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Examination of Race and Gender Differences in Predictors of Neuropsychological Decline and Development of Alzheimer's Disease

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Abstract

Objective: Black adults are diagnosed with Alzheimer's disease (AD) at higher rates than White adults. Biopsychosocial risk factors that differentially affect individuals by race, including health, education, and APOE e4, may explain these findings. Some research suggests that the risk for AD associated with the APOE e4 allele may differ by race. Gender differences in AD have also been identified but remain understudied. We examined race, APOE status, vascular risk factors, education, and the interaction of APOE e4 status and race as predictors of cognitive decline and the development of Alzheimer's disease between genders in a large longitudinal sample of older adults.

Method: Participants (N=4336) were selected from the National Alzheimer's Coordinating Center's Uniform Data Set who completed measures of verbal fluency, naming, and immediate/delayed story memory across 5 years. Analyses were stratified by gender. Follow up interactions examined statistical significance of differences.

Results: APOE e4 by race interactions were largely non-significant and dropped from most models. When controlling for health, education, referral source, and Uniform Data Set form (when applicable), few racial differences in cognitive performance over time emerged. Black participants obtained lower scores than White participants on a majority of baseline measures. Race findings did not differ by gender. Hypertension was more strongly predictive of decline in delayed memory among women.

Conclusions: Analyses did not support that APOE e4 differentially affects Black individuals. Hypertension may be a more relevant risk factor among women. Results raise questions regarding the accuracy of baseline scores in predicting decline for Black individuals.

Introduction

Black individuals are approximately two times more likely than White individuals to be diagnosed with Alzheimer's Disease (AD; Alzheimer's Association, 2009; Mayeda et al., 2016; Mehta and Yeo, 2017). Despite rates of AD declining overall (Langa et al., 2017), rates of AD diagnosis among Black individuals remain stagnant (Rajan et al., 2019). Some research suggests that racial discrepancies in diagnosis are not observed when controlling for known risk factors of AD, including education, age, sex, gender[1], and other health conditions (Rodriguez et al., 2018; Yaffe et al., 2013). In the Unites States (US) education and health disparities persist (Carter-Pokras et al., 2013; Park et al 2019), and higher rates of AD among racial and ethnic minorities may be related to higher burden of these combined risk factors (e.g., Alzheimer's Association, 2018; Mayed et al., 2016; Yaffe et al., 2013) and not due to biological differences in race (Graff-Radford et al., 2016). Structural racism (i.e., design of institutions in the US that is inequitable to racial/ethnic groups, is culturally reinforced, and fosters discriminatory beliefs; Cee & Ford, 2015; Krieger, 2014; Reskin, 2012) leads to lower quality of education and healthcare among ethnic/racial minorities, including Black Americans. A growing body of research supports structural racism as a cause for health discrepancies (see Bailey et al., 2017, for a review).

In addition to health and social factors rooted in structural racism in the US, presence of the genetic biomarker Apolipoprotein E e4 (APOE e4) has been identified as one biological risk factor for AD that may differ across Black and White individuals. Although presence of the e4 allele increases risk of AD in all racial/ethnic groups (Murrell et al., 2006), early studies suggested that the risk may vary disproportionately across various racial/ethnic groups (Green et al., 2002, Kalaria et al., 1997, Sahota et al., 1997). It remains a topic of debate whether this represents a biological difference or is the result of health inequalities. The presence of APOE e4 is more common in Black individuals (e.g., Barnes et al., 2013; Graff-Radford et al., 2016; Rajan et al., 2019), and a recent study of adults with cognitive decline from a variety of causes found that Black participants demonstrated AD neuropathologic features (i.e., neurofibrillary degeneration, neuritic and diffuse plaques) more frequently than White participants (Graff-Radford et al., 2016). However, when controlling for APOE e4 status, there was no relationship between race and the presence of AD pathology, suggesting that APOE e4 may account for AD neuropathologic differences by race. Further, other studies found no race differences in the degree of risk for AD conferred by presence of APOE e4 (Fillenbaum et al., 2001, Graff-Radford et al., 2002, Jun et al., 2010).

Fewer studies have examined any cause (i.e., not specific to AD) cognitive decline in the context of APOE e4. One large population-based community study (Barnes et al., 2013) observed that, when controlling for age, gender, education, and vascular risk burden, decline in episodic memory among Black and White participants who had the e4 allele did not differ. However, when controlling for covariates listed above, presence of the e4 allele was related to a faster rate of decline in semantic and working memory for White adults relative to Black adults (Barnes et al., 2013). Rajan and colleagues (2019) found that APOE was

[1]"Gender" refers to self-identified expression of masculine/feminine traits while "sex" refers to biologically determined features. Participants self-identified and no biological measure of sex was available, thus the term gender is used throughout the manuscript.

associated with similar cognitive decline between Black and White participants. Thus, the relationship of APOE e4 to racial differences in AD risk and general cognitive decline remains unclear.

One methodological element that may add to the inconsistent findings surrounding cognitive decline in the context of APOE e4 is the nature of the samples used in analyses. Differing trajectories of decline are observed in samples that examine population-based community sample, samples with any cause of cognitive decline, or AD specific samples). Two early cross-sectional clinical studies observed that Black participants with AD evidenced more severe cognitive impairment at earlier ages compared to White participants (Shadlen et al, 1999; Welsh et al., 1995). However, these studies only included older adults with existing cognitive decline, included small sample sizes of Black participants, and did not examine change over time due to their cross-sectional nature. One much larger longitudinal study that examined rates of decline on a composite cognitive measure (i.e., the Mini-Mental State, a measure of episodic memory, and an oral perceptual speed task) among individuals with MCI and AD found that rate of cognitive decline did not vary by race (Wilson et al., 2010). Another large longitudinal study of individuals who developed AD over a period of 18 years found that, among those who developed AD, decline was faster among White adults relative to Black adults when controlling for age, sex, and educational attainment (Rajan et al, 2017).

Large longitudinal studies of cognitive decline generally do not observe race differences in the trajectories of decline. For example, in one large population-based community sample, although the risk for AD diagnoses among Black adults was twice that of White adults, White adults did not evidence faster cognitive decline across time compared to Black adults (Weuve et al., 2018). Further, Black individuals declined more slowly in the domain of executive functioning. Baseline differences were observed, such that Black participants obtained lower baseline scores in all cognitive domains, which were largely accounted for by education. In another population-based sample, Rajan and colleagues (2017) observed that there was no difference in cognitive decline by race among individuals who did not develop AD or any dementia diagnosis. Conversely, in further analysis of data from the same sample, there were more Black participants who showed rapid and moderate decline, but fewer who showed slow decline; rates of Black and White participants with slow decline were similar. However, this study did not control for vascular health risk factors (Rajan et al., 2019).

Taken together, these studies suggest that, although Black participants are more likely to be diagnosed with AD, trajectories of cognitive decline are less clear. Overall, rates of decline among general aging populations do not support race differences, and findings within MCI or AD are mixed. Researchers largely agree that health and education disparities contribute to race differences in diagnosis of AD. Given inconsistent findings across studies, there is a need to further replicate past research in this area through examining predictors of cognitive decline and whether these predictors operate differently across racial groups.

As noted above, other health and sociodemographic factors must be considered when examining risk for AD and cognitive decline across different racial groups. Consideration of factors that might contribute to differences in neuropsychological test performance are crucial. On average, Black older adults perform more poorly on neuropsychological

measures than White older adults (Weuve et al., 2018; Zahodne et al, 2016). This is largely believed to be due to health and education disparities in the US, as cognition is affected by many factors that may vary by race/ethnicity on a population level (Green et al., 2002).

Known health risk factors for AD and cognitive decline include hypertension (Rouch et al., 2015) and diabetes (Lu et al., 2015). Rates of these health risk factors are frequently observed to be higher in Black compared to White individuals (e.g., Graff-Radford et al., 2016; Weuve et al., 2018; Wilson et al., 2010). Furthermore, level of education is related to scores on cognitive tests (Manly et al., 2002; Stern et al., 1994). Interestingly, the association between education and global cognitive functioning is more than twice as large for Black compared to White individuals (Jean et al., 2019). This may reflect not only years of education, but quality of educational opportunities (Manly et al., 2002), which is hard to quantify in research. These findings suggest that cognitive impairment seen at baseline during an AD evaluation may reflect different causal mechanisms, which may explain the general pattern suggested by longitudinal studies (i.e., less severe cognitive decline in Black individuals with AD). However, few studies have examined the relationship of these risk factors to rate of cognitive decline in different racial groups.

Gender differences are also important to consider when examining cognitive decline. It is well established that women are at a higher risk for the development of AD. Women account for nearly two thirds of individuals aged 65 years and older with AD in the U.S. (Alzheimer's Association, 2019; Hebert et al., 2013), are twice as likely as men to receive a diagnosis of dementia after age 60 (Nebel et al., 2018) and evidence higher rates of amnestic MCI than men (Cusky et al., 2016; Roberts et al., 2012).

Hormonal changes associated with menopause in women may contribute to gender differences in AD (Mielke et al., 2014). Menopause is associated with reduced brain glucose metabolism, increased development of amyloid plaques, reduced brain-derived neurotrophic factor, and reduced gray and white matter in brain areas associated with AD (Mosconi et al., 2017). Gender differences in hypertension are also well established (Ramirez & Sullivan, 2018). Although men typically have higher rates of hypertension than women prior to menopause, women's rates of hypertension exceed men's post-menopause (Ramirez & Sullivan, 2018). Thus, research suggests that risk factors for AD may function differently in men and women, and additional research on risk factors that are specific to gender is needed (Mielke, 2018).

Given the known gender differences in AD and key biological differences in aging, it is critical that researchers examine risk factors within genders. Due to the well-established gender differences in the trajectories by which biological factors confer risk for AD, it has been argued that pooled analyses of gender may not yield relevant results for each gender (Mielke, 2018; Ramirez & Sullivan, 2018). Thus, the present study used a stratified analytic approach, then followed up with analyses to determine whether there were statistically significant interactions between gender and predictors of decline that differed by gender.

The Present Study

Given mixed findings in the extant literature, research regarding whether APOE e4 differentially predicts AD and rate of cognitive decline by race in older adults requires replication in longitudinal analyses that consider the role of sex/gender in race differences in APOE e4 and both the development of AD and presence of any-cause cognitive decline from a nonclinical baseline. The present study sought to expand upon prior work through examining the interaction of APOE e4 and race in a large, mixed treatment seeking/non-treatment seeking sample that had no cognitive impairment at baseline, stratified by gender.

The first aim was to evaluate race differences in development of AD over 10 years when controlling for other known risk factors. We hypothesized that known risk factors (APOE e4, education, hypertension, and diabetes) would be related to conversion to AD. We hypothesized that race would be related to AD, such that Black individuals would be more likely to develop AD over follow-up, but that controlling for known risk factors would account for race differences. Finally, given that some studies suggest that APOE status is not equally predictive of AD risk for Black and White individuals, we included a race by APOE interaction term in our model. The second study aim was to examine race differences in cognitive decline in older adults across 10 years when controlling for known risk factors and to determine whether an interaction between race and APOE e4 predicts cognitive decline. We hypothesized that Black participants would evidence lower cognitive scores at baseline but decline less than White participants over time. We also hypothesized that known risk factors of APOE e4, education, hypertension, and diabetes would be related to decline in scores. We explored the interaction of APOE status and race in the prediction of cognitive decline. The third aim was to examine the above hypotheses within each gender. We first stratified analyses by men and women, then conducted exploratory follow-up analyses to examine the interactions of gender and race and gender and APOE e4 status.

Method

Data was utilized from the National Alzheimer's Coordinating Center (NACC), a nationwide network of Alzheimer's Disease Research Centers (ADRCs) that collect clinical data on patients who seek care related to memory concerns. Specifically, the present study used the Uniform Data Set (UDS; Morris et al., 2006), which was incorporated at the NACC in 2005 to standardize collection of data. To maximize length of follow-up and number of participants, we used all existing forms of the UDS. Revisions of the UDS (1.2– 3.0; see Weintraub et al., 2018 for more information) have introduced different neuropsychological tasks to measure the same construct. To standardize these measures in the current study, z-scores were calculated based on first visit (normal cognition) data for the specific sample used in the present analyses.

Participants

Participant data were utilized from the NACC's UDS, and the initial sample was comprised of $N = 28{,}684$ individuals[2] who were seen between 2005 and 2017. The study sample was limited to participants who identified as White or Black, were 50 or older at baseline, and had no diagnosis of AD or other neurocognitive disorders at baseline. The sample was

further restricted to participants who remained cognitively healthy for the duration of the study and those who developed AD during the duration of participation. Individuals with a major neurocognitive disorder with a different etiology were excluded. Although AD is commonly comorbid with additional etiologies and it can be difficult to isolate AD specific decline, this exclusion criteria was imposed to reduce the risk of including primarily non-AD causes of decline. Based on these inclusion criteria, the available sample included 7459 older adults (mean age at baseline = 71.33, SD = 9.45; 62% female; 83.9% White). An additional 251 participants were excluded for missing data regarding race (N=7208). Due to previous research regarding bias in NACC referral source, only participants with a clearly identified referral source (i.e., identified as by a professional or non-professional such as family/friends) were included (N=4336). The NACC database also includes individuals with unknown referral source or referred by "other" (i.e., media or other ADC/non-ADC solicitation), however these participants were not included in the study sample. Number of participants lost to follow-up across the five years are presented in Table 1. Due to missing data regarding AD diagnosis, an additional 632 participants were excluded from survival analyses (Final N for Aim 1=3704; 2798 with normal cognition at all visits and 906 diagnosed with probable AD during follow-up).

Measures

All data were collected at ADRCs at the time of the participants' visits. Measures used from the NACC data for the present analyses included participant demographics, health history, clinician judgment of symptoms and diagnosis, genetic data, and neuropsychological tests of verbal fluency, naming, and immediate/delayed story memory. Health history (i.e., diagnosis of diabetes or hypertension) was obtained through self-report. For both health variables, disease was coded as "present" if participants reported current or past diagnosis of either disorder at any time point. Diabetes type was not included in analyses. Disease duration and treatment were not available in the dataset used. AD Diagnosis (coded as normal cognition or AD) was determined from the Clinician Judgment of Symptoms, such that participants in the AD group had a diagnosis of possible or probable AD (UDS 1.2–2.0) or presumed etiologic diagnosis of Alzheimer's Disease based on the National Institute on Aging and Alzheimer's Association 2011 criteria (UDS 3.0; McKhann et al., 2011), as determined by health care providers at their ADRC visits. All cognitive measures were converted to z-scores based on norms derived from the initial visit data when all participants had normal cognition. This standardization allows for direct comparison of results on different versions of tests given across UDS 2.0 and 3.0. Validation research from the time of the test change implementation suggests that there is good correlation between tasks; thus, longitudinal comparisons can be made (Monsell et al., 2014).

Fluency: Category Fluency.—The category fluency task involves providing a semantic category to the examinee, so that the examinee can provide as many examples of the category (in the NACC database, categories of animals and vegetables) as possible within a specified time. This test is commonly used in neuropsychological settings and has been

[2]N used in the original sample is not reflective of the full NACC dataset and was specific to the criteria applied to our customized data file. Data was utilized from the September 2018 data freeze.

demonstrated to be related to cognitive decline in Alzheimer's disease (Morris et al., 1989; Cerhan et al., 2002).

Naming: Boston Naming Test and Multilingual Naming Test.—The Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2001) is used to assess confrontation naming. It has been normed in a variety of samples and shows high internal consistency and test-retest reliability (Lezak et al., 2012). It appears to be sensitive to anomia experienced in certain neurological conditions, and often specifically in Alzheimer's disease (Huff et al., 1986; Morris et al., 1989). The Multilingual Naming Test was developed to assess anomia and naming ability across diverse populations (Gollan et al., 2012) and has been shown to be sensitive to naming impairment in Alzheimer's disease (Ivanova et al., 2013). It replaced the Boston Naming Test in the UDS 3.0 for its applicability to a broader range of patients (Weintraub et al., 2018).

Memory: Logical Memory I and II and Craft Story 21.—Logical Memory I and II from the Wechsler Memory Scale (WMS) and the Craft Story 21 from Craft et al. (2000) are both measures of immediate and delayed memory of a short story read by the examiner to the examinee. The Logical Memory subtest is commonly used and supported to assess semantically related verbal memory (Kent, 2013), but may be prone to practice effects for individuals who do not have impaired cognition (Gavett et al., 2016). Craft Story 21 was used initially to measure verbal memory in individuals with Alzheimer's disease (Craft et al., 2000). It was selected for the UDS 3.0 for its demonstrated use in diverse populations and potential to reduce practice effects in NACC participants (Weintraub et al., 2018).

Data Analytic Strategy

Aim 1 analysis involved a Cox proportional hazards regression to predict risk of AD based on time to diagnosis (i.e., age at diagnosis) run using IBM SPSS Statistics for Mac, version 26 (IBM Corp., Armonk, N.Y., USA). Survival time was operationalized as age at diagnosis for individuals in the AD diagnostic group and age at most recent visit for individuals in the normal cognition group. A binary variable denoted AD diagnosis. Race was entered as a first step; APOE status, education, baseline age, diabetes, hypertension, referral source, and a race by APOE status interaction were added in a second step. Nonsignificant race by APOE status interactions were dropped from the final model. Bonferroni corrections were applied by aim to minimize risk of familywise type 1 error. Two models were run (one for each gender); thus, significance was set at $p<.025$.

Aim 2 analyses were completed using Mplus 8 Editor, V1.6 (Muthén & Muthén, 2017). A series of multilevel models were used to determine predictors of decline in the cognitive domains described above. Participants were included regardless of conversion to AD in order to examine cognitive decline overall. A two-level mixed modeling approach was utilized to increase robustness to missing values and allow for repeated testing (Gueorguieva & Krystal, 2004; Misangyi et al., 2016). Level 1 included all within-level variables (i.e., time-varying) and level 2 included all between-level variables (i.e., baseline variables). A linear time variable was created by setting the initial visit year to 0 to account for time in level one of the models. All measures were coded to reflect time since first visit in years. All

analyses were based on a random intercept, random slope model. Slope was included at the within level and entered as a random effect at the between level. Missing data was adjusted for using robust maximum likelihood estimation. Race (Black/White), APOE status (present/absent e4 allele) education, diabetes, and hypertension were included as predictors. Referral source was included as a covariate in all models based on previous research (Gleason et al., 2019). Due to the change in tests for naming and immediate/delayed memory between UDS form version 2.0 and 3.0, a binary variable control variable that denoted form version was included in models predicting naming and memory outcomes. Analyses were stratified by gender. Non-significant interactions were removed from the models. Tables present the final models with no significant interactions. Ten models were run; thus significance was set at $p<.005$ after Bonferroni corrections.

For aim 3, predictors of cognitive decline that emerged differently for men and women in aims 1 and 2 were further analyzed. Exploratory race by gender and gender by e4 status interactions were also conducted for all outcomes. Follow-up models assessing for interactions between gender and predictor were examined to determine whether differences in slope were statistically significant for men and women. Non-significant interactions were removed from models and significant interactions were probed to determine the direction of significance. Six models were run for Aim 3; thus, significance was set at $p<.008$ after Bonferroni corrections.

Results

Bivariate correlations for each gender were run to examine whether factors to be entered into the model were related to conversion to AD. Among men, presence of APOE e4 allele and diabetes were related to conversion to AD. Among women, presence of APOE e4 allele and hypertension were related to conversion to AD. Correlations stratified by gender are present in Table 2. Demographic variables and comparisons by race are presented in Table 3. Statistical values are included in Table 4 for aim 1, Tables 5 (women) and 6 (men) for aim 2, and Tables 7 and 8 for aim 3. Tables represent final models with non-significant interactions removed.

Aim 1

Women.—The interaction between race and APOE e4 status was not significant and was dropped from the model, $p=0.441$. For women, race did not predict AD diagnosis in the first step or after other predictors were added. APOE e4 status was associated with AD diagnosis, such that APOE e4 carriers had increased risk of AD diagnosis compared to non-carriers. Women with hypertension had higher risk of AD diagnosis than those without hypertension. Baseline age was also related to survival; for each additional year of age at baseline, risk of AD diagnosis reduced slightly. Individuals referred by a professional referral source had increased risk for AD diagnosis. Education and diabetes were not related to risk of AD diagnosis.

Men.—The interaction between race and APOE e4 status was not significant among men and was dropped from the model, $p=.463$. For men, race did not predict AD diagnosis in the first step or after other predictors were added. APOE affected AD risk, such that APOE

e4 carriers had increased risk of AD diagnosis compared to non-carriers. Baseline age was also related to survival; for each additional year of age at baseline, risk reduced slightly. Men who were referred by professional sources were at a higher risk for AD diagnosis. Education, diabetes, and hypertension were not related to risk of AD diagnosis.

Aim 2

Naming—The interaction between race and APOE e4 status was nonsignificant for both slope (p_{women}=.400, p_{men}=.267) and intercept (p_{women} =.065, p_{men} = .747) and was dropped.

Women.: Lower baseline scores were associated with being Black, having fewer years of education, being referred by a professional, and completing an earlier UDS form. Faster decline was associated with being referred by a professional, completing a later UDS form, and having lower scores at baseline. Carrying the e4 allele, race, education, hypertension, and diabetes were not related to score trajectories on this measure among women.

Men.: Lower baseline scores were related to being Black, having fewer years of education, and being referred by a professional. Faster decline was associated with baseline score, being referred by a professional, and completing a later UDS form. Race, presence of the e4 allele, education, hypertension and diabetes were not related to score trajectories.

Fluency-Vegetables—For the outcome of semantic fluency- vegetables, the interaction between race and APOE e4 status was nonsignificant for both slope (p_{women} =.390, p_{men} =.235) and intercept (p_{women} =.888, p_{men} =.211) and was dropped from all models.

Women.: Lower baseline scores were related to being Black, having fewer years of education, having hypertension, and being referred by a professional. Faster decline was related to hypertension and having a lower score at baseline. No other study variables were significantly related to decline.

Men.: Lower baseline scores were related to being referred by a professional. Faster decline was associated with presence of the e4 allele, being referred by a professional, and having a lower score at baseline. Race, education, hypertension, and diabetes were not related to score trajectories on this measure.

Fluency- Animals—The interaction between race and APOE was nonsignificant after Bonferroni corrections for both slope (p_{women}=.039, p_{men}=.219) and intercept (p_{women}=.052, p_{men}=.828) and was dropped.

Women.: Lower baseline score was related to being Black, having fewer years of education, having hypertension and being referred by a professional. Faster decline was associated with carrying the e4 allele, being White, hypertension, being referred by a professional, and a lower score at baseline. Education and diabetes were not related to score trajectories on this measure.

Men.: Being Black and being referred by a professional were associated with a lower baseline score. Faster decline was associated with being referred by a professional and

having a lower score at baseline. Carrying the e4 allele, race, education, hypertension, and diabetes were not related to score trajectories on this measure.

Immediate Memory—The interaction between race and APOE e4 status was nonsignificant for both slope (p_{women}=.241, p_{men}=.219) and intercept (p_{women}=.249, p_{men}=.828) and was dropped.

Women.: Lower baseline scores were associated with being Black, having fewer years of education, and being referred by a professional. Faster decline was associated with presence of the e4 allele, having hypertension, being referred by a professional, completing a later UDS form, and having a lower score at baseline. The association between hypertension and decline was marginal after Bonferroni corrections (p=.006). Race, education and diabetes were not related to score trajectories on this measure.

Men.: Being Black and being referred by a professional were associated with a lower baseline score. Faster decline was related to carrying the e4 allele, being referred by a professional, completing a later UDS form, and having a lower score at baseline. Carrying the e4 allele was marginally associated with decline after Bonferroni corrections (p=.007). Race, education, hypertension, and diabetes were not related to score trajectories.

Delayed Memory—Among both men and women, the interaction between race and APOE e4 status was nonsignificant for both slope (p_{women}=.706, p_{men}=.085) and intercept (p_{women}=.794, p_{men}=.724); thus, they were dropped from the models.

Women.: Being Black, having fewer years of education, having hypertension, being referred by a professional, and later UDS form, were associated with a lower baseline score. Faster decline was associated with presence of the e4 allele, having hypertension, being referred by a professional, later UDS form, and lower scores at baseline. Race, education and diabetes were not related to score trajectories on this measure.

Men.: Being Black and being referred by a professional were associated with a lower baseline score. Faster decline was associated later UDS form, being referred by a professional, and having a lower score at baseline. Race, presence of the e4 allele, education, hypertension, and diabetes were not related to score trajectories on this measure.

Aim 3

Conversion to AD—Stratified analyses suggested a difference in hypertension predicting AD risk for males and females, such that hypertension was a significant predictor for women but not men. Follow up analyses indicated that, although the interaction between gender and hypertension in the combined sample trended towards significance, it was not significant after Bonferroni corrections were applied (p=.034). Exploratory interactions between race and gender (p=.697) and gender and ApoE4 status (p=.874) were not significant.

Cognitive Decline.

Naming.: No significant interactions emerged for exploratory interactions of e4 status by gender (p=.421), and race by gender (p=.716).

Fluency-Vegetables.: Gender stratified models suggested that hypertension predicted decline in women, but not men. A model including gender by hypertension and exploratory gender by race and gender by e4 status was run. Results were non-significant for gender by race, (p=.933), and gender by hypertension, (p=.060) interactions thus were removed from the models. When the non-significant interactions were removed from the model, the interaction between gender and e4 status was no longer significant.

Fluency-Animals.: Gender stratified models suggested that hypertension predicted decline in women, but not men. However, follow-up interaction and exploratory gender by race, (p=.369), and gender by e4 status, (p=.019), indicted non-significant results after Bonferroni corrections.

Immediate memory.: Gender stratified models suggested that hypertension predicted decline in women, but not men. The follow-up interaction, (p=.704), and exploratory gender by race, (p=.858), and gender by e4 status, (p=.858), indicted non-significant results.

Delayed memory.: Gender stratified models suggested that hypertension and presence of the e4 allele predicted decline in women, but not men. Follow up interactions and exploratory race by gender interactions indicated nonsignificant results regarding gender by e4 status, (p=.318), and gender by race, (p=.624) and were dropped from the model. A significant interaction emerged regarding gender and hypertension. Although individual probes were non-significant after Bonferroni corrections, the direction of the association between hypertension and delayed memory differed between men and women. Hypertension was associated with greater decline (B=−.018, SE=.009, 95%CI= −.035- −.003 p=.046) among women, but not men (B=.021, SE=.011, 95%CI= −.002- .043, p=.068).

Discussion

In the present study, we examined race, APOE e4 status, vascular risk factors, and education as predictors of cognitive decline and the development of AD in a longitudinal sample of older adults taken from the NACC dataset. We utilized a large sample of participants with normal cognition at baseline who completed neurocognitive, genetic, and demographic questionnaires at several time points over a five-year-period. Overall, our results replicate prior research suggesting that race differences in AD risk and cognitive decline reflect complex associations between underlying biopsychosocial differences and disparities for which race is merely a proxy. Results support the need to consider the role that many biopsychosocial factors play in AD risk and cognitive decline differences in Black and White Individuals. Results further extend prior research with novel findings regarding gender differences.

Race Differences

Survival analysis results did not support race differences in diagnosis of AD when controlling for referral source, UDS form version (when applicable), APOE e4 status, education, age, and vascular risk factors. Further, Black participants (both male and female) did not evidence differences in rate of cognitive decline over time for any outcomes except animal fluency, where Black women evidenced *slower* decline than White women. These findings conflict with older studies regarding AD risk and race (e.g., Shadlen et al, 1999; Welsh et al., 1995), but add to a growing body of more recent literature that suggests the relationship of race to AD risk is more complex and tied to other sociodemographic and health factors (e.g., Barnes et al., 2013; Wilson et al., 2010; Weuve et al., 2018).

Our findings indicated consistently lower baseline cognitive scores among Black participants, whether male or female, even when controlling for relevant covariates. These findings are consistent with those observed by Weuve and colleagues (2018). This is particularly interesting to note given that both samples were cognitively healthy at baseline, although our sample included treatment seeking participants, unlike Weuve and colleagues (2018). One explanation for these baseline differences is potential bias in testing instruments (Manly et al., 2002; Stern et al., 1994). Some neuropsychological tests do not have full measurement invariance across sex/gender and racial/ethnic groups (Avila et al., 2020), which complicates valid interpretation of neurocognitive performance in these groups. Another contributing factor to our baseline differences is education, which has been linked to cognitive performance and cognitive decline in prior studies (e.g., Walker, Batchelor, & Shores, 2009; Weuve et al., 2018; Zahodne et al, 2016). Although we controlled for years of education in our analyses, we were not able to control for quality of education. Research supports that racial disparities in quality of early education, and childhood adversity may explain cognitive functioning later in life (Lamar et al., 2019; Sisco et al., 2015; Zhang et al., 2016). Future studies should consider the contribution of additional education factors such as school segregation, level of community funding, and adverse childhood experiences that impact academic involvement and quality. Additional social risk factors that vary by race may also be relevant. For example, perceived discrimination (Barnes et al., 2013) and perceived stress (Turner et al., 2017) are associated with poorer performance on neurocognitive tests and baseline differences could also be related to sociodemographic disparities that were not controlled for in our study.

Our finding of slower decline in animal fluency among Black women is consistent with one prior study that observed slower decline among Black adults in the domain of executive functioning in a community dwelling, non-treatment seeking presentation (Weuve et al., 2018). However, this finding is inconsistent with other studies that showed no differences in decline across race (Barnes et al., 2013; Rajan et al., 2017), and we did not see this interaction for vegetable fluency or for any other cognitive variables in our own sample. Although participants across these studies were all cognitively healthy at baseline, our sample differed from those utilized by Barnes and colleagues (2013), Rajan and colleagues (2017), and Weuve and colleagues (2018) in that our participants were mixed treatment and non-treatment seeking individuals. Due to the mixed nature of our sample, it is possible that a higher percentage of participants had subtle, pre-clinical declines at baseline, despite

our inclusion criteria of only individuals who showed normal cognitive performance at baseline. Regardless, the majority of recent research does not support previous assertions that Black adults decline more quickly than White adults when controlling for health and sociodemographic factors, and our results add to this body of literature. Future research including additional risk factors for cognitive decline that may explain race differences is needed to clarify inconsistencies among these studies.

Taken together, this body of research reinforces assertions that race differences in cognitive decline in the US are attributable to health and education disparities derived from structural racism. Our findings also highlight the importance of examining baseline level of function and slope separately in longitudinal studies of racial disparities in cognitive decline in older adults. Future research should include additional sociocultural variables that may explain low baseline scores in order to determine the relevance of low baseline scores in cognitive decline across race.

APOE e4, Cognitive Decline, and Race

Consistent with prior research, APOE e4 status was a significant predictor of both cognitive decline and development of AD across both male and female participants. Further, we did not find race or gender differences in APOE e4 risk in the presence of other known risk factors. Overall, our results, along with other larger studies, suggest that APOE status is a useful prognosticator for both Black and White older adults (Ashford, 2004; Liu et al., 2013; Saunders et al., 1993; van der Lee et al., 2018).

Our results were inconsistent with previous assertions that APOE e4 status differentially affects cognitive decline for Black and White individuals (Green et al., 2002, Kalaria et al., 1997, Sahota et al., 1997), but replicate findings from more recent studies and studies with larger samples suggesting no racial differences in the association between APOE status and risk for AD (Fillenbaum et al., 2001; Graff-Radford et al., 2002; Jun et al., 2010). In our sample, a higher percentage of Black participants carried at least one e4 allele (i.e., 34.1% of White; 37.1% of Black), although this difference was not significant and was smaller than what was been observed in other samples (Barnes et al., 2013; Evans et al., 2003; Graff-Radford et al., 2016; Rajan et al., 2019). It is possible that this difference reflects differences in the study sample. Barnes and colleagues (2013), Evans and colleagues (2003), and Rajan and colleagues (2019) utilized community cohort samples that did not include treatment seeking adults. If indeed APOE e4 is more strongly associated with decline among White adults as some previous population-based studies have suggested, it is possible that the proportion of White adults with the APOE e4 allele who enroll in a treatment related study would be greater than that observed in the general population. The study by Graff-Radford and colleagues (2016) used a post-mortem sample with known dementia. Further, the sample used by Graff-Radford and colleagues (2016) had substantially fewer Black participants compared to White, which may have influenced findings (i.e., 110 Black participants, 2500 White participants).

Health Risk Factors and Gender

Stratified analyses suggested that predictors of AD and decline may differ by gender. Specifically, hypertension predicted conversion to AD and decline in vegetable fluency, animal fluency, immediate memory, and delayed memory among women but not men. However, follow-up analyses indicated that, after Bonferroni corrections, there was no significant interaction between gender and hypertension in predicting AD diagnosis or cognitive decline in any domain except delayed memory, with hypertension predicting decline more strongly for women than men. These results support recent assertions that health risk factors operate differently by gender (Meilke, 2018). Gender differences in hypertension may be particularly important to consider in research regarding AD, given the known gender differences in the development of hypertension during aging and the role of menopause in worsening hypertension amongst adult women (Ramirez & Sullivan, 2018). Future research is needed to understand the mechanisms by which hypertension may operate differently in women than men in predicting cognitive decline. Diabetes did not emerge as a risk factor predicting AD diagnosis or decline, regardless of gender.

Although not a main aim of our study, it is also notable that professional referral source predicted AD diagnosis and was consistently related to baseline scores and decline among both men and women. Referral source has been identified as a potential confounding variable within this database (Gleason et al., 2019); thus, the present study included referral source as a covariate in analyses and restricted the sample to individuals referred by professional and non-professional referral sources. Indeed, referral source was significantly related to many of our outcomes of interest, suggesting that individuals referred by a professional evidenced greater decline in many areas relative to those referred by friends and family. It is possible that those referred by professionals were concerned about their cognition or evidenced pre-clinical decline. Our results highlight the importance of considering referral source in studies of aging. Future research should consider referral source and measure participant concerns at baseline to contextualize the sample and rule out potential confounds in population-based research.

Lastly, survival analyses indicated that, for both men and women, for each additional year of age at baseline risk of AD diagnosis reduced slightly. This finding may seem counterintuitive given that age is one of the most robust risk factors for AD (Alzheimer's Association, 2021), however this finding reflects the age when participants began the study rather than the age of diagnosis. It is possible that individuals who joined the study at an earlier age had greater cognitive concerns and existing decline and thus were more likely to be treatment seeking. Unfortunately, participants' motives for joining the study were not measured. Future research should consider additional participant sampling and self-selection factors such as referral source and motivation for participation, as these sample characteristics may influence findings.

Limitations

Limitations include a majority White (88%) and female (59.8%) sample. Although we had relatively large samples to examine Black/White differences in AD risk and cognitive decline, we did not examine other racial/ethnic groups due to disproportionately small

sample sizes of other racial/ethnic groups in the NACC dataset utilized. Thus, our results cannot generalize to other racial and ethnic groups. Analyses were also limited to a small number of cognitive domains, which differed from some past studies and did not allow for direct comparison with their results. Further, it is important to note that, although we attempted to isolate AD specific decline through our participant inclusion, it has been well documented that there is a high level of comorbidity between AD and other etiologies of cognitive decline (e.g., Lo & Jagust, 2012; Matthews et al., 2009) and individual contributions of multiple etiologies can be difficult to disentangle. Additionally, although we included health risk factors, we were unable to include treatment status, severity, or duration of these health risk factors, which may affect the relevance of these predictors in risk for AD and cognitive decline. Further, although analyses accounted for missing data statistically, attrition rates were fairly high over the five-year span (Table 1). Moreover, although the present study expanded upon previous research by examining gender interactions, the sampling method used self-reported sex, and biological markers of sex were not included in the NACC dataset. Thus, the biological or genetic basis of sex/gender reported could not be confirmed.

Lastly, there are some limitations associated with using the NACC database that may limit generalization to the greater aging population. Findings may not generalize to purely community-based samples or pure clinic-based settings. There may be self-selection effects of individuals who agree to participate in research, even if they are recruited from a clinical setting. Some studies have observed higher risk for MCI and dementia in the NACC dataset compared to other cohort studies of aging, which may relate to selection effects (Qian et al., 2017).

Conclusions

Overall, results of the present study and past research suggest that when, controlling for other known risk factors, Black individuals decline at the same rate if not more slowly than White individuals and are equally likely to be diagnosed with AD, regardless of APOE status or gender. However, there were consistent differences in baseline cognitive scores between White and Black individuals, even after controlling for referral source, UDS form (when applicable), health related variables, and education. Our findings have important implications for clinical practice and diagnosis of AD among racial groups. Given the baseline findings, it is important to be cautious when interpreting low baseline cognitive scores as evidence to support a neurocognitive diagnosis without evidence of decline. Further, factors other than AD may explain low scores on neuropsychological measures at baseline. It is important to consider the larger biopsychosociocultural context for individuals being assessed and to be wary of over-interpreting scores when additional factors may better explain low scores.

Our results also suggest that presence of APOE e4 was predictive of AD diagnosis and of cognitive decline, regardless of race or gender. Consistent with prior research, these results point to the importance of the e4 allele as an indicator of risk. Finally, our results suggest the potential for hypertension to be a stronger risk factor for cognitive decline for females than for males. These findings require replication in further research.

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Table 1.

Attrition and Demographics over 5 years

	N	% Women	%White	Mean Years Education
Baseline	4336	59.8	88	16.23
Year 1	4324	59.8	88	16.22
Year 2	4269	59.8	88.1	16.22
Year 3	4018	69.2	88.2	16.19
Year 4	3215	61.1	87.8	16.22
Year 5	2475	62.5	87.7	16.16

Table 2.

Bivariate correlations of baseline study variables.

Men (N=1744)						
	1.	**2.**	**3.**	**4.**	**5.**	**6.**
1. Conversion to AD	-	.19**	.03	.06*	−.01	−.04
2. APOE e4 status		-	−.01	.00	−.01	.03
3. Hypertension			-	.13**	.01	.12**
4. Diabetes				-	.01	.13**
5. Years of Education					-	−.08**
6. Race						-
Women (N=2592)						
	1.	**2.**	**3.**	**4.**	**5.**	**6.**
1. Conversion to AD	_-	.17**	.10**	.01	−.03	−.025
2. APOE e4 status		-	−.03	−.00	.02	.38
3. Hypertension			-	.20**	−.13**	.26**
4. Diabetes				-	−.06**	.22**
5. Years of Education					-	−.09**
6. Race						-

* p<.05

** p<.01

*** p<.001

Table 3.

T-tests and Chi Squares Among Study Variables and Conversion to Alzheimer's Disease (AD)

Men (N=1744)			
	% Diagnosed with AD		**Statistic**
Race	Black	White	$\chi^2(1, 1337) = 2.44$, $p = .12$
	31.5%	30.9%	
APOE e4 allele	Absent	Present	$\chi^2(1, 1251) = 46.90$, $p < .001$
	23.2%	41.6%	
Hypertension	Absent	Present	$\chi^2(1, 1337) = 1.25$, $p = .26$
	29.1%	32.0%	
Diabetes	Absent	Present	$\chi^2(1,1337) = 4.12$, $p = .04$
	29.8%	37.1%	
Referral Source	Non-professional	Professional	$\chi^2(1,1337) = 88.62$, $p < .001$
	22.3%	47.3%	
Years of Education	No AD $M = 16.76$, $SD = 4.82$	AD $M = 16.65$, $SD = 7.69$	$t(1335) = .32$, $p = .75$
Women (N=2592)			
	Descriptive Data		**Statistic**
Race	Black	White	$\chi^2(1, 2367) = 1.45$, $p = .23$
	18.6%	21.3%	
APOE e4 allele	Absent	Present	$\chi^2(1, 2200) = 61.34$, $p < .001$
	15.5%	29.7%	
Hypertension	Absent	Present	$\chi^2(1, 2367) = 23.24$, $p < .001$
	16%	24.2%	
Diabetes	Absent	Present	$\chi^2(1, 2367) = .30$, $p = .58$
	20.7%	22.1%	
Referral Source	Professional	Non-professional	$\chi^2(1, 2367) = 73.19$, $p < .001$
	16.7%	33.2%	
Years of Education	No AD $M = 15.95$, $SD = 5.84$	AD $M = 15.44$, $SD = 7.16$	$t(2365) = 1.63$, $p = .10$

Table 4:

Survival Analyses Examining Conversion to Alzheimer's Disease Stratified by Gender

Men (N=1337)					
	B	**SE**	**p**	**HR**	**95% HR CI**
Step 1					
Race	−.20	.26	.43	.82	.49–1.36
Step 2					
Race	−.21	.27	.43	.81	.48–1.36
APOE e4	1.03	.13	<.001	2.80	2.19–3.58
Education	.01	.01	.10	1.01	1.00–1.03
Baseline Age	−.13	.01	<.001	.88	.86-.90
Diabetes	.24	.18	.17	1.27	.90–1.80
Hypertension	−.03	.13	.80	.97	.74–1.26
Referral Source	.86	.13	<.001	2.36	1.85–3.02
Women (N=2397)					
	B	**SE**	**p**	**HR**	**95% CI for HR**
Step 1					
Race	−.21	.16	.18	.81	.59–1.10
Step 2					
Race	−.31	.17	.07	.74	.53–1.02
APOE e4	1.07	.11	<.001	2.92	2.34–3.66
Education	−.00	.01	.92	1.00	.98–1.02
Baseline Age	−.11	.01	<.001	.90	.88-.92
Diabetes	.09	.17	.61	1.09	.78–1.54
Hypertension	.30	.13	.02	1.35	1.05–1.74
Referral Source	.83	.12	<.001	2.30	1.81–2.91

Table 5.

Temporal Association between Predictors and Cognitive Performance for Women

Naming		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Baseline Score						
Race *(Black/White)*	−.779	.073	−.922	−.636	0.46	<.001
Education	.014	.005	.005	.023	1.01	.003
Diabetes *(yes/no)*	−.088	.070	−.225	.048	0.92	.204
Hypertension *(yes/no)*	−.067	.042	−.149	.015	0.94	.110
Referral Source *(professional/non)*	−.328	.055	−.436	−.221	0.72	<.001
UDS Change (*yes/no)*	.526	.101	.328	.723	1.69	<.001
Cognitive Decline						
Baseline score	.079	.015	.049	.109	1.08	<.001
APOE status *(e4 allele yes/no)*	−.030	.012	−.054	−.006	0.97	.015
Race *(Black/White)*	.027	.015	−.001	.056	1.03	.059
Education	−.001	.002	−.005	.003	1.00	.515
Diabetes *(yes/no)*	.006	.016	−.025	.036	1.01	.722
Hypertension *(yes/no)*	−.029	.014	−.055	−.002	0.97	.037
Referral Source *(professional/non)*	−.125	.020	−.165	−.085	0.88	<.001
UDS Change (*yes/no)*	−.220	.044	−.306	−.134	0.80	<.001
Semantic Fluency-Vegetables		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	
Baseline Score						
Race *(Black/White)*	−.246	.049	−.341	−.151	0.78	<.001
Education	.014	.004	.006	.022	1.01	.001
Diabetes *(yes/no)*	−.037	.056	−.147	.072	0.96	.504
Hypertension *(yes/no)*	−.179	.039	−.256	−.078	0.84	<.001
Referral Source *(professional/non)*	−.395	.046	−.484	−.277	0.67	<.001
Cognitive Decline						
Baseline score	.020	.004	.012	.029	1.02	<.001
APOE status *(e4 allele yes/no)*	−.017	.009	−.034	.000	0.98	.057
Race *(Black/White)*	.021	.010	.002	.040	1.02	.034
Education	−.001	.001	−.002	.000	1.00	.039
Diabetes *(yes/no)*	−.008	.012	−.031	.016	0.99	.530
Hypertension *(yes/no)*	−.029	.009	−.046	−.011	0.97	.001
Referral Source *(professional/non)*	−.019	.010	−.039	.001	0.98	.068

Naming		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Semantic Fluency-Animals		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	
Baseline Score						
Race *(Black/White)*	−.613	.049	−.710	−.516	0.54	<.001
Education	.020	.005	.011	.030	1.02	<.001
Diabetes *(yes/no)*	−.040	.055	−.148	.067	0.96	.464
Hypertension *(yes/no)*	−.228	.040	−.307	−.149	0.80	<.001
Referral Source *(professional/non)*	−.362	.047	−.453	−.271	0.70	<.001
Cognitive Decline						
Baseline score	.019	.004	.012	.027	1.02	<.001
APOE status *(e4 allele yes/no)*	−.030	.008	−.046	−.015	0.97	<.001
Race *(Black/White)*	.043	.009	.026	.060	1.04	<.001
Education	−.001	.000	−.002	.000	1.00	.011
Diabetes *(yes/no)*	−.005	.010	−.025	.014	1.00	.592
Hypertension *(yes/no)*	−.024	.008	−.040	−.008	0.98	.003
Referral Source *(professional/non)*	−.029	.009	−.047	−.011	0.97	.002
Immediate Memory		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Baseline Score						
Race *(Black/White)*	−.459	.050	−.556	−.362	0.63	<.001
Education	.016	.004	.008	.023	1.02	<.001
Diabetes *(yes/no)*	−.040	.057	−.152	.072	0.96	.481
Hypertension *(yes/no)*	−.107	.041	−.187	−.027	0.90	.009
Referral Source *(professional/non)*	−.450	.047	−.542	−.358	0.64	<.001
UDS Change (*yes/no)*	.259	.104	.056	.462	1.30	.012
Cognitive Decline						
Baseline score	.042	.005	.033	.051	1.04	<.001
APOE status *(e4 allele yes/no)*	−.047	.010	−.068	−.027	0.95	<.001
Race *(Black/White)*	.026	.012	.003	.050	1.03	.025
Education	−.001	.001	−.002	.001	1.00	.482
Diabetes *(yes/no)*	−.007	.014	−.035	.021	0.99	.640
Hypertension *(yes/no)*	−.028	.010	−.048	−.008	0.97	.006
Referral Source *(professional/non)*	−.071	.012	−.094	−.047	0.93	<.001
UDS Change (*yes/no)*	−.289	.033	−.354	−.223	0.75	<.001

Naming		**Model**			
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Delayed Memory		**Model**			
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	
Baseline Score						
Race *(Black/White)*	−.467	.052	−.569	−.366	0.63	<.001
Education	.015	.004	.008	.022	1.02	<.001
Diabetes *(yes/no)*	−.066	.060	−.184	.051	0.94	.270
Hypertension *(yes/no)*	−.117	.042	−.199	−.034	0.89	.005
Referral Source *(professional/non)*	−.475	.042	−.570	−.379	0.62	<.001
UDS Change (*yes/no)*	.380	.103	.179	.581	1.46	<.001
Cognitive Decline						
Baseline score	.031	.004	.023	.039	1.03	<.001
APOE status *(e4 allele yes/no)*	−.043	.010	−.062	−.024	0.96	<.001
Race *(Black/White)*	.017	.011	−.004	.038	1.02	.118
Education	−.001	.001	−.002	.001	1.00	.232
Diabetes *(yes/no)*	−.008	.013	−.034	.019	0.99	.568
Hypertension *(yes/no)*	−.030	.010	−.049	−.012	0.97	.002
Referral Source *(professional/non)*	−.054	.011	−.075	−.033	0.95	<.001
UDS Change (*yes/no)*	−.258	.030	−.316	−.200	0.77	<.001

Baseline N=2592

Table 6.

Temporal Association between Predictors and Cognitive Performance for Men

Naming		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Baseline Score						
Race *(Black/White)*	−.640	.120	−.875	−.405	0.53	<.001
Education	.017	.005	.007	.027	1.02	.001
Diabetes *(yes/no)*	−.032	.079	−.187	.124	0.97	.691
Hypertension *(yes/no)*	.011	.060	−.107	.128	1.01	.856
Referral Source *(professional/non)*	−.506	.062	−.629	−.384	0.60	<.001
UDS Change (*yes/no)*	.228	.174	−.114	.569	1.26	.192
Cognitive Decline						
Baseline score	.163	.036	.093	.234	1.18	<.001
APOE status *(e4 allele yes/no)*	−.018	.018	−.053	.017	0.98	.310
Race *(Black/White)*	.036	.027	−.017	.089	1.04	.179
Education	−.004	.003	−.010	.003	1.00	.279
Diabetes *(yes/no)*	.028	.021	−.014	.070	1.03	.197
Hypertension *(yes/no)*	−.002	.021	−.043	.040	1.00	.942
Referral Source *(professional/non)*	−.157	.024	−.203	−.110	0.85	<.001
UDS Change (*yes/no)*	−.239	.073	−.381	−.097	0.79	.001
Semantic Fluency-Vegetables		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Baseline Score						
Race *(Black/White)*	−.138	.076	−.287	.010	0.87	.067
Education	.010	.004	.001	.018	1.01	.030
Diabetes *(yes/no)*	−.094	.065	−.221	.034	0.91	.149
Hypertension *(yes/no)*	.005	.047	−.087	.096	1.01	.923
Referral Source *(professional/non)*	−.504	.046	−.594	−.413	0.60	<.001
Cognitive Decline						
Baseline score	.023	.005	.014	.033	1.02	<.001
APOE status *(e4 allele yes/no)*	−.029	.009	−.048	−.011	0.97	.002
Race *(Black/White)*	.014	.017	−.019	.048	1.01	.411
Education	−.002	.001	−.004	.000	1.00	.095
Diabetes *(yes/no)*	.006	.012	−.018	.029	1.01	.634
Hypertension *(yes/no)*	.010	.009	−.009	.028	1.01	.308
Referral Source *(professional/non)*	−.050	.009	−.068	−.032	0.95	<.001

Naming		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Semantic Fluency-Animals		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	
Baseline Score						
Race *(Black/White)*	−.350	.092	−.530	−.170	0.70	<.001
Education	.007	.006	−.004	.018	1.01	.226
Diabetes *(yes/no)*	−.123	.070	−.260	.014	0.88	.077
Hypertension *(yes/no)*	.006	.051	−.094	.106	1.01	.905
Referral Source *(professional/non)*	−.574	.050	−.672	−.476	0.56	<.001
Cognitive Decline						
Baseline score	.024	.005	.014	.035	1.02	<.001
APOE status *(e4 allele yes/no)*	−.022	.010	−.042	−.002	0.98	.029
Race *(Black/White)*	.022	.016	−.010	.054	1.02	.179
Education	−.001	.001	−.003	.001	1.00	.178
Diabetes *(yes/no)*	.010	.013	−.016	.036	1.01	.453
Hypertension *(yes/no)*	.022	.010	.002	.043	1.02	.031
Referral Source *(professional/non)*	−.069	.010	−.089	−.049	0.93	<.001
Immediate Memory		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Baseline Score						
Race *(Black/White)*	−.454	.079	−.607	−.300	0.64	<.001
Education	.013	.006	.001	.024	1.01	.036
Diabetes *(yes/no)*	.011	.070	−.127	.148	1.01	.880
Hypertension *(yes/no)*	−.008	.053	−.113	.096	0.99	.876
Referral Source *(professional/non)*	−.613	.052	−.715	−.511	0.54	<.001
UDS Change (*yes/no)*	.167	.134	−.096	.431	1.18	.213
Cognitive Decline						
Baseline score	.051	.006	.038	.063	1.01	<.001
APOE status *(e4 allele yes/no)*	−.035	.013	−.059	−.010	1.01	.007
Race *(Black/White)*	.023	.020	−.017	.062	1.02	.261
Education	−.001	.001	−.004	.002	1.00	.417
Diabetes *(yes/no)*	.001	.017	−.032	.034	1.02	.971
Hypertension *(yes/no)*	.012	.013	−.014	.038	1.01	.348
Referral Source *(professional/non)*	−.090	.013	−.116	−.064	1.01	<.001
UDS Change (*yes/no)*	−.226	.042	−.309	−.143	1.04	<.001

Naming		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Delayed Memory		**Model**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	
Baseline Score						
Race *(Black/White)*	−.525	.080	−.682	−.369	0.59	<.001
Education	.013	.006	.002	.024	1.01	.021
Diabetes *(yes/no)*	.007	.070	−.131	.145	1.01	.921
Hypertension *(yes/no)*	−.020	.052	−.121	.082	0.98	.707
Referral Source *(professional/non)*	−.607	.051	−.707	−.508	0.54	<.001
UDS Change (*yes/no)*	.341	.131	.084	.598	1.41	.009
Cognitive Decline						
Baseline score	.039	.005	.029	.048	1.04	<.001
APOE status *(e4 allele yes/no)*	−.023	.011	−.044	−.001	0.98	.040
Race *(Black/White)*	.024	.020	−.015	.063	1.02	.227
Education	−.002	.001	−.004	.000	1.00	.112
Diabetes *(yes/no)*	−.009	.015	−.038	.021	0.99	.557
Hypertension *(yes/no)*	.013	.011	−.010	.035	1.01	.264
Referral Source *(professional/non)*	−.076	.011	−.097	−.054	0.93	<.001
UDS Change (*yes/no)*	−.176	.034	−.243	−.108	1.04	<.001

Baseline N=1744

Table 7.

Interactions between Gender and Predictors of Diagnosis of Alzheimer's Disease.

	B	SE	p	HR	95% CI for HR
Step 1					
Race	−.29	.13	.03	.75	.58–.97
Step 2					
Race	−.26	.14	.06	.77	.58–1.01
APOE e4	1.03	.08	<.001	2.81	2.38–3.31
Education	.00	.01	.47	1.00	.99–1.02
Gender	−.31	.09	<.001	.74	.62–.87
Baseline Age	−.12	.01	<.001	.89	.88–.91
Diabetes	.17	.12	.17	1.18	.93–1.50
Hypertension	.15	.09	.10	1.16	.97–1.40
Referral Source	.81	.09	<.001	2.25	1.90–2.67
Step 3					
Race	−.29	.14	.04	.75	.57–.99
APOE e4	1.03	.08	<.001	2.81	2.39–3.31
Education	.01	.01	.40	1.01	1.00–1.01
Gender	−.56	.15	<.001	.57	.43–.76
Baseline Age	−.12	.01	<.001	.89	.88–.91
Diabetes	.17	.12	.18	1.18	.93–1.50
Hypertension	−.42	.29	.14	.66	.37–1.15
Referral Source	.82	.09	<.001	2.26	1.91–2.68
Gender*Hypertension	.37	.18	.04	1.45	1.02–2.06

Baseline N=3704

Table 8.

Interactions between Gender and Predictors of Cognitive Decline

Naming		**Models**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Gender*APOE e4	.014	.018	−.020	.049	1.01	.421
Gender*Race	−.010	.027	−.063	.044	0.99	.716
Semantic Fluency-Vegetables						
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Gender*APOE e4	.014	.013	−.011	.040	1.01	.266
Gender*Race (*dropped)*	.002	.019	−.036	.040	1.00	.933
Gender*Hypertension *(dropped)*	−.018	.009	−.036	.001	0.98	.060
Semantic Fluency-Animals						
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Gender*APOE e4	.029	.012	.005	.052	1.03	.019
Gender*Race	.016	.018	−.019	.052	1.02	.369
Gender*Hypertension	.002	.009	−.017	.020	1.00	.849
Immediate Memory		**Models**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Gender*APOE e4	.016	.015	−.014	.045	1.02	.294
Gender*Race	.004	.023	−.040	.048	1.00	.858
Gender*Hypertension	−.004	.012	−.027	.018	1.00	.704
Delayed Memory		**Models**				
	B	***SE***	**CI (low)**	**CI (high)**	**OR**	***p***
Gender*APOE e4 *(dropped)*	−.014	.015	−.043	.014	0.99	.318
Gender*Race *(dropped)*	−.011	.022	−.054	.033	0.99	.624
Gender*Hypertension	−.039	.014	−.066	−.009	0.96	.007

Baseline N=4336