

FEATURED ARTICLE

Risk of Alzheimer's disease and related dementia by sex and race/ethnicity: The Multiethnic Cohort Study

Unhee Lim¹  | Songren Wang² | Song-Yi Park¹ | David Bogumil² | Anna H. Wu² | Iona Cheng³ | Christopher A. Haiman² | Loïc Le Marchand¹ | Lynne R. Wilkens¹ | Lon White^{4,5} | V. Wendy Setiawan²

¹ Cancer Epidemiology Program, University of Hawaii Cancer Center, University of Hawaii at Manoa, Honolulu, Hawaii, USA

² Department of Population and Public Health Sciences, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA

³ Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA

⁴ Pacific Health Research and Education Institute, Honolulu, Hawaii, USA

⁵ John A Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii, USA

Correspondence

Unhee Lim, University of Hawaii Cancer Center, 701 Ilalo Street, Honolulu, HI 96813, USA. Email: ULim@cc.hawaii.edu

Lon White and V. Wendy Setiawan contributed equally to this work.

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 for 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 apolipoprotein E (APOE) e4 carriers.

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 (ADRDs) among Americans age 65 and older are more prevalent in women than in 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} whereas others have suggested higher age-adjusted risks in women⁴ 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 have

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. The review also suggested that more data are needed, especially for other 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 were 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 comprises ≈60% women, with ≈75% from several underrepresented racial/ethnic groups in the United States. 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 45 to 75 years of age 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 they 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 because 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 & 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

RESEARCH IN CONTEXT

1. **Systematic review:** Studies are limited for the comparison of Alzheimer's disease (AD) and Alzheimer's disease and related disorders (ADRDs) risks across multiple racial/ethnic populations.
2. **Interpretation:** Using a linkage to Medicare claims data within the Multiethnic Cohort Study, we report differences in the diagnostic incidence of AD and ADRD by sex and across six racial/ethnic groups and assess the role of education, cardiometabolic conditions, deaths from competing causes, and apolipoprotein E (APOE) genotype. In particular, our findings are novel regarding the disparity in Native Hawaiians.
3. **Future directions:** Future research is needed to identify the yet unknown contributors to the ADRD disparity and to mitigate them in the context of genetic risk.

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 ($n = 2266$; Chinese, Korean, Samoan, or other ethnicities¹⁴) due to small sample sizes, who were younger than 64 years at the start of the MEC-Medicare linkage ($n = 4887$), or who were enrolled in the Medicare for less than 2 years ($n = 6681$). In addition, 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 ($n = 2160$), 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 ($n = 1171$) 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 intake.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 Table S1. 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 found 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 cases²⁵; 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 Medicare²⁷ 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 7364 AD and 16,410 ADRD cases: genotype information was available on 1021 AD and 2451 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 (December 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 Although 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: that is, 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 Figure S1, 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 Latinos. Cardiometabolic conditions were reported more frequently among non-Whites, particularly 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 had the least. Among the subset of participants with a known APOE genotype ($n = 16,034$ or $\approx 15\%$ of the study population), a higher proportion of e4 risk allele carriers was observed in African Americans (37%) and Native Hawaiians (35%) compared with others (20%–23%). Table S2 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

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 participant	13,895	4694	32,432	20,756	7121	26,898
Women, %	65	53	54	53	57	54
Age at ADRD follow-up start, mean years \pm SD	71.7 \pm 5.1	69.9 \pm 4.2	71.0 \pm 4.8	69.8 \pm 4.2	69.2 \pm 3.9	70.4 \pm 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: \geq 1 per year	7	3	2	5	4	3
Out-patient claims: \geq 1 per year	55	47	60	51	57	61
APOE genotype availability, n (%)	3735 (27%)	NA	4689 (14%)	2721 (13%)	2390 (34%)	2499 (9%)
Number of ϵ 4 allele, % of individuals with genotype data						
0 (ϵ 3/ ϵ 3, ϵ 3/ ϵ 2 or ϵ 2/ ϵ 2)	63	-	80	77	65	78
1 (ϵ 3/ ϵ 4 or ϵ 2/ ϵ 4)	33	-	20	23	32	22
2 (ϵ 4/ ϵ 4)	4	-	0	0	3	0

\approx 2-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 versus 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 (Table S3), 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 (Table S4), women showed a significantly higher risk for AD-only but lower risks for VD-only and for LBD-only and 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 Amer-

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 ^a	Person-years	ASDIR	Hazard Ratio (95% CI)		
					Model 1	Model 2	Model 3
(a) AD							
Women	4561	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	2803	13,389	454,877	6.08	1.00 (ref)	1.00 (ref)	1.00 (ref)
<i>P</i> for sex (all races combined)					<0.0001	<0.0001	<0.0001
Women							
African American	1002	2832	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	1454	2918	187,200	6.60	0.94 (0.87-1.02)	0.94 (0.87-1.02)	1.06 (0.97-1.15)
Latino	769	2022	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	1001	3191	140,234	6.85	1.00 (ref)	1.00 (ref)	1.00 (ref)
<i>P</i> for race/ethnicity					<0.0001	<0.0001	<0.0001
Men							
African American	402	1989	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	3962	147,930	5.55	0.89 (0.81-0.98)	0.90 (0.81-1.00)	0.99 (0.90-1.10)
Latino	553	2535	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	3449	113,687	6.07	1.00 (ref)	1.00 (ref)	1.00 (ref)
<i>P</i> for race/ethnicity					<0.0001	<0.0001	<0.0001
<i>P</i> for race/ethnicity by sex					0.26	0.46	0.52
(b) ADRD							
Women	9792	9406	574,019	17.01	1.03 (1.00-1.11)	1.01 (0.98-1.04)	1.15 (1.12-1.19)
Men	6618	10,769	443,287	15.33	1.00 (ref)	1.00 (ref)	1.00 (ref)
<i>P</i> for sex (all races combined)					<0.0001	0.49	<0.0001
Women							
African American	2175	2061	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	2994	2192	181,323	14.76	0.89 (0.84-0.94)	0.87 (0.82-0.92)	0.97 (0.92-1.03)
Latino	1609	1609	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	2214	2473	136,053	16.38	1.00 (ref)	1.00 (ref)	1.00 (ref)
<i>P</i> for race/ethnicity					<0.0001	<0.0001	<0.0001
Men							
African American	1005	1557	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	2151	3114	144,076	13.84	0.87 (0.81-0.93)	0.85 (0.80-0.91)	0.94 (0.88-1.01)
Latino	1250	2066	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)

(Continues)

TABLE 2 (Continued)

	Events	Competing events*	Person-years	ASDIR	Hazard Ratio (95% CI)		
					Model 1	Model 2	Model 3
White	1629	2807	110,818	15.50	1.00 (ref)	1.00 (ref)	1.00 (ref)
<i>P</i> for race/ethnicity					<0.0001	<0.0001	<0.0001
<i>P</i> for race/ethnicity by sex					0.045	0.055	0.39

Note: 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.

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

Abbreviations: AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementia; CI, confidence interval.

*Competing events refer to deaths due to other (non-ADRD) causes among individuals who have not been diagnosed 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	N (%)	AD		ADRD	
		N	HR (95% CI)	N	HR (95% CI)
Women	8002	525		1197	
ε2/ε2 & ε2/ε3	805 (10%)	44	0.98 (0.71–1.36)	109	0.95 (0.77–1.17)
ε3/ε3	4962 (62%)	254	1.0 (ref)	649	1.0 (ref)
ε2/ε4 & ε3/ε4	2045 (26%)	204	2.22 (1.84–2.69)	390	1.67 (1.47–1.91)
ε4/ε4	190 (2%)	23	3.43 (2.22–5.29)	49	3.00 (2.23–4.03)
<i>P</i> -trend for genotype			< 0.0001		< 0.0001
Men	8014	495		1,251	
ε2/ε2 & ε2/ε3	837 (10%)	33	0.72 (0.50–1.03)	115	0.89 (0.72–1.08)
ε3/ε3	5088 (63%)	270	1.0 (ref)	709	1.0 (ref)
ε2/ε4 & ε3/ε4	1935 (24%)	161	1.70 (1.39–2.08)	375	1.48 (1.30–1.68)
ε4/ε4	154 (2%)	31	5.20 (3.54–7.64)	52	3.21 (2.41–4.28)
<i>P</i> -trend for genotype			< 0.0001		< 0.0001
<i>P</i> for genotype by sex			0.04		0.63

Note: 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, ε2/ε2 through ε4/ε4. 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.

Abbreviations: AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementia; CI, confidence interval.

icans, 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. Although LBD-only included a limited number of cases, LBD of mixed etiology showed a trend of elevated risks among African Americans and Latinos. Table S5 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 ε3/ε3 genotype was most common (62% in women, 63% in men), followed by carriers of one ε4 allele (26%, 24%), one or two ε2 alleles without ε4 (10%, 10%), and two ε4 alleles (2%, 2%). Compared to the individuals with ε3/ε3, AD and ADRD risks approximately doubled in association with each additional copy of ε4 (all *p*-trends < .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).

Table S6 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 HRs between the highest- versus 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 ϵ 4 carrier status (Table 4), the racial/ethnic disparities in fully adjusted models (Model 2) were significant only among non-carriers ($p = .01$ for AD; $p < .0001$ for ADRD) and not among carriers ($p = .48$ for AD; $p = .10$ 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 \approx 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, although the APOE ϵ 4 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 sig-

nificantly 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 ϵ 4 has varied widely in previous studies depending on the AD definition and source population, with odds ratios for ϵ 4/ ϵ 4 versus ϵ 3/ ϵ 3 in the range of 12 to 16 in Whites and 2 to 7 in African Americans, Latinos, and Asians.³³⁻³⁷ In our multi-ethnic sample, we observed approximate doubling of the risk of late-onset AD and ADRD with each additional copy of the ϵ 4 risk allele and also detected a trend of ADRD risk reduction associated with the ϵ 2 allele as reported.³⁸ It is important to note that our results illustrate the racial/ethnic difference in the risk allele frequency as an important contributor to the AD/ADRD disparity. The ϵ 4 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 ϵ 4 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 ϵ 4 risk allele, although the interaction did not reach statistical significance. The reasons are not clear but may be due to the predominant effects of ϵ 4 risk allele on AD clinicopathology, as demonstrated for amyloid deposition, atrophy rates, and cognitive decline,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, the latter of which is consistent with the Rush Alzheimer's brain pathology

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% CI)	
				Model 1	Model 2
(a) AD					
Number of $\epsilon 4$ 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)
<i>P</i> for race/ethnicity				0.0068	0.014
Number of $\epsilon 4$ 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)
<i>P</i> for race/ethnicity				0.49	0.48
<i>P</i> for race/ethnicity by APOE				0.62	0.56
(b) ADRD					
Number of $\epsilon 4$ 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)
<i>P</i> for race/ethnicity				< 0.0001	< 0.0001
Number of $\epsilon 4$ 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)
<i>P</i> for race/ethnicity				0.022	0.10
<i>P</i> for race/ethnicity by APOE				0.79	0.67

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 $\epsilon 4$ 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 $\epsilon 4$ 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.

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.

Abbreviations: AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementia; CI, confidence interval.

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 used broadly 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 (standard deviation [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. Although 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. In addition, 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.

ACKNOWLEDGMENTS

This work was supported by grants from the National Cancer Institute and a supplement from the National Institute on Aging at the U.S. National Institutes of Health to the Multiethnic Cohort Study (U01 CA164973; CA164973 08S1). The funding organizations played no role in the design and conduct, the management and analysis of the data, the interpretation of results, or the preparation of the article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Unhee Lim, V. Wendy Setiawan, Lynne R. Wilkens, and Loïc Le Marchand were responsible for the study concept and design. Christopher

A. Haiman and Loïc Le Marchand provided the genetic data. Songren Wang, Song-Yi Park, V. Wendy Setiawan, and Unhee Lim were responsible for the data analysis in consultation with Lynne R. Wilkens and Lon White. Unhee Lim and V. Wendy Setiawan drafted and revised the manuscript. All authors, including David Bogumil, Anna H. Wu, and Iona Cheng provided input on the draft and revisions. Unhee Lim is the guarantor and was responsible for the overall study.

ORCID

Unhee Lim  <https://orcid.org/0000-0001-6221-7190>

REFERENCES

1. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2021;17:327-406.
2. Kawas C, Gray S, Brookmeyer R, Fozard J, Zonderman A. Age-specific incidence rates of Alzheimer's disease: the Baltimore longitudinal study of aging. *Neurology*. 2000;54:2072-2077.
3. Tom SE, Hubbard RA, Crane PK, et al. Characterization of dementia and Alzheimer's disease in an older population: updated incidence and life expectancy with and without dementia. *Am J public health*. 2015;105:408-413.
4. Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. *Neurology*. 1997;48:132-138.
5. Matthews FE, Stephan BC, Robinson L, et al. A two decade dementia incidence comparison from the cognitive function and ageing studies I and II. *Nat Commun*. 2016;7:11398.
6. Mielke MM, Ferretti MT, Iulita MF, Hayden K, Khachaturian AS. Sex and gender in Alzheimer's disease—does it matter? *Alzheimers Dement*. 2018;14:1101-1103.
7. Nebel RA, Aggarwal NT, Barnes LL, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. *Alzheimers Dement*. 2018;14:1171-1183.
8. Mehta KM, Yeo GW. Systematic review of dementia prevalence and incidence in United States race/ethnic populations. *Alzheimers Dement*. 2017;13:72-83.
9. National Institute of Neurological Disorders and Stroke. Alzheimer's disease-related dementias (ADRD) summit 2016 prioritized research milestones. <https://aspe.hhs.gov/alzheimers-disease-related-dementias-ardr-summit-2016-prioritized-research-milestones#Topic32016>
10. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement*. 2016;12:216-224.
11. Meng X, D'Arcy C. Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One*. 2012;7:e38268.
12. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. *Alzheimers Dement*. 2015;11:718-726.
13. Cuyvers E, Sleegers K. Genetic variations underlying Alzheimer's disease: evidence from genome-wide association studies and beyond. *Lancet Neurol*. 2016;15:857-868.
14. Kolonel LN, Henderson BE, Hankin JH, et al. A Multiethnic Cohort in Hawaii and Los Angeles: baseline characteristics. *Am J Epidemiol*. 2000;151:346-357.
15. Kolonel LN, Altshuler D, Henderson BE. The Multiethnic Cohort study: exploring genes, lifestyle and cancer risk. *NatRevCancer*. 2004;4:519-527.
16. Kaufman JS. Epidemiologic analysis of racial/ethnic disparities: some fundamental issues and a cautionary example. *Soc Sci Med*. 2008;66:1659-1669.

17. Setiawan VW, Virnig BA, Porcel J, et al. Linking data from the Multiethnic Cohort study to Medicare data: linkage results and application to chronic disease research. *Am J Epidemiol.* 2015;181:917-919.
18. Lim U, Wilkens LR, Albright CL, Novotny R, Le Marchand L, Kolonel LN. University of Hawai'i cancer center connection: bias in self-reported anthropometry in relation to adiposity and adulthood weight gain among postmenopausal caucasian and Japanese American women. *Hawaii J Med Public Health.* 2013;72:445-449.
19. Patterson RE, Emond JA, Natarajan L, et al. Short sleep duration is associated with higher energy intake and expenditure among African-American and non-Hispanic white adults. *J Nutr.* 2014;144:461-466.
20. Stram DO, Hankin JH, Wilkens LR, et al. Calibration of the dietary questionnaire for a Multiethnic Cohort in Hawaii and Los Angeles. *Am J Epidemiol.* 2000;151:358-370.
21. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol.* 2017;134:171-186.
22. De Reuck J, Deramecourt V, Cordonnier C, et al. The incidence of post-mortem neurodegenerative and cerebrovascular pathology in mixed dementia. *J Neurol Sci.* 2016;366:164-166.
23. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology.* 2007;69:2197-2204.
24. Barker WW, Luis CA, Kashuba A, et al. Relative frequencies of Alzheimer disease, lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida brain bank. *Alzheimer Dis Assoc Disord.* 2002;16:203-212.
25. Frisoni GB, Boccardi M, Barkhof F, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. *Lancet Neurol.* 2017;16:661-676.
26. Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM. Prevalence of dementia subtypes in United States Medicare fee-for-service beneficiaries, 2011-2013. *Alzheimers Dement.* 2017;13:28-37.
27. Taylor DH Jr, Fillenbaum GG, Ezell ME. The accuracy of Medicare claims data in identifying Alzheimer's disease. *J Clin Epidemiol.* 2002;55:929-937.
28. Xiong C, Luo J, Coble D, Agboola F, Kukull W, Morris JC. Complex interactions underlie racial disparity in the risk of developing Alzheimer's disease dementia. *Alzheimers Dement.* 2020;16:589-597.
29. Austin PC, Fine JP. Practical recommendations for reporting fine-gray model analyses for competing risk data. *Stat Med.* 2017;36:4391-4400.
30. Park SY, Shvetsov YB, Kang M, et al. Changes in diet quality over 10 years are associated with baseline sociodemographic and lifestyle factors in the Multiethnic Cohort study. *J Nutr.* 2020;150:1880-1888.
31. Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health.* 2014;14:643.
32. Medaglia JD, Pasqualetti F, Hamilton RH, Thompson-Schill SL, Bassett DS. Brain and cognitive reserve: translation via network control theory. *Neurosci Biobehav R.* 2017;75:53-64.
33. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta analysis consortium. *JAMA : J Am Med Ass.* 1997;278:1349-1356.
34. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet.* 2007;39:17-23.
35. Murrell JR, Price B, Lane KA, et al. Association of apolipoprotein E genotype and Alzheimer disease in African Americans. *Arch Neurol.* 2006;63:431-434.
36. Blue EE, Horimoto A, Mukherjee S, Wijsman EM, Thornton TA. Local ancestry at APOE modifies Alzheimer's disease risk in Caribbean Hispanics. *Alzheimers Dement.* 2019;15:1524-1532.
37. Jia L, Xu H, Chen S, et al. The APOE epsilon4 exerts differential effects on familial and other subtypes of Alzheimer's disease. *Alzheimers Dement.* 2020;16:1613-1623.
38. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol.* 2013;9:106-118.
39. Emrani S, Arain HA, DeMarshall C, Nuriel T. APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer's disease: a systematic review. *Alzheimers Res Ther.* 2020;12:141.
40. Barnes LL, Leurgans S, Aggarwal NT, et al. Mixed pathology is more likely in black than white decedents with Alzheimer dementia. *Neurology.* 2015;85:528-534.
41. Akushevich I, Yashkin AP, Kravchenko J, Ukraintseva S, Stallard E, Yashin AI. Time trends in the prevalence of neurocognitive disorders and cognitive impairment in the United States: the effects of disease severity and improved ascertainment. *J Alzheimers Dis (JAD).* 2018;64:137-148.
42. Zhu CW, Ornstein KA, Cosentino S, Gu Y, Andrews H, Stern Y. Misidentification of dementia in Medicare claims and related costs. *J Am Geriatr Soc.* 2019;67:269-276.
43. Taylor DH Jr, Ostbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: the case of dementia revisited. *J Alzheimers Dis (JAD).* 2009;17:807-815.
44. Chen Y, Tysinger B, Crimmins E, Zissimopoulos JM. Analysis of dementia in the US population using Medicare claims: insights from linked survey and administrative claims data. *Alzheimers Dement.* 2019;5:197-207.
45. Conroy SM, Shariff-Marco S, Yang J, et al. Characterizing the neighborhood obesogenic environment in the Multiethnic Cohort: a multi-level infrastructure for cancer health disparities research. *CCC.* 2018;29:167-183.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Lim U, Wang S, Park S-Yi, et al. Risk of Alzheimer's disease and related dementia by sex and race/ethnicity: The Multiethnic Cohort Study. *Alzheimer's Dement.* 2022;18:1625-1634.
<https://doi.org/10.1002/alz.12528>