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RESEARCH ARTICLE

A novel neuroimaging signature for ADRD risk stratification in the community

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Abstract

INTRODUCTION: Early risk stratification for clinical dementia could lead to preventive therapies. We identified and validated a magnetic resonance imaging (MRI) signature for Alzheimer's disease (AD) and related dementias (ARDR).

METHODS: An MRI ADRD signature was derived from cortical thickness maps in Framingham Heart Study (FHS) participants with AD dementia and matched controls. The signature was related to the risk of ADRD and cognitive function in FHS. Results were replicated in the University of California Davis Alzheimer's Disease Research Center (UCD-ADRC) cohort.

RESULTS: Participants in the bottom quartile of the signature had more than three times increased risk for ADRD compared to those in the upper three quartiles ($P < 0.001$). Greater thickness in the signature was related to better general cognition ($P < 0.01$) and episodic memory ($P = 0.01$). Results replicated in UCD-ADRC.

DISCUSSION: We identified a robust neuroimaging biomarker for persons at increased risk of ADRD. Other cohorts will further test the validity of this biomarker.

KEYWORDS
Alzheimer's disease, biomarker, dementia, epidemiology, neuroimaging, risk prediction

1 | BACKGROUND

An increasing segment of the population in the United States is becoming older and more diverse,[1–4] demanding precision medicine approaches to reduce the impending public health burden of late-onset dementia. Our understanding of the multiple life-course contributing risk factors to dementia,[5–7] even dementia clinically attributable to Alzheimer's disease (AD), is evolving to recognize mixed underlying pathologies, particularly among community-based samples[8–11] and across diverse races/ethnicities.[12,13] Furthermore, systematic analyses

of various pathologies suggest an even more complex relationship between any specific pathology and future cognitive decline.[11,14]

Brain magnetic resonance imaging (MRI)–derived measures are suitable, non-invasive biomarkers associated with various degenerative neuropathologies[15,16] that can be applied to large at-risk populations. Several previous attempts have been made at creating a structural imaging signature to identify persons at risk of clinical AD. Early approaches used a guided selection of specifically vulnerable regions that differed between AD and cognitively normal individuals.[17] Such a "signature approach" encompasses exploratory, data-driven methods for selecting brain features most strongly associated with the outcome of interest that generally differentiates cognitively normal from demented individuals. These methods vary from the use of brain voxel locations or regions of interest.[18] Feature selection techniques include machine learning,[18] voxel aggregation into signature regions,[17] and systematic testing and selection from a list of regions of interest.[19] Efforts of these methods differ from classification into discrete categories to predicting continuous outcomes. A recent review of deep learning methods finds excellent discrimination between cognitively normal and AD cohorts.[20] Most of these studies, however, have used highly selected clinical samples, emphasizing the detection of AD pathology as the primary driver of dementia. Such an approach will not necessarily generalize to the diverse US population, which is more likely to have multiple pathologies contributing to dementia,[8] particularly for non-White individuals for whom non-AD pathologies may be more common.[12,13]

In this work, we aimed to identify and validate a brain MRI AD and related dementias (ADRD) signature that can predict the development of clinical dementia, including the AD phenotype, in the community based on data from the Framingham Heart Study (FHS). We further replicate our results in a diverse community-based sample[21] from the University of California Davis Alzheimer's Disease Research Center (UCD-ADRC).

RESEARCH IN CONTEXT

1. **Systematic review**: The literature review included traditional sources (e.g., PubMed). Brain magnetic resonance imaging–derived biomarkers are suitable for the identification of persons at risk of dementia. However, most current approaches have used selected clinical samples and are unlikely to generalize to diverse populations as they present with multiple pathologies contributing to dementia. Relevant references are cited.
2. **Interpretation**: Our work led to the identification of a cortical signature biomarker strongly associated with incident all-cause and Alzheimer's disease (AD) dementia in a well-characterized community cohort. Results were replicated in an independent and more diverse cohort.
3. **Future directions**: The present work developed a robust neuroimaging marker of AD and related dementias for stratification of persons at risk of dementia, which will be important to assess in other populations. Additional work is warranted to identify risk and protective factors associated with differences in the cortical thickness of this region.

2 | METHODS

2.1 | Study design

A flowchart of the study design is presented in Figure 1. Our development and testing samples were derived from FHS. Briefly, the FHS is an ongoing population-based, longitudinal cohort study initiated in 1948 to prospectively investigate the risk factors associated with cardiovascular disease. It gathers data on a comprehensive range of biological and lifestyle risk factors and cardiovascular, neurological, and other disease outcomes across three generations of participants. The original cohort enrolled 5209 women and men from Framingham, Massachusetts, and participants have been under continuous surveillance through biennial examinations assessing medical, physical, and laboratory measures.[22] In 1971, 5214 children of the original cohort and their spouses were enrolled in the study. These participants, referred as the offspring cohort, have undergone similar examinations to the original cohort, every 4 to 6 years.[23] We included participants from the original and offspring cohorts who completed an MRI at the 26th and 7th examination cycles, respectively.

Our replication sample included participants from the UCD-ADRC.[21] The UCD-ADRC cohort was initiated in 2000 to enroll participants aged ≥ 60 years from diverse race/ethnic backgrounds in the East Bay and Sacramento areas of Northern California, with the aim of maximizing sample heterogeneity in education and cognitive function to better understand the risk factors that influence onset and trajectories of cognitive impairment.[21] This cohort has been evaluated an average of $5.6 \pm 3.3^{2-16}$ times over $5.6 \pm 4.0^{1-17}$ years with clinical, neuroimaging, and cognitive assessments. All participants signed an informed consent. For this study, we included participants who underwent brain MRI examination at their initial visit with an average time between visit and MRI of 0.09 ± 0.11 years. The study is overseen by the institutional review board of the UCD.

2.2 | Neuroimaging examination

2.2.1 | FHS

The methods for brain MRI examination have been described before.[24] Participants underwent neuroimaging by a variety of MRI machines varying in field strength, from 1T to 1.5T. Imaging data were transferred to a central location for processing and analyzed by operators who were blinded to clinical characteristics at the Imaging of Dementia and Aging Laboratory directed by Dr. DeCarli at the UCD.

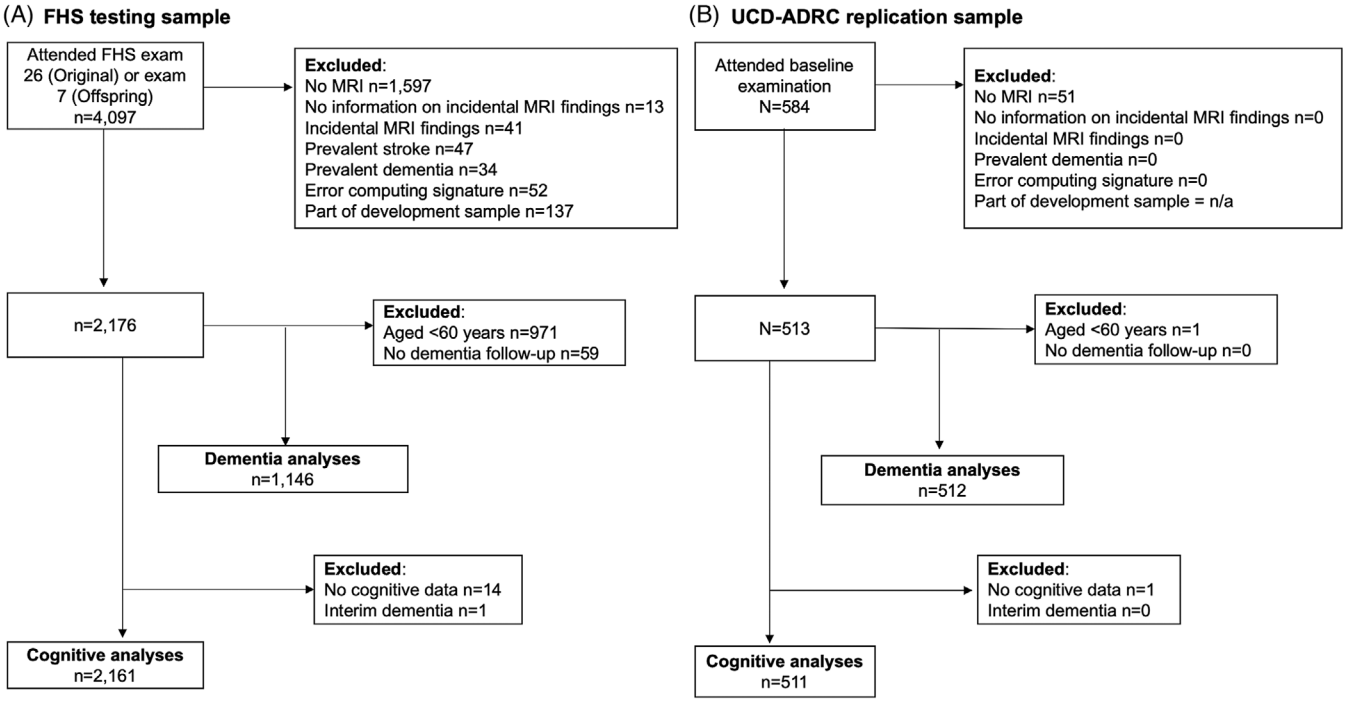

FIGURE 1 Study design flowchart. FHS, Framingham Heart Study; MRI, magnetic resonance imaging; UCD-ADRC, University of California Davis Alzheimer's Disease Research Center.

2.2.2 | UCD-ADRC

All the participants in the UCD-ADRC longitudinal diversity cohort were scanned using a harmonized sequence that included high-resolution 3DT1 and fluid-attenuated inversion recovery (FLAIR) imaging. Most participants (56%) were scanned on a GE 1.5T system followed by a Siemens 3T system. A minority of participants (17%) were scanned on the Philips 1.5T platform.

2.3 | Dementia ascertainment

2.3.1 | FHS

Dementia surveillance in the FHS has been consistent throughout time in all cohorts.[25] In the original cohort, cognitive status has been monitored since 1975 with a comprehensive neuropsychological battery.[26] Participants were flagged if they scored below predefined scores on the general battery or, since 1982, education-based Mini-Mental State Examination (MMSE) cutoffs, experiencing a 3-point decline since the most recent examination, or a 5-point overall decline compared to any previous examination. Participants identified as having possible mild cognitive impairment (MCI) or being at risk for developing dementia were invited to undergo additional neurological and neuropsychological examination every year onward until either the development of dementia, or if two consecutive evaluations showed normal status, in which case they returned to baseline tracking. Additional examination was also pursued whenever memory loss symptoms were self- or family-reported, upon referral by a physician or an FHS investigator, or through annual health status updates.[27] The offspring cohort followed similar monitoring to the original cohort since 1991.[28] In addition to this tracking, a subjective memory question assessed since 1979 was used for retrospective ascertainment of cognitive status in the offspring cohort. A dementia panel including at least one neurologist and one neuropsychologist reviewed in detail each case of possible dementia. The diagnosis of dementia was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,[29] criteria, and that of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[30] Participants were required to survive for at least 6 months after the onset of symptoms.

2.3.2 | UCD-ADRC

Dementia diagnosis followed standard criteria established by the National Institute on Aging Alzheimer's Disease Research Centers,[31] which is based on a clinical assessment of the presence or absence of dementia and, when present, its severity using the Clinical Dementia Rating Scale. More recently, clinical diagnosis also incorporates the 2011 National Institute on Aging–Alzheimer's Association (NIA-AA) criteria for AD, which stipulates an etiology for both MCI and dementia.[32] Although none of the UCD-ADRC participants enrolled in the study were demented at first observation, 180 (35%) were diagnosed with MCI.

2.4 | MRI post-processing pipeline

All MRIs were processed in the IDeA laboratory using an in-house pipeline. Briefly, a convolutional neural network was used to remove non-brain elements on MRI and derive total cerebral intracranial volume (TCV).[33] Intensity non-homogeneities were removed[34] and the 3DT1 images were segmented into gray matter, white matter, and cerebrospinal fluid tissues using a Bayesian probabilistic method.[35] Cortical thickness was determined using the three-tissue segmented images using the DiReCT method.[36] FLAIR images were processed through linear co-registration to 3DT1, followed by skull removal and segmentation of white matter hyperintensities (WMH).[37] B-spline registration[38] with an age-appropriate template structural brain image[39] was performed for use in voxel-wise analysis, as reported previously.[40] To derive Dickerson's signature,[17] we used FreeSurfer v 6.0 to generate a gray matter thickness region based on previous work[41,42] aggregating eight brain regions: medial temporal gyrus, temporal pole, inferior temporal gyrus, supramarginal gyrus, superior parietal lobule, precuneus, middle frontal gyrus, and superior frontal gyrus.

2.5 | ADRD signature

For the development sample, we selected the most recent MRI (up to 2018) from 210 FHS participants in the original and offspring cohorts, 70 who had prevalent AD dementia at the time of MRI and 140 age- and sex-matched participants who were dementia free at the time of MRI. Quantification of cortical thickness for each image was performed using the DiReCT diffeomorphism-based application[36] applied to the segmented gray matter mantle in an image native space. Tissue segmentation input to the DiReCT application was generated by our in-house pipeline as described above. Native space gray matter density maps were then deformed to template space via B-spline parameters previously computed in our pipeline.

Non-parametric *t* value cluster significance computations[43] were used to generate an "unbiased" statistical region of interest (sROI), correcting for multiple comparisons over many image voxels while simultaneously aggregating voxel between-group comparisons into significant clusters. The *t* value significant clusters are computed from tests of the null hypothesis of no relation between outcome and individual voxel brain measures. If the null hypothesis is true, then permuting the association between brain image and clinical diagnosis should generate maximal associated cluster sizes of voxels of similar volume to those of the actual regressions when aggregated over the image.[43] To compute these significant clusters, we performed 10,000 iterations, randomly permuting clinical diagnosis under the assumption of a null association. We retained clusters from the original regressions whose size was in the top fifth percentile of the size distribution. We performed this analysis at separate *t* thresholds in the range from 3.0 to 6.5 with increments of 0.5. This is useful for delineating the regions of significant association at variable association strengths.[42] These levels are displayed in Figure 2. For simplicity in the analyses of group differences, however, our sROI consisted of all clusters at $t \geq 3.0$.[44]

The computed ADRD signature ROI was then applied to compute gray matter mean densities in stroke- and dementia-free participants from the FHS (testing sample, non-overlapping with the development sample) and UCD-ADRC (replication sample) cohorts.

2.6 | Cognitive assessments

2.6.1 | FHS

A comprehensive neuropsychological battery was administered by trained staff. We considered a range of cognitive tests assessing several cognitive domains, including delayed episodic memory (Logical Memory—delayed), abstract reasoning (Similarities), and executive function (Trail Making Test Part B-Part A, TMT B-A). For interpretation purposes, TMT scores were re-signed such that higher values indicate a faster time of completion, similar to other cognitive tasks. We also derived a measure of general cognitive function using principal component analysis from distinct cognitive domains as previously described.[45]

2.6.2 | UCD-ADRC

This cohort follows the Spanish–English Neuropsychological Assessment Scales (SENAS) battery,[46] administered in English or Spanish. Psychometrically matched measures across scales and language versions were derived from item response theory to create scores representing the domains of executive function (i.e., Category Fluency, Phonemic/Letter Fluency, Digit Span Backward, Visual Span Backward, List Sorting—1 list, List Sorting—2 list) and episodic memory (i.e., Word List Learning—1, Word List Learning—2, Spatial Configuration Learning).[47]

2.7 | Statistical analysis

Analyses were performed in the testing sample from FHS and replication sample from UCD-ADRC using identical methods (Figure 1).

In our primary analysis, we used Cox proportional hazard models to assess the association between thickness in the cortical ADRD signature and incidence of all-cause and AD dementia up to 10-year follow-up in participants aged ≥ 60 years. The ADRD signature was modeled as a continuous measure (multiplied by 10 units) and by quartile categories, which compared each of the upper three quartiles to the bottom quartile (referent category) and the bottom versus upper three quartiles (referent category) to explore threshold effects. In persons with incident dementia, the follow-up time was measured in years from the MRI examination used to derive the ADRD signature and until disease onset. Persons who did not develop dementia within 10 years after the MRI examination were censored at the last date when they were known to be cognitively normal up to 10 years after their MRI or at death. Primary models were adjusted for age and sex. Secondary models were additionally adjusted for other brain MRI markers of

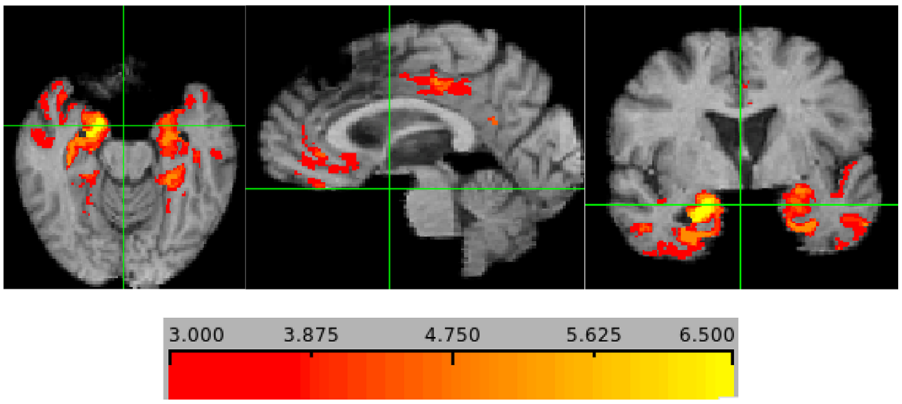

FIGURE 2 Strengths of significant association (regression *t* values) for gray matter thickness in Alzheimer's disease (AD) dementia cases versus cognitively healthy controls after accounting for multiple comparisons. Cluster masks significantly associated with AD versus normal cognition were computed separately for thresholds of *t* values from 3 to 6.5, in increments of 0.5. This highlights areas of differing but significant association strengths. However, gray matter density means over the $t \geq 3$ cluster were used for the analyses.

dementia, including total brain volume, hippocampal volume, and white matter hyperintensities, all expressed as the percentage of intracranial volume. Analyses were repeated with clinically consistent AD dementia as the outcome. Additional analyses examined the cross-sectional association between the ADRD signature and cognitive function in dementia-free participants using linear regression models adjusting for age, sex, and education, without age restrictions.

To further compare the performance of our ADRD signature with existing neuroimaging predictors of dementia, we performed a head-to-head comparison with Dickerson's cortical signature,[17] cortical thickness, and hippocampal volume. Cox proportional hazard models were used to assess the association between neuroimaging predictors and risk of all-cause or AD dementia in the FHS sample using the same analytical strategy as described above. The *C* statistic was also derived to quantify the predictive discrimination of neuroimaging predictors.

Finally, we performed additional exploratory analyses to contextualize our results. First, we analyzed a subsample of the UCD-ADRC sample to explore the utility of the cortical ADRD signature in predicting conversion to all-cause and AD dementia among participants with MCI. Second, we performed stratified analyses by race/ethnicity in UCD-ADRC to assess generalizability. Third, we related apolipoprotein E (*APOE*) genotype (presence of at least one $\varepsilon 4$ allele vs. none) to the ADRC signature to determine potential genetic predisposition to atrophy patterns characteristic of our ADRD signature. Fourth, we tested for interactions between the ADRD signature and sex on dementia and cognitive outcomes, and further performed sex-stratified analyses. Significant interactions were set at $P < 0.1$. Significant results for other analyses were set at $P < 0.05$.

3 | RESULTS

3.1 | Participants' characteristics

Table 1 describes the samples included at each stage in the study. At baseline, the FHS testing sample included 1146 participants (mean age 70.1 ± 7.2 years, 53% women); the UCD-ADRC replication sample included 513 participants (mean age 74.7 ± 6.8 years, 61% were women).

3.2 | Validation and replication of the ADRD signature in independent samples

Table 2 presents association results between the ADRD signature and incident all-cause and AD dementia. In our primary analysis adjusting for age and sex, every 10th of a point increase in thickness in the AD dementia ROI signature was significantly associated with a 20% and 21% reduced risk of all-cause and AD dementia, respectively, in FHS (all-cause dementia hazard ratio [HR] = 0.80 [95% confidence interval (CI) 0.75–0.85], $P < 0.001$; AD dementia HR = 0.79 [95% CI 0.73–0.85], $P < 0.001$). Results were consistently replicated in UCD-ADRC (all-cause dementia HR = 0.74 [95% CI 0.70–0.78], $P < 0.001$; AD dementia HR = 0.73 [95% CI 0.68–0.77], $P < 0.001$). Modeled as a categorical variable, we observed an overall lower risk for all-cause and AD dementia in each of the upper quartiles of the ADRD signature compared to the bottom quartile. These results were significant in both samples and slightly stronger in UCD-ADRC. Finally, we observed > 3-fold increased risk of all-cause (HR = 3.38 [95% CI 2.21–5.16], $P < 0.001$) and AD dementia (HR = 3.35 [95% CI 2.04–5.50], $P < 0.001$) in FHS participants within the lowest ADRD signature quartile, compared to those in the upper three quartiles. Replication results were slightly stronger in UCD-ADRC, with > 5-fold increased risk of all-cause (HR = 5.09 [95% CI 3.52–7.37], $P < 0.001$) and AD dementia (HR = 5.89 [95% CI 3.92–8.85], $P < 0.001$). Kaplan–Meier curves further show incident rates for all-cause and AD dementia for participants in the bottom versus upper three quartiles of the ADRD signature (Figure 3).

In secondary models, additional adjustment by hippocampal and WMH volumes decreased the magnitude of the HRs, but associations remained largely significant, indicating the ADRD signature ROI's predictive power for all-cause and AD dementia goes beyond these classic MRI markers.

TABLE 1 Participants' characteristics.

	FHS			
	Development sample	Dementia sample (testing)	Cognition sample (testing)	UCD-ADRC (replication)
All-dementia/AD/N[a]	70/70/210	95/69/1146	0/0/2161	130/108/513
Age at MRI, mean (± SD)	82.4 (± 7.7)	70.1 (± 7.2)	62.5 (± 10.2)	74.7 ± 6.8
Women, *n* (%)	126 (60.0%)	612 (53.4%)	1172 (54.2%)	311(61%)
APOE ε4 (≥1 ε4 allele), *n* (%)	52 (25.2%)	224 (20.3%)	435 (21.0%)	188 (38.5%)
Education, *n* (%)				
Less than high school	33 (15.7%)	65 (5.7%)	80 (3.7%)	87(17%)
High school	77 (36.7%)	377 (32.9%)	612 (28.3%)	99(19%)
Some college	51 (24.3%)	342 (29.8%)	639 (29.5%)	109(21%)
College	49 (23.3%)	362 (31.6%)	832 (38.5%)	218(42%)
Race, *n* (%)				
White	100%	100%	100%	248(48%)
Black	0%	0%	0%	119(23%)
Other	0%	0%	0%	29 (5.7%)
Hispanic ethnicity, *n* (%)	1 (0.5%)	5 (0.4%)	7 (0.3%)	117 (22.8%)
MRI markers				
ADRD signature ROI, cm^2	1.82 ± 0.38	2.20 ± 0.26	2.25 ± 0.25	2.18 ±0.33
Dickerson's signature, cm^2		1.55 ± 0.19	1.57 ± 0.17	1.47 + 0.22
Cortical thickness, cm^2		1.50 ± 0.17	1.53 ± 0.17	1.49 ± 0.21
Hippocampal volume, cm^3		6.52 ± 0.73	6.63 ± 0.74	6.1 ± 0.79
Total brain volume, cm^3		944.71 ± 99.11	970.02 ± 103.67	896.08 ± 92.31
WMH volume, cm^3		0.92 [0.47–2.00]	0.68 [0.32–1.20]	6.23 [2.60–13.61]
Cognitive measures[b]				
Executive function			0.33 [−0.06, 0.62]	−0.03 ± 0.64
Episodic memory			0.14 ± 0.89	−0.16 ± 0.90
General cognition			0.18 ± 0.85	

Abbreviations: ADRD, Alzheimer's disease and related dementias; *APOE*, apolipoprotein E; FHS, Framingham Heart Study; MRI, magnetic resonance imaging; ROI, region of interest; SD, standard deviation; UCD-ADRC, University of California Davis Alzheimer's Disease Research Center; WMH, white matter hyperintensity.

[a]Development sample reflects prevalent cases, testing, and replication samples incident cases.

[b]Represents standardized values in each cohort.

3.3 | Associations between the ADRD signature and cognitive function

In line with the results described above, we observed significant associations between the ADRD signature and cognitive function in primary models adjusted for age, sex, and education in a younger sample from FHS (Table 3). Greater thickness in the ADRD signature ROI was cross-sectionally associated with better measures of episodic memory (Beta ± standard error, 0.02 ± 0.01, $P = 0.011$) and general cognitive function (0.02 ± 0.01, $P = 0.009$). In the older UCD-ADRC cohort, we observed significant associations for greater thickness in the ADRD signature ROI with better episodic memory (0.08 ± 0.01, $P < 0.001$) and executive function (0.03 ± 0.01, $P < 0.001$). Modeled as a categorical variable, having a cortical thickness in the bottom quartile of the ADRD signature was associated with poorer episodic memory and executive function in UCD-ADRC, and poorer general cognitive function in FHS, compared to those in the upper three quartiles. Additional adjustment for MRI markers in secondary models led to similar results.

3.4 | Head-to-head comparison of dementia neuroimaging markers

When modeled continuously, higher values for all the neuroimaging markers were significantly associated with a decreased risk of all-cause and AD dementia (risk reduction ranging from 8% to 21% and 11% to 22%, respectively) independent of age and sex (Table 4). More striking differences in effect estimates were observed when

TABLE 2 Association between the cortical AD signature and 10-year risk of all-cause and AD dementia.

	FHS validation sample			UCD-ADRC replication sample		
	Cases/N	HR [95% CI]	*P* value	Cases/N	HR [95% CI]	*P* value
All-cause dementia						
Model 1						
ADRD signature/10	94/1146	0.80 [0.75–0.85]	<0.001	130/513	0.74 [0.70–0.78]	<0.001
ADRD signature, quartiles						
Q1 (referent)	56/286	1.0		69/128	1.0	
Q2	17/287	0.38 [0.22–0.66]	<0.001	31/128	0.33 [0.22–0.51]	<0.001
Q3	10/287	0.25 [0.12–0.49]	<0.001	21/129	0.21 [0.12–0.35]	<0.001
Q4	11/286	0.25 [0.13–0.49]	<0.001	9/128	0.07 [0.03–0.14]	<0.001
Q2–4 (referent)	38/860	1.0		61/385	1.0	
Q1	56/286	3.38 [2.21–5.16]	<0.001	69/128	5.09 [3.52–7.37]	<0.001
Model 2						
ADRD signature/10	93/1122	0.89 [0.83–0.96]	0.002	130/512	0.78 [0.73–0.83]	<0.001
ADRD signature, quartiles						
Q1 (referent)	55/275	1.0			1.0	
Q2	17/279	0.55 [0.31–0.98]	0.042	69/128	0.46 [0.29–0.72]	<0.001
Q3	10/284	0.40 [0.20–0.81]	0.011	31/128	0.30 [0.18–0.52]	<0.001
Q4	11/284	0.46 [0.23–0.92]	0.028	21/129	0.10 [0.05–0.20]	<0.001
Q2–4 (referent)	38/847	1.0		9/128	1.0	
Q1	55/275	2.09 [1.33–3.29]	0.002	61/385	3.48 [2.33–5.21]	<0.001
Alzheimer's disease dementia						
Model 1						
ADRD signature/10	69/1146	0.79 [0.73–0.85]	<0.001	108/513	0.73 [0.68–0.77]	<0.001
ADRD signature, quartiles						
Q1 (referent)	42/286	1.0		61/128	1.0	
Q2	11/287	0.35 [0.18–0.68]	0.002	22/128	0.27 [0.16–0.44]	<0.001
Q3	9/287	0.32 [0.15–0.66]	0.002	18/129	0.20 [0.12–0.35]	<0.001
Q4	7/286	0.23 [0.10–0.51]	<0.001	7/128	0.06 [0.03–0.14]	<0.001
Q2–4 (referent)	27/860	1.0		47/385	1.0	
Q1	42/286	3.35 [2.04–5.50]	<0.001	61/128	5.89 [3.92–8.85]	<0.001
Model 2						
ADRD signature/10	69/1122	0.89 [0.81–0.97]	0.006	108/512	0.77 [0.71–0.82]	<0.001
ADRD signature, quartiles						
Q1 (referent)	42/275	1.0		61/128	1.0	
Q2	11/279	0.52 [0.26–1.05]	0.066	22/128	0.37 [0.22–0.62]	<0.001
Q3	9/284	0.52 [0.25–1.11]	0.093	18/129	0.29 [0.16–0.52]	<0.001
Q4	7/284	0.43 [0.19–1.01]	0.054	7/128	0.09 [0.04–0.20]	<0.001
Q2–4 (referent)	27/847	1.0		47/385	1.0	
Q1	42/275	2.01 [1.18–3.43]	0.010	61/128	4.06 [2.60–6.34]	<0.001

Abbreviations: AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; CI, confidence interval; FHS, Framingham Heart Study; HR, hazard ratio; MRI, magnetic resonance imaging; UCD-ADRC, University of California Davis Alzheimer's Disease Research Center.

Model 1: Adjusted for age and sex.

Model 2: Adjusted for age, sex, and MRI markers (i.e., total brain volume, hippocampal volume, and white matter hyperintensities) expressed as the percentage of intracranial volume.

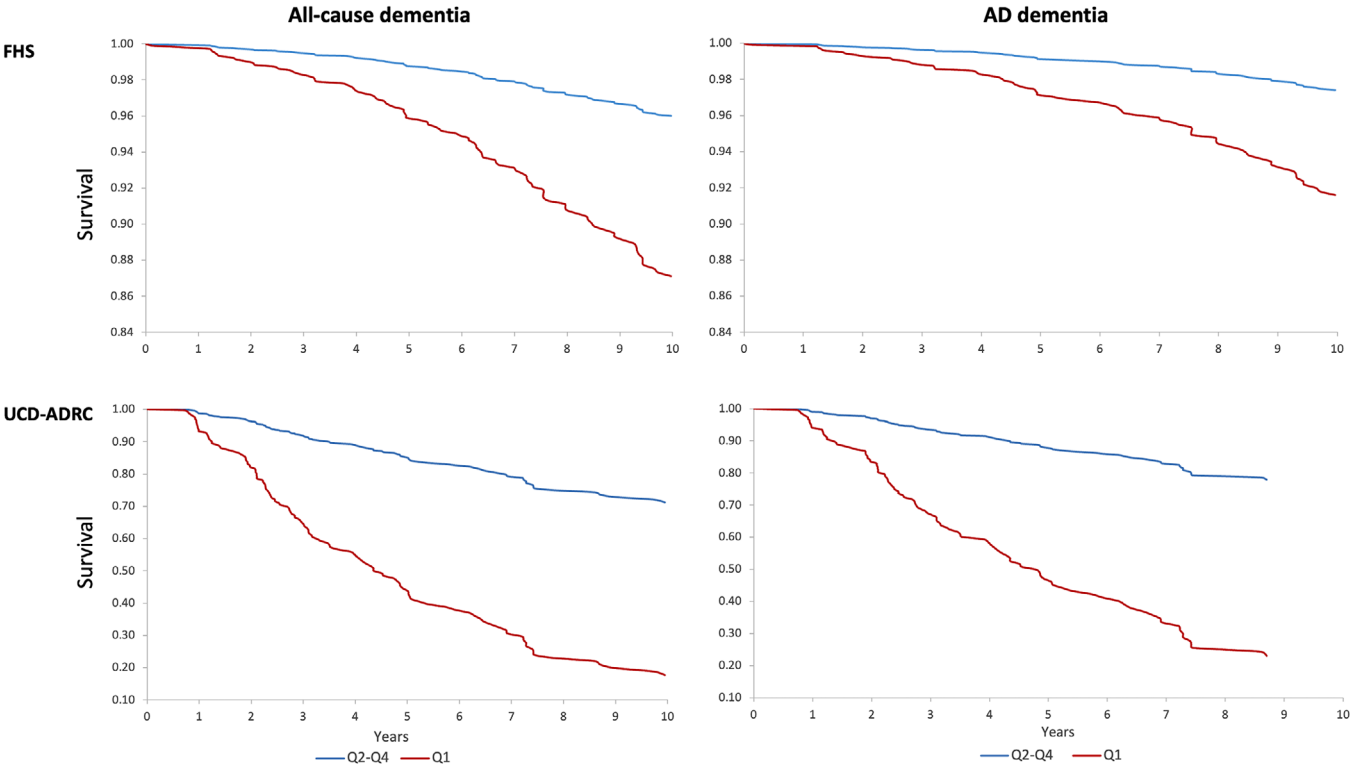

FIGURE 3 Kaplan–Meier curves showing rates for AD dementia and all-cause dementia by ADRD signature classification (Q1 vs. Q2-Q4). AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; FHS, Framingham Heart Study; UCD-ADRC, University of California Davis Alzheimer's Disease Research Center

neuroimaging markers were modeled categorically. Participants in the bottom quartile of Dickerson's signature, cortical thickness, and hippocampal volume were almost twice as likely to develop all-cause dementia compared to those in the upper three quartiles, whereas the same classification based on our ADRD signature predicted a > 3-fold risk. Similar results were observed for AD dementia. Secondary models additionally accounting for other MRI measures revealed that only associations for the ADRD signature remained significant. Finally, the ADRD signature showed higher or equivalent *C* statistic values (but not lower) compared to other neuroimaging predictors.

3.5 | Exploratory analyses

A subanalysis among UCD-ADRC participants with MCI revealed that every 10th of a point increase in thickness in the AD dementia ROI signature was significantly associated with a 13% reduced risk of conversion to all-cause dementia (HR = 0.87 [95% CI 0.81–0.93], $P < 0.001$) and 16% reduced risk of conversion to AD dementia (HR = 0.84 [95% CI 0.78–0.90], $P < 0.001$) independent of age and sex. Further, participants in the lowest ADRD signature quartile were twice as likely to convert to all-cause dementia (HR = 2.0 [95% CI 1.3–3.0], $P < 0.001$) and more than twice as likely to convert to AD dementia (HR = 2.5 [95% CI 1.6–3.9], $P < 0.001$), compared to those in the upper three quartiles. Results were significant although decreased in magnitude after additional adjustment for MRI markers (Table S1 in supporting information).

Stratified analyses by race/ethnicity in the UCD-ADRC sample showed overall similar effect estimates between non-Hispanic White and Black participants for the primary models, especially for AD dementia (Table S2 in supporting information). Observed associations between the ADRD signature and all-cause or AD dementia risk among Black participants were significant. Although following the same direction, the effect estimates observed in Hispanic participants tended to be weaker and most were borderline significant, likely because this group contributed the smaller number of cases (14 all-cause, 9 AD dementia).

Additionally, we observed no significant associations between the presence of at least one *APOE* ε4 allele and the ADRD signature in either the FHS or the UCD-ADRC cohorts (Table S3 in supporting information).

Finally, we found significant interactions between the ADRD signature and sex on incident all-cause dementia and cognitive function, although these were not consistent across cohorts. For instance, men in the bottom quartile of the ADRD signature had a > 5-fold increase in all-cause dementia risk, versus a 2-fold risk among women, but only in FHS. Further, being in the bottom quartile of the ADRD signature was related to poorer episodic memory among women in FHS, whereas the ADRD signature was related to poorer executive function among men in UCD-ARDC. Sex-specific differences are presented in Tables S4 and S5 in supporting information.

TABLE 3 Cross-sectional association between the cortical ADRD signature and cognitive function.

	FHS validation sample			UCD-ADRC replication sample		
Cognitive outcomes[a]	***N***	**Beta ± SE**	***P* value**	***N***	**Beta ± SE**	***P* value**
Episodic memory						
Model 1						
ADRD signature/10	2157	0.02 ± 0.01	0.011	512	0.08 ± 0.01	<0.001
ADRD signature, Q1 vs. Q2–4	2157	−0.06 ± 0.04	0.147	512	−0.66 ± 0.08	<0.001
Model 2						
ADRD signature/10	2126	0.02 ± 0.01	0.013	511	0.05 ± 0.01	<0.001
ADRD signature, Q1 vs. Q2–4	2126	−0.06 ± 0.04	0.159	511	−0.45 ± 0.08	<0.001
Executive function						
Model 1						
ADRD signature/10	2135	0.00 ± 0.01	0.895	512	0.03 ± 0.01	<0.001
ADRD signature, Q1 vs. Q2–4	2135	−0.04 ± 0.03	0.297	512	−0.26 ± 0.06	<0.001
Model 2						
ADRD signature/10	2105	−0.01 ± 0.01	0.136	511	0.03 ± 0.01	<0.001
ADRD signature, Q1 vs. Q2–4	2105	0.01 ± 0.03	0.743	511	−0.23 ± 0.06	<0.001
General cognitive function						
Model 1						
ADRD signature/10	2124	0.02 ± 0.01	0.009			
ADRD signature, Q1 vs. Q2-4	2124	−0.12 ± 0.03	<0.001			
Model 2						
ADRD signature/10	2095	0.01 ± 0.01	0.304			
ADRD signature, Q1 vs. Q2–4	2095	−0.08 ± 0.04	0.023			

Model 1: adjusted for age, sex, and educational attainment.
Model 2: adjusted for age, sex, educational attainment, and MRI markers (i.e., total brain volume, hippocampal volume, and white matter hyperintensities) expressed as the percentage of intracranial volume.
[a]Cognitive outcomes were modeled as standardized values.
Abbreviations: ADRD, Alzheimer's disease and related dementias; FHS, Framingham Heart Study; MRI, magnetic resonance imaging; SE, standard error; UCD-ADRC, University of California Davis Alzheimer's Disease Research Center.

4 | DISCUSSION

In the community-based study that included predominantly non-Hispanic White participants, we identified a neuroimaging biomarker strongly associated with incident all-cause and AD dementia. The signature was obtained through the application of a voxel-based permutation method designed to identify significant differences in cortical thickness from a subgroup of participants with AD dementia compared to age- and sex-matched individuals known to remain cognitively normal for at least 10 years after their MRI.

Subsequent validation and replication of this ADRD signature in two community-based cohorts proved strong associations with incident all-cause and AD dementia. When mean thickness in the ADRD signature was considered continuously, greater thickness was related to lower dementia incidence with close effect sizes in both samples. These confirmatory results further strengthen the general applicability of this finding as an MRI risk measure for incident dementia. Most associations remained despite adjustment for other MRI measures such as total brain, hippocampal, and WMH volumes in secondary analyses, supporting the unique contributions of this anatomical region to identifying individuals at risk for future dementia. Analysis of the ADRD signature by quartiles of distribution further suggested results consistent with threshold effects. We also show that the 10-year risk for dementia among individuals in the lowest quartile of the ADRD signature was increased greater than three times for the FHS cohort and nearly six times for the UCD-ADRC cohort. A higher risk in the UCD-ADRC cohort likely reflects the inclusion of participants with MCI. Individuals in the lowest ADRD signature quartile were also significantly more likely to be adjudicated a clinical dementia diagnosis compared to individuals in the higher quartiles in both cohorts. Survival estimates from parametric survival in the UCD-ADRC cohort found a 5%, 9%, 20%, and 50% likelihood of dementia incidence at 2, 3, 5, and 10 years, respectively, based on estimates for a cognitively normal, non-Hispanic White female 74.7 years of age. In summary, this "unbiased" ADRD signature is associated with both all-cause and clinical AD dementia in a large cohort of non-Hispanic White individuals, as well as a diverse cohort including Black and Hispanic adults. Stratified analyses by race/ethnicity show overall good generalizability to

TABLE 4 Head-to-head comparison of neuroimaging dementia markers in the FHS validation sample.

	Neuroimaging signatures			
	ADRD signature	**Dickerson's**	**Cortical thickness**	**Hippocampal volume**
All-cause dementia				
Model 1	94/1146	94/1146	94/1146	94/1146
Continuous				
HR [95% CI]	0.80 [0.75–0.85]	0.85 [0.77–0.94]	0.79 [0.71–0.88]	0.92 [0.89–0.96]
P value	<0.001	0.001	<0.001	<0.001
C stat [SE]	0.84 [0.02]	0.81 [0.02]	0.82 [0.02]	0.81 [0.02]
Q1 vs. Q2–4				
HR [95% CI]	3.38 [2.21–5.16]	1.83 [1.20–2.77]	1.97 [1.31–2.97]	1.57 [1.01–2.43]
P value	<0.001	0.005	0.001	0.044
C stat [SE]	0.84 [0.02]	0.81 [0.02]	0.82 [0.02]	0.81 [0.02]
Model 2	93/1122	93/1122	93/1122	93/1122
Continuous				
HR [95% CI]	0.89 [0.83–0.96]	0.93 [0.85–1.02]	0.90 [0.80–1.00]	0.98 [0.93–1.02]
P value	0.002	0.142	0.055	0.250
C stat [SE]	0.87 [0.02]	0.87 [0.02]	0.87 [0.02]	0.86 [0.02]
Q1 vs. Q2–4				
HR [95% CI]	2.09 [1.33–3.29]	1.41 [0.91–2.19]	1.48 [0.97–2.28]	0.86 [0.52–1.42]
P value	0.002	0.120	0.072	0.554
C stat [SE]	0.87 [0.02]	0.87 [0.02]	0.87 [0.02]	0.86 [0.02]
AD dementia				
Model 1	69/1146	69/1146	69/1146	69/1146
Continuous				
HR [95% CI]	0.79 [0.73–0.85]	0.84 [0.75–0.94]	0.78 [0.68–0.89]	0.89 [0.86–0.93]
P value	<0.001	0.003	<0.001	<0.001
C stat [SE]	0.87 [0.02]	0.85 [0.02]	0.85 [0.02]	0.87 [0.02]
Q1 vs. Q2–4				
HR [95% CI]	3.35 [2.04–5.50]	1.76 [1.08–2.86]	2.13 [1.32–3.42]	2.13 [1.28–3.54]
P value	<0.001	0.024	0.002	0.004
C stat [SE]	0.86 [0.02]	0.85 [0.02]	0.85 [0.02]	0.86 [0.02]
Model 2	69/1122	69/1122	69/1122	69/1122
Continuous				
HR [95% CI]	0.89 [0.81–0.97]	0.93 [0.83–1.04]	0.89 [0.78–1.01]	0.96 [0.91–1.01]
P value	0.006	0.180	0.079	0.098
C stat [SE]	0.91 [0.01]	0.90 [0.01]	0.90 [0.01]	0.90 [0.01]
Q1 vs. Q2–4				
HR [95% CI]	2.01 [1.18–3.43]	1.33 [0.80–2.21]	1.60 [0.97–2.63]	0.99 [0.56–1.75]
P value	0.010	0.269	0.065	0.969
C stat [SE]	0.91 [0.01]	0.90 [0.01]	0.91 [0.01]	0.90 [0.01]

Abbreviations: AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; CI, confidence interval; FHS, Framingham Heart Study; HR, hazard ratio; MRI, magnetic resonance imaging; SE, standard error.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, and MRI markers (i.e., total brain volume, hippocampal volume [except hippocampal signature], and white matter hyperintensities) expressed as the percentage of intracranial volume.

Black and Hispanic older adults, although larger studies need to confirm these findings due to the smaller samples included in this work, especially for Hispanics. Associations were also independent of other common AD-related measures such as age, sex, and education. It is interesting to note that no associations were observed between the *APOE ε4* genotype and the ADRD signature, suggesting little genetic predisposition to AD contributes to this phenotype. Further analyses exploring sex interactions highlighted differences between women and men, particularly when modeling the bottom quartile of the ADRD signature. However, these findings were inconsistent across cohorts, and more research on sex-specific differences is needed to confirm these findings.

A subsequent head-to-head comparison of neuroimaging markers of AD dementia showed overall stronger associations between our ADRD signature and dementia risk independent of age and sex, particularly comparing the bottom to the upper three quartiles of distribution. These associations remained significant after the inclusion of additional neuroimaging measures only for our ADRD signature, providing additional evidence of the robustness of this marker above and beyond other existing neuroimaging markers.

The anatomical distribution of the ADRD ROI is strikingly similar to that reported by Fjell et al.[48] from a longitudinal study of cognitively normal individuals that incorporated medial temporal as well as cingulate and inferior frontal regions. Although Fjell et al. believed the frontal regions reflect normal aging, distinct from AD, our data suggest that they are areas of similar vulnerability to dementia that may occur with AD or other dementia pathologies. The notion of brain structures specifically vulnerable to certain diseases has been previously reported[16,49,50] as has the notion that differences in cortical thickness could be used to distinguish AD from normal aging.[17] More recent work further suggests that this approach can be used to identify relationships between brain structure and cognitive performance within specific domains.[42] The unique aspect of this work is the a priori application to less select community-based and diverse study cohorts. Given our increasing understanding of the multiple and complex pathological processes that lead to dementia in community-based[8,10,11,14] and diverse populations,[12,13] we did not assess correlations between the ADRD signature and AD pathology (i.e., markers of amyloid and tau deposition). Such an "unbiased" ADRD signature likely identifies brain regions of common susceptibility to dementia independent of pathology,[50] and consequently, may be of greater general use to identify individuals at risk of ADRD that can be targeted for early treatments or preventive strategies.

There are multiple strengths to this study. First, participants were recruited from the community. Second, the ADRD signature was developed on a select group of participants with highly probable AD dementia compared to a select group at very low risk for dementia. Third, the resulting ROI was applied at a single time point to predict incident dementia in two non-overlapping cohorts of diverse participants. The result showed excellent predictability in both cohorts indicating that this approach could stratify persons at increased risk of ADRD in the community. This study, however, is not without some limitations. First, the FHS sample received less frequent dementia evaluations, leading to potential issues regarding interval censoring. Second, the pathological specificity of the ROI cannot be determined from this study. Future work will be required to evaluate risk and protective factors that may be associated with differences in cortical thickness of this region. Third, because of a lack of specificity, these results do not immediately translate into preventative or therapeutic targets. Further work is necessary to clarify the conditions by which this particularly vulnerable brain region is affected.

Despite these limitations, this study clearly demonstrates the utility of identifying a brain region of specific vulnerability and testing the association with incident dementia among a diverse group of individuals recruited from the community. Future work is needed to replicate these findings in other larger diverse community-based studies as well as more clearly identify potential risk factors for future therapeutic and preventive interventions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided written informed consent at each examination. The FHS protocols and participant consent forms were approved by the institutional review board of Boston University School of Medicine. The UCD-ADRC is overseen by the institutional review board of the University of California at Davis.

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SUPPORTING INFORMATION

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

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