern is inconsistent across cognitive domains, with some studies showing conflicting[11,12,15] or null[14,16–19] results, even within the same study,

depending on the cognitive assessment used. For example, Swan and colleagues found that male *APOE* ε4 carriers had a faster rate of decline in executive function and verbal memory than female *APOE* ε4 carriers,[15] whereas Beydoun and colleagues[17] found no sex difference in the relationship of *APOE* ε4 and transition to clinically defined mild cognitive impairment (MCI) or AD. At the same time they found that *APOE* ε4 was more strongly associated with impairment in delayed recall among women than among men.

The inconsistent findings may arise from the use of clinical and community samples drawn using non-probability methods, which often results in selective samples of highly educated, urban respondents in select regions of the country.[9,13–18] These respondents may volunteer for the study for reasons that differ by gender and are related to dementia.[20,21] Researcher-defined inclusion criteria (e.g., age and health status) may also lead to healthy survivor bias,[22] particularly as men typically die at younger ages compared to women, resulting in older male participants who are disproportionately healthier compared to their peers who did not survive.[23,24] These factors complicate efforts to determine if the observed sex differences are genuine or artifacts of sampling or study design.

Our study uses prospective data from the Health and Retirement Study (HRS) to examine sex differences in the relationship between *APOE* ε4 and (1) cognitive decline and (2) dementia onset in a sample in which the men and women are representative of the U.S. population of non-Hispanic Black and White midlife and older adults. The HRS study design addresses two key weaknesses in previous research. First, by using probability sampling, the HRS ensures that all potential respondents are identified and it can adjust for participation bias through sampling weights, unlike studies using convenience samples.[25] Second, HRS follows participants from midlife onward, regardless of their health status, even if they move into nursing homes.[26] When participants are unable to complete cognitive tests, proxy reports are used.[27] These features help minimize sample attrition and allow the HRS to adjust for it with sampling weights, thereby reducing concerns about healthy survivor bias, a common issue in clinical studies.

RESEARCH-IN-CONTEXT

1. **Systematic review**: We reviewed the literature using traditional (e.g., PubMed) sources. There is a body of evidence that shows sex differences in the strength of apolipoprotein E ε4 allele (*APOE* ε4) for Alzheimer's disease (AD) and cognitive decline. These studies often, but not always, report that female *APOE* ε4 carriers transition to dementia at higher rates and experience faster cognitive decline than their male counterparts. Inconsistent findings may be due, in part, to the use of non-probability samples that are highly selective and researcher-defined inclusion criteria that can lead to healthy survivor bias.
2. **Interpretation**: In a nationally representative sample of older White and Black adults in the United States, we found no sex differences in the relationship between *APOE* ε4 and cognitive decline or dementia onset.
3. **Future directions**: Our findings should be replicated in other U.S. probability samples that include additional racial and ethnic groups, as well as in international samples, to determine the robustness of our results. Studies that use more comprehensive measures of cognitive function and dementia should be prioritized.

2 | METHODS

2.1 | Study population

Data come from the HRS, a nationally representative, prospective study of U.S. adults age 50 and older.[26] The HRS is a multistage area probability sample of age-eligible households selected from primary sampling units chosen from U.S. Metropolitan Statistical Areas (MSAs) and non-MSA counties, with an oversampling of minorities. Since 1992, the HRS has conducted core interviews with age-eligible respondents and their spouses approximately every 2 years. The HRS uses a steady-state design that replenishes the sample with younger cohorts every 6 years to ensure that it remains nationally representative of the U.S. population age 50 and older. Genetic data collection began in 2006 among community-dwelling respondents who completed a face-to-face interview.[28] This design allowed the HRS to construct sample weights that accounted for differential participation in the genetic data collection using detailed respondent information. Respondents who provided salivary DNA from 2006 to 2012, had apolipoprotein E (*APOE*) genotyped. The HRS maintains a panel response rate of 74.4% as of 2018.[29]

For models estimating cognitive decline, we restricted our sample to HRS respondents interviewed between 2006 and 2018, who participated in salivary DNA data collection and for whom *APOE* genotype was publicly available, who were age and cohort-eligible, and who self-reported as non-Hispanic Black or White (n = 15,312). Next, using principal component analysis (PCA), HRS generated 10 PCs to account for population stratification. We used loadings on PCs 1 and 2 to exclude respondents whose genetic ancestry fell outside the range that HRS identified as European or African ancestry (n = 738).[30] Finally, we excluded respondents who were missing data on cognition during the period of observation (n = 7), *APOE* genotype (n = 71), or education (n = 40), or who had a zero-sampling weight (n = 18). This resulted in a final analytic sample of 11,572 non-Hispanic White (hereafter White) and 2867 non-Hispanic Black (hereafter Black) respondents.

In models assessing dementia onset, we excluded respondents with dementia onset before age 65 (n = 290) (i.e., early-onset dementia) or before 2006 (n = 366), or who were not observed at or after age 65 (n = 2939). We excluded respondents born before 1924 (n = 1062) to minimize healthy survivor bias. This resulted in a final analytic sample of 8297 White respondents and 1509 Black respondents.

2.2 | Measures

2.2.1 | Cognitive function

In each survey year, the HRS administered the validated Telephone Instrument for Cognitive Status (TICS) to assess cognitive function by phone, face-to-face, or, in 2018, online for a small subset (8%) of respondents.[27] The TICS consists of immediate and delayed 10-word recall tests, a serial 7 s subtraction test, and a counting backward test. We summed across all TICS items, resulting in a composite score of *cognitive function* that ranged from 0 to 27, and higher scores reflect better cognitive function. We subtracted 1 point from the TICS if a respondent completed the TICS online in 2018 to account for mode differences.[31]

2.2.2 | Dementia status

We assessed dementia status using established cut points.[32] If a respondent completed the TICS, they were classified as having cognitive impairment consistent with dementia if their TICS score was ≤6. If a respondent did not complete the TICS, we used a proxy's assessment of their memory and limitations in five instrumental activities of daily living *and* the interviewer's assessment of how difficult it was for them to complete the interview due to cognitive limitations. Proxy scores ranged from 0 to 11; higher scores indicated greater impairment. We classified respondents with proxy scores of 6 or higher as having cognitive impairment consistent with *dementia*. This categorization has good predictive ability when compared with classification from a consensus panel of experts in neuropsychiatric assessments of dementia.[27]

2.2.3 | *APOE* genotype

Two genetic variants (rs7412 and rs429358) contribute to three *APOE* alleles (ε2, ε3, and ε4), resulting in six potential *APOE* genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4). Genotyping was performed using TaqMan allelic discrimination single-nucleotide polymorphism (SNP) assays. HRS imputed *APOE* status from previously genotyped array data that used the 1000 Genomes Cosmopolitan Reference Panel (phase 3) if genotyping did not pass quality control (one or both SNPs failed). This resulted in dosage data for rs7412 and rs429358, which the HRS used to determine a "best guess genotype" and infer the *APOE* isoform. Per HRS recommendations, we dropped respondents with a posterior probability <0.8 on imputations of rs7412 ($n = 20$) or rs429358 ($n = 76$).[28] Overall, *APOE* was imputed for 1511 respondents in the cognitive decline sample and 1055 respondents in the dementia-onset sample. We dichotomized *APOE* as *APOE* ε4 carriers versus non-carriers because more refined classifications yielded similar findings but resulted in small cell sizes for the ε4/ε4 genotype (Table S1).

2.2.4 | Covariates

We included *sex*, birth *cohort*, interview *mode* (face-to-face or phone/web), *years of schooling* completed (0–17 years), if *APOE* was *imputed* (yes/no), and *ancestry-specific PCs*, which include the first 10 PCs identified through PC analysis to account for population stratification. For the dementia-onset models, we included an indicator of whether the respondent's cognition assessment was ever determined by proxy (yes/no).

2.3 | Statistical analysis

We estimated the level and change in cognitive function using linear mixed models to account for observations nested within persons and varying numbers of observations per person.[33] Age represents time and is centered at age 70, respondents' mean age over the observation period, and divided by 10. Thus each unit increase in age represents change over a decade.

Unconditional linear mixed models supported a quadratic specification of age. All models included sex, *APOE* genotype, and sex × *APOE* genotype to estimate sex differences in the relationship between *APOE* genotype and level of cognitive function, after adjusting for covariates. We interacted age with all variables to assess whether these factors were associated with the rate of cognitive decline. We did not interact quadratic age with covariates because it did not improve model fit. It is important to note that models that did not include quadratic age yielded inferences similar to those we present (results available upon request).

We used Cox proportional hazards models to estimate the risk of transitioning to dementia at or after age 65.[34] We calculated the age at dementia onset as the midpoint between respondents' last non-demented assessment and the first time they were observed with dementia. Respondents who left the study with no dementia or did not have dementia by the end of the study period were censored at their last observation. Hazard models included sex, *APOE* genotype, and sex × *APOE* genotype to estimate sex differences in the relationship between *APOE* genotype and the hazard of dementia, after adjusting for covariates.

We estimated several additional models to determine the robustness of our findings. First, we re-estimated the main models after restricting our nationally representative sample to respondents who shared characteristics of clinical samples—that is, highly educated and urban residents. Next, we investigated healthy survivor bias and attrition in our cognitive decline sample by (1) restricting to younger respondents (<75 years), (2) assigning everyone who died during the study period a value of 6 on the TICS (the threshold for dementia classification) at their last observation, and (3) restricting to respondents who provided at least four observations. We examined the influence of mortality in the dementia-onset sample by (1) restricting to younger respondents (<75 years) and (2) estimating a competing risk model that

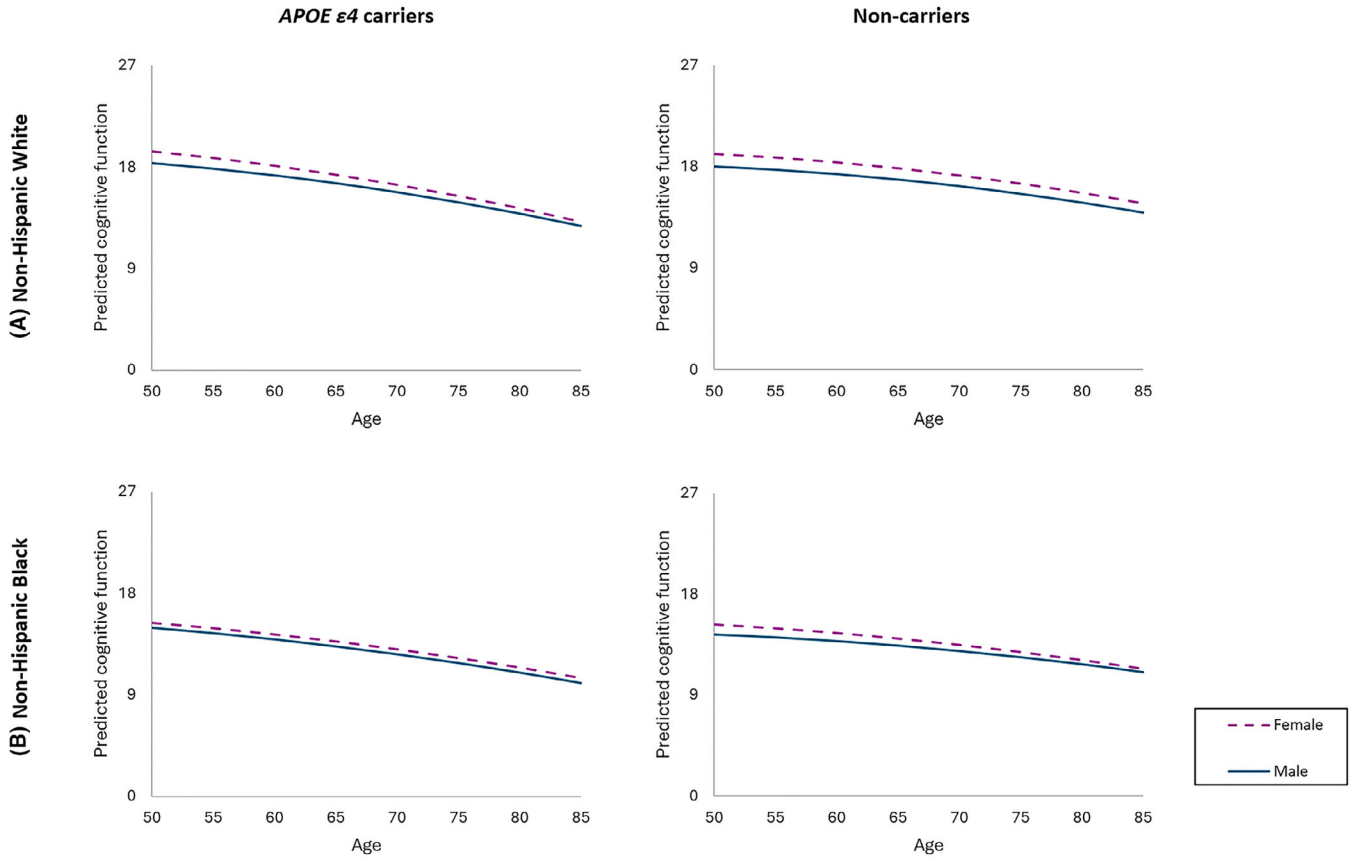

FIGURE 1 Predicted cognitive function by sex across age among non-Hispanic White (A) and Black (B) adults ages 50 and older (HRS 2006–2018). Predicted scores were calculated using margins in Stata 18 from race-stratified estimates from Model 1 that hold covariates constant at their race-specific means. Predicted scores are reported in Tables S3 and S5. Post hoc race differences were not tested, but potential race differences are discussed in the supplementary material. HRS, Health and Retirement Study.

estimated the probability of dementia accounting for the probability of transitioning to death.[34]

Given that several studies report a sex × *APOE* ε4 interaction for memory decline,[11,14,15,17] we also estimated linear mixed models predicting episodic memory (sum of the immediate and delayed recall scores from the TICS) in the full sample and for highly educated, urban residents, and younger respondents (<75 years). Finally, we re-estimated the main models for cognitive function, episodic memory, and dementia status excluding ε2/ε4 carriers, consistent with some previous studies.[9,13–16,18] We discuss results from these models in the Sensitivity Analysis section.

We used person-level sample weights constructed to account for the complex sampling design of the HRS, sample non-response and respondent attrition, and participation in the genetic data collection.[35] If respondents did not have sample weights for the genetic data collection (n = 451), we used their sampling weight from their last core interview, which accounts for all but participation in the genetic data collection. Because most studies estimating sex × *APOE* genotype on cognitive decline and dementia onset restrict analyses to White respondents, we stratify analyses by self-reported race for comparability with other studies.

We conducted weighted analyses in Stata version 18 (StataCorp, LLC) using *mixed* for models estimating cognitive decline and *stcox* for models estimating dementia onset.[36] We used *margins* to calculate predicted cognitive function scores and *stcurve* to calculate the weighted survivor function of dementia onset across age by sex, race, and *APOE* genotype and to plot the values in Figures 1 (cognitive decline) and 2 (dementia onset). When using *margins*, covariates were set to their sample mean. We used a two-tailed test, with statistical significance reached at $p < 0.05$.

3 | RESULTS

3.1 | Sample characteristics

Table 1 describes the sample used to estimate cognitive decline by sex and race. Among White adults, women had significantly higher cognitive function scores than men at their first (mean = 16.9, women; mean = 16.3, men; $p < 0.01$) and last (mean = 15.4, women; mean = 15.1, men; $p = 0.01$) observations. *APOE* ε4 prevalence did not differ by sex; about 26% of White men and women were *APOE*

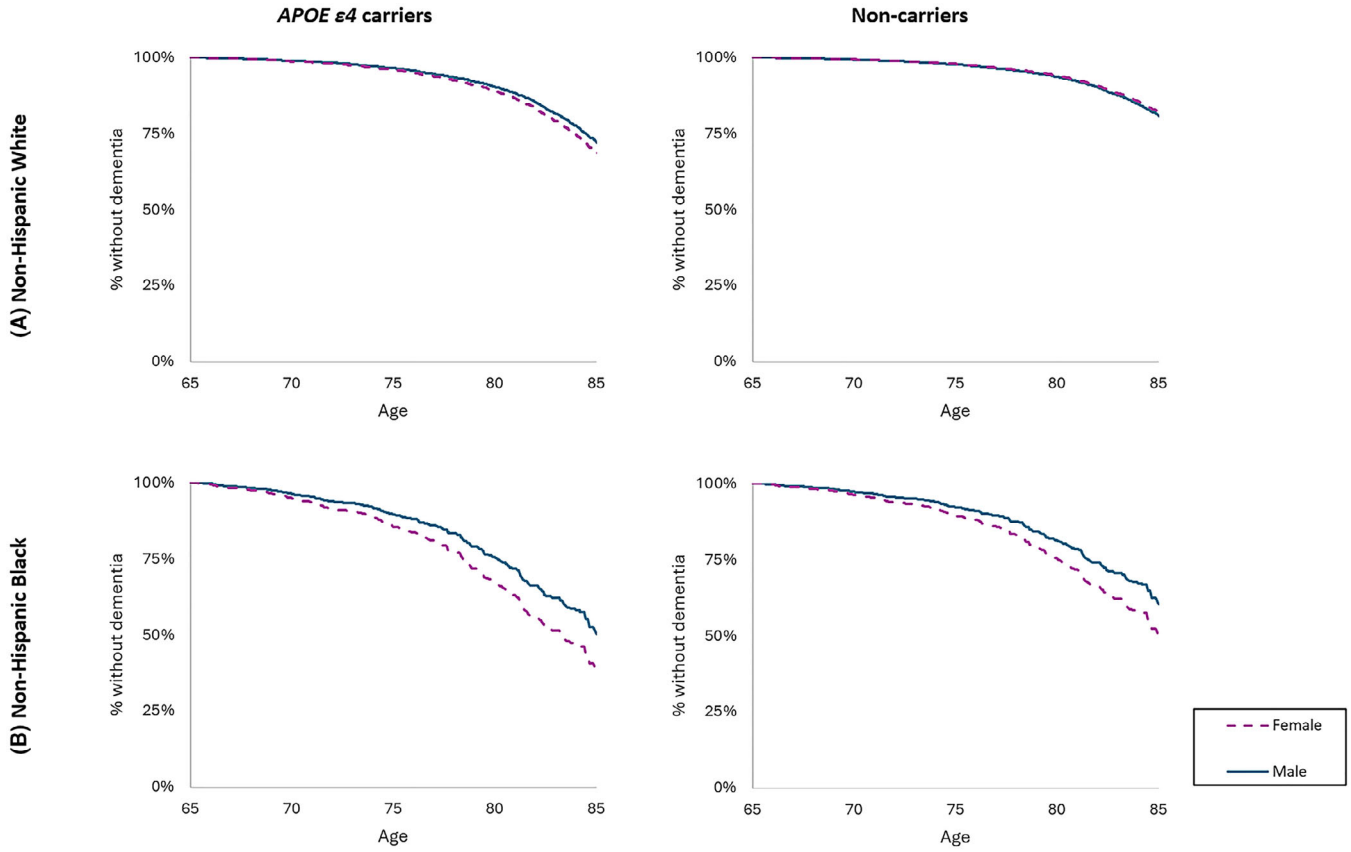

FIGURE 2 Survival curves of dementia onset by sex among non-Hispanic White (A) and Black (B) adults ages 65 and older (HRS, 2006–2018). Survival estimates were calculated using *stcurve* in Stata 18 from race-stratified models. Post hoc race differences were not tested, but potential race differences are discussed in the supplementary material. HRS, Health and Retirement Study.

ε4 carriers ($p = 0.81$). Among Black adults, women had significantly higher cognitive function scores than men only at their first observation (mean = 13.8, women; mean = 13.0, men; $p < 0.01$). The prevalence of *APOE* ε4 was similar by sex: 37.9% of women and 40.9% of men were *APOE* ε4 carriers ($p = 0.22$).

Table 2 describes the sample used to estimate the hazard of dementia onset by sex and race. During the study period, 8.0% of White men and 9.3% of White women transitioned to dementia ($p = 0.03$), whereas 13.8% of Black men and 16.2% of Black women transitioned to dementia ($p = 0.24$). For both groups, the prevalence of *APOE* ε4 was similar by sex.

3.1.1 | *APOE* ε4×sex associations with cognitive decline

Figure 1A plots predicted cognitive function scores across age by sex for White adults. Predicted cognitive function scores were derived from linear mixed model estimates reported in Table S2 (Model 1) using *margins* in Stata 18. Predicted scores and their 95% confidence intervals (CIs) are reported in Table S3. Cognitive function was significantly lower at age 70 among *APOE* ε4 carriers than among non-carriers (Table S2 Model 1: $b_{age70} = -0.5$; 95% CI: −0.7, −0.3) and their rate of cognitive decline was faster (Table S2 Model 1: $b_{change} = -0.4$; 95% CI: −0.6, −0.3). There was no statistically significant difference in this pattern by sex (Table S2 Model 1: $b_{age70} = -0.3$; 95% CI: −0.6, 0.0; $b_{change} = -0.1$; 95% CI: −0.3, 0.1).

Figure 1B plots predicted cognitive function scores across age by sex for Black adults. We report linear mixed model estimates in Table S4 (Model 1) and predicted scores in Table S5. At age 70, there was no statistically significant difference in cognitive function by *APOE* ε4 carrier status (Table S4 Model 1; $b_{age70} = -0.4$; 95% CI: −1.0, 0.2); however, *APOE* ε4 carriers had faster cognitive decline than non-carriers (Table S4 Model 1; $b_{change} = -0.5$; 95% CI: −0.9, −0.1). These patterns did not differ statistically by sex (Table S4 Model 1: $b_{age70} = -0.1$; 95% CI: −0.8, 0.6; $b_{change} = 0.2$; 95% CI: −0.3, 0.7).

3.1.2 | *APOE* ε4 × sex associations with dementia onset

Figure 2A plots the weighted survival function estimating dementia onset during the study period across age and by sex for White adults. Hazard ratios and estimated survival functions were calculated using *stcurve* in Stata 18 reported in Tables S6 (Model 1) and S7. *APOE* ε4 carriers had a higher risk of transitioning to dementia (Table S6 Model 1:

TABLE 1 Descriptive statistics for sample estimating cognitive decline by sex and race (HRS, 2006–2018).

	No. (%)					
	Non-Hispanic White (n = 11,572)			Non-Hispanic Black (n = 2867)		
Characteristic	Male	Female	p-value	Male	Female	p-value
Cognitive function, first observation, mean (SE)	16.3 (0.06)	16.9 (0.06)	<0.01	13.0 (0.17)	13.8 (0.14)	<0.01
Cognitive function, last observation, mean (SE)	15.1 (0.07)	15.4 (0.07)	0.01	12.1 (0.20)	12.6 (0.15)	0.06
APOE ε4	1307 (26.2)	1700 (25.9)	0.81	454 (40.9)	650 (37.9)	0.21
Age at first observation, mean (SE), y	62.4 (0.14)	63.4 (0.15)	<0.01	60.4 (0.28)	61.0 (0.25)	0.08
Age at last observation, mean (SE), y	70.0 (0.15)	71.3 (0.15)	<0.01	67.3 (0.28)	68.5 (0.26)	<0.01
Birth cohort			<0.01			0.23
<1924	367 (4.9)	581 (7.3)		36 (2.3)	78 (3.5)	
1924–1930	723 (8.4)	887 (10.5)		67 (4.8)	95 (7.0)	
1931–1941	1779 (21.3)	2134 (21.4)		296 (16.1)	447 (16.2)	
1942–1947	662 (19.8)	997 (17.3)		114 (17.1)	204 (16.6)	
1948–1953	804 (25.6)	977 (23.2)		288 (35.1)	443 (33.7)	
1954–1959	723 (20.0)	938 (20.4)		327 (24.6)	472 (23.1)	
Interview mode, first observation			0.02			0.30
In person	1650 (32.8)	2283 (35.2)		251 (26.4)	466 (28.8)	
Phone	3408 (67.2)	4231 (64.8)		877 (73.6)	1273 (71.2)	
Interview mode, last observation			0.14			0.42
In person	1791 (40.8)	2279 (39.2)		412 (39.6)	699 (41.6)	
Phone or internet	3267 (59.2)	4235 (60.8)		716 (60.4)	1040 (58.4)	
Imputed *APOE*	524 (9.8)	728 (10.5)	0.27	93 (9.1)	166 (10.4)	0.39
Years of education, mean (SE), y	13.7 (0.04)	13.3 (0.03)	<0.01	12.1 (0.12)	12.4 (0.08)	0.03
No. of respondents (unweighted)	5058	6514		1128	1739	
Person-period observations	25,627	34,954		5263	8846	
Average observations per person	5.1	5.4		4.7	5.1	

Note: Data are *N* (%) unless otherwise specified. Unweighted *N* reported. Weighted percentages and means reported. Percentages may not add up to 100 due to rounding. Means across sex were compared using an adjusted Wald test. Percentages across sexes were compared using Pearson's chi-square test.
Abbreviations: *APOE*, apolipoprotein E; HRS, Health and Retirement Study; SE, standard error.

HR = 1.54; 95% CI: 1.19, 1.98) than non-carriers, but this relationship did not differ statistically by sex (Table S6 Model 1: HR = 1.22; 95% CI: 0.89, 1.67).

Figure 2B plots the weighted survival function estimating dementia onset during the study period across age and by sex for Black adults. Hazard ratios and estimated survival functions are reported in Tables S8 (Model 1) and S9. Among Black adults, the risk of dementia onset did not vary by *APOE* ε4 status (Table S8 Model 1: HR = 1.37; 95% CI: 0.84, 2.20), and this null association did not differ by sex (Table S8 Model 1: HR = 1.02; 95% CI: 0.57, 1.82).

3.2 | Sensitivity analyses

Models that restricted our nationally representative sample to respondents with characteristics similar to those found in clinical samples (Tables S2 and S4 for cognitive decline and Tables S6 and S8 for dementia onset for White and Black adults, respectively) did not show sex differences.

Models that investigated healthy survivor and attrition bias in the sample estimating cognitive decline (Tables S10 and S11) also showed no sex differences in the relationship between *APOE* and cognitive decline for either White or Black adults. In the dementia-onset sample, accounting for healthy survivor bias (Tables S6 and S8, Model 4) and the competing risk of mortality (Table S12) also showed no sex differences in either group.

Finally, we found no sex differences in the *APOE* ε4 relationship with memory decline among White or Black adults (Tables S13 and S14) in the full sample (Model 1) or after restricting to the highly educated (Model 2), urban residents (Model 3), or younger respondents (Model 4). After excluding ε2/ε4 carriers (Tables S6 and S8 [Model 5, dementia onset], Table S15 [cognitive function, episodic memory]) results were unchanged with two exceptions: White female *APOE* ε4 carriers had lower cognitive function at age 70 (Table S15: $b_{\text{cognitive function at age 70}} = -0.3$; 95% CI: −0.6, 0.0, $p = 0.04$) and lower episodic memory at age 70 ($b_{\text{episodic memory at age 70}} = -0.2$; 95% CI: −0.5, −0.0, $p = 0.04$) than male *APOE* ε4 carriers. With adjustment for multiple comparisons within outcome and race,

TABLE 2 Descriptive statistics for sample estimating dementia onset by sex and race (HRS, 2006–2018).

	No. (%)					
	Non-Hispanic White respondents ($n = 8297$)			Non-Hispanic Black respondents ($n = 1509$)		
Characteristic	Male	Female	*p*-value	Male	Female	*p*-value
Transitioned to dementia	400 (8.0)	538 (9.3)	0.03	114 (13.8)	176 (16.2)	0.24
APOE ε4	940 (26.1)	1232 (26.1)	0.99	229 (38.3)	340 (36.9)	0.66
Age at first observation, mean (SE), y	64.3 (0.15)	64.9 (0.14)	<0.01	62.8 (0.34)	62.6 (0.29)	0.62
Age at last observation, mean (SE), y	74.0 (0.13)	75.0 (0.13)	<0.01	72.1 (0.32)	72.5 (0.28)	0.26
Birth cohort			<0.01			0.78
1924–1930	693 (12.2)	859 (15.4)		53 (7.0)	64 (8.5)	
1931–1941	1737 (31.4)	2088 (32.0)		249 (25.2)	375 (24.4)	
1942–1947	625 (28.2)	958 (25.2)		93 (26.3)	175 (24.9)	
1948–1953	583 (28.2)	754 (27.4)		180 (41.5)	320 (42.3)	
Interview mode, first observation			0.22			0.41
In person	1483 (42.5)	1978 (44.1)		187 (35.2)	352 (37.9)	
Phone	2155 (57.5)	2681 (55.9)		388 (64.8)	582 (62.1)	
Interview mode, last observation			0.04			0.62
In person	1302 (41.3)	1616 (38.6)		205 (41.5)	378 (43.2)	
Phone or internet	2336 (58.7)	3043 (61.4)		370 (58.5)	556 (56.8)	
Cognition ever given by proxy	362 (8.6)	387 (7.0)	0.01	67 (10.7)	68 (5.7)	<0.01
Imputed *APOE*	376 (9.9)	529 (10.9)	0.22	47 (9.0)	103 (11.9)	0.19
Years of education, mean (SE), y	13.8 (0.05)	13.3 (0.04)	<0.01	12.3 (0.17)	12.7 (0.10)	0.07
No. of respondents (unweighted)	3638	4659		575	934	

Note: Data are *N* (%) unless otherwise specified. Unweighted *N* reported. Weighted percentages and means reported. Percentages may not add up to 100 due to rounding. Means across sex were compared using an adjusted Wald test. Percentages across sexes were compared using Pearson's chi-square test.
Abbreviations: *APOE*, apolipoprotein E; SE, standard error.

these two sex × *APOE* ε4 interactions were no longer statistically significant.

4 | DISCUSSION

Using a nationally representative sample of older White and Black adults, we found no sex differences in the relationship between *APOE* ε4, cognitive decline, and dementia onset. Our results call into question existing knowledge derived mostly from clinical and community-based samples that often, although not always, find that *APOE* ε4 is associated with faster cognitive decline or a higher risk of dementia among women (Table S16 for summary). Because clinical and community-based samples are often highly selective—that is, highly educated and live in urban areas—we conducted additional analyses to determine if we would find sex differences among HRS respondents who shared characteristics similar to the participants of clinical studies. We found no such pattern.

Our results suggest that prior reports of sex differences may be due to the use of non-probability samples, which can introduce sex-differential participation bias, defined as *unmeasured* gender differences in why people participate in a clinical study (e.g., health-seeking behaviors, personality, health, and social factors) rather than sex-differentiated genetic risk.[20,37–39] Non-probability sampling methods do not provide the researcher with the means to identify nonresponders or their characteristics, making it impossible to evaluate or correct for participation bias.[25] In addition, covariate adjustment alone cannot address this bias, further highlighting the need for probability sampling methods like those used in HRS to ensure accurate and representative results.

Researcher-defined sample inclusion/exclusion criteria may also explain inconsistencies in identifying sex differences in the *APOE* ε4 and cognition relationship. For example, some researchers exclude ε2/ε4 genotypes,[9,13–16,18] whereas others do not.[11,12,17,19] When we excluded this group, we identified two statistically significant sex × *APOE* ε4 interactions for cognitive function and episodic memory among White adults that were no longer statistically significant after multiple test corrections. Differences in inclusion criteria can also affect *APOE* ε4 prevalence across studies that use the same data, with potential implications for the inferences drawn. Using data from the Baltimore Longitudinal Study of Aging, Beydoun et al.[17] reported statistically significant sex differences in *APOE* ε4 frequency in their sample (23% for men, 31.2% for women), whereas Williams et al.[13] did not, which may be why the two studies reported conflicting sex differences in *APOE* ε4 and cognitive decline.

4.1 | Strengths and limitations

Our study has several strengths. First, the HRS sampling design, including the construction and use of sampling weights, avoids sex-differential participation bias found in non-probability samples. Second, we assessed both cognitive decline *and* dementia onset to compare with prior studies and to determine if sex differences in the *APOE* ε4 relationship are found in a younger sample before healthy survivor bias affects validity. Third, our sample includes both older White and Black adults, an important addition to the literature that relies almost exclusively on samples of White older adults.

Our study includes limitations. Our dementia measure is based on respondent tests or proxy reports, not neurological assessments, and does not differentiate between AD and other dementias. Still, it shows good predictive validity compared to expert neuropsychiatric classifications.[29] Although TICS is a validated measure of cognitive function, it does not capture all cognitive domains examined previously in the *APOE* ε4 × sex literature and may be less sensitive to small changes in cognitive decline.[40] Respondents, however, were followed for an average of 7–8 years, thereby increasing the opportunity to capture cognitive decline during the observation period. Our sample included only 228 White and 117 Black adults with the ε4/ε4 genotype, limiting our ability to estimate sex differences in homozygotes, although patterns for homozygotes were similar to those for ε4 carriers. Finally, our findings are generalizable only to non-Hispanic Black and White adults, as small sample sizes for other racial/ethnic groups in the HRS limited broader analysis.

4.2 | Conclusions

Our study is one of the first to estimate sex differences in *APOE* ε4, cognitive decline, and dementia onset in a nationally representative sample of older White and Black adults. The findings indicate similar associations between *APOE* ε4, cognitive decline, and dementia onset for both men and women. This underscores the importance of using probability samples in genetic and dementia research. Future work should replicate these findings in other U.S. probability samples that include additional racial and ethnic groups and more comprehensive cognitive and dementia measures, as well as in international samples, to test the robustness of our results.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

CONSENT STATEMENT

The HRS collects consent during data collection. Informed consent was obtained from all respondents involved in the study.

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REFERENCES

1. Bakulski KM, Vadari HS, Faul JD, et al. Cumulative genetic risk and *APOE* ε4 are independently associated with dementia status in a multiethnic, population-based cohort. *Neurol Genet*. 2021;7:e576. doi:10.1212/NXG.0000000000000576
2. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921-923.
3. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA*. 1993;90:1977-1981. doi:10.1073/pnas.90.5.1977
4. Fortea J, Pegueroles J, Alcolea D, et al. *APOE4* homozygosity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;30:2093. doi:10.1038/s41591-024-02931-w
5. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: a meta-analysis. *JAMA*. 1997;278:1349-1356. doi:10.1001/jama.1997.03550160069041
6. Ward A, Crean S, Mercaldi CJ, et al. Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology*. 2012;38:1-17. doi:10.1159/000334607
7. Fillenbaum GG, Landerman LR, Blazer DG, Saunders AM, Harris TB, Launer LJ. The relationship of *APOE* genotype to cognitive functioning in older African-American and Caucasian community residents. *J Am Geriatr Soc*. 2001;49:1148-1155. doi:10.1046/j.1532-5415.2001.49230.x
8. Small BJ, Rosnick CB, Fratiglioni L, Bäckman L. Apolipoprotein E and cognitive performance: a meta-analysis. *Psychol Aging*. 2004;19:592-600. doi:10.1037/0882-7974.19.4.592
9. Altmann A, Tian L, Henderson VW, Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the *APOE*-related risk of developing Alzheimer's disease. *Ann Neurol*. 2014;75:563-573. doi:10.1002/ana.24135
10. Neu SC, Pa J, Kukull W, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer's disease: a meta-analysis. *JAMA Neurology*. 2017;74:1178-1189. doi:10.1001/jamaneurol.2017.2188
11. Lehmann DJ, Refsum H, Nurk E, et al. Apolipoprotein E ε4 and impaired episodic memory in community-dwelling elderly people: a marked sex difference. The Hordaland Health Study. *J Neurol Neurosurg Psychiatry*. 2006;77:902-908. doi:10.1136/jnnp.2005.077818
12. Reinvang I, Winjevoll IL, Rootwelt H, Espeseth T. Working memory deficits in healthy APOE epsilon 4 carriers. *Neuropsychologia*. 2010;48:566-573. doi:10.1016/j.neuropsychologia.2009.10.018

13. Williams OA, An Y, Armstrong NM, et al. Apolipoprotein E ε4 allele effects on longitudinal cognitive trajectories are sex and age dependent. *Alzheimers Dement*. 2019;15:1558-1567. doi:10.1016/j.jalz.2019.07.011
14. Walters S, Contreras AG, Eissman JM, et al. Associations of sex, race, and apolipoprotein E alleles with multiple domains of cognition among older adults. *JAMA Neurology*. 2023;80:929-939. doi:10.1001/jamaneurol.2023.2169
15. Swan GE, Lessov-Schlaggar CN, Carmelli D, Schellenberg GD, La Rue A. Apolipoprotein E ε4 and change in cognitive functioning in community-dwelling older adults. *J Geriatr Psychiatry Neurol*. 2005;18:196-201. doi:10.1177/0891988705281864
16. Sundermann EE, Tran M, Maki PM, Bondi MW. Sex differences in the association between apolipoprotein E ε4 allele and Alzheimer's disease markers. *Alzheimers Dement*. 2018;10:438-447. doi:10.1016/j.dadm.2018.06.004
17. Beydoun MA, Boueiz A, Abougergi MS, et al. Sex differences in the association of the apolipoprotein E epsilon 4 allele with incidence of dementia, cognitive impairment, and decline. *Neurobiol Aging*. 2012;33(4):720-731.e4. doi:10.1016/j.neurobiolaging.2010.05.017
18. Reas ET, Laughlin GA, Bergstrom J, Kritz-Silverstein D, Barrett-Connor E, McEvoy LK. Effects of *APOE* on cognitive aging in community-dwelling older adults. *Neuropsychology*. 2019;33:406-416. doi:10.1037/neu0000501
19. O'Shea DM, Galvin JE. Female *APOE* ε4 carriers with slow rates of biological aging have better memory performances compared to female ε4 carriers with accelerated aging. *J Alzheimers Dis*. 2023;92:1269-1282. doi:10.3233/JAD-221145
20. Pirastu N, Cordioli M, Nandakumar P, et al. Genetic analyses identify widespread sex-differential participation bias. *Nat Genet*. 2021;53:663-671. doi:10.1038/s41588-021-00846-7
21. Weuve J, Proust-Lima C, Power MC, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimers Dement*. 2015;11:1098-1109. doi:10.1016/j.jalz.2015.06.1885
22. Smith LH. Selection Mechanisms and their consequences: understanding and addressing selection bias. *Curr Epidemiol Rep*. 2020;7:179-189. doi:10.1007/s40471-020-00241-6
23. Crimmins EM, Zhang YS. Aging populations, mortality, and life expectancy. *Annu Rev Sociol*. 2019;45:69-89. doi:10.1146/annurev-soc-073117-041351
24. Woolf S, Schoomaker H. Life expectancy and mortality rates in the United States, 1959-2017. *JAMA*. 2019;322:1996-2016. doi:10.1001/jama.2019.16932
25. Heeringa SG, West BT, Berglund PA. *Applied Survey Data Analysis*. 2nd ed. Chapman & Hall/CRC Press; 2017.
26. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort profile: the Health and Retirement Study (HRS). *Int J Epidemiol*. 2014;43:576-585. doi:10.1093/ije/dyu067
27. Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the Health and Retirement Study and the Aging, Demographics, and Memory Study. *J Gerontol B Psychol Sci Soc Sci B*. 2011;66 Suppl 1:i162-i171. doi:10.1093/geronb/gbr048
28. Faul JD, Collins S, Smith JA, Zhao W, Kardia S, Weir DR. APOE *and Serotonin Transporter Alleles – Early Release*. University of Michigan; 2021. Accessed January 15, 2024. https://hrsdata.isr.umich.edu/sites/default/files/documentation/data-descriptions/1629310147/File-Description-for-APOE-and-Serotonin.pdf
29. HRS Staff. HRS Core Interview Sample Sizes and Response Rates. Institute for Social Research, University of Michigan; 2023. Accessed January 15, 2024. https://hrs.isr.umich.edu/documentation/survey-design/response-rates
30. Ware E, Schmitz L, Faul J, et al. HRS Polygenic Scores – 2006-2010 Genetic Data. University of Michigan; 2021.
31. Domingue BW, McCammon RJ, West BT, Langa KM, Weir DR, Faul J. The mode effect of web-based surveying on the 2018 U.S. Health and Retirement Study measure of cognitive functioning. *J Gerontol B Psychol Sci Soc Sci*. 2023;78:1466-1473. doi:10.1093/geronb/gbad068
32. Langa KM, Weir DR, Kabeto M, Sonnega A. Langa-Weir classification of cognitive function (1995-2020). University of Michigan; 2023. Accessed July 1, 2024. https://hrsdata.isr.umich.edu/sites/default/files/documentation/data-descriptions/1695907706/Data_Description_Langa_Weir_Classifications2020_V2.pdf
33. Singer JD, Willett JB. *Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence*. New York: Oxford University Press; 2003.
34. Kleinbaum DG, Klein M. *Survival Analysis: A Self-Learning Text*. 3rd ed. New York: Springer; 2012.
35. HRS Staff. Sampling Weights: Revised for Tracker 2.0 and Beyond. Survey Research Center, Institute for Social Research, University of Michigan; 2019. Accessed January 20, 2024. https://hrsonline.isr.umich.edu/sitedocs/wghtdoc.pdf
36. Stata Corp. Stata Statistical Software. Release 18.0: StataCorp LLC; 2023.
37. Knudsen AK, Hotopf M, Skogen JC, Øverland S, Mykletun A. The health status of nonparticipants in a population-based health study: The Hordaland Health Study. *Am J Epidemiol*. 2010;172:1306-1314. doi:10.1093/aje/kwq257
38. Drivsholm T, Eplov LF, Davidsen M, et al. Representativeness in population-based studies: a detailed description of non-response in a Danish cohort study. *Scand J Public Health*. 2006;34:623-631. doi:10.1080/14034940600607616
39. Schoeler T, Speed D, Porcu E, Pirastu N, Pingault J-B, Kutalik Z. Participation bias in the UK Biobank distorts genetic associations and downstream analyses. *Nat Hum Behav*. 2023;7:1216-1227. doi:10.1038/s41562-023-01579-9
40. van den Berg E, Ruis C, Biessels GJ, Kappelle LJ, Van Zandvoort MJ. The Telephone Interview for Cognitive Status (Modified): relation with a comprehensive neuropsychological assessment. *J of Clin and Exp Neuropsychology*. 2012;34:598-605.

SUPPORTING INFORMATION

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

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