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Risk of Alzheimer's Disease and Related Dementia by Sex and Race/Ethnicity: The Multiethnic Cohort Study

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Abstract

Introduction: Data are limited for comparison of sex- and race/ethnicity-specific risks of Alzheimer's disease and related dementia (ADRD).

Methods: In the population-based Multiethnic Cohort, we estimated the age-standardized diagnostic incidence rate (ASDIR) and relative risk of late-onset ADRD (n=16,410) among 105,796 participants based on Medicare claims (1999-2014) by sex and race/ethnicity.

Results: The ASDIR for ADRD was higher for women (17.0 per 1000 person-years) than men (15.3) and varied across African Americans (22.9 in women, 21.5 in men), Native Hawaiians (19.3, 19.4), Latinos (16.8, 14.7), Whites (16.4, 15.5), Japanese Americans (14.8, 13.8) and Filipinos (12.5, 9.7). Similar risk patterns were observed for AD. Adjustment for education and cardiometabolic diseases attenuated the differences. Accounting for deaths from competing causes increased the sex difference, while reducing the racial/ethnic differences. Less racial/ethnic disparity was detected among *APOE* e4 carriers.

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Authors' contributions: U.L., V.W.S., L.R.W. and L.LM. were responsible for the study concept and design. C.A.H and L.LM. provided the genetic data. S.W., S.P., V.W.S. and U.L were responsible for the data analysis in consultation with L.R.W. and L.W. U.L. and V.W.S. drafted and revised the manuscript. All authors, including D.B., A.W. and I.C., provided input on the draft and revisions. U.L. is the guarantor and was responsible for the overall study.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Discussion: More research is needed to understand the sex and racial/ethnic differences in ADRD.

Keywords

Alzheimer's dementia; dementia with Lewy bodies; diagnostic incidence rates; frontotemporal dementia; prospective studies; racial/ethnic disparities; vascular dementia

1. Introduction

Late-onset Alzheimer's disease (AD) and related dementias (ADRD) among Americans age 65 and older are more prevalent in women than men [1]. After accounting for women's longer life expectancy, however, studies have been inconsistent on sex differences. Some have reported similar age-adjusted rates of AD or dementia by sex [2, 3], while others suggested higher age-adjusted risks in women [4] or men [5]. These discrepancies have been in part attributed to different distributions of risk factors by sex in the past studies, including education, cardiometabolic conditions and genetic susceptibilities [6], which underscored the importance of evaluating risk factor characteristics for rate comparisons, as well as for better understanding of the etiology, treatment and prevention strategies [7].

Similarly, AD/ADRD research to date lacks direct comparison of multiple racial/ethnic populations in the context of risk factor distributions. A systematic review of the past studies that each included one or two minority groups suggested that dementia incidence is higher among African Americans and Caribbean Latinos compared with Mexican Americans, Whites or Japanese Americans, but more data are needed, especially for Asian Americans, Pacific Islanders and American Indians [8]. Therefore, recent priorities were placed in leveraging existing population-based cohorts that were not specifically designed for AD/ADRD research [9]. For example, multiple racial/ethnic groups were compared in the Kaiser Permanente Northern California (KPNC) data, where the age-adjusted rate of incident dementia was highest among African Americans, followed by American Indians and Alaska Natives, Latinos, Pacific Islanders, Whites and Asian Americans [10]. Although the racial/ethnic differences in this study between African Americans and Asian Americans was only slightly attenuated from a 1.73- to 1.65-fold with adjustment for cardiometabolic condition history, the study lacked information on the conditions before age 60 and other key risk factors, such as education [11], lifestyle factors [12], and apolipoprotein E (*APOE*) genotype [13].

In this report, we compared the diagnostic incidence rate of AD and ADRD in the Multiethnic Cohort Study (MEC), an ongoing, long-term follow-up study of middle-aged and older adults among residents of Hawaii and Los Angeles County [14]. The MEC population is comprised of ~60% women, with ~75% from several underrepresented racial/ethnic groups in the U.S. The MEC has amassed comprehensive information on disease and lifestyle histories using uniform protocols and has germline genotype data in a subset. Thus, in addition to comparing age-standardized rates of AD and ADRD across sex-racial/ethnic groups, we examined any remaining differences after accounting for education and history of cardiometabolic conditions as potential mediators while adjusting for death from

competing risks, lifestyle factors and, in a subset, the *APOE* genetic polymorphisms as potential confounders, in order to evaluate their role in explaining the AD/ADRD risk differences.

2. Methods

2.1. Study population

The MEC was established in 1993-1996 with over 215,000 women and men aged 45-75 years who completed and returned a mailed questionnaire [14]. Potential participants received a cover letter, along with the questionnaire, explaining the study and that participation was voluntary. The participants were generally representative of the age-eligible residents of Hawaii and Los Angeles, California [15] and consisted mostly of five targeted racial/ethnic groups, including African Americans, Native Hawaiians, Japanese Americans, Latinos and Whites, with smaller representation of other groups including Filipinos [14]. Self-reported race/ethnicity was used for the cohort design and current analysis since self-identified race/ethnicity as a social construct is thought to capture different lived experiences and related individual behaviors and contextual factors that are likely associated with health disparities beyond biological differences [16]. In addition to linkage with the National Death Index for vital status, the cohort has been linked to the Centers for Medicare and Medicaid (CMS) administrative enrollment and claims data since 1999 for all major chronic conditions [17]. The institutional review boards of the University of Hawaii and the University of Southern California approved the study protocol. These boards agree that implicit consent was granted by return of a completed baseline questionnaire.

For the current analysis, we used the MEC linkage with the Medicare claims for the fee-for-service beneficiaries (n=123,186) over the follow-up between 1999 and 2014 [17]. We excluded participants who were not from the six racial/ethnic groups mentioned above (n=2,266; Chinese, Korean, Samoan or other ethnicities [14]) due to small sample sizes, who were younger than 64 years at the start of the MEC-Medicare linkage (n=4,887), or who were enrolled in the Medicare for less than 2 years (n=6,681). Also, among those remaining on Medicare for 2 years or longer, in order to ascertain new cases of ADRD ("diagnostic incidence"), we excluded those who claimed AD/ADRD within the first 2 years of the Medicare linkage or their individual Medicare coverage, whichever came later (n=2,160), who reported history of AD on a MEC follow-up questionnaire administered around the time of Medicare linkage (1999-2002; n=223), or who had missing data on their baseline questionnaire for their education (n=1,171) or diagnostic history of cardiometabolic conditions (heart disease, stroke, diabetes or hypertension) (n=2). As a result, a total of 105,796 participants were included in this analysis.

2.2. Covariate data

On the MEC baseline questionnaire, participants provided detailed information regarding demographics, education, medical history, smoking history, weight and height, and habitual levels of physical activity and dietary intakes [14]. The self-reported questionnaire responses have been shown to correlate well in calibration studies of reported anthropometry

against technician measurements [18], reported physical activity against energy expenditure estimated with doubly labeled water [19], and reported dietary intake on the MEC quantitative food frequency questionnaire against intake assessed from multiple 24-hour recalls [20]. For the current analysis, we utilized the MEC baseline covariates above and also the mean Medicare usage based on in-patient or out-patient claims (≥1 vs. <1 per year for each) over the follow-up.

2.3. APOE genotype

We compiled genotyping array data available from over 20 genome-wide association studies (GWAS) conducted in the MEC, which covered five primary racial/ethnic groups but not Filipinos. Acquisition of the *APOE* genotypes and genetic ancestries is described in Supplemental Digital Content and Supplementary Table 1. Of the 105,796 participants, 16,034 participants had *APOE* genotype data. .

2.4. Outcome ascertainment

We examined AD and also broad-definition of ADRD based on the following considerations: AD pathology is commonly found in dementia cases of mixed or unknown etiology [21-24]; accurate AD diagnosis requires costly imaging/biomarker tests and may not have been available in many cases [25]; and AD/ADRD diagnosis typically takes a gradual process even for individuals who have access to accurate tests [26]. We defined ADRD by combining the approach by Medicare [27] and by Goodman et al. [26] and categorized ADRD cases into common subtypes of not otherwise specified (NOS) dementia, AD-only, AD of mixed etiology (with any other subtypes), vascular dementia (VD)-only, and Lewy body dementia (LBD)-only: frontotemporal dementia cases, also included in ADRD, were too few for separate analysis (Supplemental Digital Content). As a result, the current analysis included 7,364 AD and 16,410 ADRD cases: genotype information was available on 1,021 AD and 2,451 ADRD cases.

2.5. Statistical analysis

Age-standardized, annual diagnostic incidence rates (ASDIRs) of AD and ADRD for up to 14.0 years of follow-up (median = 8.1 years) among the 12 sex-racial/ethnic groups were determined with left truncation at age 64 and age-standardization based on the U.S. 2000 standard population. A Cox proportional hazards model with age as the time metric was used to compare the covariate-adjusted relative risk of AD or ADRD in hazard ratios (HRs) and 95% confidence intervals (CIs) for each non-White group compared to Whites by sex. The follow-up for AD/ADRD ascertainment began 2 years after the Medicare coverage start date or January 1, 1999, whichever came later, and ended at the earliest of the following dates: the first claim date for AD/ADRD, the date of death, or the end of the follow-up (Dec 31, 2014).

Minimally-adjusted Cox regression models (Model 1 in tables) included age at cohort entry, when cardiometabolic conditions were reported, and age at AD/ADRD follow-up start date on Medicare. Fully-adjusted models (Model 2) additionally adjusted for education, cohort baseline history of cardiometabolic conditions and the average Medicare usage over the follow-up for in-patient or out-patient care. Considering that AD/ADRD is highly dependent

on age and aging-associated comorbidities, we also compared the HRs of AD/ADRD in a Fine-Gray competing risk model, where the at-risk denominator was the AD/ADRD-free individuals plus deaths from other diseases (Model 3) [28]. While the HRs from the Cox proportional hazards and competing risk models are not directly comparable [29], our purpose was to test the heterogeneity across racial/ethnic groups under the competing risk-adjusted setting: i.e., compare the HRs for the highest- and lowest-risk groups in each model. The sex-racial/ethnic HRs were examined with further adjustment for the following lifestyle characteristics at cohort baseline: cigarette smoking status (never, former, current) and pack-years, BMI, physical activity (hours/week of sitting activities and of moderate to vigorous activities), alcohol consumption (g/day), and overall diet quality [30]. The p-value for the overall sex or racial/ethnic difference was obtained from the Wald Chi-square test for their main effect. The p-value for heterogeneity in the racial/ethnic difference by sex was obtained based on the interaction term between race/ethnicity and sex in a combined model. We also performed an exploratory mediation analysis based on the paradigm shown in Supplementary Figure 1, with education and cardiometabolic history as mediators and age, sex, Medicare usage and lifestyle as confounders for the racial/ethnic difference in AD/ADRD risks.

For the participants with available *APOE* genotype data, the ASDIRs and HRs for AD/ADRD were determined as described above with additional adjustment for or stratification by the *APOE* e4 carrier status. Further details on the statistical analysis are provided in Supplemental Digital Content.

3. Results

Table 1 shows the participant characteristics by racial/ethnic groups. Compared to other groups, African Americans included more women, and African Americans and Japanese Americans were slightly older. The proportion of those who completed college or higher education was lower among non-Whites, especially in Latinos. Cardiometabolic conditions were reported more frequently among non-Whites, particularly in African Americans. African Americans also showed higher Medicare usage for in-patient services, followed by Latinos and Native Hawaiians. Whites and Japanese Americans had the most out-patient services, and Filipinos, the least. Among the subset of participants with a known *APOE* genotype (n=16,034 or ~15% of the study population), a higher proportion of e4 risk allele carriers was observed in African Americans (37%) and Native Hawaiians (35%) compared to others (20-23%). Supplementary Table 2 shows that the individuals with *APOE* genotype data were overall similar to all study participants in risk factor distributions and that the majority of the MEC Latinos were of Mexican descent.

In Table 2, the ASDIR per 1000 person-years was higher in women than men for AD (7.3 vs. 6.1) and ADRD (17.0 vs. 15.3) and varied around two-fold across the six racial/ethnic groups for AD (ranging 4.6-9.5 in women, 3.6-8.0 in men) and ADRD (12.5-22.9 in women, 9.7-21.5 in men). When age differences were more finely adjusted for using continuous age variables in Cox regression (**Model 1**), the sex difference was more pronounced for AD (HR for women vs. men = 1.17; 95% confidence interval (CI): 1.11-1.23) than ADRD (HR=1.03; 1.00-1.07). With Whites as the reference, African Americans showed the highest

age-adjusted relative risk for AD in women (HR=1.37) and for ADRD in women and men (HRs=1.39 and 1.37), whereas Native Hawaiians had the highest risk for AD among men (HR=1.35). Age-adjusted HRs for AD and ADRD were almost all significantly lower among Filipinos and Japanese Americans compared to Whites. Although HRs for AD and ADRD were higher among Latino women compared to White women, the risks were similar in Latino and White men. When education and history of cardiometabolic conditions were further accounted for (**Model 2**), the sex difference remained significant only for AD. The racial/ethnic disparity attenuated somewhat based on the fold difference between the highest vs. lowest HRs but remained statistically significant and retained the same racial/ethnic ranks, with higher risks observed in African Americans and Native Hawaiians, and lower risks in Asian Americans, compared to Whites. Among Latinos, however, the adjustments in Model 2 led to substantially lower relative risks for ADRD (HR changed from 1.06 to 0.93 in women and from 0.96 to 0.87 in men).

The above proportional hazards models assume that the probability of AD/ADRD among the deceased would be the same as the survived had they continued to live, when the competing risk models were used for potentially different probabilities (Table 2, **Model 3**), the extent of the sex differences in AD/ADRD risks were increased, whereas racial/ethnic differences were further reduced. Additional adjustment for lifestyle characteristics did not reduce the racial/ethnic heterogeneity notably (data not shown). In an exploratory mediation analysis (Supplementary Table 3), we found that education and history of cardiometabolic conditions mediate a substantial proportion of the racial/ethnic differences in AD/ADRD risks.

When common ADRD subtypes were examined in Cox regression adjusted for age, education and cardiometabolic conditions (Supplementary Table 4), women showed a significantly higher risk for AD-only but lower risks for VD-only and for LBD-only or LBD of mixed etiology. A generally consistent pattern of racial/ethnic risk differences was observed for NOS dementia, AD-only, and AD of mixed etiology, with higher risks for African Americans and Native Hawaiians, lower risks in Asian Americans and similar risks in Latinos, compared to Whites. For VD-only and VD of mixed etiology, African Americans and Native Hawaiians again showed a trend of higher risks compared with Whites, whereas Filipinos and Latinos had a trend of lower risks. While LBD-only included a limited number of cases, LBD of mixed etiology showed a trend of elevated risks among African Americans and Latinos. Supplementary Table 5 shows a slightly younger mean age at claim diagnosis for AD of mixed etiology compared to others.

Table 3 presents the *APOE* genotype frequencies by sex and their associations with AD and ADRD in Cox models adjusted for age and population stratification. The genotype distribution was similar between women and men, showing that the e3/e3 genotype was most common (62% in women, 63% in men), followed by carriers of one e4 allele (26%, 24%), one or two e2 alleles without e4 (10%, 10%) and two e4 alleles (2%, 2%). Compared to the individuals with e3/e3, AD and ADRD risks approximately doubled in association with each additional copy of e4 (all p-trends < 0.0001), although the association was stronger for AD than for ADRD and the *APOE*-AD association was stronger in men than women (p-heterogeneity by sex = 0.04).

Supplementary Table 6 shows the ASDIR and HRs for AD and ADRD as in Table 2 but limited to the participants with *APOE* genotype data, thus excluding Filipinos. The racial/ethnic differences for AD and ADRD risks based on the range of age-adjusted HR's between the highest- vs. lowest-risk groups were reduced with additional adjustment for *APOE* genotype (**Model 1a** vs. **Model 1**), and further with adjustment for education and cardiometabolic conditions (**Model 2a** vs. **Model 1a**). In stratified analysis by the *APOE* e4 carrier status (Table 4), the racial/ethnic disparities in fully-adjusted models (**Model 2**) were significant only among non-carriers (p=0.01 for AD; p<0.0001 for ADRD) and not among carriers (p=0.48 for AD; p=0.10 for ADRD).

4. Discussion

In this large population-based cohort with high representation of women and understudied racial/ethnic minorities, we observed a 17% higher age-adjusted risk of late-onset AD among women compared to men and a ~2-fold difference in age-adjusted diagnostic incidence of AD and ADRD across six racial/ethnic groups of African American, Native Hawaiian, European, Latino, Japanese, and Filipino ancestries. This finding confirmed some of the past reports of slightly higher AD risks among women even after accounting for their longer lifespan [4], replicated previous reports that the risk of developing dementia is highest among African Americans and lowest among Asian Americans [8, 10], and added a novel observation that the dementia risk is also high in Native Hawaiians, a group that has not been studied separately. We also observed that some of the established risk factors likely mediate part of the racial/ethnic disparity in our stepwise-adjusted regression models and an exploratory mediation analysis. The racial/ethnic gap for this highly aging-dependent disease would have been larger were it not for premature deaths from other competing causes in higher-risk racial/ethnic groups, whereas part of the higher risk in women appeared to be due to greater competing causes in men. The racial/ethnic relative risk pattern for overall ADRD was comparable for ADRD subtypes of NOS dementia, AD-only and AD of mixed etiology, with some differences observed in VD and LBD. Another notable finding was that, while the *APOE* e4 variant had a strong association with AD/ADRD risks and confounded the racial/ethnic risk differences, the racial/ethnic disparity was more pronounced among non-carriers of the risk allele.

The racial/ethnic rates and risk patterns of ADRD in the MEC, based on the administrative Medicare claims data, were comparable to those observed in the KPNC study based on clinical assessment [10]. Specifically, the sex-combined ADRD rates in the MEC were slightly lower compared to the rates of all dementia in KPNC for African Americans (22.2 in MEC vs. 26.6 in KPNC, per 1000 person-years), Latinos (15.7 vs. 19.6), Whites (16.3 vs. 19.3) and Asian Americans (14.0 vs. 15.2) [10]. Our findings of similar or slightly higher AD/ADRD risks among Latinos of mostly Mexican ethnicity compared to Whites are consistent with previous observations that Latinos of Mexican descent may not have as high risks as some other groups, such as Caribbean Latinos [8]. In this first study on Native Hawaiians separately, we report a significantly higher sex-combined ADRD rate in this group compared to Whites (19.7 vs. 16.3) and a high risk for AD among Native Hawaiian men, even above the risk for African American men.

We observed an attenuation of the racial/ethnic difference in dementia risks when the history of cardiometabolic conditions was adjusted for, which along with the mediation analysis results supports that the metabolic disease disparity contributes to part of the dementia disparity [31]. A similar mediating effect was observed by education, an important protective factor against dementia for its role in early development of neural network and cognitive reserve [11, 32]. For example, Latinos in the MEC on average had lower education and a higher prevalence of cardiometabolic conditions compared to Whites, and their relative risk for AD/ADRD became significantly less than the risk in Whites when these differences were accounted for. Although other known risk factors, including recent smoking, physical inactivity, higher mid-life BMI and poor diet quality, were associated with increased risk of AD and ADRD as expected, their adjustment did not meaningfully attenuate the racial/ethnic disparities beyond that obtained with adjustment for education and cardiometabolic conditions. Future in-depth analyses of detailed lifestyle data in the MEC may provide further insight.

The effect size of *APOE* e4 has varied widely in previous studies depending on the AD definition and source population, with odds ratios for e4/e4 vs. e3/e3 in the range of 12-16 in Whites and 2-7 in African Americans, Latinos and Asians [33-37]. In our multiethnic sample, we observed approximately doubling of the risk of late-onset AD and ADRD with each additional copy of the e4 risk allele and also detected a trend of ADRD risk reduction associated with the e2 allele as reported [38]. Importantly, our results illustrate the racial/ethnic difference in the risk allele frequency as an important contributor to the AD/ADRD disparity. The e4 frequency was substantially higher among African Americans than in Latinos, Whites and Asian Americans, as documented [33], and also high among Native Hawaiians, which is a novel finding. Adjustment for the e4 distribution moderated some of the racial/ethnic disparity in AD and ADRD risks. Finally, the racial/ethnic disparity was more pronounced among non-carriers of the e4 risk allele, although the interaction did not reach statistical significance. The reasons are not clear but may be due to the predominant effects of e4 risk allele on AD clinico-pathology, as demonstrated for amyloid deposition, atrophy rates, and cognitive declines [39], which may leave less risk variation among carriers from other race/ethnicity-related risk factors. Compared to the previous small-scale studies that did not allow for stratified analyses [1], our findings further underscore the importance of considering this strong genetic risk factor in AD/ADRD disparity research.

In our analysis of broadly defined ADRD [1, 26], the most common subtype was NOS. For known common subtypes, women showed a higher risk for AD-only but lower risks for VD-only and LBD compared to men. As with overall ADRD, higher risks for AD and VD were observed among African Americans and Native Hawaiians. Native Hawaiians and Japanese Americans showed lower risks for LBD-only, whereas Latinos and African Americans had a higher risk for LBD of mixed etiology, latter of which is consistent with the Rush Alzheimer's brain pathology study, where African Americans had a higher frequency of LBD mixed with AD pathology compared to Whites [40].

Our study has a number of strengths, including the prospective design, the large number of cases from a population-based cohort, the unique racial/ethnic diversity, and the availability of relevant covariates and *APOE* genotype in a subset. Limitations of our study include

the use of diagnosis codes in the Medicare claims data for AD/ADRD definitions. This approach has been broadly used to estimate the prevalence and trends of dementia in the U.S. population [26, 41] and is often the only viable option in large population-based cohorts with limited access to medical records. Although the Medicare claims-based approach has been noted for potential misclassification, especially under-detection of cases [42], this approach has yielded reasonable concordance with clinical assessment-based case identification [43, 44], which is also evidenced in our similar rate estimates as in clinical studies. Therefore, we are cautiously optimistic that our relative risk estimates are generalizable to the racial/ethnic populations of the study areas and other comparable populations broadly. Another limitation is that we adjusted for the history of cardiometabolic conditions at cohort baseline at age 45 and older, which was on average 16.6 years (SD=4.4) prior to the first diagnostic claims for AD/ADRD, in order to maximize the sample size without attrition in follow-up responses. While this approach may have better reflected mid-life exposures, which have shown a stronger association with AD/ADRD than conditions at older ages [1], an adjustment for updated, time-varying cardiometabolic disease status may have shown greater attenuation of the racial/ethnic disparity in AD/ADRD. Also, our analysis of socioeconomic status (SES) or social determinants of health was limited to educational attainment. Future analyses in the MEC will interrogate neighborhood SES and social contextual indicators available from residential history-based information over the entire follow-up [45], which will more adequately account for their multi-level effects on racial/ethnic health disparities.

In conclusion, our findings emphasize a slight sex difference in AD risks and a substantial racial/ethnic disparity in AD/ADRD risks, likely resulting from both genetic and environmental factors, and other yet undescribed risk factors. Future studies of AD and ADRD risk and risk factors should give careful consideration to sex and racial/ethnic differences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Characteristics of participants for the Multiethnic Cohort analysis of ADRD (N = 105,796).

	African Am.	Filipino	Japanese Am.	Latino	Native Haw.	White
Number of participants	13,895	4,694	32,432	20,756	7,121	26,898
Women, %	65	53	54	53	57	54
Age at ADRD follow-up start, mean years ± SD	71.7 ± 5.1	69.9 ± 4.2	71.0 ± 4.8	69.8 ± 4.2	69.2 ± 3.9	70.4 ± 4.7
Education, %						
≤ 8th grade	8	15	3	38	4	3
High school	33	25	34	30	49	22
Vocational school/some college	35	24	30	21	29	31
Graduated college	12	25	19	5	10	20
Graduate/professional school	12	11	14	6	8	25
Cardiometabolic conditions, %						
Heart disease	12	7	6	9	8	7
Stroke	4	2	2	2	2	2
Diabetes	14	11	10	14	13	5
Hypertension	54	42	39	34	44	28
Medicare usage, %						
In-patient claims: ≥ 1 per year	7	3	2	5	4	3
Out-patient claims: ≥ 1 per year	55	47	60	51	57	61
APOE genotype availability, n (%)	3,735 (27%)	NA	4,689 (14%)	2,721 (13%)	2,390 (34%)	2,499 (9%)
Number of e4 allele, % of individuals with genotype data						
0 (e3/e3, e3/e2 or e2/e2)	63	-	80	77	65	78
1 (e3/e4 or e2/e4)	33	-	20	23	32	22
2 (e4/e4)	4	-	0	0	3	0

Table 2.

Diagnostic incidence of AD and ADRD by sex and race/ethnicity in the Multiethnic Cohort Study (1999-2014; N = 105,796).

	Events	Competing Events*	Person-years	ASDIR	Hazard Ratio (95% Confidence Interval) Model 1	Model 2	Model 3
(a) Alzheimer's Disease (AD)							
Women	4,561	12,266	592,678	7.32	1.17 (1.11-1.23)	1.12 (1.07-1.18)	1.27 (1.21-1.33)
Men	2,803	13,389	454,877	6.08	1.00 (ref)	1.00 (ref)	1.00 (ref)
P for sex (all races combined)					<0.0001	<0.0001	<0.0001
Women							
African American	1,002	2,832	88,315	9.54	1.37 (1.26-1.50)	1.28 (1.17-1.40)	1.25 (1.14-1.37)
Filipino	111	395	25,420	4.58	0.71 (0.58-0.86)	0.72 (0.59-0.87)	0.77 (0.63-0.93)
Japanese American	1,454	2,918	187,200	6.60	0.94 (0.87-1.02)	0.94 (0.87-1.02)	1.06 (0.97-1.15)
Latino	769	2,022	114,723	7.76	1.15 (1.04-1.26)	1.05 (0.95-1.17)	1.11 (1.00-1.24)
Native Hawaiian	224	908	36,786	7.65	1.16 (1.00-1.34)	1.10 (0.95-1.28)	1.07 (0.92-1.24)
White	1,001	3,191	140,234	6.85	1.00 (ref)	1.00 (ref)	1.00 (ref)
P for race/ethnicity					< 0.0001	< 0.0001	< 0.0001
Men							
African American	402	1,989	44,755	7.85	1.27 (1.12-1.43)	1.26 (1.10-1.43)	1.19 (1.05-1.35)
Filipino	80	528	22,211	3.56	0.60 (0.47-0.75)	0.63 (0.50-0.80)	0.69 (0.55-0.87)
Japanese American	927	3,962	147,930	5.55	0.89 (0.81-0.98)	0.90 (0.81-1.00)	0.99 (0.90-1.10)
Latino	553	2,535	99,739	6.19	1.04 (0.93-1.16)	1.00 (0.88-1.13)	1.08 (0.96-1.22)
Native Hawaiian	160	926	26,555	7.99	1.35 (1.13-1.60)	1.27 (1.06-1.52)	1.22 (1.02-1.46)
White	681	3,449	113,687	6.07	1.00 (ref)	1.00 (ref)	1.00 (ref)
P for race/ethnicity					< 0.0001	< 0.0001	< 0.0001
P for race/ethnicity by sex					0.26	0.46	0.52
(b) Alzheimer's Disease and Related Dementia (ADRD)							
Women	9,792	9,406	574,019	17.01	1.03 (1.00-1.11)	1.01 (0.98-1.04)	1.15 (1.12-1.19)
Men	6,618	10,769	443,287	15.33	1.00 (ref)	1.00 (ref)	1.00 (ref)
P for sex (all races combined)					<0.0001	0.49	<0.0001
Women							
African American	2,175	2,061	84,398	22.92	1.39 (1.31-1.47)	1.24 (1.16-1.32)	1.22 (1.15-1.30)
Filipino	278	322	24,783	12.53	0.79 (0.70-0.89)	0.79 (0.69-0.89)	0.84 (0.74-0.95)
Japanese American	2,994	2,192	181,323	14.76	0.89 (0.84-0.94)	0.87 (0.82-0.92)	0.97 (0.92-1.03)
Latino	1,609	1,609	111,684	16.79	1.06 (0.99-1.13)	0.93 (0.87-1.00)	0.99 (0.92-1.06)
Native Hawaiian	522	749	35,778	19.33	1.21 (1.10-1.33)	1.13 (1.03-1.25)	1.06 (0.96-1.17)
White	2,214	2,473	136,053	16.38	1.00 (ref)	1.00 (ref)	1.00 (ref)
P for race/ethnicity					< 0.0001	< 0.0001	< 0.0001
Men							
African American	1,005	1,557	43,054	21.51	1.37 (1.26-1.48)	1.31 (1.21-1.42)	1.25 (1.15-1.35)
Filipino	208	440	21,859	9.72	0.63 (0.54-0.72)	0.64 (0.55-0.74)	0.71 (0.62-0.83)
Japanese American	2,151	3,114	144,076	13.84	0.87 (0.81-0.93)	0.85 (0.80-0.91)	0.94 (0.88-1.01)

	Events	Competing Events*	Person-years	ASDIR	Hazard Ratio (95% Confidence Interval)		
					Model 1	Model 2	Model 3
Latino	1,250	2,066	97,610	14.71	0.96 (0.89-1.03)	0.87 (0.81-0.95)	0.95 (0.88-1.03)
Native Hawaiian	375	785	25,870	19.44	1.30 (1.16-1.46)	1.19 (1.06-1.33)	1.12 (0.99-1.25)
White	1,629	2,807	110,818	15.50	1.00 (ref)	1.00 (ref)	1.00 (ref)
P for race/ethnicity					< 0.0001	< 0.0001	< 0.0001
P for race/ethnicity by sex					0.045	0.055	0.39

ASDIR (age-standardized diagnostic incidence rate per 1000 person-years)

*Competing events refer to deaths due to other (non-ADRD) causes among individuals who have not been diagnosed for AD or ADRD.

Model 1: Cox proportional hazards regression model adjusted for age at cohort entry and age at Medicare follow-up start

Model 2: includes Model 1 adjustments + education, history of heart disease, stroke, diabetes or hypertension at cohort baseline, and mean annual Medicare usage (in-patient, out-patient) over follow-up

Model 3: includes Model 2 adjustments in a competing risk model accounting for deaths due to other causes

P for race/ethnicity for the overall racial/ethnic difference was obtained from the Wald Chi-square test for the main effect of race/ethnicity in the sex-stratified Cox regression model for AD or ADRD. P for race/ethnicity by sex for the heterogeneity of the racial/ethnic differences between women and men was obtained based on the interaction term between sex and race/ethnicity in the combined Cox regression model for AD or ADRD.

Table 3.

APOE genotypes and their association with AD and ADRD by sex in the Multiethnic Cohort Study (1999-2014; N = 16,016).

***APOE* Genotype**		**AD**		**ADRD**	
	N (%)	**N**	**HR (95% CI)**	**N**	**HR (95% CI)**
Women	8,002	525		1,197	
e2/e2 & e2/e3	805 (10%)	44	0.98 (0.71-1.36)	109	0.95 (0.77-1.17)
e3/e3	4,962 (62%)	254	1.0 (ref)	649	1.0 (ref)
e2/e4 & e3/e4	2,045 (26%)	204	2.22 (1.84-2.69)	390	1.67 (1.47-1.91)
e4/e4	190 (2%)	23	3.43 (2.22-5.29)	49	3.00 (2.23-4.03)
P-trend for genotype			< 0.0001		< 0.0001
Men	8,014	495		1,251	
e2/e2 & e2/e3	837 (10%)	33	0.72 (0.50-1.03)	115	0.89 (0.72-1.08)
e3/e3	5,088 (63%)	270	1.0 (ref)	709	1.0 (ref)
e2/e4 & e3/e4	1,935 (24%)	161	1.70 (1.39-2.08)	375	1.48 (1.30-1.68)
e4/e4	154 (2%)	31	5.20 (3.54-7.64)	52	3.21 (2.41-4.28)
P-trend for genotype			< 0.0001		< 0.0001
P for genotype by sex			0.04		0.63

The sex-stratified Cox proportional hazards regression models were each adjusted for age at cohort entry, age at Medicare follow-up start, and genetic ancestry (genetic ancestry proportion variables for African, East Asian, Native American and Polynesian ancestries, with European ancestry as the reference). Of 16,034 participants with *APOE* genotype data, 18 were removed for missing genetic ancestry information. The p-trend for the *APOE* genotype associations was estimated by including a numeric variable for the *APOE* genotype categories ordered as above, e2/e2 through e4/e4. The p for genotype by sex for the difference in the genotype-AD/ADRD association between women and men was obtained based on the interaction term between sex and the *APOE* genotype trend variable in a combined Cox regression model for AD or ADRD.

Table 4.

Diagnostic incidence of AD and ADRD by *APOE* genotype and race/ethnicity in the Multiethnic Cohort Study (1999-2014; N = 16,034).

	Events	Person-years	ASDIR	Hazard Ratio (95% Confidence Interval) Model 1	Model 2
(a) Alzheimer's Disease (AD)					
Number of e4 allele = 0					
African American	167	24445	575.5	1.40 (1.08-1.81)	1.33 (1.02-1.74)
Japanese American	192	41205	422.1	0.99 (0.77-1.27)	0.93 (0.71-1.20)
Latino	109	23611	531.0	1.28 (0.96-1.69)	1.12 (0.83-1.52)
Native Hawaiian	43	14394	445.1	1.02 (0.70-1.46)	0.92 (0.63-1.34)
White	90	19202	420.7	1.00 (ref)	1.00 (ref)
P for race/ethnicity				0.0068	0.014
Number of e4 alleles = 1 or 2					
African American	172	13858	1152.8	1.12 (0.85-1.49)	1.16 (0.87-1.54)
Japanese American	81	9190	889.4	0.89 (0.64-1.23)	0.91 (0.66-1.27)
Latino	42	5900	913.1	0.93 (0.63-1.37)	0.94 (0.62-1.42)
Native Hawaiian	56	7850	1064.0	0.99 (0.69-1.41)	1.05 (0.73-1.52)
White	69	6730	1002.7	1.00 (ref)	1.00 (ref)
P for race/ethnicity				0.49	0.48
P for race/ethnicity by *APOE*				0.62	0.56
(b) Alzheimer's Disease and Related Dementia (ADRD)					
Number of e4 allele = 0					
African American	460	23568	1729.3	1.46 (1.25-1.70)	1.34 (1.14-1.58)
Japanese American	482	40201	1134.7	0.92 (0.79-1.08)	0.85 (0.73-1.00)
Latino	270	23024	1390.2	1.14 (0.96-1.36)	1.00 (0.83-1.20)
Native Hawaiian	128	14077	1306.8	1.08 (0.87-1.34)	0.96 (0.77-1.21)
White	244	18734	1205.7	1.00 (ref)	1.00 (ref)
P for race/ethnicity				< 0.0001	< 0.0001
Number of e4 alleles = 1 or 2					
African American	361	13154	2698.5	1.30 (1.06-1.59)	1.24 (1.00-1.52)
Japanese American	171	8877	2070.5	1.03 (0.82-1.30)	1.02 (0.81-1.29)
Latino	98	5717	2291.0	1.14 (0.87-1.48)	1.04 (0.78-1.38)
Native Hawaiian	110	7669	2195.7	1.00 (0.77-1.29)	0.99 (0.76-1.30)
White	127	6455	1964.0	1.00 (ref)	1.00 (ref)
P for race/ethnicity				0.022	0.10
P for race/ethnicity by *APOE*				0.79	0.67

ASDIR (age-standardized diagnostic incidence rate per 1000 person-years)

Model 1: Cox proportional hazards regression model adjusted for age at cohort entry and age at Medicare follow-up start

Model 2: includes Model 1 adjustments + education, history of heart disease, stroke, diabetes or hypertension at cohort baseline, and mean annual Medicare usage (in-patient, out-patient) over follow-up

Note: P for race/ethnicity for the overall racial/ethnic difference was obtained from the Wald Chi-square test for the main effect of race/ethnicity in the sex-combined Cox regression model for AD or ADRD stratified by the *APOE* e4 risk allele carrier status. P for race/ethnicity by *APOE* for the heterogeneity of the racial/ethnic differences between non-carriers and carriers of the *APOE* e4 risk allele was obtained based on the interaction term between the *APOE* genotype trend variable and race/ethnicity in the combined Cox regression model for AD or ADRD.