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Received: 18 July 2026 | Revised: 2 October 2026 | Accepted: 6 October 2026

DOI: 10.1002/dad2.70526

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Digital completion time relates more strongly to Alzheimer's disease-type atrophy than to vascular burden in a community cohort

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Funding information
Taiju Life Social Welfare Foundation

Abstract

INTRODUCTION: Slowing on digital cognitive testing may reflect Alzheimer's disease (AD)-type atrophy, small-vessel disease, or both. Single-outcome studies cannot determine whether slowing preferentially reflects one type of brain change or general brain health. We tested whether response-time features from the tablet-based Cognitive Assessment for Dementia, iPad version 2 (CADi2) were more strongly associated with AD-type atrophy than with vascular burden.

METHODS: In 1163 community-dwelling adults undergoing brain-health screening (Izumo cohort, 2019–2025), CADi2 response-time features predicted two primary MRI markers from one framework under repeated nested cross-validation: Alzheimer's disease likelihood score (ADLS; similarity to an AD-type atrophy pattern) and normalized white matter lesion (WML) volume. The primary metric was the incremental observed–predicted correlation (ΔR) over age and sex. Silent brain infarcts, microbleeds, and a composite small vessel disease score were additional vascular outcomes.

RESULTS: CADi2 features improved prediction of ADLS ($\Delta R = +0.054$, 95% confidence interval [CI] +0.010 to +0.095) but not WML ($\Delta R = -0.006$). The improvement reflected completion time, not accuracy. Because predictive headroom differed, we repeated the comparison in residual space. There, the increment correlated about twice as strongly with ADLS as with WML ($r = 0.160$ vs. 0.080; $p = 0.044$), although both remained significant. A parallel contrast against the composite vascular score gave $\Delta r = 0.100$ ($p = 0.008$).

DISCUSSION: Digital completion time was preferentially, but not exclusively, associated with AD-type atrophy (neurodegeneration axis) relative to vascular burden. Because ADLS indexes an atrophy pattern rather than amyloid or tau pathology, these cross-sectional findings characterize a structural phenotype.

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KEYWORDS
Alzheimer's disease, CADi2, digital cognitive testing, machine learning, neurodegeneration, structural MRI, white matter lesions

Highlights

- Digital slowing related more closely to Alzheimer's disease (AD)-type atrophy than to vascular burden
- Incremental value for white matter lesions, infarcts, and microbleeds was near zero
- The asymmetry persisted after accounting for unequal predictive headroom
- The signal came from response latency rather than accuracy on the digital test
- The association was graded, not absolute, and concerns a structural phenotype only

1 | BACKGROUND

Alzheimer's disease (AD) is increasingly defined biologically through biomarkers rather than solely as a clinical syndrome,[1] but established biomarkers such as amyloid positron emission tomography (PET) and cerebrospinal fluid assays are costly, invasive, and impractical at the population scale.[1,2] In several countries, including Japan, community-based brain-health screening with magnetic resonance imaging (MRI) ("brain dock") is widely implemented, highlighting the need for scalable tools that complement such frameworks.

Conventional screening instruments, including the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), have limited sensitivity to subtle cognitive decline,[3–6] motivating approaches that extend beyond summary scores. Process-based measures such as response latency may capture subtle processing inefficiencies not reflected in summary scores alone,[7–11] and digital platforms make timing-based metrics feasible even in unsupervised settings.[12] The Cognitive Assessment for Dementia, iPad version 2 (CADi2), a self-administered tablet-based screening tool developed in Japan, automatically records response accuracy and completion time.[8,9]

The two CADi2 metrics differ fundamentally. The total score is discrete and bounded at 10 points; in populations with preserved cognitive function, most individuals cluster near the ceiling, and the measure loses sensitivity to subtle decline. Completion time is continuous and unbounded, resolving small shifts in processing efficiency. In our previous work in cognitively unimpaired adults, completion time was associated with hippocampal and medial temporal atrophy, whereas the total score showed no significant regional association.[7] Accuracy and latency may index distinct processes, with slowing preceding accuracy decline. Thus, completion time is a candidate behavioral signal that may be sensitive to subtle neurodegenerative changes.

However, the neural substrate of slowing is not unitary. Age-related slowing can arise from white matter lesions attributable to cerebral small vessel disease (SVD),[13,14] and from Alzheimer's disease-type atrophy; slowed processing speed is the classic cognitive hallmark of vascular impairment,[13] and white matter hyperintensity burden independently predicts cognitive decline.[15] The two processes differ in their structural signatures yet both degrade processing efficiency, and whether digital slowing preferentially reflects one over the other has not been directly examined.

Crucially, demonstrating that a behavioral measure specifically reflects a pathology requires more than showing that it predicts that pathology. Demonstrating association with one pathology does not show that a measure preferentially reflects that pathology. Most digital cognition studies evaluate only a single outcome and, therefore, cannot determine whether an observed association is pathology-weighted or reflects general brain health. Comparing a neurodegenerative outcome with a vascular outcome cannot establish the biological basis of digital slowing. However, it can test whether slowing is more closely associated with one type of change than the other. We therefore framed our question in relative terms: whether digital slowing is more strongly associated with AD-type atrophy than with vascular changes.

Two MRI-derived measurements were used for this comparison. The Alzheimer's disease likelihood score (ADLS) is a machine-learning structural-MRI measure that quantifies the degree to which the brain exhibits an AD-type atrophy pattern on a continuous scale.[16,17] Because ADLS integrates whole-brain morphometry, it indexes the neurodegeneration (N) axis and is not a biomarker of amyloid or tau pathology; throughout this paper, "Alzheimer's disease-type" (AD-type) denotes only this structural phenotype. White matter lesion (WML) volume, derived from the same framework (Brain Anatomical Analysis using Diffeomorphic Deformation, BAAD), was used to index the vascular burden. Comparing these measures within one cohort and framework may clarify whether CADi2 features are more closely linked to AD-type atrophy or to vascular burden. Because WML volume represents only one component of SVD, we further examined silent brain infarcts, cerebral microbleeds, and a composite SVD burden score. Accordingly, we evaluated whether CADi2 features provide incremental predictive value for ADLS, whether the same features also provide incremental value for WML, and how the predictive value varies across cognitive levels.

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RESEARCH IN CONTEXT

Digital completion time relates more strongly to Alzheimer's disease-type atrophy than to vascular burden in a community cohort

1. **Systematic review**. We searched PubMed and screened references for studies on digital cognitive testing, response-time metrics, and magnetic resonance imaging (MRI) markers of Alzheimer's disease-type atrophy and small vessel disease. Prior single-outcome studies cannot determine whether such measures preferentially reflect one type of brain change or are non-specific.
2. **Interpretation**. Within one cohort and framework, Cognitive Assessment for Dementia, iPad version 2 (CADi2) completion-time features added incremental value for an Alzheimer's disease-type atrophy marker (Alzheimer's disease likelihood score [ADLS]) but not for white matter lesions, silent infarcts, microbleeds, or total small vessel disease burden. The asymmetry persisted after accounting for unequal predictive headroom, yet the residual association with vascular burden remained significant: a difference in the strength of association, not a dissociation. Without amyloid or tau biomarkers, ADLS captures a structural atrophy phenotype, not confirmed Alzheimer's disease pathology.
3. **Future directions**. This asymmetry should be replicated in independent longitudinal cohorts, extended to the amyloid and tau axes, and combined with blood-based biomarkers.

2 | METHODS

2.1 | Study design and participants

This retrospective observational study used data from the Izumo cohort of the Comprehensive Epidemiological Research on Neurological Diseases by Brain Checkup System (CEREBs), an ongoing community-based "brain dock" screening and longitudinal follow-up project for cerebrovascular disease and dementia risk factors, conducted at Shimane Institute of Health Science. We studied Japanese adults who underwent structural MRI and cognitive assessment between June 2019 (the start of item-level CADi2 data collection) and March 2025. Baseline evaluations comprised age, sex, medical and medication history, blood tests, electrocardiography, and cognitive testing (MMSE and CADi2,[8,9] other instruments administered but not analyzed here). This study was exploratory rather than confirmatory.

This study was approved by the Medical Ethics Committee of Shimane University Faculty of Medicine (approval number 2225; approval date May 12, 2016) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

2.2 | Missing data

Five participants without MMSE scores were excluded. The model variables (age, sex, CADi2 measures) had no missing values, so a complete-case analysis was used; missing values in some descriptive-only variables were not imputed.

2.3 | MRI acquisition and analysis

MRI was performed on the same day as blood tests using a Philips 3.0-Tesla scanner, with T1-weighted, T2-weighted, FLAIR, and T2*-weighted sequences (Supplementary Materials); images were converted to NIfTI format. Periventricular hyperintensities (PVH) and deep subcortical white matter hyperintensities (DSWMH) were rated visually on FLAIR images, while ADLS and WML were derived quantitatively from T1-weighted images processed by BAAD (version 4.4.0), a voxel-based morphometry (VBM) framework described previously,[17] images were aligned to the anterior commissure–posterior commissure (AC–PC) line, resampled to 1-mm^3 voxels, segmented, and warped into Montreal Neurological Institute (MNI) space.

2.4 | Outcome measures

Both outcomes were derived within BAAD from the same T1-weighted images, but differed in biological meaning and computation. The neurodegenerative marker was the log-transformed ADLS, a score derived by applying a support vector machine to VBM features to estimate the likelihood of an AD-type atrophy pattern (range 0-1; higher = greater similarity).[16,17] A natural-log transformation was applied to reduce skewness. The vascular marker was WML volume normalized to total intracranial volume (TIV) and log-transformed (WML/TIV).

To extend the vascular characterization, silent brain infarcts (lacunes of presumed vascular origin) and cerebral microbleeds were rated according to STRIVE criteria,[18] by board-certified radiologists blinded to clinical and cognitive data, and a modified total SVD burden score (range 0–3) was computed following Staals et al.,[19] full scoring criteria and two deviations from the original definitions,[19,20] are given in the Supplementary Materials.

2.5 | Convergent validity of WML volume

To assess the convergent validity of BAAD-derived WML (log WML/TIV), we examined its association with visual PVH and DSWMH ratings (0–4, Shinohara classification,[21] Japanese Brain Dock Guidelines 2019,[22]); because volumetric quantification uses T1-weighted images and visual ratings use independent FLAIR images,

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agreement reflects cross-sequence convergent validity. Associations were assessed using Spearman's rank correlation (bootstrap 95% CIs), the Jonckheere–Terpstra trend test, and the Kruskal–Wallis test with Holm-corrected Dunn post hoc tests.

2.6 | Digital cognitive predictors

CADi2 automatically records the accuracy and completion time of each item.[8,9] Predictors comprised total score, total and item-level completion times, age, and sex, standardized for the linear and ridge models. Time-ratio features (each item's time divided by the total) were included only in the tree-based models (XGBoost, residual stacking), since these compositional features induce multicollinearity in linear models.

2.7 | Model development and evaluation

Terminology: "prediction" here means out-of-fold estimation of a concurrently acquired MRI marker under cross-validation. It denotes cross-sectional association, not temporal precedence, forecasting, or causation.

We compared eight models—(1) age only, (2) age + total score, (3) age + total completion time, (4) age + total score + total time, (5) multivariable linear regression, (6) ridge regression, (7) XGBoost, and (8) a two-stage residual-stacking model (XGBoost on ridge residuals)—with sex as a covariate throughout. Performance was evaluated using repeated nested cross-validation (10-fold outer, five repeats; three-fold inner tuning, where the ridge penalty and XGBoost hyperparameters were tuned), separating tuning from evaluation to reduce optimistic bias. The purpose was not to select the single best predictor, but to examine whether any neurodegenerative–vascular asymmetry depended on the choice of model.

2.8 | Incremental value and comparison between outcomes

The primary interest was whether the CADi2 features provided any incremental value over models based on age and sex. The primary metric was ΔR, the change in the Pearson correlation coefficient between the observed outcome and its out-of-fold prediction when CADi2 features were added to the age + sex model, with 95% paired-bootstrap CIs computed on the same participants (2000 resamples); the change in the mean absolute error (MAE), denoted ΔMAE, was also assessed. ΔR was computed for ADLS and WML. The same sensitivity analysis was repeated for additional vascular outcomes (silent brain infarcts, cerebral microbleeds, total SVD burden score); for these outcomes the increment was quantified as the change in the area under the receiver operating characteristic curve (ΔAUC) for the two binary outcomes and as ΔR for the ordinal total SVD burden score, with 95% paired-bootstrap confidence intervals (CIs) computed as above; see the Supplementary Materials.

ΔR is bounded by how well the age + sex model already predicts each outcome, and a near-ceiling base correlation leaves little room for further increase; apparent asymmetry could therefore reflect unequal predictive headroom rather than a genuine difference in the strength of association. To test this with a headroom-independent metric, we computed, for every participant, the residualized outcome (observed minus age + sex out-of-fold prediction) and the model's increment (full-model minus age + sex out-of-fold prediction), and correlated them (Pearson) within each outcome's age- and sex-residual space; this semi-partial-style correlation is not bounded by base-model accuracy. The two correlations were compared using a subject-level bootstrap (10,000 resamples, recomputed on the same resampled participants per replicate), from which the two-sided *p*-value and 95% CI for the difference were derived. Analyses of the additional vascular outcomes (silent brain infarcts, cerebral microbleeds, and total SVD burden score) were conducted after the initial peer review and reported as secondary, supportive analyses rather than confirmatory tests. The definitions of these outcomes, including the WMH threshold and exclusion of the perivascular space component, were fixed before the outcomes were analyzed, and all vascular outcomes examined were reported.

2.9 | Supplementary analyses

As an exploratory secondary analysis, we assessed discrimination of ADLS positivity (raw ADLS cutoff 0.5) using the AUC; because predicted probabilities were compressed under class imbalance, only the threshold-free AUC is reported (Supplementary Materials). To examine whether the incremental value varied with global cognition without imposing a cutoff, we computed the local observed–predicted correlation in sliding windows across the MMSE distribution (width 120 participants, step 20), and computed SHapley Additive exPlanations (SHAP) values from the full-data XGBoost model to identify the features contributing most to ADLS prediction.

2.10 | Software

Analyses were conducted in R version 4.5.1 using caret, glmnet, and xgboost for modeling; SHAP values were computed with xgboost's built-in TreeSHAP. MRI processing used BAAD 4.4.0. The full package list is given in the Supplementary Materials.

3 | RESULTS

3.1 | Participant characteristics

Of 1,168 consecutive participants, five were excluded for missing MMSE data, leaving 1163 for analysis (Figure 1); mean age was 62.1 ± 12.6 years, and 643 (55.3%) were male. Mean MMSE was 28.5 ± 1.9, CADi2 total score 9.5 ± 0.8, and total completion time 86.9 ± 24.2 seconds. Median WML/TIV was 1.07×10^{-3} (interquartile

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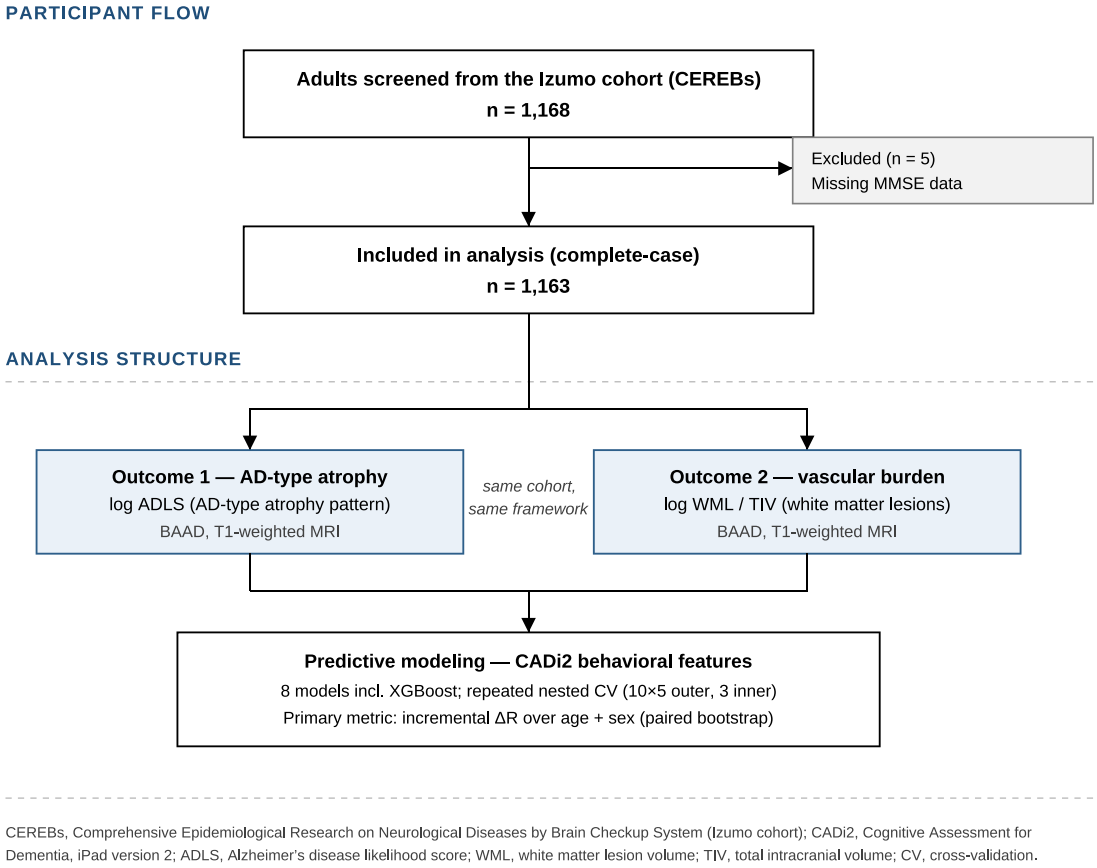


FIGURE 1 Participant flow and analysis structure. Upper panel, participant selection (1168 screened; five excluded for missing MMSE; 1163 analyzed). Lower panel, the two contrasting MRI-derived outcomes (ADLS, AD-type atrophy; WML, vascular burden) and the shared predictive-modeling framework. AD, Alzheimer's disease (AD; ADLS, Alzheimer's disease likelihood score (BAAD-derived); MMSE, Mini-Mental State Examination; WML, white matter lesion.

range [IQR] 0.61–2.23 × 10^{-3}) and median ADLS 0.121 (IQR 0.042–0.314); baseline characteristics are summarized in Table 1.

3.2 | Convergent validity of WML volume

BAAD-derived WML volume (from T1) agreed with the visual ratings from the independent FLAIR images: log WML/TIV correlated strongly with PVH grade (Spearman $\rho = 0.752$; 95% CI, 0.722–0.779) and DSWMH grade ($\rho = 0.720$; 95% CI, 0.690–0.749), increasing monotonically across grades (Jonckheere–Terpstra and Kruskal–Wallis, $P < 0.001$); the most severe grades were infrequent, so some post hoc comparisons did not reach significance. This cross-sequence agreement supported convergent validity and justified the use of WML as the primary vascular outcome (Tables S1a, and S1b; Figure S1).

3.3 | Incremental value for the neurodegenerative and vascular outcomes

Adding CADi2 features to the age + sex model significantly improved prediction of ADLS. XGBoost gave the largest ΔR (+0.054; 95% CI, +0.010 to +0.095; $p = 0.013$) and a significant reduction in MAE ($p = 0.003$). The observed–predicted correlation rose from 0.218 for age + sex to $r = 0.272$ (95% CI, 0.217–0.324) (Figure 2; Table 2). For WML, age + sex already predicted log-WML/TIV well ($r = 0.689$; 95% CI, 0.657–0.718), and adding CADi2 did not improve out-of-fold prediction (XGBoost $\Delta R = -0.006$; 95% CI, −0.017 to +0.005; $p = 0.30$); this asymmetry was observed across all models (Table S2a).

Extended vascular characterization (silent brain infarcts, cerebral microbleeds, total SVD burden score) showed the same pattern as WML: every increment was near zero (ΔAUC for the two binary outcomes, ΔR for the total SVD burden score) and well below that observed for ADLS ($\Delta R = +0.054$); full results are given in the Supplementary Materials (Table S2b).

To test whether this asymmetry reflects unequal predictive headroom, we compared the increment within each outcome's age- and sex-residual space, a metric not bounded by base-model accuracy. The increment correlated about twice as strongly with the neurodegenerative as with the vascular outcome (ADLS $r = 0.160$; 95% CI, 0.104–0.216; WML $r = 0.080$; 95% CI, 0.022–0.137; $\Delta r = 0.081$; 95% CI, 0.002–0.159; $P = 0.044$). Although the vascular residual correlation was approximately half that for ADLS, it remained significantly greater than zero, indicating a difference in the strength of association

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TABLE 1 Baseline characteristics of the study participants ($N = 1,163$).

Variable	Overall ($n = 1,163$)
Age, years	62.1 (12.6)
Sex, male	643 (55.3%)
MMSE	28.5 (1.9)
CADi2 total score	9.5 (0.8)
CADi2 total time, s	86.9 (24.2)
Total intracranial volume, mL	1463.4 (153.3)
Gray matter volume, mL	599.3 (59.4)
White matter volume, mL	494.4 (58.9)
WM lesion volume (T1), mL	1.59 [0.88–3.23]
WML/TIV ratio ($\times 10^{-3}$)	1.07 [0.61–2.23]
ADLS (AD likelihood score)	0.121 [0.042–0.314]
PVH grade	
Grade 0	569 (48.9%)
Grade 1	409 (35.2%)
Grade 2	158 (13.6%)
Grade 3	24 (2.1%)
Grade 4	3 (0.3%)
DSWMH grade	
Grade 0	316 (27.2%)
Grade 1	497 (42.7%)
Grade 2	300 (25.8%)
Grade 3	45 (3.9%)
Grade 4	5 (0.4%)
Silent brain infarct, present	111 (9.5%)
Cerebral microbleeds, present	157 (13.5%)
Total SVD burden score (0–3)	
Score 0	698 (60.0%)
Score 1	338 (29.1%)
Score 2	101 (8.7%)
Score 3	26 (2.2%)

Note: Data are mean (SD) for approximately symmetric continuous variables, median [IQR] for right-skewed variables (WM lesion volume, WML/TIV ratio, ADLS), and *n* (%) for categorical variables. Silent brain infarcts and cerebral microbleeds were rated according to the STRIVE criteria. The total SVD burden score assigns one point each for the presence of silent brain infarcts, the presence of cerebral microbleeds, and white matter hyperintensity burden (PVH grade ≥3 or DSWMH grade ≥2); see Supplementary Materials for two deviations from the original definition. Neurodegenerative (ADLS) and vascular (WML volume, silent brain infarcts, cerebral microbleeds, total SVD burden score) MRI markers are presented.
Abbreviations: ADLS, Alzheimer's disease likelihood score (BAAD-derived); CADi2, Cognitive Assessment for Dementia, iPad version 2; DSWMH, deep subcortical white matter hyperintensity; IQR, interquartile range; MMSE, Mini-Mental State Examination; PVH, periventricular hyperintensity; SD, standard deviation; SVD, small vessel disease; TIV, total intracranial volume; WM, white matter; WML, white matter lesion.

rather than an absence of association with vascular burden. A parallel comparison against the total SVD burden score showed the same pattern (score $r = 0.061$; 95% CI, 0.003–0.118; $\Delta r = 0.100$; 95% CI, 0.026–0.170; $p = 0.008$; Supplementary Materials, Table S3).

3.4 | Exploratory analysis of incremental value across cognitive levels

In an exploratory, non-prespecified sliding-window analysis, the observed–predicted correlation for log-ADLS was highest in the middle of the MMSE range (peaking around MMSE 25–26) and attenuated among the most cognitively preserved participants (MMSE 28–30), while the age + sex model showed no comparable peak (Figure 3).

3.5 | Classification and feature attribution

Classification of ADLS positivity (raw ADLS ≥ 0.5) is reported in Table S4. In the SHAP analysis, age was most influential, followed by CADi2 total completion time and several item-level completion-time and time-ratio features, with total score contributing least (Figure 4; Table S5).

4 | DISCUSSION

In this community-based cohort of 1163 adults, CADi2 features improved the prediction of an MRI-derived marker of AD-type atrophy (ADLS) but not of WML—an effect that was modest but reproducible (XGBoost $\Delta R = +0.054$), driven by completion time rather than accuracy, despite WML being highly predictable from age and sex. We interpreted these findings as a difference in degree rather than a dissociation. Digital slowing was more closely associated with AD-type atrophy than with vascular burden, although associations with both were observed. Because ADLS corresponds to the neurodegeneration (N) axis of the amyloid/tau/neurodegeneration (AT[N]) framework rather than a measure of amyloid or tau pathology, "AD-type" here denotes a structural phenotype, not confirmed Alzheimer's disease pathology.

4.1 | Interpreting the asymmetry between the outcomes

The central contribution is methodological as much as empirical. Single-outcome studies cannot determine whether a behavioral measure is more closely associated with one pathological process than another. By comparing neurodegenerative and vascular outcomes within the same cohort and framework, we addressed this question directly.

The asymmetry was evident across analyses. CADi2 features improved prediction of ADLS, showed little incremental value for vascular outcomes, and remained more strongly associated with ADLS

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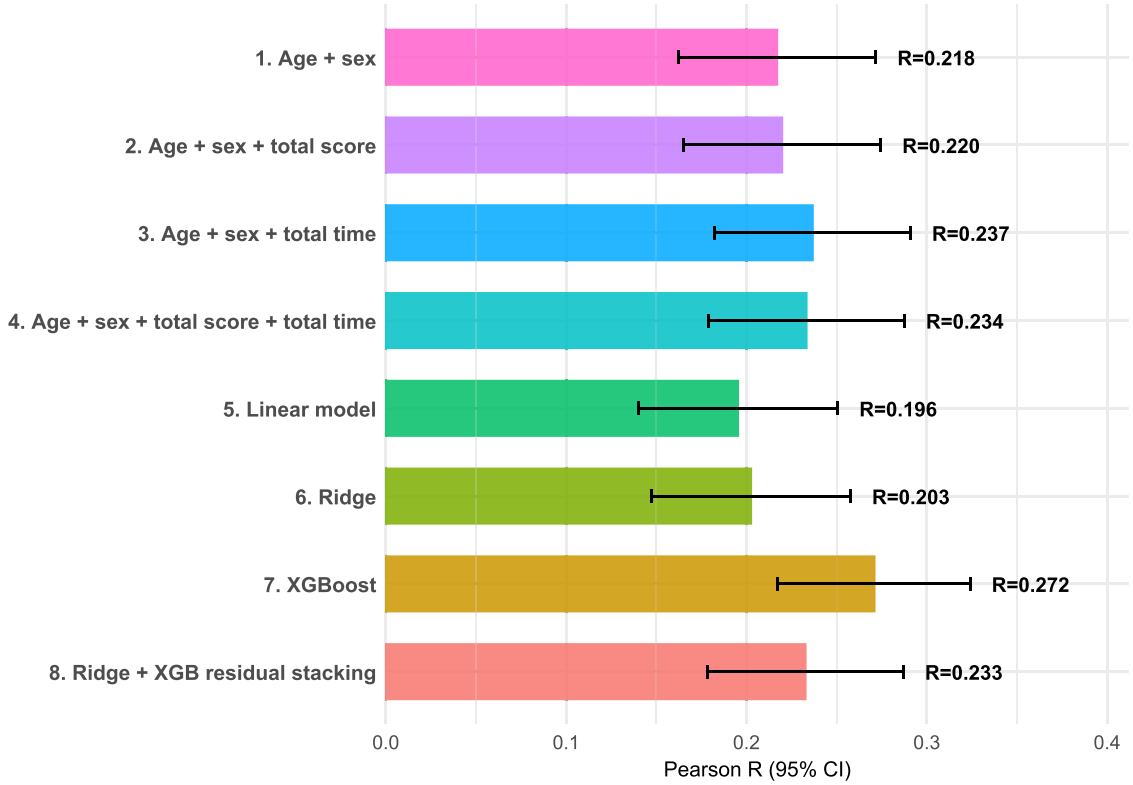


FIGURE 2 Predictive performance of all eight candidate models for log-transformed ADLS in the full sample ($N = 1,163$). Bars show the Pearson correlation between observed and out-of-fold predicted values with 95% confidence intervals from repeated nested cross-validation. XGBoost achieved the highest correlation. ADLS, Alzheimer's disease likelihood score (BAAD-derived).

TABLE 2 Predictive performance of candidate models for the neurodegenerative (ADLS) and vascular (WML) MRI markers.

Model	*R* (95% CI)	Δ*R* vs. age + sex	95% CI	*p*-value
Outcome: ADLS (Alzheimer's disease-type atrophy pattern) — full sample, *N* = 1163				
Age + sex (reference)	0.218 (0.162–0.272)	—	—	—
Age + sex + total score	0.220 (0.165–0.274)	+0.001	−0.005 to +0.007	0.62
Age + sex + total time	0.237 (0.182–0.291)	+0.020	−0.004 to +0.042	0.11
XGBoost	**0.272 (0.217–0.324)**	**+0.054**	**+0.010 to +0.095**	**0.013**
Ridge + XGB residual stacking	0.233 (0.178–0.287)	+0.018	—	—
Outcome: WML (white matter lesion burden) — full sample, *N* = 1163				
Age + sex (reference)	0.689 (0.657–0.718)	—	—	—
Age + sex + total time	0.691 (0.660–0.720)	+0.002	−0.002 to +0.007	0.30
XGBoost	**0.682 (0.651–0.712)**	**−0.006**	**−0.017 to +0.005**	**0.30**

Note: *R*, Pearson correlation between observed and out-of-fold predicted log-transformed outcome (repeated nested cross-validation, 10 × 5 outer, three-fold inner). Δ*R*, change in the Pearson correlation between observed and out-of-fold predicted values when the listed predictors are added to the age + sex base model, with 95% paired-bootstrap CIs (2,000 resamples). Bold rows mark the primary comparison. Representative models are shown; the Pearson R for all eight candidate models for ADLS is shown in Figure 2. Adding CADi2 features improved out-of-fold estimation of ADLS but not of WML, despite WML being highly predictable from age and sex. In the headroom-independent residual-space analysis, CADi2 features remained significantly associated with both outcomes, with a stronger association for ADLS. Additional vascular outcomes (silent brain infarcts, cerebral microbleeds, total SVD burden score) are reported in the Supplementary Materials. ADLS reflects the neurodegeneration (N) axis of the AT(N) framework, a structural phenotype rather than confirmed Alzheimer's disease pathology. R is the Pearson correlation between observed and out-of-fold predicted log-transformed outcome under repeated nested cross-validation; Δ*R* is the change in the observed–predicted correlation from adding the listed predictors to the age + sex base model, with 95% paired-bootstrap confidence intervals. CADi2 features improved the prediction of ADLS but not WML, indicating an asymmetry between the outcomes
Abbreviations: ADLS, Alzheimer's disease likelihood score; CADi2, Cognitive Assessment for Dementia iPad version 2; CI, confidence interval; SVD, small vessel disease; WML, white matter lesion volume.

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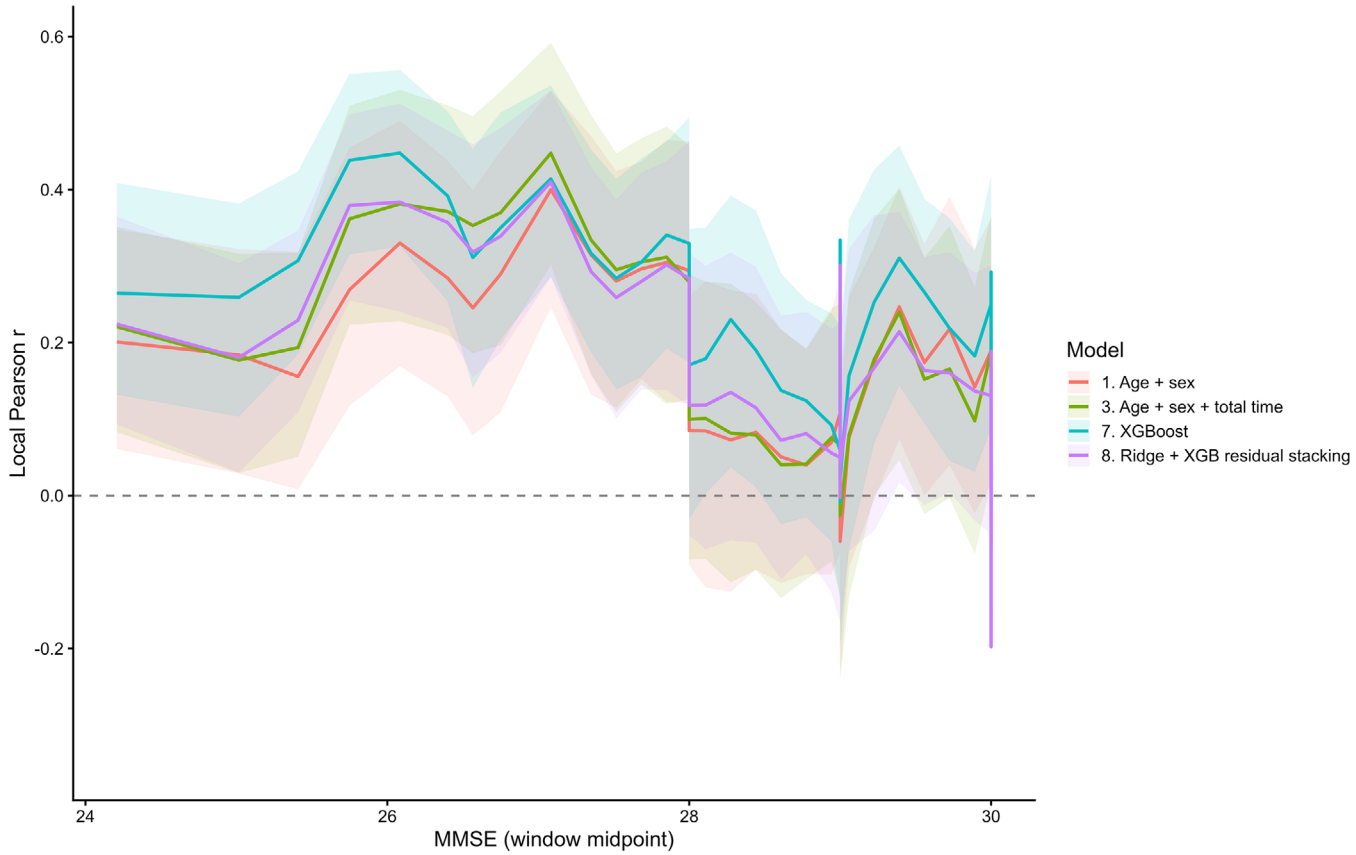


FIGURE 3 Sliding-window local performance across the MMSE distribution (window $n = 120$, step = 20). Local Pearson correlation between observed and out-of-fold predicted log-ADLS peaked in the middle of the MMSE range (around MMSE 25–26) and was attenuated among the most cognitively preserved participants (MMSE 28–30). This analysis was exploratory only, as the cross-sectional design is insufficient to establish a stage-dependent biological relationship. Each point represents a window of 120 consecutive participants ordered by MMSE, plotted at the midpoint MMSE of that window; windows advance in steps of 20 participants. Shaded bands are 95% confidence intervals. ADLS, Alzheimer's disease likelihood score (BAAD-derived); MMSE, Mini-Mental State Examination.

than with vascular measures in residual space. Together, these findings support a difference in the strength of association rather than a dissociation.

This interpretation is consistent with evidence that medial temporal atrophy, but not white matter hyperintensity burden, predicts cognitive decline,[23] and that neurodegenerative and vascular burden contribute independently to cognitive impairment.[24,25] Our findings suggest that digital completion time may be more closely associated with AD-type atrophy than with vascular brain changes.

4.2 | Variation across cognitive levels and the primacy of latency

The correlation for ADLS peaked in the middle of the MMSE range and attenuated among the most cognitively preserved participants. One explanation is that the coupling between behavioral slowing and AD-type structural change becomes resolvable only once neurodegeneration perturbs processing efficiency.[26,27] This analysis was exploratory and cross-sectional and cannot establish a stage-dependent relationship, which requires longitudinal confirmation. The signal was carried by latency rather than accuracy (Figure 4), which is mechanistically coherent: a bounded 10-point score saturates near the ceiling while continuous latency remains sensitive to small efficiency shifts. This aligns with our prior finding that completion time, not total score, tracked medial temporal atrophy in unimpaired adults,[7] and with literature in which process-based metrics outperform summary scores.[10,11]

4.3 | Explanation for the weaker association with vascular burden

Processing-speed slowing is the classic signature of vascular impairment,[13] and may extend across domains,[14] so why was completion time less closely related to vascular burden here? WML volume was chosen as the primary vascular outcome for being continuously quantifiable across the sample.[28] Nevertheless, WML volume is neither SVD itself nor the cognitive impairment it produces, so completion time may capture some of its cognitive consequences without necessarily tracking this particular index. Moreover, the association between completion time and ADLS was not fully accounted for by WML volume. After adjustment for WML volume, the association

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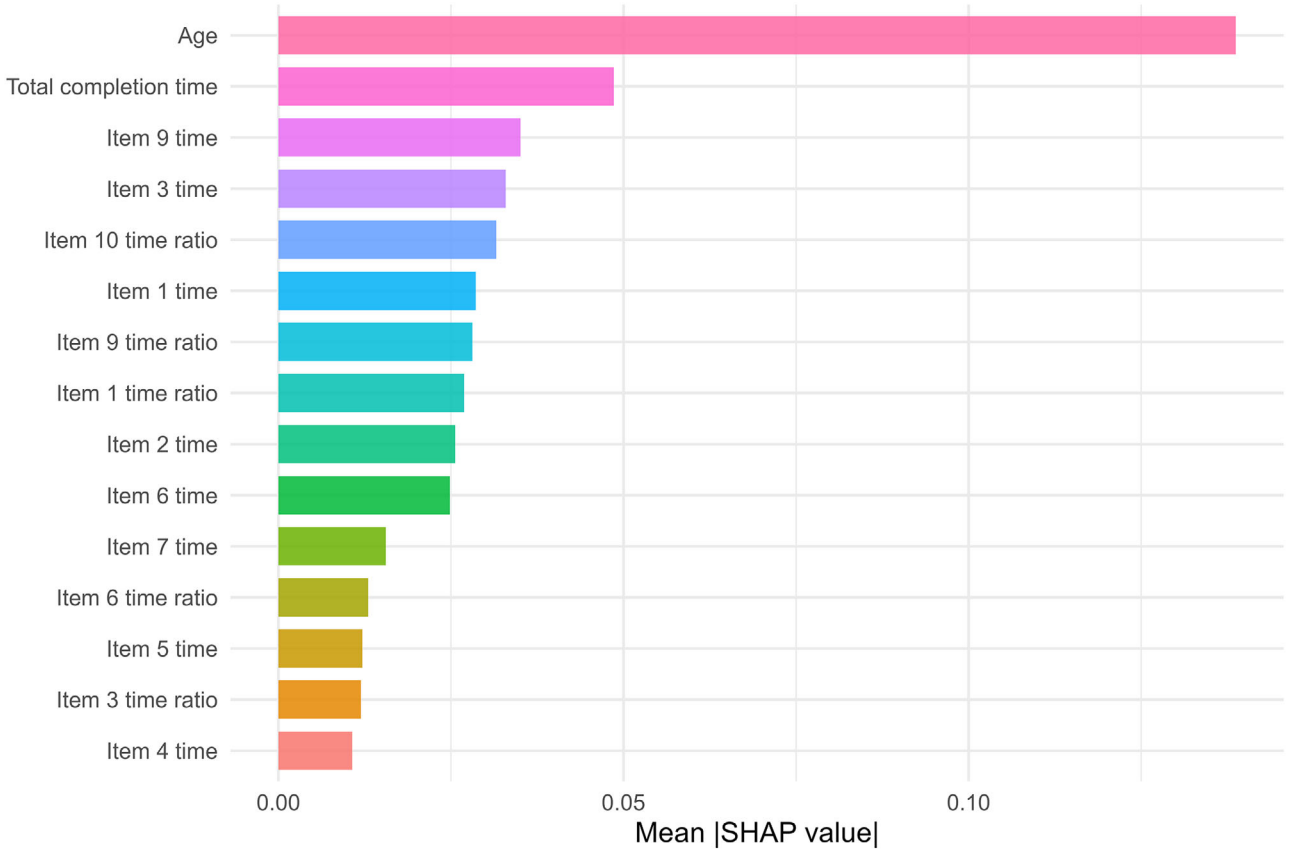


FIGURE 4 SHAP () feature importance for the final full-data XGBoost model predicting log-ADLS. Age was the most influential predictor, followed by CADi2 total completion time and several item-level completion-time variables; CADi2 total score contributed little, indicating that the incremental signal was carried by latency rather than accuracy. ADLS, Alzheimer's disease likelihood score (BAAD-derived); CADi2, Cognitive Assessment for Dementia, iPad version 2; SHAP, SHapley Additive exPlanations.

was attenuated, but persisted, and was numerically strongest among participants in the higher-lesion strata. This attenuation is difficult to interpret here. WML and ADLS both increase with age and are therefore correlated; so adjusting for WML also removes part of the shared ADLS variance and may weaken the association through over-adjustment. Taken together, these observations are compatible with a contribution beyond vascular burden but do not establish one; equally, they do not exclude a vascular contribution, and no causal inference can be drawn from these cross-sectional data (Tables S6a and S6b).

4.4 | Limitations

The main limitation is the absence of AD-specific biomarkers: neither amyloid or tau imaging nor validated blood-based markers were available. ADLS indexes similarity to an AD-type atrophy pattern and cannot attribute the underlying neurodegeneration to AD, so our findings concern a structural phenotype on the neurodegeneration axis, not AD pathology. The study was single-cohort and cross-sectional without external validation; because vascular–cognitive relationships change over time,[29] independent and ideally longitudinal confirmation is required.

Although extended to discrete lesions and a composite score, the vascular comparison does not fully capture SVD: this largely healthy screening cohort included few participants at the severe end, and the composite omitted the perivascular space component. The preferential association is therefore graded and specific to the contrasts examined, and remains untested against other contributors to slowing: motor speed, touchscreen familiarity, mood, medication use, and generalized age-related slowing. Because age is entered first and is collinear with CADi2's vascular information, that contribution is estimated conservatively, making the asymmetry a lower bound. The additional vascular outcomes were also coarse—silent brain infarcts and microbleeds were uncommon (9.5% and 13.5%) and the composite had four levels—so power to detect a small increment was low, and these near-zero increments are weak evidence of absence rather than evidence of no association. Their bootstrap intervals were computed at the participant level, conditional on the out-of-fold predictions, and exclude variability across cross-validation repeats.

The outcomes may also differ in measurement precision, which could itself contribute to the asymmetry: WML volume was derived

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from T1 rather than FLAIR and should carry greater error, attenuating its associations. The agreement with independent FLAIR ratings (ρ = 0.72–0.75) and the predictability of WML from age and sex (r = 0.689) argue against noise dominance but do not establish comparable reliability, and rater reliability was not formally assessed. Nor are the two outcomes independent contrasts: both derive from the same T1-weighted images within the same BAAD pipeline, so segmentation and registration error is shared. The magnitude of the residual-correlation difference should therefore be interpreted with caution.

Finally, this voluntary cohort was enriched for cognitively preserved individuals and the effect sizes were small ($\Delta R \approx 0.05$). Such effects are uninformative for individual-level estimation and are best regarded as group-level, hypothesis-generating observations; any role would lie in population-level pre-screening within multimodal frameworks, alongside emerging markers such as plasma p-tau217,[30–32] not in standalone use.

Within a single community cohort and framework, digital cognitive completion time was more closely associated with an MRI-derived AD-type atrophy marker than with vascular burden, though associated with both. This graded preference, carried by latency rather than accuracy, is consistent with a signal weighted toward AD-type atrophy relative to the vascular measures examined. Confirmation in biomarker-characterized longitudinal cohorts is required before any screening application could be considered.

ACKNOWLEDGMENTS

The authors used a generative artificial intelligence (AI) assistant to support English-language editing and formatting of the manuscript. It was not used to generate scientific content, data, or analyses, and all interpretations are the authors' own. This study was supported by a grant from the Taiju Life Social Welfare Foundation in 2021. The funders played no role in the design, data collection, data analysis, or reporting of this study.

CONFLICT OF INTEREST STATEMENT

MI is an executive director and stockholder of ERISA Co., Ltd., which develops the CADi2. KI, NO, TT, and AN have received speaker honoraria and related personal fees from pharmaceutical companies, and AN has received research funding from Johnson & Johnson K.K., outside the submitted work. Author disclosures are available in the Supporting Information.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of Shimane University Faculty of Medicine (approval number 2225; approval date May 12, 2016) and conducted in accordance with the Declaration of Helsinki.

CONSENT STATEMENT

Written informed consent was obtained from all participants before enrollment.

REPORTING GUIDELINE

The study was conducted in accordance with the STROBE guidelines for observational studies, and the completed checklist is provided as a supplementary file.

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How to cite this article: Iwasa K, Omori N, Ishida M, Tanaka T, Nagai A. Digital completion time relates more strongly to Alzheimer's disease-type atrophy than to vascular burden in a community cohort. *Alzheimer's Dement*. 2026;18:e70526. https://doi.org/10.1002/dad2.70526

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