Title

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Journal

Alzheimers & Dementia: The Journal of the Alzheimers Association, 20(12)

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Publication Date

2024-12-01

DOI

10.1002/alz.14345

Peer reviewed

Received: 13 April 2024 | Revised: 18 September 2024 | Accepted: 21 September 2024

DOI: 10.1002/alz.14345

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Biological validation of peak-width of skeletonized mean diffusivity as a VCID biomarker: The MarkVCID Consortium

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Funding information
National Institute of Neurological Disorders and Stroke (NINDS), Grant/Award Numbers: U24NS100591, UH2NS100599, UH2NS100605, UH2NS100588, UH2NS100608, UH2NS100606, UH2NS100598, UH2NS100614, U01NS125513

Abstract

BACKGROUND: Peak-width of skeletonized mean diffusivity (PSMD), a neuroimaging marker of cerebral small vessel disease (SVD), has shown excellent instrumental properties. Here, we extend our work to perform a biological validation of PSMD.

METHODS: We included 396 participants from the Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID-1) Consortium and three replication samples (Cohorts for Heart and Aging Research in Genomic Epidemiology = 6172, Rush University Medical Center = 287, University of California Davis Alzheimer's Disease Research Center = 567). PSMD was derived from diffusion tensor imaging using an automated algorithm. We related PSMD to a composite measure of general cognitive function using linear regression models adjusting for confounders.

RESULTS: Higher PSMD was associated with lower general cognition in MarkVCID-1 independent of age, sex, education, and intracranial volume (Beta [95% confidence interval], −0.8 [−1.2, −0.4], $P < 0.001$). These findings were replicated in independent samples. Furthermore, PSMD explained cognitive status above and beyond white matter hyperintensities.

Alison M. Luckey and Saptaparni Ghosh contributed equally to this study.

DISCUSSION: Our biological validation work supports the pursuit of larger clinical validation studies evaluating PSMD as a susceptibility/risk biomarker of small vessel disease contributing to cognitive impairment and dementia.

KEYWORDS
biomarker, cognitive impairment, diffusion tensor imaging, peak-width of skeletonized mean diffusivity, small vessel disease, vascular contributions to cognitive impairment and dementia

Highlights

- Peak-width of skeletonized mean diffusivity (PSMD) is a novel small vessel disease neuroimaging biomarker.
- A prior instrumental validation study demonstrated that PSMD is a robust biomarker.
- This biological validation study shows that high PSMD relates to worse cognition.
- PSMD explains cognitive function above and beyond white matter hyperintensities.
- Future clinical validation will assess PSMD as a vascular contribution to cognitive impairment and dementia biomarker in clinical trials.

1 | BACKGROUND

Cerebrovascular pathology is present to varying degrees in most adults suffering from cognitive impairment.[1–4] Although the vascular contributions to cognitive impairment and dementia (VCID) are significant, it is challenging to determine the number of people impacted due to the frequent co-occurrence of VCID with other etiologies.[5–7] Advances in neuroimaging have identified a high prevalence of white matter damage in persons with VCID, leading to the consensus that slow progressive changes in the brain related to cerebral small vessel disease (SVD) are a major mechanism involved in VCID.[8,9] As life expectancy increases worldwide, the global burden of age-related cognitive impairment, including presumed vascular etiology, will rise.[10] Therefore, any intervention that alleviates the burden of VCID should be investigated.

Despite the pressing need to develop VCID biomarkers, only a few can reliably detect and track SVD changes leading to VCID, and these have yet to be approved by regulatory agencies for use in clinical trials.[6,11] Currently, the most used neuroimaging marker of SVD in epidemiological settings is white matter hyperintensities (WMH). WMH burden has been associated with a decline in memory and executive function,[12] risk of stroke,[13] mild cognitive impairment (MCI), and dementia.[13,14] However, the etiology of WMH remains undetermined, as growing research suggests they are not only of vascular origin but can be driven by Alzheimer's disease (AD)-related processes.[15,16] Although extensive research has been carried out on WMH at the population level, a rigorous and systematic biomarker validation informing an individual's risk for VCID has yet to be conducted for WMH and other SVD markers.

To address the need for VCID biomarkers, the National Institute on Neurological Disorders and Stroke (NINDS) initiated the Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID) Consortium (https://markvcid.partners.org), which aims to deliver high-quality, rigorously validated biomarkers within a defined US Food and Drug Administration category and context of use that can be incorporated into large-scale clinical AD/AD and related dementias (ADRD) clinical trials, including for VCID. MarkVCID has developed standardized protocols for multi-site enrollment, clinical and cognitive testing, handling of fluid samples,[17] and neuroimaging data acquisition.[18] The present paper describes results from the biological validation of a neuroimaging-based biomarker kit, peak-width of skeletonized mean diffusivity (PSMD), one of 11 biomarkers selected to undergo instrumental (i.e., reliability across users, sites, and time points) and biological (i.e., association with clinically meaningful aspects of VCID, such as cognition) validation in the first phase of MarkVCID (MarkVCID-1).

Diffusion tensor imaging (DTI) enables the characterization of brain white matter microstructure by taking advantage of the diffusion properties of water molecules naturally restricted by white matter fibers. PSMD is derived from two DTI central tendency metrics, mean diffusivity (MD) and fractional anisotropy (FA), in which higher and lower values reflect increased white matter fluid preceding neurodegeneration and axonal loss, respectively.[19] In contrast, PSMD is a dispersion metric derived from a histogram analysis, which adds another layer of understanding by quantitatively reflecting the heterogeneity in MD values across the voxels of the white matter skeleton. Therefore, higher PSMD values indicate greater heterogeneity, increased water dispersion, and white matter microstructural damage.[19] PSMD has been acknowledged as a novel imaging marker reflecting vascular brain injury.[20] High values of PSMD have been observed in both sporadic and monogenic forms of SVD, and to a lesser extent in neurodegenerative disease, making it attractive as a VCID biomarker.[19] Previous studies have related higher PSMD to poorer processing speed,[19,21,22]

memory,[21,22] and visuospatial function,[21] domains most often affected in patients with SVD-related cognitive impairment.[10,23] However, current knowledge is limited by a lack of diversity and relatively small sample sizes.

We have recently reported results from a comprehensive instrumental validation study demonstrating PSMD's excellent inter-rater reliability, test–retest repeatability, and inter-scanner reproducibility.[24] As the next step of biomarker development, this study aimed to (1) perform a biological validation by relating PSMD to cognitive function in the MarkVCID-1 cohort and three independent replication samples and (2) to assess whether PSMD explains cognitive function above and beyond WMH as a biomarker of SVD.

RESEARCH IN CONTEXT

1. **Systematic review**: Peak-width of skeletonized mean diffusivity (PSMD) is a novel cerebral small vessel disease marker derived from diffusion imaging with robust instrumental properties. The current study performed a biological validation to assess the association between PSMD and general cognitive function in the Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID-1) Consortium and three independent replication samples. To evaluate the biological relevance of PSMD, the authors reviewed publicly available literature using traditional sources (e.g., PubMed). References to these sources are appropriately cited.
2. **Interpretation**: Our findings suggest that higher PSMD is strongly related to lower cognitive function across diverse samples in terms of age, race/ethnicity, and education. PSMD also explained additional variation in cognitive function beyond white matter hyperintensities.
3. **Future directions**: The next step in biomarker development will focus on the clinical validation of PSMD. MarkVCID-2 will evaluate PSMD as a susceptibility/risk and disease monitoring biomarker for clinical trials of vascular contributions to cognitive impairment and dementia.

2 | METHODS

2.1 | Study design and sample

2.1.1 | MarkVCID-1 cohort

The data used in this study were acquired as part of MarkVCID-1, which consisted of seven project sites: Johns Hopkins University School of Medicine (JHU); Rush University Medical Center & Illinois Institute of Technology (RUSH/IIT); Universities of California at San Francisco, Davis, and Los Angeles (UCSF/UCD/UCLA); University of Kentucky (UKY); University of New Mexico Health Sciences Center (UNM); University of Southern California (USC); and the University of Texas Health Science Center at San Antonio (UTHSCSA, operating as part of the Cohorts for Heart and Aging Research in Genomic Epidemiology [CHARGE] consortium site); and a central coordinating center (Massachusetts General Hospital) working with the NINDS and the National Institute on Aging under cooperative agreements. A detailed description of the MarkVCID-1 protocols regarding participant enrollment, clinical assessments, and cognitive testing can be found elsewhere.[17] A brief description of the enrollment characteristics is summarized in Table S1 in supporting information.

2.1.2 | Replication cohorts

Existing data from three independent samples were used for replication. The first included CHARGE, which contributed data from four population-based cohorts: the Age Gene/Environment Susceptibility-Reykjavik (AGES),[25] the Atherosclerosis Risk in Communities (ARIC) Study,[26] the Coronary Artery Risk Development in Young Adults (CARDIA) Study,[27,28] and the Framingham Heart Study (FHS) Third Generation and Omni 2 cohorts.[29] The second and third samples included data from community-based samples from RUSH,[30–32] and the UCD Alzheimer's Disease Research Center (UCD-ADRC). A description of each sample is provided in the supporting information.

Participants from the MarkVCID-1 cohort with unstable major medical illness, major primary psychiatric disorders, prevalent stroke, or dementia at the time of the magnetic resonance imaging (MRI), or other neurological disorders that might confound the assessment of neuroimaging markers were excluded from the analysis. Similar exclusion criteria were used for the replication cohorts if this information was available; all participants were dementia- and stroke-free at baseline. Institutional review boards approved all participating studies, and study participants provided written informed consent. Details on study-specific approvals are presented in the supporting information.

2.2 | MRI acquisition

2.2.1 | MarkVCID-1

The detailed MarkVCID-1 neuroimaging protocol is described elsewhere.[18] Briefly, to accommodate for both scan time and accuracy, the diffusion-weighted imaging (DWI) protocol uses a single-shell (b = 1000 s/mm^2) and 40-direction diffusion sequence with a voxel size of 2.0 × 2.0 × 2.0 mm^3 and six b = 0 s/mm^2. The reverse polarity data were used to estimate and correct image distortions in the DTI data. T1-weighted and fluid-attenuated inversion recovery (FLAIR) sequences were used to quantify the extent of WMH in the brain. Acquisition times for these sequences were 6 and 7 minutes, respectively. The three-dimensional T1-weighted multi-echo magnetization-prepared rapid-acquisition gradient

echo (ME-MPRAGE) used a sagittal-plane acquisition, four echoes, and a voxel size of 1.0 × 1.0 × 1.0 mm^3. The high-resolution 3D-FLAIR incorporated a sagittal-plane acquisition with a voxel size of 1.0 × 1.0 × 1.0 mm^3.

2.2.2 | Replication samples

MRI scans were performed at each site separately and have been detailed previously.[24] The image acquisition protocol and segmentation methods used to derive the MRI measurements in each cohort are summarized in Table S2 in supporting information. Briefly, the magnetic field strength of the scanners used in the different studies ranged from 1.5 to 3.0 Tesla. All cohorts used a single-shell DWI acquisition, with non–b-zero values equal to 1000 s/mm^2. The reverse polarity data was used in the RUSH cohort only. CARDIA, UCD-ADRC, and RUSH used a 2 × 2 × 2 mm^3 resolution, whereas AGES, ARIC, and FHS used 1.7 × 1.7 × 3, 2.7 × 2.7 × 3, and 1.8 × 1.8 × 5 mm^3, respectively. The UCD-ADRC protocols evolved over time; the cohort was divided into two samples. The first sample (UCD-ADRC-1, n = 388) used a DWI protocol including 26 gradient directions, whereas the second sample (UCD-ADRC-2, n = 179) included 65 gradient directions.

2.3 | Estimation of PSMD and WMH

Briefly, the measurement of PSMD requires the mapping of FA, MD, radial diffusivity, and axial diffusivity. The PSMD pipeline includes the following steps: (1) linear and non-linear registration of FA volumes to the standard space FMRIB FSL 1-mm FA template, (2) creation of a white matter skeleton using Tract-Based Spatial Statistics (TBSS) in FSL,[33] (3) projection of FA data onto a skeleton derived from the standard space template thresholded at a lower-bound FA value of 0.2 to exclude predominantly non–white matter voxels,[34] (4) projection of MD volumes onto the mean FA skeleton using the FA-derived projection parameters and further thresholded with a template skeleton mask to reduce cerebrospinal fluid (CSF) partial volume contamination, (5) calculation of PSMD as the difference between the 95th and 5th percentiles of the voxel-based MD values within the participant's skeletonized MD, and (6) storage of PSMD in a text file.

The WMH kit requires three inputs: high resolution 3D T1-weighted image, a raw FLAIR image, and a binary brain mask. The algorithm, previously described,[35] returns a four-component (CSF, gray matter, white matter, and WMH) grayscale segmented image volume in the native space of the 3D T1-weighted volume along with a segmented mask of WMH. Each study used automated methods to derive WMH, either using the previously described WMH kit[24] or a similar method (AGES-Reykjavik,[36] RUSH[37]).

The PSMD and WMH biomarker kits consist of a protocol, script, and instructions. These are available on the MarkVCID-1 website (https://markvcid.partners.org/consortium-protocols-resources). It takes ≈ 12 and 90 minutes to process PSMD and WMH on a standard desktop computer, respectively. All MRIs collected by MarkVCID-1 sites were processed at UTHSCSA and UCD sites to derive PSMD and WMH.[18,24] Replication cohorts derived PSMD and WMH independently using similar procedures.

2.4 | General cognitive function

Although the MarkVCID-1 sites used the same cognitive battery based on the Uniform Data Set 3 protocol, replication cohorts administered different neuropsychological batteries. To ensure that the cognitive outcome was comparable across samples, we derived a metric of general cognitive function (g-factor) in each sample based on available cognitive tests. The derived composite score was later standardized following previous methods.[38] Briefly, the g-factor was calculated by extracting the first un-rotated principal component derived from neuropsychological tests assessing at least three distinct cognitive domains. This global composite score has been used extensively in CHARGE cohorts. The cognitive tests selected for the g-factor in each sample are detailed in Table S3 in supporting information.

2.5 | Covariates

Educational background was self-reported, and participants were divided into four groups: no high school diploma, high school diploma, some college attendance but no 4-year degree, and college degree or higher. Intracranial volume, measured in cm^3, was determined from the WMH kit[24] or with similar cohort-specific methods (refer to Table S4 in supporting information). Intracranial volume was included as a covariate per a prior finding demonstrating that total intracranial volume influences PSMD measures.[39] The time difference between MRI and neuropsychological assessment was measured in days (if not performed at the same examination). Other site-specific covariates included site, center, batch, or race/ethnicity if linked with the site.

Additional vascular risk factors were considered for secondary analyses. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medication, or a history of hypertension. Diabetes was defined as ≥ 8 hours of fasting glucose ≥ 126 mg/dL, previous history of diabetes, or use of insulin or any hypoglycemic medications. Smoking status was self-reported and defined as current smoking versus past/never.

2.6 | Statistical analysis

PSMD and WMH were naturally log-transformed to achieve normal distributions. For the MarkVCID-1 sample, data from different sites were pooled for analysis (version dated January 17, 2022). The analysis in the MarkVCID-1 cohort used generalized estimating equations (GEE) to determine the association of PSMD with the g-factor, accounting for differences in study sites. For replication cohorts, linear regression models were used to determine the association between

PSMD and the g-factor. Our primary model (Model 1) was adjusted for age at MRI examination, age^2, sex, education, intracranial volume, time difference between MRI and cognitive assessment (if applicable), and site-specific covariates (if applicable).

A secondary model (Model 2) adjusted for diabetes, smoking status, and hypertension in addition to the Model 1 covariates. This exploratory model was conceived to assess whether PSMD was related to cognition independent of classical vascular factors contributing to VCID and routinely obtained in clinical settings.

Analyses in the MarkVCID-1 and validation samples were performed independently, following a common analysis plan. For the CHARGE cohorts, each cohort was analyzed separately, and estimates were meta-analyzed using fixed-effect models as they were considered a single site for biological validation.

Finally, to investigate the contribution of PSMD to explain cognitive function above and beyond WMH, we compared the adjusted R-squared from a model including WMH as the independent variable (instead of PSMD) to the R-squared from another including both PSMD and WMH. This comparison was done in MarkVCID-1 and three additional cohorts representing the younger (FHS) and older (AGES) spectrum of participants from the CHARGE consortium, as well as in RUSH, which includes a more diverse sample. Covariate adjustments were the same as those in Model 1.

3 | RESULTS

3.1 | Participants' characteristics

The demographic and clinical characteristics of the participants in each cohort are summarized in Table 1. MarkVCID-1 included data from 396 participants across seven recruiting sites, including JHU ($n = 58$), UCSF ($n = 36$), UCD ($n = 4$), UKY ($n = 103$), UNM ($n = 48$), USC ($n = 46$), and UTHSCSA ($n = 101$). The mean age of the MarkVCID-1 sample was 71.7 ± 8 years, making this cohort older than FHS and CARDIA but younger than the other replication cohorts. The MarkVCID-1 sample included 63% women, 40% Hispanic, and 7% Black adults. Roughly 80% of MarkVCID-1 participants have graduated from college (53%) or attended some college (26%). Regarding vascular risk factors, 19% of individuals in MarkVCID-1 had diabetes, 63% had hypertension, and 36% reported current smoking.

The CHARGE sample included data from 6172 participants across four cohorts, including AGES ($n = 2568$), ARIC ($n = 1402$), CARDIA ($n = 351$), and FHS ($n = 1851$). RUSH and UCD-ADRC included data from 287 and 567 participants, respectively. The mean age of the samples in the replication cohorts ranged from 48 to 77 years; FHS had on average the youngest participants (48 ± 9 years), and RUSH and UCD-ADRC-1 had on average the oldest participants (77 ± 7 years). The population was predominately non-Hispanic White, with ARIC, CARDIA, RUSH, and UCD-ADRC contributing 21% to 61% Black participants. Hispanic participant representation ranged from 9% to 40%. The percentage of women in the replication cohorts ranged from 18% to 66%. Vascular risk factors varied widely in the replication cohorts, including the proportion of individuals with diabetes (5% to 38%), smoking (5% to 58%), and hypertension (21% to 76%).

As expected, PSMD and WMH burden values tended to increase with the age of the cohort. The median PSMD ranged from 2.2 to 4.8 10^{-4} mm^2/s, and that of WMH from 0.6 to 13.9 cm^3.

3.2 | Association between PSMD and cognition in MarkVCID-1 and replication cohorts

Association results between PSMD and general cognitive function are summarized in Table 2 for all cohorts. Our primary analysis in the MarkVCID-1 cohort showed a significant association between higher PSMD and lower cognitive function (Beta [95% confidence interval], P value], −0.8 [−1.2, −0.4], $P < 0.001$) independent of age, sex, education, and intracranial volume.

Similar results were observed in replication samples. Meta-analysis results for CHARGE cohorts showed that higher PSMD was associated with lower cognitive function (−1.0 [−1.1, −0.8], $P < 0.001$) in the primary model. Individually, all cohorts showed a consistent direction of effects (Figure S1 in supporting information). Higher PSMD values were also related to lower cognitive function in RUSH (−1.5 [−2.0, −0.9], $P < 0.001$) and UCD-ADRC samples (UCD-ARDC-1: −0.8 [−1.1, −0.5], $P < 0.001$; UCD-ARDC-2: −0.7 [−1.0, −0.4], $P < 0.001$) in primary models. Results from secondary models remained virtually unchanged after additional adjustment for vascular risk factors.

3.3 | Association between WMH and cognition in MarkVCID-1 and replication cohorts

In addition to PSMD, we further investigated the association between WMH burden and cognitive function in MarkVCID-1 and replication cohorts. Results are summarized in Table 3. We observed significant associations between higher WMH volumes and lower cognitive function in MarkVCID-1 (−0.08 [−0.15, −0.01], $P = 0.021$). These results were replicated in the CHARGE cohort (−0.07 [−0.09, −0.04], $P < 0.001$), with all individual cohorts showing a consistent direction of effects (Figure S2 in supporting information). Similar associations were found in the RUSH (−0.13 [−0.22, −0.04], $P = 0.003$) and UCD-ADRC samples (UCD-ARDC-1: −0.10 [−0.17, −0.02], $P = 0.009$; UCD-ARDC-2: −0.12 [−0.16, −0.08], $P < 0.001$). These findings remained consistent in secondary models after additional adjustments for vascular risk factors.

3.4 | Contribution of PSMD to cognitive function beyond WMH

We assessed whether PSMD could explain cognitive function above and beyond WMH in MarkVCID-1 and three additional cohorts. In MarkVCID-1, FHS, AGES, and RUSH cohorts, PSMD explained an additional 1.8%, 0.2%, 2.5%, and 4.4% of the variance in cognitive function

TABLE 1 Population characteristics in each cohort.

		CHARGE cohorts (N = 6172)					UCD-ADRC	
	MarkVCID-1	AGES	ARIC	CARDIA	FHS	RUSH	UCD-1	UCD-2
N	396	2568	1402	351	1851	287	388	179
Age, mean (SD), years	71.7 (8.0)	76.4 (5.2)	76.2 (5.3)	50.5 (3.4)	48.1 (8.9)	77.3 (6.6)	77.1 (7.2)	76.3 (7.3)
Women, N (%)	248 (62.6%)	1469 (57.2%)	860 (61.3%)	185 (52.7%)	961 (51.9%)	52 (18%)	226 (58.2%)	118 (65.9%)
Race								
Non-Hispanic White	342 (86.4%)	100%	924 (65.9%)	234 (66.7%)	1754 (94.8%)	96 (33.5%)	189 (48.7%)	90 (50.3%)
Black/African American	26 (6.6%)		478 (34.1%)	117 (33.3%)		176 (61.3%)	80 (20.9%)	39 (21.2%)
Other	28 (7.1%)				97 (5.2%)	9 (3.1%)	118 (30.4%)	51 (28.5%)
Hispanic ethnicity	158 (39.9%)					27 (9.4%)	93 (24.0%)	41 (22.9%)
Education								
Less than high school	25 (6.3%)	582 (22.7%)	209 (14.9%)	9 (2.6%)	7 (0.4%)	6 (2.2%)	59 (15.2%)	16 (8.9%)
High school diploma	58 (14.7%)	1307 (50.9%)	575 (41%)	50 (14.3%)	221 (11.9%)	38 (13.6%)	91 (23.5%)	33 (18.4%)
Some college	102 (25.8%)	404 (15.7%)	618 (44.1%)	205 (58.4%)	532 (28.7%)	71 (25.5%)	85 (21.9%)	38 (21.2%)
College	211 (53.3%)	275 (10.7%)		87 (24.8%)	1091 (58.9%)	164 (58.8%)	153 (39.4%)	92 (51.4%)
Diabetes	76 (19.2%)	275 (10.7%)	482 (34.8%)	18 (5.2%)	91 (4.9%)	53 (18%)	149 (38.4%)	48 (26.8%)
Smoking	143 (36.1%)	1477 (57.5%)	73 (5.2%)	131 (37.3%)	154 (8.3%)	111 (39%)	–	–
Hypertension	249 (62.9%)	1619 (63.1%)	1065 (76%)	75 (21.4%)	402 (21.7%)	200 (70%)	296 (76.3%)	107 (59.8%)
Time difference between MRI and NP exam (days)	1.8 (0.14)	–	–	–	0.8 (11.0)	–	54.8 (36.5)	62.1 (69.4)
Intracranial vol., cm^3	1331 (157)	1497 (146)	1370 (154)	1364 (146)	1262 (127)	1276 (124)	1312 (142)	1357 (138)
WMH, cm^3, Median [Q1, Q3]	7.5 [1.5, 8.2]	13.0 [7.0, 26.0]	11.6 [6.5, 20.9]	0.6 [0.3, 1.0]	0.8 [0.2, 0.9]	6.2 [2.5, 14.1]	13.9 [3.8, 16.2]	3.6 [1.2, 10.4]
PSMD, 10^{-4} mm^2/s	3.0 [2.5, 3.4]	4.0 [3.0, 4.0]	3.3 [3.0, 3.8]	2.3 [2.2, 2.5]	2.2 [2.0, 2.4]	2.6 [2.3, 2.9]	3.2 [1.7, 4]	4.8 [2.3, 18.0]

Note: Mean (SD); Median [Q1, Q3]; N (%).

Abbreviations: AGES, Age Gene/Environment Susceptibility-Reykjavik; ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in Young Adults; FHS, Framingham Heart Study; MarkVCID, Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia; MRI, magnetic resonance imaging; NP, neuropsychological; PSMD, peak-width of skeletonized mean diffusivity; RUSH, Rush University Medical Center; SD, standard deviation; UCD-ADRC, University of California at Davis Alzheimer's Disease Research Center; WMH, white matter hyperintensity.

TABLE 2 Association between PSMD and general cognitive function.[a]

	Model 1		Model 2	
Cohort	**β [95% CI]**	***P* value**	**β [95% CI]**	***p* value**
MarkVCID-1 ($n = 396$)	−0.8 [−1.2, −0.4]	<0.001	−0.9 [−1.3, −0.4]	<0.001
CHARGE ($n = 6156$)	−1.0 [−1.1, −0.8]	<0.001	−0.9 [−1.1, −0.8]	<0.001
RUSH ($n = 287$)	−1.5 [−2.0, −0.9]	<0.001	−1.4 [−2.0, −0.8]	<0.001
UCD-ADRC-1[b] ($n = 388$)	−0.8 [−1.1, −0.5]	<0.001	−0.8 [−1.1, −0.5]	<0.001
UCD-ADRC-2[b] ($n = 179$)	−0.7 [−1.0, −0.4]	<0.001	−0.8 [−1.2, −0.4]	<0.001

Notes: CARDIA (of CHARGE) removed 16 participants due to missing covariates. Model 1 is adjusted for age, age^2, sex, education level, and intracranial volume. Model 2 is additionally adjusted for vascular risk factors: hypertension, diabetes, and smoking status.
Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CHARGE; Cohorts for Heart and Aging Research in Genomic Epidemiology; CI, confidence interval; DWI, diffusion weighted imaging; MarkVCID, Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia; PSMD, peak-width of skeletonized mean diffusivity; RUSH, Rush University Medical Center; UCD-ADRC, University of California Davis Alzheimer's Disease Research Center.
[a]General cognitive function was calculated as the first un-rotated principal component obtained from neuropsychological tests assessing at least three different cognitive domains.
[b]Samples differ based on the DWI protocol.

TABLE 3 Association between WMH and general cognitive function.[a]

	Model 1		Model 2	
Cohort	**β [95% CI]**	***p* value**	**β [95% CI]**	***p* value**
MarkVCID-1 ($n = 396$)	−0.08 [−0.15, −0.01]	0.021	−0.09 [−0.16, −0.02]	0.017
CHARGE ($n = 6156$)	−0.07 [−0.09, −0.04]	<0.001	−0.06 [−0.09, −0.04]	<0.001
RUSH ($n = 287$)	−0.13 [−0.22, −0.04]	0.003	−0.12 [−0.21, −0.04]	0.006
UCD-ADRC-1[b] ($n = 388$)	−0.10 [−0.17, −0.02]	0.009	−0.10 [−0.17, −0.03]	0.009
UCD-ADRC-2[b] ($n = 179$)	−0.12 [−0.16, −0.08]	<0.001	−0.12 [−0.16, −0.08]	<0.001

Notes: CARDIA (of CHARGE) removed 16 participants due to missing covariates. Model 1 is adjusted for age, age^2, sex, education level, and intracranial volume. Model 2 is additionally adjusted for vascular risk factors: hypertension, diabetes, and smoking status.
Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CHARGE; Cohorts for Heart and Aging Research in Genomic Epidemiology; CI, confidence interval; DWI, diffusion weighted imaging; MarkVCID, Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia; PSMD, peak-width of skeletonized mean diffusivity; RUSH, Rush University Medical Center; UCD-ADRC, University of California Davis Alzheimer's Disease Research Center; WMH, white matter hyperintensity.
[a]General cognitive function was calculated as the first un-rotated principal component obtained from neuropsychological tests assessing at least three different cognitive domains.
[b]Samples differ based on the DWI protocol.

compared to WMH in the primary model, respectively. The adjusted R-squared values for models including only PSMD, only WMH, and both (PSMD and WMH) for each cohort are summarized in Table S5 in supporting information.

4 | DISCUSSION

The MarkVCID consortium aims to generate a suite of high-quality validated biomarkers that inform on individual outcomes within a defined category and context of use, and which can be distributed as kits including computing scripts, protocols, and training materials for future implementation into large-scale, multi-site VCID clinical trials. PSMD was one of 11 kits studied in depth by the first phase of the consortium. Although several studies have shown higher PSMD is related to lower cognitive function,[19] a rigorous, multi-site biomarker validation has not been done. Our instrumental validation work was recently published,[24] and here we discuss the biological validation of the PSMD biomarker kit and its potential to become a fully validated VCID susceptibility/risk biomarker for lower cognitive function, including cognitive decline over time (longitudinal) and in diverse populations.

The current study shows that higher PSMD is cross-sectionally associated with lower general cognitive function in the MarkVCID-1 cohort. These results were consistently replicated across the three independent samples from CHARGE, RUSH, and UCD-ADRC after considering demographic factors. Furthermore, our results suggest that PSMD may be a more sensitive biomarker than WMH for explaining cognitive function variability, particularly in older adults. Together, these findings support the use of PSMD as a robust neuroimaging biomarker in VCID studies.

In exploratory models, we observed that the association between higher PSMD and lower general cognition remained virtually

unchanged after additional adjustments for hypertension, diabetes, and smoking status. We did not pursue a comprehensive evaluation of vascular risk factors reported related to cognition through other mechanisms, such as atherosclerosis[40] and body mass index/obesity.[41] Future studies could assess the utility of PSMD as a VCID biomarker across different strata of vascular risk to improve precision.

PSMD has been studied in populations with diverse clinical presentations. Higher PSMD values are seen among adults with greater white matter burden, such as patients with a genetic form of severe SVD (e.g., cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]/ cerebral autosomal-recessive arteriopathy with subcortical infarcts and leukoencephalopathy [CARASIL]), followed by those with an underlying condition of cerebral amyloid angiopathy, sporadic SVD, AD, and MCI, whereas cognitively healthy adults from the community displayed lower PSMD values.[20] Moreover, when investigating neurocognitive correlates of PSMD, Baykara et al. identified a strong association between high PSMD and slower processing speed in CADASIL patients.[19] The same association was detected in sporadic SVD and memory clinic patients with high WMH burden; however, this association was weaker than in the CADASIL sample.[19] In community-based healthy individuals, Deary et al. found that higher PSMD was also related to lower visuospatial and general cognition and, to a lesser extent, poor verbal and crystallized memory.[21] These cognitive domains are typically first impacted by SVD, further suggesting PSMD can capture relevant clinical manifestations of VCID at the early stages of SVD. Another prospective community-based study related PSMD to baseline and 3-year follow-up processing speed and Montreal Cognitive Assessment, although they did not evaluate cognitive change due to the short follow-up.[22] In population-based samples, PSMD has been recently associated with executive function,[42] verbal and semantic fluency, and cognitive inhibition.[43] Taken together, the current literature suggests PSMD is related to several cognitive domains, an advantageous characteristic given the multiplicity of cognitive decline in aging and aging being a leading catalyst in SVD etiology.

Similar to the current research, some studies have assessed whether PSMD explains additional variance in cognition beyond other MRI/DTI measures. PSMD explained additional variance in processing speed compared to WMH volume, lacunar volume, brain parenchymal volume, and microbleed counts in samples with different clinical presentations, including CADASIL, sporadic SVD, and memory clinic SVD patients.[19] Broadening clinical correlates beyond processing speed, PSMD explained additional variance in visuospatial function and general cognitive ability compared to WMH volume, FA, MD, and perivascular spaces.[21] Similarly, PSMD outperformed four established SVD markers (i.e., WMH, enlarged perivascular spaces, microbleeds, lacune infarcts, and MD) when predicting global cognition.[44] Last, PSMD outperformed WMH and MD in inhibition and delayed memory.[43]

Although no genome-wide association studies of PSMD have been published to date, a recent investigation exploring the lifetime impact of WMH genetic risk variants reported four WMH risk loci near *SH3PXD2A*, *NMT1*, *KLHL24*, and *VCAN* that were associated with PSMD in younger adults from the i-SHARE cohort.[45] Notably, higher PSMD was related to slower information processing speed in the same cohort. Together, these findings highlight genetic variation could potentially influence white matter microstructure and cognitive performance since early adulthood, and further supports PSMD as a sensitive marker. However, more research is needed to evaluate the genetic underpinnings of PSMD.

White matter microstructural disruption is present in cerebral SVD and other vascular and neurodegenerative diseases. Individually, multiple features of white matter damage, including WMH and lacunes, have consistently been associated with a higher incidence of stroke and dementia, including AD and vascular dementia, attributing some disease burden to SVD.[46] The role of PSMD as a biomarker of these diseases has yet to be fully understood. However, a recent study compared five DTI-based markers, including PSMD, MD, network global efficiency, DSEG θ, and WM histogram-derived PC1 across six independent cohorts of participants along the continuum of SVD severity, monogenetic SVD, and MCI.[47] This study reported that baseline PSMD predicted dementia conversion within 2 to 9 years in cohorts of both mild and severe SVD and MCI. More interesting, PSMD was able to better predict conversion to vascular and mixed than AD dementia in participants with mild SVD. Although other DTI markers may have had comparable predictive ability, PSMD was the only fully automated marker.

Together, the ability of PSMD to predict conversion to dementia differentially across subtypes, sensitivity to early white matter damage, correlation with cognitive function, and ease of quantification may have important implications for future clinical research and practice.

4.1 | Strengths and limitations

Our study has several strengths, including a rigorous biological validation plan, large sample size, and diversity of study samples in terms of age, race/ethnicity, and study settings, including community-based and ADRC samples. The PSMD kit is readily available for use and includes a protocol, script, and instructions, which are publicly available to the scientific community on the MarkVCID website (https://markvcid.partners.org/). Additionally, the DTI sequence has been optimized for several major MRI scanners and is also available on the MarkVCID website. We acknowledge, however, several limitations. Although we strived to include a diverse sample, a large proportion of the samples were non-Hispanic White. Further efforts are needed to increase diversity in biomarker studies, which is one of the main milestones for MarkVCID-2. Further, brain MRI/DTI incurs non-negligible costs, and PSMD may not be a suitable biomarker in study settings with limited resources. Finally, while the PSMD kit may be used for early detection of SVD, the current results are cross-sectional, and additional research is needed to assess the utility of PSMD in longitudinal studies. MarkVCID-2 will address the potential of PSMD to predict cognitive change and VCID onset as a marker of risk prediction and disease monitoring.

5 | CONCLUSIONS

In summary, this comprehensive biological validation study suggests that PSMD is related to general cognition across diverse samples, potentially explaining more variation in cognitive function than a classic cerebrovascular marker, WMH. PSMD has ideal biomarker qualities for the AD/ADRD clinical trial pipeline. It is non-invasive, fully automated, fast, and has excellent reliability, repeatability, and reproducibility,[24] enabling PSMD to be routinely used to process numerous samples and in multi-site studies. Additional longitudinal validation studies assessing the use of PSMD as a surrogate endpoint of cerebral SVD are underway.

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ACKNOWLEDGMENTS

We thank all the participants and their research partners for their contributions to this research study. Data collection and sharing for this project was funded by National Institute of Neurological Disorders and Stroke (NINDS) as part of the MarkVCID Consortium (U24NS100591, UH2NS100599, UH2NS100605, UH2NS100588, UH2NS100608, UH2NS100606, UH2NS100598, UH2NS100614, U01NS125513). Additional funding sources are reported in the supplementary material.

CONFLICT OF INTEREST STATEMENT

Dr. Luckey, Dr. Ghosh, Ms. Bernal, Dr. Chen-Pin Wang, Dr. Fadaee, Dr. Snoussi, Mr. Velarde Dediós, Mr. Trevino, Dr. Goss, Ms. Hillmer, Dr. Lu, Dr. Gold, Dr. Bauer, Dr. Stables, Dr. Danny J.J. Wang, Dr. Beiser, Dr. Fornage, Dr. Mosley, Dr. Launer, Dr. Guðnason, Dr. Rosenberg, Mr. Baljeet Singh, Herpreet Singh, Ms. Schwab, Dr. Helmer, Dr. Himali, Dr. Caprihan, Dr. Maillard, and Dr. Satizabal have no conflicts of interest to report. Dr. Arfanakis is on the advisory board for an External Advisory Committee, NIH-funded clinical research study titled "Determinants of Incident Stroke Cognitive Outcomes and Vascular Effects on RecoverY Network (DISCOVERY)." Dr. Staffaroni is a consultant to Alector, Lilly/Prevail, Passage Bio, and Takeda. He receives licensing fees as the developer of digital cognitive tests not used in this study. Dr. Kramer has received royalties from Pearson, Inc. Dr. Greenberg is a consultant for Roche (payment to Dr. Greenberg), Washington University/IQVIA (payment to Dr. Greenberg), Bayer (payment to Dr. Greenberg), and Biogen (payment to Dr. Greenberg), and receives royalties or licenses from Up-To-Date (payment to Dr. Greenberg). Dr. Habes is a consultant for Biogen on ARIA. Dr. Seshadri is a consultant for Biogen. Dr. DeCarli is a consultant to Novartis on a safety trial for heart failure. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human participants provided informed consent.

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SUPPORTING INFORMATION

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

How to cite this article: Luckey AM, Ghosh S, Wang C-P, et al. Biological validation of peak-width of skeletonized mean diffusivity as a VCID biomarker: The MarkVCID Consortium. *Alzheimer's Dement*. 2024;20:8814–8824. https://doi.org/10.1002/alz.14345