

Cumulative Genetic Risk and *APOE* $\epsilon 4$ Are Independently Associated With Dementia Status in a Multiethnic, Population-Based Cohort

Kelly M. Bakulski, PhD, Harita S. Vadari, MPH, Jessica D. Faul, PhD, MPH, Steven G. Heeringa, PhD, Sharon L.R. Kardia, PhD, Kenneth M. Langa, MD, PhD, Jennifer A. Smith, PhD, Jennifer J. Manly, PhD, Colter M. Mitchell, PhD, Kelly S. Benke, PhD, and Erin B. Ware, PhD, MPH

Correspondence
Dr. Bakulski
bakulski@umich.edu

Neurol Genet 2021;7:e576. doi:10.1212/NXG.0000000000000576

Abstract

Objective

Alzheimer disease (AD) is a common and costly neurodegenerative disorder. A large proportion of AD risk is heritable, and many genetic risk factors have been identified. The objective of this study was to test the hypothesis that cumulative genetic risk of known AD markers contributed to odds of dementia in a population-based sample.

Methods

In the US population-based Health and Retirement Study (waves 1995–2014), we evaluated the role of cumulative genetic risk of AD, with and without the *APOE* $\epsilon 4$ alleles, on dementia status (dementia, cognitive impairment without dementia, borderline cognitive impairment without dementia, and cognitively normal). We used logistic regression, accounting for demographic covariates and genetic principal components, and analyses were stratified by European and African genetic ancestry.

Results

In the European ancestry sample ($n = 8,399$), both AD polygenic score excluding the *APOE* genetic region (odds ratio [OR] = 1.10; 95% confidence interval [CI]: 1.00–1.20) and the presence of any *APOE* $\epsilon 4$ alleles (OR = 2.42; 95% CI: 1.99–2.95) were associated with the odds of dementia relative to normal cognition in a mutually adjusted model. In the African ancestry sample ($n = 1,605$), the presence of any *APOE* $\epsilon 4$ alleles was associated with 1.77 (95% CI: 1.20–2.61) times higher odds of dementia, whereas the AD polygenic score excluding the *APOE* genetic region was not significantly associated with the odds of dementia relative to normal cognition 1.06 (95% CI: 0.97–1.30).

Conclusions

Cumulative genetic risk of AD and *APOE* $\epsilon 4$ are both independent predictors of dementia in European ancestry. This study provides important insight into the polygenic nature of dementia and demonstrates the utility of polygenic scores in dementia research.

From the Department of Epidemiology (K.M.B., S.L.R.K., J.A.S.), School of Public Health, University of Michigan; Survey Research Center (H.S.V., J.D.F., S.G.H., K.M.L., C.M.M., E.B.W.), Institute for Social Research, University of Michigan; VA Center for Clinical Management Research (K.M.L.), Ann Arbor, MI; Department of Neurology (J.J.M.), Columbia University, and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain (J.J.M.), New York; and Department of Mental Health (K.S.B.), Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.

Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the NIH.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Glossary

AD = Alzheimer dementia; AUC = area under the curve; BMI = body mass index; CI = confidence interval; CIND = cognitive impairment—no dementia; *df* = degrees of freedom; GWAS = genome-wide association study; HRS = Health and Retirement Study; PC = principal component; PGS = polygenic score; ROC = receiver operating characteristic; SNP = single nucleotide polymorphism.

Dementia is characterized by progressive cognitive decline, leading to a loss of independence. The population of those aged 65+ years is estimated to grow from 55 million in 2019 to 88 million in 2050, and the number of people with dementia is predicted to increase.¹ In 2019, the estimated health care, long-term care, and hospice costs associated with dementia were \$290 billion.¹ Heritability estimates for dementia attribute 50–80% of risk to genetic factors.² The most common dementia genetic susceptibility locus is in the *APOE* gene, represented by multiple alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$). In European and African ancestry samples, *APOE* $\epsilon 4$ alleles increase the risk of dementia, although they are neither necessary nor sufficient for disease.^{3,4} Understanding etiologic factors is essential for dementia prevention and potential treatment.

Alzheimer disease (AD) is implicated in 70% of dementia cases,⁵ and late-onset AD is the more common and sporadic form of AD. Late-onset AD genome-wide association studies (GWASs) have identified many single nucleotide polymorphisms (SNPs).⁶ Based on this a priori knowledge of AD genetics, cumulative genetic risk of AD can be summarized using polygenic scores (PGSs). In a recent familial AD study of non-Hispanic White participants, an unweighted PGS constructed using 19 genome-wide significant AD SNPs, observed a 1-SD unit increase in the PGS was associated with 1.29 times increased odds of clinically diagnosed late-onset AD (95% confidence interval [CI]: 1.21–1.37), relative to unaffected family members.⁷ The utility of a weighted AD PGS, independent of *APOE*, has not been tested in multiple ancestries or with population-based dementia outcomes.

We investigated whether cumulative genetic risk of AD—over and above the risk established by the *APOE* $\epsilon 4$ allele—was associated with dementia or cognitive impairment in 2 genetic ancestries. In a large, population-based study, the Health and Retirement Study (HRS), we characterized the utility of AD PGS in European ancestry as well as African ancestry, where the PGS may have value, albeit as a less informative instrument given the European-based GWAS weights. We provide important insight into the genetic correlates of dementia and demonstrate the utility of AD PGSs in dementia research across ancestries.

Methods

Health and Retirement Study

The HRS is a US nationally representative, longitudinal panel cohort study of adults older than 50 years ($n \sim 22,000$,

per wave).⁸ The HRS was collected biennially beginning in 1992, through face-to-face interviews, mail-in surveys, and leave-behind questionnaires, with samples obtained for genotyping (2006–2012). This analysis included 10 waves (1995–2014). The HRS is sponsored by the National Institute on Aging (U01AG009740) and is conducted by the University of Michigan. Informed consent was obtained from all participants.

Standard Protocol Approvals, Registrations, and Patient Consents

The Health and Retirement Study is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan. Before each interview, participants are provided with a written informed consent information document. At the start of each interview, all respondents are read a confidentiality statement and give oral consent by agreeing to do the interview. The University of Michigan Institutional Review Board approved the collection of these data (HUM00061128 and HUM00056464). This secondary data analysis was exempt and not regulated as determined by the University of Michigan Institutional Review Board (HUM00128220).

Cognitive Outcome

Cognition status at each wave was assigned using the Langa-Weir method.⁹ Cognition status at 3 levels (dementia, cognitive impairment–no dementia [CIND], and normal cognition) was assigned using survey instruments. For missing values, multivariate, regression-based imputation and variance estimation were used.¹⁰ The Langa-Weir method was validated against a clinically evaluated subsample of the HRS where 76% of self-respondents and 84% of proxy respondents were correctly classified with dementia.¹¹

Cognition can fluctuate between waves. We were interested in cumulative cognitive status; thus, we constructed summary cognition measures based on all available wave-specific values (ranging from 3 to 10 waves). Observations were excluded if the participant was less than 60 years old at cognitive assessment. Participants were assigned 1 of 5 possible summary cognitive statuses: dementia, CIND, borderline CIND, cognitively normal, and unclassified (table e-1, links.lww.com/NXG/A393). Unclassified summary cognitive status participants were excluded.

Genetic Variables

Genetic data (waves 2006, 2008, and 2010) were downloaded from dbGap (phs000428.v2.p2). Saliva DNA was genotyped on the Illumina Human Omni-2.5-4v1 and Illumina Human

Omni-2.5-8v1 Quad BeadChips¹² at the Center for Inherited Disease Research. Autosomal SNPs were filtered on missing call rate >5% and minor allele frequency <5%. The highly variant lactase gene, *HLA* gene, 8p23, and 17q21.31 regions were excluded.

Genetic ancestry was identified through principal component (PC) analysis on independent genome-wide SNPs. The European ancestry sample included all self-reported non-Hispanic White participants within 1 SD of the mean for eigenvector 1 (n = 9,991 non-Hispanic White/European ancestry). The African ancestry sample included all self-reported non-Hispanic Black participants within 2 SDs of the mean of eigenvector 1 and 1 SD of the mean for eigenvector 2 (n = 2,279 non-Hispanic Black/African ancestry). In the HRS analytic sample, self-reported race/ethnicity and genetic ancestry are perfectly correlated by selection, eliminating our ability to test for effects in discordant or mixed racial/ancestral groups. To create sample eigenvectors for population stratification covariates, PC analysis was performed again within each ancestry sample.

Two genetic variants (rs7412 and rs429358) contribute to 3 *APOE* alleles ($\epsilon 2$, $\epsilon 3$, and $\epsilon 4$). One of 6 *APOE* genotypes ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$) was assigned using 1000 Genomes Project imputation.¹³ Primary analyses indicated the binary presence of the $\epsilon 4$ allele. Sensitivity analyses included additional *APOE* genotype categorizations.

Cumulative genetic risk of AD was calculated using PGS¹² with the following formula:

$$\text{PGS}_i = \sum_{j=1}^J W_j G_{ij}$$

where *i* is individual (*i* = 1 to *N*), *j* is SNP (*j* = 1 to *J*), and *W* is the GWAS meta-analysis effect size for SNP *j*. *G* is the number of variant alleles genotyped (0, 1, or 2), for individual *i* at SNP *j*. Effect estimates were derived from an AD meta-analysis GWAS (stage 1) in European ancestry with 21,982 cases and 41,944 controls.⁶ Summary statistics were downloaded from the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (niagads.org/datasets/ng00075). We identified SNPs that overlapped between the HRS measured genotypes and the AD GWAS summary statistics,⁶ after removing the region on chromosome 19 containing the linkage disequilibrium block of the *APOE* gene (chr19:45384477-45432606, GRCh37/hg19) from the summary statistics. After evaluating PGS developed across multiple *p* value thresholds for outcome association,¹⁴ SNPs with *p* < 0.01 in the summary statistics were included in the PGS.

Although the AD GWAS was conducted in individuals of European ancestry, we conducted our analyses in both European and African ancestry samples. We note the HRS recommendation¹² that “PGSs for other ancestry groups may not

have the same predictive capacity” and “users (should) perform analyses separately by ancestral group and adjust for PCs.” We emphasize the need for large GWAS on non-European ancestries with available summary statistics to advance the knowledge in this field. AD PGSs were *z*-score standardized within ancestry.

Covariates

Information on sex (female and male) and years of education was collected at the first HRS visit. At last cognitive assessment, we considered respondent age and year in our analyses.

In sensitivity models, we included additional dementia risk factors: smoking behavior,¹⁵ alcohol use,¹⁶ body mass index (BMI),¹⁷ and history of hypertension,¹⁸ diabetes,¹⁹ depressive symptoms,²⁰ and stroke.²¹ History of hypertension (no/yes), diabetes (no/yes), smoking (never, former, or current), and alcohol use (never/yes) were assessed at the last cognitive visit using variables from the RAND Center for the Study of Aging, which is supported by the National Institute of Aging and Social Security Administration.²² If the last cognitive visit was face to face, we preferentially used the concurrent measured BMI (kg/m²), followed by the participant's self-reported BMI at that wave. If these 2 values were missing, we selected prior wave measured BMI followed by prior wave self-reported BMI. Depressive symptoms, measured by the 8-item Center for Epidemiological Scales—Depression questionnaire, were averaged across all waves concurrent to and prior to the last cognitive measure. This value was dichotomized at the ancestry-specific mean of depressive symptoms. At each wave, participants were queried on their history of stroke or TIA. This information was used to construct a summary variable for ever having a stroke (no/yes) at the last year of cognitive assessment.

Statistical Analysis

Analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R (version 3.5.1). We calculated univariate and bivariate descriptive statistics. Multiple covariates (sex, age, *APOE* $\epsilon 4$, and education) violated the proportional odds assumptions. Thus, we used separate logistic regressions to model the odds of impaired cognition (dementia, CIND, or borderline CIND) with normal cognition as the reference. Analyses were stratified by ancestry (European and African). Stratification is essential given genetic architecture varies by ancestry, the PGSs were created using European ancestry weights,⁶ and risk factor profiles vary across groups.²³

Model 1 included age and year of last visit, sex, educational attainment, and 2 ancestry-specific genetic PCs. Model 2 added one of the AD genetic components (model 2a: AD PGS; model 2b: *APOE* $\epsilon 4$ status) to model 1. Model 3 added both genetic components to model 1.

Sensitivity Analyses

To assess robustness to methodological and analytic decisions, we conducted several sensitivity analyses. First, to assess

potential linear deviations among pairs of AD PGSs, we tested correlation (Pearson) between an AD PGS without variants in the *APOE* gene region (removing 444 variants from chr19: 45384477-45432606, GRCh37/hg19 from the summary statistics; table e-2, links.lww.com/NXG/A393), to a PGS including *APOE* gene region variants. Second, to examine the effect of different *p* value cutoffs for variants included in the AD PGS, we compared the performance of AD PGS developed using variable GWAS *p* value thresholds ($p_T = 1, 0.3, 0.1, 0.05, 0.01, 0.001$) in model 2a. Third, to account for potential survival bias, logistic models were repeated after removing the oldest HRS cohorts, Assets and Health Dynamics (AHEAD: birth year <1924) and Children of the Depression Era (CODA: birth years 1923–1930). Fourth, to test whether the effect of AD PGS was different in the presence of *APOE* and vice versa, we tested for multiplicative interaction between *APOE* and the AD PGS. Fifth, to characterize the *APOE* locus, a set of logistic regression models examined a 3-level *APOE* variable, based on the number of $\epsilon 4$ copies (0, 1, and 2). We did not have enough individuals in the protective $\epsilon 2/\epsilon 2$ haplotype (<1% of the total sample in each ancestry) to assess. Sixth, to assess the potential role of health behaviors on the relationships presented, we included model 3 variables as well as history of hypertension, diabetes, smoking, alcohol use, stroke, and depressive symptoms (model 4).

Receiver Operating Characteristic Curve

To evaluate classification capability, receiver operating characteristic (ROC) curves were estimated using areas under the curve (AUC) of logistic models of dementia vs normal cognition. C-statistics from models 2a, 2b, 3, and 4 were compared with model 1 to assess whether the addition of AD PGS, *APOE* $\epsilon 4$ status, or the combination of AD PGS and *APOE* $\epsilon 4$ status improved the classification ability over that of the model 1. We further evaluated the AUC of model 3 (with both AD PGS and *APOE* $\epsilon 4$ status) relative to model 2b (only *APOE* $\epsilon 4$ status) to determine whether the addition of AD PGS improved the classification of dementia and normal cognition over and above *APOE* $\epsilon 4$ status.

Attributable Fraction

To determine the proportion of the dementia burden that would be reduced in the absence of elevated cumulative genetic risk, we calculated the attributable fraction for adjusted impaired cognition vs normal cognition regression models. We first compared those in the highest 20th percentile of AD PGS with those in the lowest 20th percentile of AD PGS. Next, we compared those with at least 1 copy of *APOE* $\epsilon 4$ with those without the allele. We calculated the population attributable fractions and confidence intervals using the AF package with the case-control option.

Data Availability

All HRS survey data are publicly available (hrs.isr.umich.edu/data-products). The genetic data are available from the dbGaP database (accession phs000428.v2.p2). Analytic code is also publicly available (github.com/bakulskilab).

Results

Sample Description

Analyses were performed in both European ($n = 8,399$) and African ($n = 1,605$) ancestry samples (figure e-1, links.lww.com/NXG/A393). In the European ancestry sample, 8.6% were classified with dementia, 8.5% with CIND, and 15.0% with borderline CIND (table e-3). In the African ancestry sample, 16.9% were classified with dementia, 21.8% with CIND, and 19.4% with borderline CIND. The proportion of cases in each cognitive status differed by ancestry ($p < 0.001$).

The majority of the participants in the samples were female (European = 57.0%; African = 63.1%). The average age at the participant's last cognition visit was 75.3 years ($SD = 9.04$) in the European ancestry group and 72.2 years ($SD = 8.83$) in the African ancestry group. Sex, age, education, year of last visit, and *APOE* $\epsilon 4$ status differed by ancestry ($p < 0.01$). The prevalence of *APOE* $\epsilon 4$ was lower in the European sample (26.3%) than in the African sample (36.9%). Hypertension, diabetes, smoking, alcohol use, and stroke status also differed by ancestry ($p \leq 0.001$). AD PGSs were normally distributed within ancestries.

Bivariate Analyses

In the European ancestry sample, there were differences in demographic characteristics by summary cognitive status (dementia, CIND, borderline CIND, and normal) (table 1). The mean age at last visit of those with dementia (84.2 years; $SD = 7.73$) was higher than those with normal cognition (72.9 years; $SD = 8.17$). The mean years of education were lower in those with dementia (11.9 years; $SD = 2.90$) compared with those with normal cognition (13.7 years; $SD = 2.31$). Among participants with impaired cognition, there were higher proportions of *APOE* $\epsilon 4$ carriers and history of hypertension, diabetes, stroke and depression, compared to those with normal cognition ($p < 0.001$). Lower mean BMI, less alcohol use, and lower proportions of current smokers were observed in those with impaired cognition compared with normal cognition ($p < 0.001$). PGS for AD, with and without the *APOE* gene region, was higher with impaired cognition ($p < 0.003$) (figure e-2, links.lww.com/NXG/A393).

In the African ancestry sample, the mean age at last visit of those with dementia (78.8; $SD = 9.16$) was higher than those with normal cognition (68.4; $SD = 6.84$). The mean years of education were lower among those with dementia (9.49 years; $SD = 3.82$), relative to those with normal cognition (13.3 years; $SD = 2.35$). Among those with impaired cognition, there was a higher proportion of participants with history of hypertension, diabetes, stroke, and depression compared to participants with normal cognition ($p < 0.01$). Higher mean BMI and more alcohol use were observed in those with normal cognition relative to impaired cognition ($p < 0.01$). PGS for AD, with and without the *APOE* gene region, was higher with impaired cognition ($p < 0.005$).

Table 1 Bivariate Analyses of Covariates by Cognition Status Stratified by Ancestry Among Health and Retirement Study (HRS) Participants With Core Measurements Taken From 1995 to 2014

	European ancestry (n = 8,399)					African ancestry (n = 1,605)				
	Normal (n = 5,708)	Borderline CIND (n = 1,256)	CIND (n = 711)	Dementia (n = 724)	p Value	Normal (n = 672)	Borderline CIND (n = 312)	CIND (n = 350)	Dementia (n = 271)	p Value
AD polygenic score (no APOE)^a	-0.03 (1.01)	0.09 (0.98)	0.02 (1.00)	0.03 (0.99)	0.003	-0.10 (1.01)	0.00 (1.03)	-0.02 (0.96)	0.15 (0.96)	0.007
AD polygenic score (with APOE)	-0.03 (1.00)	0.10 (0.99)	0.03 (0.98)	0.06 (1.01)	<0.001	-0.10 (1.01)	0.00 (1.03)	-0.02 (0.96)	0.15 (0.96)	0.005
APOE variant status^b	—									—
ε2/ε2	29 (0.51)	12 (0.96)	5 (0.70)	1 (0.14)		6 (0.89)	5 (1.60)	7 (2.00)	2 (0.74)	
ε2/ε3	780 (13.7)	144 (11.5)	83 (11.7)	72 (9.94)		89 (13.2)	41 (13.1)	49 (14.0)	40 (14.8)	
ε2/ε4	117 (2.05)	23 (1.83)	17 (2.39)	26 (3.59)		23 (3.42)	19 (6.09)	16 (4.57)	19 (7.01)	
ε3/ε3	3,528 (61.8)	738 (58.8)	408 (57.4)	391 (54.0)		337 (50.1)	153 (49.0)	173 (49.4)	111 (41.0)	
ε3/ε4	1,161 (20.3)	306 (24.4)	183 (25.7)	211 (29.1)		188 (28.0)	80 (25.6)	95 (27.1)	85 (31.4)	
ε4/ε4	93 (1.63)	33 (2.63)	15 (2.11)	23 (3.18)		29 (4.32)	14 (4.49)	10 (2.86)	14 (5.17)	
APOE ε4 binary status^c										<0.001
No ε4 allele	4,337 (76.0)	894 (71.2)	496 (69.8)	464 (64.1)		432 (64.3)	199 (63.8)	229 (65.4)	153 (56.5)	0.093
ε4 allele present	1,371 (24.0)	362 (28.8)	215 (30.2)	260 (35.9)		240 (35.7)	113 (36.2)	121 (34.6)	118 (43.5)	
Age at last visit	72.9 (8.17)	78.1 (8.54)	80.8 (8.40)	84.2 (7.73)	<0.001	68.4 (6.84)	71.4 (7.76)	75.1 (8.94)	78.8 (9.16)	<0.001
Year of last visit										<0.001
2006	122 (2.1)	40 (3.2)	36 (5.1)	17 (2.4)		8 (3.0)	10 (2.9)	6 (1.9)	9 (1.3)	
2008	318 (5.6)	116 (9.2)	65 (9.1)	66 (9.1)		32 (11.8)	32 (9.1)	11 (3.5)	20 (3.0)	
2010	274 (4.8)	108 (8.6)	68 (9.6)	103 (14.2)		29 (10.7)	34 (9.7)	11 (3.5)	27 (4.0)	
2012	347 (6.1)	165 (13.1)	105 (14.8)	164 (22.7)		39 (14.4)	25 (7.1)	19 (6.1)	28 (4.2)	
2014	4,647 (81.4)	827 (65.8)	437 (61.5)	374 (51.7)		163 (60.2)	249 (71.1)	265 (84.9)	588 (87.5)	
Sex										0.004
Male	2,403 (42.1)	582 (46.3)	333 (46.8)	295 (40.7)		226 (33.6)	116 (37.2)	147 (42.0)	103 (38.0)	0.067
Female	3,305 (57.9)	674 (53.7)	378 (53.2)	429 (59.3)		446 (66.4)	196 (62.8)	203 (58.0)	168 (62.0)	
Education years	13.7 (2.31)	12.6 (2.37)	11.6 (2.70)	11.9 (2.90)	<0.001	13.3 (2.35)	12.2 (2.37)	10.3 (2.90)	9.49 (3.82)	<0.001
Cohort										<0.001
AHEAD	371 (6.50)	212 (16.9)	176 (24.8)	275 (38.0)		12 (1.79)	11 (3.53)	38 (10.9)	54 (19.9)	
CODA	428 (7.50)	172 (13.7)	126 (17.7)	147 (20.3)		5 (0.74)	10 (3.21)	34 (9.71)	30 (11.1)	
Remaining HRS cohorts	4,909 (86.0)	872 (69.4)	409 (57.5)	302 (41.7)		655 (97.5)	291 (93.3)	278 (79.4)	187 (69.0)	

Continued

Table 1 Bivariate Analyses of Covariates by Cognition Status Stratified by Ancestry Among Health and Retirement Study (HRS) Participants With Core Measurements Taken From 1995 to 2014 (continued)

	European ancestry (n = 8,399)					African ancestry (n = 1,605)				
	Normal (n = 5,708)	Borderline CIND (n = 1,256)	CIND (n = 711)	Dementia (n = 724)	p Value	Normal (n = 672)	Borderline CIND (n = 312)	CIND (n = 350)	Dementia (n = 271)	p Value
BMI (kg/m²) at last visit	29.0 (6.14)	28.2 (6.11)	27.3 (6.22)	25.5 (5.36)	<0.001	31.5 (7.31)	30.7 (7.13)	30.2 (7.48)	27.7 (6.49)	<0.001
Ever hypertension										<0.001
No	2,090 (36.6)	330 (26.3)	186 (26.2)	190 (26.2)		134 (19.9)	61 (19.6)	43 (12.3)	29 (10.7)	
Yes	3,618 (63.4)	926 (73.7)	525 (73.8)	534 (73.8)		538 (80.1)	251 (80.4)	307 (87.7)	242 (89.3)	
Diabetes status										<0.001
No	4,420 (77.4)	910 (72.5)	488 (68.6)	540 (74.6)		437 (65.0)	180 (57.7)	198 (56.6)	148 (54.6)	
Yes	1,288 (22.6)	346 (27.5)	223 (31.4)	184 (25.4)		235 (35.0)	132 (42.3)	152 (43.4)	123 (45.4)	
Stroke status										<0.001
No	5,303 (92.9)	1,074 (85.5)	576 (81.0)	508 (70.2)		620 (92.3)	282 (90.4)	286 (81.7)	184 (67.9)	
Yes	405 (7.10)	182 (14.5)	135 (19.0)	216 (29.8)		52 (7.74)	30 (9.62)	64 (18.3)	87 (32.1)	
Depression status										<0.001
Low CESD^d	3,996 (70.0)	700 (55.7)	360 (50.6)	361 (49.9)		477 (71.0)	206 (66.0)	169 (48.3)	123 (45.4)	
High CESD	1,712 (30.0)	556 (44.3)	351 (49.4)	363 (50.1)		195 (29.0)	106 (34.0)	181 (51.7)	148 (54.6)	
Smoking status										<0.001
Never	2,509 (44.0)	503 (40.0)	267 (37.6)	329 (45.4)		288 (42.9)	129 (41.3)	129 (36.9)	108 (39.9)	
Former	2,686 (47.1)	621 (49.4)	365 (51.3)	365 (50.4)		289 (43.0)	131 (42.0)	168 (48.0)	128 (47.2)	
Current	513 (8.99)	132 (10.5)	79 (11.1)	30 (4.14)		95 (14.1)	52 (16.7)	53 (15.1)	35 (12.9)	
Alcohol status										<0.001
No	2,420 (42.4)	725 (57.7)	488 (68.6)	565 (78.0)		395 (58.8)	198 (63.5)	254 (72.6)	220 (81.2)	
Yes	3,288 (57.6)	531 (42.3)	223 (31.4)	159 (22.0)		277 (41.2)	114 (36.5)	96 (27.4)	51 (18.8)	

Abbreviations: AHEAD = asset and health dynamics among the oldest old; CESD = Center for Epidemiologic Studies for Depression Scale; CIND = cognitive impairment–no dementia; CODA = children of the depression study.

The analytic sample includes participants at least 3 visits of cognition measured from ages 60 years and older with an assigned cognition status and complete genetic information. Analysis was split by genetic ancestry determined by principal component analysis: European ancestry (n = 8,399) and African ancestry (n = 1,605). Associations by race between cognition status (normal, borderline CIND, CIND, and dementia) were tested by ancestry. Categorical variables are represented by n (%) with χ^2 test for association. Continuous variables are represented by mean (SD) with analysis of variance test for association.

^a Weights derived from Kunkle et al. (IGAP, 2019).⁶

^b APOE status was genotyped using 2 single nucleotide polymorphisms (rs7412 and rs429358) resulting in 3 alleles of APOE. The frequencies listed are of the possible allelic combinations.

^c Binary status was determined by the presence of the ϵ 4 allele in participants.

^d Binary cutoff determined by ancestry-specific median of all CESD measures before last cognitive assessment.

Adjusted Association of Genetics With Dementia Outcomes

Logistic regression models were run separately by ancestry (table 2). In the European ancestry sample, age and education

(model 1) were associated with each impaired cognitive status relative to normal cognition ($p < 0.0001$). AD PGS, without the APOE gene region, was associated with dementia compared with normal cognition (model 2a: OR = 1.13, 95% CI:

Table 2 Odds Ratios (ORs) of Cognitive Status, Relative to Normal Status, Explained by 1 SD Increase of Polygenic Score and the Presence of an *APOE ε4* Allele in Participants in the Health and Retirement Study (HRS), of European and African Ancestries, Adjusted for Age, Sex, Education, Year of Last Visit, Genetic Principal Component (PC) 1, and Genetic PC 2

	N	Model 2a			Model 2b			Model 3			Model 4		
		OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
European ancestry	8,399												
Polygenic score													
Normal	5,708	Ref						Ref			Ref		
Borderline CIND	1,256	1.15	1.08–1.23	<0.0001	—	—	1.14	1.07–1.21	<0.0001	1.13	1.06–1.21	<0.0001	
CIND	711	1.06	0.97–1.16	0.188	—	—	—	1.05	0.96–1.14	0.298	1.05	0.96–1.15	0.288
Dementia	724	1.13	1.03–1.24	0.008	—	—	—	1.10	1.00–1.20	0.049	1.10	0.99–1.21	0.07
<i>APOE ε4</i>													
Normal	5,708				Ref			Ref	—	—	Ref	—	
Borderline CIND	1,256	—	—	—	1.46	1.26–1.69	<0.0001	1.43	1.24–1.65	<0.0001	1.45	1.25–1.68	<0.0001
CIND	711	—	—	—	1.74	1.43–2.11	<0.0001	1.73	1.43–2.10	<0.0001	1.70	1.39–2.07	<0.0001
Dementia	724	—	—	—	2.46	2.02–2.99	<0.0001	2.42	1.99–2.95	<0.0001	2.30	1.86–2.85	<0.0001
African ancestry	1,605												
Polygenic score													
Normal	672	Ref			—	—	—	Ref			Ref		
Borderline CIND	312	1.06	0.87–1.29	0.562	—	—	—	1.06	0.87–1.30	0.555	1.07	0.86–1.28	0.519
CIND	350	0.96	0.76–1.20	0.702	—	—	—	0.96	0.76–1.20	0.706	0.92	0.74–1.16	0.46
Dementia	271	1.29	0.98–1.70	0.072	—	—	—	1.29	0.97–1.70	0.076	1.25	0.95–1.65	0.141
<i>APOE ε4</i>													
Normal	672	—	—	—	Ref			Ref			Ref		
Borderline CIND	312	—	—	—	1.10	0.82–1.47	0.541	1.10	0.82–1.47	0.534	1.12	0.84–1.51	0.443
CIND	350	—	1.08	0.78–1.50	0.644	1.08	0.78–1.50	0.648	1.14	0.81–1.61	0.45		
Dementia	271	—			1.77	1.20–2.61	0.004	1.77	1.20–2.61	0.004	1.74	1.15–2.63	0.009

Abbreviations: BMI = body mass index; CI = confidence interval; CIND = cognitive impairment–no dementia. Final model was additionally adjusted for by BMI, hypertension, diabetes, stroke, depression, smoking, and alcohol. Logistic regressions were performed on data subset.

Model 2a: $\beta_0 + \beta_1(\text{Polygenic score}) + \beta_2(\text{age at last visit}) + \beta_3(\text{sex}) + \beta_4(\text{educational attainment}) + \beta_5(\text{year of last visit}) + \beta_6(\text{PC1}) + \beta_7(\text{PC2})$.

Model 2b: $\beta_0 + \beta_1(\text{APOE } \epsilon 4) + \beta_2(\text{age at last visit}) + \beta_3(\text{sex}) + \beta_4(\text{educational attainment}) + \beta_5(\text{year of last visit}) + \beta_6(\text{PC1}) + \beta_7(\text{PC2})$.

Model 3: $\beta_0 + \beta_1(\text{Polygenic score}) + \beta_2(\text{APOE } \epsilon 4) + \beta_3(\text{age at last visit}) + \beta_4(\text{sex}) + \beta_5(\text{educational attainment}) + \beta_6(\text{year of last visit}) + \beta_7(\text{PC1}) + \beta_8(\text{PC2})$.

Model 4: $\beta_0 + \beta_1(\text{Polygenic score}) + \beta_2(\text{APOE } \epsilon 4) + \beta_3(\text{age}) + \beta_4(\text{sex}) + \beta_5(\text{educational attainment}) + \beta_6(\text{year of last visit}) + \beta_7(\text{PC1}) + \beta_8(\text{PC2}) + \beta_9(\text{BMI}) + \beta_{10}(\text{hypertension}) + \beta_{11}(\text{diabetes}) + \beta_{12}(\text{stroke}) + \beta_{13}(\text{depression}) + \beta_{14}(\text{smoking}) + \beta_{15}(\text{alcohol})$.

1.03–1.24). *APOE ε4* status was also associated with dementia compared with normal cognition (model 2b: OR = 2.46, 95% CI: 2.02–2.99). In model 3, both AD PGS and *APOE ε4* status were significantly and independently associated with dementia relative to normal cognition. A 1 SD increase in AD PGS was associated with a 1.10 (95% CI: 1.00–1.20) times higher odds of dementia relative to normal cognition in European ancestry. Carrying an *APOE ε4* allele was associated with 2.42 (95% CI: 1.99–2.95) times higher odds of dementia, relative to normal cognition in European ancestry.

In the African ancestry sample, age and education (model 1) were associated with each abnormal cognitive status relative

to normal cognition ($p < 0.003$). AD PGS, without the *APOE* gene region, was not associated with dementia compared with normal cognition (model 2a: OR = 1.29, 95% CI: 0.98–1.70). *APOE ε4* status was associated with dementia compared with normal cognition (model 2b: OR = 1.77, 95% CI: 1.20–2.61). In model 3, *APOE ε4* status remained significantly associated with dementia relative to normal cognition (OR = 2.10, 95% CI: 1.34–3.28).

Sensitivity Analyses

We compared the primary AD PGS excluding the *APOE* gene region to an AD PGS including the *APOE* gene region using a correlation test. These 2 AD PGSSs were highly correlated ($r_{\text{European}} = 0.9772, p < 0.0001; r_{\text{African}} = 0.9981, p < 0.0001$).

To examine the effect of GWAS p value threshold selection for SNP inclusion in the PGS, we compared PGSs developed using variable p value thresholds. Correlations between PGSs at different p value threshold cutoffs ranged from 0.30 to 0.98 in the European ancestry sample and from 0.41 to 0.99 in the African ancestry sample (table e-4, links.lww.com/NXG/A393). In the European ancestry sample in model 2a, all AD PGSs were associated with the odds of borderline CIND ($p < 0.05$), whereas no AD PGSs were associated with the odds of CIND (table e-5). The relationship between AD PGS and dementia was sensitive to pT . The AD PGS was associated with dementia status at $pT = 0.01$ and $pT = 0.001$ ($p < 0.01$), but not associated at $pTs > 0.01$. In the African ancestry sample, AD PGS was not associated with odds of impaired cognition, relative to normal cognition at any pT .

To account for potential survival bias in our study sample, the oldest HRS cohorts (AHEAD and CODA) were removed, dropping the sample size from $n = 10,004$ to $n = 7,913$ ($n_{\text{European}} = 6,492$; $n_{\text{African}} = 1,421$). In this European ancestry subset in model 3, a 1 SD increase in AD PGS was not associated with the odds of dementia OR = 1.05 (95% CI: 0.92–1.20), relative to normal cognition (table e-6, links.lww.com/NXG/A393). The presence of *APOE* $\epsilon 4$ remained associated with the odds of dementia relative to normal cognition OR = 2.60 (95% CI: 2.00–3.38). In the African ancestry subset when AHEAD and CODA were removed, the *APOE* $\epsilon 4$ relationship attenuated (from 1.77 to 1.55) but remained associated with dementia.

We tested for a multiplicative interaction between having any copies of the *APOE* $\epsilon 4$ allele and the AD PGS. There was not an interaction between *APOE* $\epsilon 4$ and the PGS excluding *APOE* region (OR_{interaction} = 1.10, $p = 0.30$). There was also not an interaction between *APOE* $\epsilon 4$ and the PGS including the *APOE* region (OR_{interaction} = 1.09, $p = 0.34$). This suggests

that the effect of the *APOE* $\epsilon 4$ allele is the same as the *APOE* region.

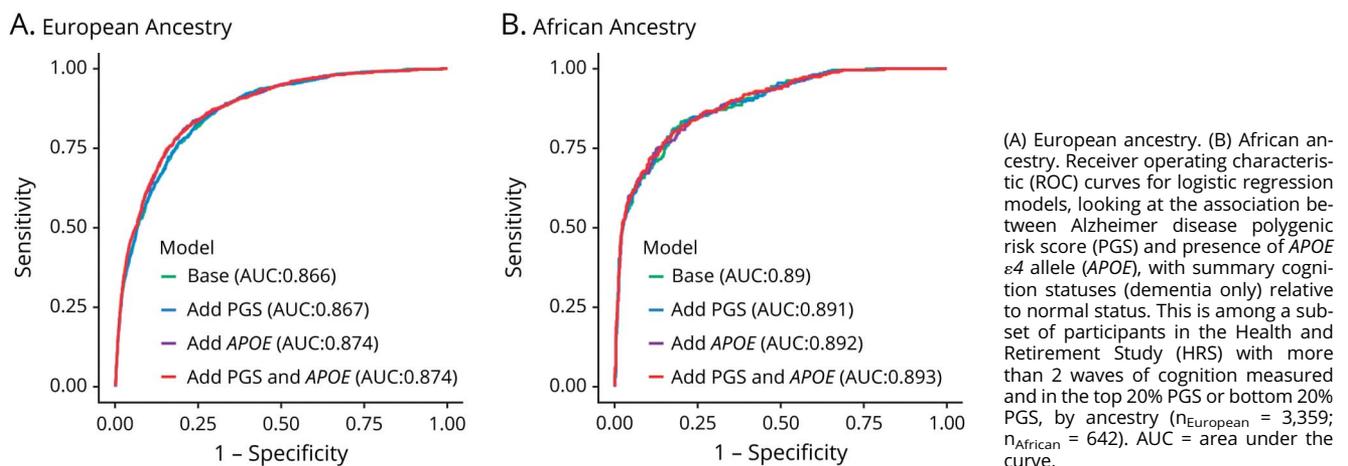
We assessed alternative *APOE* categories (table e-7, links.lww.com/NXG/A393). In European and African ancestry models, having 1 copy and having 2 copies of *APOE* $\epsilon 4$ compared with no copies both increased the odds of impaired cognition over normal cognition. Although this may indicate utility in modeling *APOE* $\epsilon 4$ as 2 indicators for 1 or 2 copies of an $\epsilon 4$ allele, the relative prevalence of 2 $\epsilon 4$ copies limits the power (prevalence < 5% in each ancestry).

To assess the robustness of our findings, we additionally adjusted for dementia risk factors (BMI, hypertension, depression, diabetes, smoking, alcohol use, and stroke) (table 2; model 4). In European ancestry, the association between *APOE* $\epsilon 4$ and the odds of dementia relative to normal cognition remained (model 4; OR = 2.30 95% CI: 1.86–2.85). The effect of AD PGS was consistent in magnitude, but nonsignificant (OR = 1.10 95% CI: 0.99–1.21). Similar associations were observed in African ancestry (*APOE* $\epsilon 4$ OR = 1.74, 95% CI: 1.15–2.63; AD PGS OR = 1.25, 95% CI: 0.95–1.65).

ROC Curve

To address the differences in dementia prediction ability and potential clinical relevance, we assessed AUC using ROC curves. In European ancestry, using model 1 as a reference (c -statistic = 0.87), adding AD PGS did not improve model discrimination ($c_{\text{difference}} = 0.001$, 95% CI: –0.0006 to 0.0018, $p = 0.30$). However, adding *APOE* $\epsilon 4$ status increased classification ($c_{\text{difference}} = 0.0075$, 95% CI: 0.0037 to 0.0114, $p = 0.0001$). Adding the AD PGS did not improve classification over the model already including *APOE* $\epsilon 4$ (model 2b: $c_{\text{model2b}} = 0.87$; $c_{\text{difference}} = 0.0001$, 95% CI: –0.0006 to 0.0008, $p = 0.77$). In African ancestry, no models performed more accurately than model 1 (table e-8, links.lww.com/NXG/A393; figure 1).

Figure 1 Classification of Dementia vs Normal Cognition Status Using Demographics, *APOE*, and Polygenic Score



Attributable Fraction

Attributable fraction analyses were restricted to a sample of the top 20th percentile AD PGS and the bottom 20th percentile AD PGS by ancestry ($n_{\text{European}} = 3,359$, $n_{\text{African}} = 642$). In the European ancestry model 3, having at least 1 copy of *APOE* $\epsilon 4$ was attributed to 21.4% (95% CI: 11.9%–30.8%; $p < 0.0001$) of dementia cases and 9.6% (95% CI: 0.9%–18.2%; $p = 0.03$) of borderline CIND cases. The AD PGS (top 20%) was attributed to 19.0% (95% CI: 8.5%–29.5%; $p < 0.0001$) of borderline CIND cases, relative to the bottom 20% of the AD PGS distribution. In the African ancestry model 3, 53.9% (95% CI: 35.7%–72.0%; $p < 0.0001$) of dementia cases were attributed to being in the top 20% of the AD PGS distribution. All other attributable fractions were not significantly different than zero (table e-9, links.lww.com/NXG/A393).

Discussion

In the large US population-based HRS panel cohort, we observed that AD PGS and *APOE* $\epsilon 4$ status had independent associations with dementia and cognitive impairment compared with normal cognition in European and African ancestry samples. These genetic factors were associated with significant attributable fractions of impaired cognition. *APOE* $\epsilon 4$ status improved classification of dementia cases; however, the AD PGS did not improve classification. Together, these findings confirm that *APOE* $\epsilon 4$ and AD PGS are powerful predictors of cognitive impairment in population-based studies, although only *APOE* $\epsilon 4$ currently provides sufficient improved classification for potential clinical utility. It should be noted that the African ancestry analysis had a smaller sample size and used weights from a European-based study of Alzheimer disease to build the PGS. Our study replicates previous *APOE* results and expands to also consider cumulative genetic risk, providing greater understanding of the genetic etiology of dementia.

APOE $\epsilon 4$ is a consistent genetic risk factor associated with AD and dementia, but it accounts for only a portion of the heritability.²⁴ In the Rotterdam study, those with a single copy of *APOE* $\epsilon 4$ had 1.7 times higher odds of dementia (95% CI: 1.0–2.9) and those with 2 copies had 11.2 times higher odds of dementia (95% CI: 3.6–35.2) compared with $\epsilon 3/\epsilon 3$.³ In our supplemental analysis, we also detected *APOE* $\epsilon 4$ dose-increasing odds for dementia relative to normal cognition (1 copy [$n = 237$]: OR = 2.29, 95% CI: 1.87–2.81; 2 copies [$n = 23$]: OR = 4.93, 95% CI: 2.82–8.62) in the European ancestry sample. To compare the highest genetic risk to the lowest genetic risk, we note that the attributable fraction analysis was performed on a sample that was 40% of the size of the primary analytic sample. This sample size and selection may have modified the relationship between *APOE* and cognitive status in the sensitivity analysis. We saw a similar *APOE* $\epsilon 4$ dose-effect pattern in the African Ancestry sample, although the observed effect size was smaller and the sample was more limited (1 copy [$n = 104$]: OR = 1.68, 95% CI: 1.12–2.51; 2

copies [$n = 14$]: OR = 2.65, 95% CI: 1.11–6.33). In an independent African-American sample, those with a single copy of *APOE* $\epsilon 4$ had 2.6 higher odds of dementia (95% CI: 1.8–3.7) and those with 2 copies had 10.5 higher odds of dementia (95% CI: 5.1–21.8), relative to $\epsilon 3/\epsilon 3$.⁴ Consistent with prior research, we observed that *APOE* $\epsilon 4$ is associated with impaired cognition in multiple ancestries and *APOE* $\epsilon 4$ status can improve classification of dementia cases in population-based samples.

Studies of AD PGS and AD or cognitive status have largely been restricted to participants of European ancestry or identifying as non-Hispanic White,^{24–29} and these studies have varied in their PGS development techniques and modeling decisions. A non-*APOE* PGS study (constructed from 19 SNPs outside the *APOE* gene) found those with the highest PGS had 62% increased late-onset AD risk over the lowest PGS.³⁰ Non-*APOE* PGS have also been used for AD-patient classification.^{31–35} One reported AD classification when including age, sex, *APOE* $\epsilon 4$, *APOE* $\epsilon 2$, and a PGS with AD-associated SNPs ($p < 0.5$) (AUC: 0.78, 95% CI: 0.77–0.80).²⁵ This study used PGS weights from a GWAS that included the study sample. In our European ancestry sample independent of the GWAS weights, our estimate of the AUC for dementia with similar covariates (any *APOE* $\epsilon 4$, *APOE* $\epsilon 2/\epsilon 2$, and PGS with AD-associated SNPs $p < 0.1$) was higher (AUC: 0.85, 95% CI: 0.83–0.86). This difference is likely due to the broader definition of our dementia phenotype. Other PGS analyses have reported AD-subtype discrimination from PGS created for AD,³⁶ revealing multiple biological mechanisms underlying AD subtypes.

A previous longitudinal analysis in the HRS ($n = 8,253$) featuring a 21 SNP AD PGS excluding *APOE* observed that a 0.1 unit increase in PGS was associated with 0.016 decreased memory score units (95% CI: –0.036 to 0.005) in European ancestry ($n = 7,172$) and 0.049 decreased memory score units (95% CI: –0.12 to 0.023) in African ancestry ($N = 1,081$) samples.³⁷ Consistent with this prior study on impaired memory, in our analysis, we observed AD PGS was associated with increased odds of dementia. We further extended our analysis, by accounting for *APOE* and adjusting for additional dementia risk factors.

In this study, we assessed the utility of transferring PGS weights from one population to another population. Allele frequencies, linkage disequilibrium patterns, and the genetic architecture can vary by ancestral populations³⁸ based on recombination and demographic histories.³⁹ Participation or inclusion in the discovery GWAS is influenced by social and behavioral factors, which relates to the applicability of the discovery GWAS results to another population.⁴⁰ Also, the background of nongenetic risk factors differs across populations, likely affecting the observed genetic signal.⁴⁰ Furthermore, in population-based studies such as the HRS, accuracy of dementia classification algorithms varies across racial/ethnic groups⁴¹ and the algorithm used in the current

study¹¹ has higher accuracy in non-Hispanic White participants. Future studies in other samples may examine heritability in diverse populations to assess whether genetic or environmental factors explain different proportions of the variance in cognitive status. With systemic differences in the outcome classification and differences in the genetic exposure (PGS) classification by ancestry in our study, it is essential to not directly compare the genetic associations across groups (European ancestry and African ancestry). We focused on the within-ancestry findings and are cautious not to overstate our results. Although trans-ancestry genetic analyses are challenging, it remains important to perform studies in multiple ancestries to demonstrate these fundamental differences, refine methods that generate AD PGSs, and call for more inclusive ancestry GWAS.

Older participants with cognitive impairments may be more likely to die of other comorbid causes, and capturing cognitively impaired cases in older age groups may be difficult.⁴² Individuals surviving to age 90 years with no cognitive impairment may skew estimates. The HRS began genetic sample collection in 2006 and *APOE* or other risk genotypes may have already influenced survival for inclusion in our analytic sample. In sensitivity analyses, we removed the older cohorts (AHEAD and CODA) to observe if our results were robust to mortality selection. Removing AHEAD and CODA in the European ancestry sample, we dropped 58.3% of dementia cases with 1 substantive change in findings: the PGS association with odds of dementia (model 3) attenuated from 1.10 (95% CI: 1.00–1.20) to 1.05 (95% CI: 0.92–1.20), whereas the *APOE* $\epsilon 4$ association increased in magnitude from 2.42 (95% CI: 1.99–2.95) to 2.60 (95% CI: 2.00–3.38). The ORs did not significantly differ between the models, indicating that mortality selection did not critically bias these results.

Dementia ascertainment in population cohorts can be highly variable. We used the Langa-Weir method that incorporates the Telephone Interview of Cognitive Status and assigns a cognition status using cut points mirroring clinical diagnosis. This method has a comparable sensitivity and specificity (sensitivity: 75%; specificity: 83%) to related methods and provides balanced accuracy with prior clinical validation.⁴¹ Outcome misclassification can introduce bias into the study, likely toward the null, and may have contributed to the null findings with the ROC analysis. Future studies may improve dementia classification. New and larger studies may increase power with greater numbers of participants with impaired cognition, particularly in diverse ancestries. Importantly, our broad outcome of dementia did not involve direct imaging or biomarker measures or clinician diagnostic evaluation and did not allow for dementia subtyping, such as AD. Studies with specific clinical AD diagnoses may have higher predictive values of AD PGS. Other challenges such as time-varying biases and nonlinear cognitive trajectory⁴³ were addressed by constructing a summary cognition status based on multiple visits. There are documented learning effects—where scores are higher the second time a participant sees a similar

examination—for these cognition tests.⁴³ Our summary cognition status excluded those with less than 3 visits, strengthening the cognitive status designation for each individual, and reducing practice effects.

Assessing outcome classification allows researchers to better understand how genetic factors can potentially contribute to clinical diagnosis of complex disease outcomes. The utility of PGS has helped to identify (for example) risk of MS,⁴⁴ Parkinson disease,⁴⁵ and cardiovascular disease.⁴⁶ AD PGSs may also predict age at AD onset, where individuals with a top quartile AD PGS had an age at onset of 75 vs an age at onset of 95 for the lowest quartile.³¹ Despite the motivation to use AD PGS in clinical practice, scientists are understandably hesitant to encourage PGS use outside of research. The risk conferred by AD PGS is calculated at a population level and may not be appropriate to predict individual risk. In addition, current AD PGSs are not created with diverse populations as the reference weights, which may provide inaccurate risk for individuals of diverse ancestries,⁴⁷ and clinical use in their present form may exacerbate health disparities.⁴⁸

In summary, AD PGS and *APOE* $\epsilon 4$ were independently associated with dementia and cognitive impairment in the large, US population-based longitudinal HRS in European and African ancestry samples. *APOE* $\epsilon 4$ was associated with improved dementia classification; however, the current AD PGS did not improve classification. There are many opportunities to improve and apply AD PGS, especially in non-European ancestries. We may eventually be able to use PGSs for primary prevention (quantifying the genetic burden in subpopulations), secondary prevention (detecting high-risk individuals for disease screening), and tertiary prevention (a potential biomarker for optimizing treatment stratification).⁴⁹ However, current AD PGSs, though associated with odds of dementia, are not sufficiently accurate enough for clinical diagnosis, particularly across ancestries.

Acknowledgment

The authors thank the participants in the Health and Retirement Study and the staff who catalogued their information.

Study Funding

This study was funded by the NIH (grant numbers R01 AG055406, R01 AG055654, R25 AG053227, R01 AG053972, R03 AG048806, and P30 AG053760). The Health and Retirement Study is sponsored by the National Institute on Aging (U01AG009740) and is conducted at the Institute for Social Research, University of Michigan.

Disclosure

The authors report no disclosures. Go to [Neurology.org/NG](https://www.neurology.org/NG) for full disclosures.

Publication History

Received by *Neurology: Genetics* June 18, 2020. Accepted in final form October 29, 2020.

Appendix Authors

Name	Location	Contribution
Kelly M. Bakulski, PhD	University of Michigan, Ann Arbor	Designed and conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content
Harita S. Vadari, MPH	University of Michigan, Ann Arbor	Major role in the acquisition of data
Jessica D. Faul, PhD, MPH	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Steven G. Heeringa, PhD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Sharon L.R. Kardia, PhD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Kenneth M. Langa, MD, PhD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Jennifer A. Smith, PhD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Jennifer J. Manly, PhD	Columbia University, New York	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Colter M. Mitchell, PhD	University of Michigan, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Kelly S. Benke, PhD	Johns Hopkins University, Baltimore, MD	Major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Erin B. Ware, PhD, MPH	University of Michigan, Ann Arbor	Designed and conceptualized the study; analyzed the data; interpreted the data; and drafted the manuscript for intellectual content

References

- Gaugler J, James B, Johnson T, Marin A, Weuve J. 2019 Alzheimer's disease facts and figures. *Alzheimers Dement* 2019;15:321–387.
- Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry* 2006;63:168–174.
- Slooter AC, Cruts M, Kalmijn S, et al. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam study. *Arch Neurol* 1998;55:964–968.
- Graff-Radford NR, Green RC, Go RCP, et al. Association between apolipoprotein E genotype and Alzheimer disease in African American subjects. *Arch Neurol* 2002;59:594–600.
- Brookmeyer R, Evans DA, Hebert L, et al. National estimates of the prevalence of Alzheimer's disease in the United States. *Alzheimers Dement* 2011;7:61–73.
- Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Abeta, tau, immunity and lipid processing. *Nat Genet* 2019;51:414–430.
- Tosto G, Bird TD, Tsuang D, et al. Polygenic risk scores in familial Alzheimer disease. *Neurology* 2017;88:1180–1186.
- Juster FT, Suzman R. An overview of the health and retirement study. *J Hum Resour* 1995;30:S7–S56.
- Langa KM, Larson EB, Crimmins EM, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Intern Med* 2017;177:51–58.
- Fisher G, Hassan H, Faul J, Rodgers W, Weir D. Health and retirement study imputation of cognitive functioning measures: 1992–2014 (final release version). Data description. 2017.
- Crimmins EM, Kim JK, Langa KM, Weir DR. Assessment of cognition using surveys and neuropsychological assessment: the health and retirement study and the aging, demographics, and memory study. *J Gerontol Ser B: Psychol Sci Soc Sci* 2011;66B:i162–i171.
- Ware EB, Schmitz LL, Gard A, Faul J. HRS Polygenic Scores: Release 2. Ann Arbor: University of Michigan Survey Research Center; 2018.
- The Genomes Project C, Auton A, Abecasis GR, et al. A global reference for human genetic variation. *Nature* 2015;526:68.
- Ware EB, Faul JD, Mitchell C, Bakulski KM. Considering the APOE locus in polygenic scores for Alzheimer's disease. medRxiv 2019:2019.2012.2010.19014365.
- Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MMB. Relation between smoking and risk of dementia and Alzheimer disease. The Rotterdam Study. *Neurology* 2007;69:998–1005.
- Xu W, Wang H, Wan Y, et al. Alcohol consumption and dementia risk: a dose-response meta-analysis of prospective studies. *Eur J Epidemiol* 2017;32:31–42.
- Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. *Neurology* 2005;65:892–897.
- Reitz C, Tang M-X, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 2007;64:1734–1740.
- Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol* 2004;61:661–666.
- Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. *Arch Neurol* 2004;61:1290–1293.
- Honig LS, Tang M-X, Albert S, et al. Stroke and the risk of Alzheimer disease. *Arch Neurol* 2003;60:1707–1712.
- Bugliari D, Campbell N, Chan C, et al. RAND HRS Data Documentation, Version P. Philadelphia: RAND Center for the Study of Aging; 2016.
- Zahodne LB, Nowinski CJ, Gershon RC, Manly JJ. Depressive symptoms are more strongly related to executive functioning and episodic memory among African American compared with non-Hispanic White older adults. *Arch Clin Neuropsychol* 2014;29:663–669.
- Logue MW, Panizzon MS, Elman JA, et al. Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. *Mol Psychiatry* 2019;24:421.
- Escott-Price V, Sims R, Bannister C, et al. Common polygenic variation enhances risk prediction for Alzheimer's disease. *Brain* 2015;138:3673–3684.
- Harris SE, Davies G, Luciano M, et al. Polygenic risk for Alzheimer's disease is not associated with cognitive ability or cognitive aging in non-demented older people. *J Alzheimers Dis* 2014;39:565–574.
- Mormino EC, Sperling RA, Holmes AJ, et al. Polygenic risk of Alzheimer disease is associated with early- and late-life processes. *Neurology* 2016;87:481–488.
- Verhaaren BFJ, Vernooij MW, Koudstaal PJ, et al. Alzheimer's disease genes and cognition in the nondemented general population. *Biol Psychiatry* 2013;73:429–434.
- Carrasquillo MM, Crook JE, Pedraza O, et al. Late-onset Alzheimer's risk variants in memory decline, incident mild cognitive impairment, and Alzheimer's disease. *Neurobiol Aging* 2015;36:60–67.
- Chouraki V, Reitz C, Maury F, et al. Evaluation of a genetic risk score to improve risk prediction for Alzheimer's disease. *J Alzheimers Dis* 2016;53:921–932.
- Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: development and validation of a polygenic hazard score. *PLoS Med* 2017;14:e1002258.
- Tan CH, Fan CC, Mormino EC, et al. Polygenic hazard score: an enrichment marker for Alzheimer's associated amyloid and tau deposition. *Acta Neuropathol* 2018;135:85–93.
- Cruchaga C, Del-Aguila JL, Saef B, et al. Polygenic risk score of sporadic late-onset Alzheimer's disease reveals a shared architecture with the familial and early-onset forms. *Alzheimers Dement* 2018;14:205–214.
- Escott-Price V, Myers AJ, Huentelman M, Hardy J. Polygenic risk score analysis of pathologically confirmed Alzheimer disease. *Ann Neurol* 2017;82:311–314.
- Lupton MK, Strike L, Hansell NK, et al. The effect of increased genetic risk for Alzheimer's disease on hippocampal and amygdala volume. *Neurobiol Aging* 2016;40:68–77.
- Adams HH, de Bruijn RF, Hofman A, et al. Genetic risk of neurodegenerative diseases is associated with mild cognitive impairment and conversion to dementia. *Alzheimers Dement* 2015;11:1277–1285.
- Marden JR, Mayeda ER, Walter S, et al. Using an Alzheimer disease polygenic risk score to predict memory decline in Black and White Americans over 14 years of follow-up. *Alzheimer Dis Assoc Disord* 2016;30:195–202.
- Martin AR, Gignoux CR, Walters RK, et al. Human demographic history impacts genetic risk prediction across diverse populations. *Am J Hum Genet* 2017;100:635–649.
- Rosenberg NA, Edge MD, Pritchard JK, Feldman MW. Interpreting polygenic scores, polygenic adaptation, and human phenotypic differences. *Evol Med Public Health* 2019;2019:26–34.
- Mostafavi H, Harpak A, Conley D, Pritchard JK, Przeworski M. Variable prediction accuracy of polygenic scores within an ancestry group. bioRxiv 2019:629949.
- Gianattasio KZ, Wu Q, Glymour MM, Power MC. Comparison of methods for algorithmic classification of dementia status in the health and retirement study. *Epidemiology* 2019;30:291–302.

42. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry* 1998;55:809–815.
43. Weuve J, Proust-Lima C, Power MC, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimers Dement* 2015;11:1098–1109.
44. De Jager PL, Chibnik LB, Cui J, et al. Integration of genetic risk factors into a clinical algorithm for multiple sclerosis susceptibility: a weighted genetic risk score. *Lancet Neurol* 2009;8:1111–1119.
45. Pihlstrom L, Morset KR, Grimstad E, Vitelli V, Toft M. A cumulative genetic risk score predicts progression in Parkinson's disease. *Mov Disord* 2016;31:487–490.
46. Tikkanen E, Havulinna AS, Palotie A, Salomaa V, Ripatti S. Genetic risk prediction and a 2-stage risk screening strategy for coronary heart disease. *Arterioscler Thromb Vasc Biol* 2013;33:2261–2266.
47. Duncan L, Shen H, Gelaye B, et al. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat Commun* 2019;10:3328.
48. Martin AR, Kanai M, Kamatani Y, Okada Y, Neale BM, Daly MJ. Clinical use of current polygenic risk scores may exacerbate health disparities. *Nat Genet* 2019;51:584–591.
49. Chasioti D, Yan J, Nho K, Saykin AJ. Progress in polygenic composite scores in Alzheimer's and other complex diseases. *Trends Genet* 2019;35:371–382.

Neurology[®] Genetics

Cumulative Genetic Risk and *APOE* $\epsilon 4$ Are Independently Associated With Dementia Status in a Multiethnic, Population-Based Cohort

Kelly M. Bakulski, Harita S. Vadari, Jessica D. Faul, et al.

Neurol Genet 2021;7;

DOI 10.1212/NXG.0000000000000576

This information is current as of March 5, 2021

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.



Updated Information & Services	including high resolution figures, can be found at: http://ng.neurology.org/content/7/2/e576.full.html
References	This article cites 44 articles, 4 of which you can access for free at: http://ng.neurology.org/content/7/2/e576.full.html##ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Alzheimer's disease http://ng.neurology.org/cgi/collection/alzheimers_disease Association studies in genetics http://ng.neurology.org/cgi/collection/association_studies_in_genetics Cognitive aging http://ng.neurology.org/cgi/collection/cognitive_aging Cohort studies http://ng.neurology.org/cgi/collection/cohort_studies MCI (mild cognitive impairment) http://ng.neurology.org/cgi/collection/mci_mild_cognitive_impairment
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://ng.neurology.org/misc/about.xhtml#permissions
Reprints	Information about ordering reprints can be found online: http://ng.neurology.org/misc/addir.xhtml#reprintsus

Neurol Genet is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.

