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RESEARCH ARTICLE

Continuous gait monitoring discriminates community-dwelling mild Alzheimer's disease from cognitively normal controls

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Abstract

Introduction: Few studies have explored whether gait measured continuously within a community setting can identify individuals with Alzheimer's disease (AD). This study tests the feasibility of this method to identify individuals at the earliest stage of AD.

Methods: Mild AD (n = 38) and cognitively normal control (CNC; n = 48) participants from the University of Kansas Alzheimer's Disease Center Registry wore a GT3x+ accelerometer continuously for 7 days to assess gait. Penalized logistic regression with repeated five-fold cross-validation followed by adjusted logistic regression was used to identify gait metrics with the highest predictive performance in discriminating mild AD from CNC.

Results: Variability in step velocity and cadence had the highest predictive utility in identifying individuals with mild AD. Metrics were also associated with cognitive domains impacted in early AD.

Discussion: Continuous gait monitoring may be a scalable method to identify individuals at-risk for developing dementia within large, population-based studies.

KEYWORDS
accelerometer, Alzheimer's disease, digital biomarker, gait

1 | INTRODUCTION

The prevalent number of Alzheimer's disease (AD) cases in the United States is projected to more than double from nearly 5 million in 2014 to nearly 14 million by 2060 and costs will rise to over $1 trillion.[1] In the absence of effective therapies to prevent or treat AD, there is growing interest in identifying cost-effective biomarkers for early identification of risk for AD. Biomarkers are useful tools for identifying individuals early in disease progression who may benefit from treatments or trials, for use as surrogate end-points for clinical trials, and as a way to better understand mechanisms of disease progression to identify targets for interventions.

Noninvasive, cost-effective biomarkers are essential to improving diagnosis of AD across multiple care settings and screening large numbers of individuals to direct them into targeted clinical trials.[2] Recently, "digital" biomarkers from sensor and mobile/wearable devices[3,4] have been suggested for early detection as an alternative to fluid and imaging markers, considering mounting evidence indicating that sensory and motor changes may precede neurologic and neurodegenerative diseases.

Prior work indicates a relationship between cognitive function and gait, considering that walking requires complex cognitive functions including executive function, attention, and depth perception.[5] Considerable work additionally indicates that subtle disturbances in gait and balance can predict falls among individuals with neurologic disorders such as Parkinson's disease (PD)[6] and healthy older adults.[7,8] Identifying gait abnormalities or impairments may also help discriminate between neurologic disease states as well as predict progression to AD. Indeed, evidence indicates the benefit of laboratory or performance-based gait measures in assisting with predicting dementia[9,10,11] and cognitive impairment.[12] Alterations in laboratory-based measures of pace and gait variability in particular have been shown to precede dementia onset, predict diagnosis, and differentiate between neurologic diseases.[13,14,15]

The majority of prior work using gait to describe and predict dementia has used laboratory or performance based gait measures, which may not accurately reflect movement in participants' usual free-living environment. Over the last 10-years, passive, accelerometer-based, body-worn devices have been used to measure physical activity and more recently as gait measures in population- and clinic-based studies. Despite important differences between gait measured in free-living versus lab settings,[16,17] there is considerable interest in measuring gait continuously in community settings because of cost and time savings, the likelihood of measuring rare events, and the ability to conduct remote assessments for patients in areas with limited healthcare professionals.[16,18]

Prior efforts have developed robust pipelines for generating quantitative gait metrics from accelerometer-based, body-worn sensors, particularly in the PD field.[19] Recently, the Deep and Frequent Phenotyping for Experimental Medicine Study (D&FP) introduced a pilot study to incorporate body-worn sensors in the measurement of gait in mild AD.[20] The Brain and Movement Group at Newcastle University have used sensors worn during performance-based tests within a laboratory setting to differentiate between dementia subtypes.[21] To our knowledge, few if any studies have explored whether gait measured continuously within a free-living community setting can differentiate between dementia disease states. Ambulatory assessment on a 24-hour basis offers the opportunity to explore whether increased time resolution, which provides close to real-time gait assessment, may more sensitively identify individuals with dementia.

In this study, we measured gait features continuously for 7 days using a body-worn accelerometer in a sample of community-dwelling older adults with mild AD and cognitively normal controls (CNC). We measured domain-specific gait parameters using a pipeline developed and validated in the PD field. We then used these parameters to explore the efficacy of gait metrics to differentiate between mild AD and CNC participants and associations with cognitive performance. This study tests the feasibility of a low-cost, scalable method to identify individuals at the earliest stage of dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional (eg, PubMed) sources as well as Google keyword searches. Prior studies have explored whether lab-based gait measures can discriminate between neurologic diseases and assist in dementia prediction. Recent work has explored the use of wearable accelerometers to measure gait in community settings. We included the relevant citations.
2. **Interpretation**: Our findings are the first to demonstrate the feasibility and predictive validity of using continuous gait monitoring in community settings to discriminate individuals with mild Alzheimer's disease (AD) from cognitively normal controls.
3. **Future directions**: These results suggest that continuous gait monitoring may be a cost-effective and scalable method to identify individuals at risk for AD and may eventually be appropriate for clinical settings. Future large, prospective studies are required to determine whether continuous gait monitoring can predict AD among cognitively normal individuals and is associated with the progression of AD pathology.

2 | METHODS

2.1 | Participants

Mild AD and CNC participants were from the University of Kansas Alzheimer's Disease Center Registry (KU-ADC). Recruitment and evaluation of participants in the KU-ADC have been reported previously.[22]

Briefly, KU-ADC participants receive annual cognitive and clinical examinations and experienced clinicians trained in dementia assessment provide consensus diagnoses (see Section 2.5, Cognitive status and psychometric test battery, below).

Participants recruited into the study underwent a full physical and neurological examination and review of medical history. Participants with mobility disability, including those confined to a bed or wheelchair, and participants with inadequate visual or auditory capacity were excluded. The KU-ADC registry excludes individuals with active (<2 years) ischemic heart disease (myocardial infarction or symptoms of coronary artery disease) or uncontrolled insulin-dependent diabetes mellitus. The study sample included individuals with mild AD, defined as a clinical dementia rating (CDR)[23] scale scores of 0.5 (very mild) or 1 (mild), and control participants, defined as a CDR score of 0.

A total of 100 community dwelling older adults with and without mild AD were recruited. Of those, N = 92 had valid actigraphy data and 86 of those participants provided valid gait data (n = 38 mild AD; n = 48 controls) (gait data processing described in Section 2.4, Gait feature extraction, below). Participant demographics are included in Table S1 in the Supporting Information. The study protocol was approved by the KU Medical Center Institutional Review Board. Participants, and/or their legally acceptable representative, provided written, informed consent.

2.2 | Physical function covariates

Whole body mass and cardiorespiratory capacity (VO_2 max) were collected due to the association of both with accelerometry and cognitive outcomes. Whole body mass was determined using a digital scale accurate to ±0.1 kg (Seca Platform Scale, Seca Corp., Columbia, MD), and height (in cm) was measured by a stadiometer with shoes off, from which body mass index (BMI; weight [kg]/[height (m)]^2) was calculated. VO_2 max was measured by a graded treadmill exercise test using a modified Bruce protocol for older adults. Participants were attached to a 12-lead electrocardiograph (ECG) to continuously monitor heart rate and rhythm.[24] Expired gases were collected continuously, and oxygen uptake and carbon dioxide production were averaged at 15-second intervals (TrueOne 2400, Parvomedics, Sandy, UT).

2.3 | Accelerometry measurement

A detailed description of accelerometry measurement has been published previously.[25] Briefly, the GT3x+ (Pensacola FL; Actigraph, 2012; 30 Hz sampling rate) is a triaxial accelerometer validated across a range of community dwelling older adults.[26] The accelerometer was placed on the dominant hip and participants were instructed to wear the device for 24 hours a day for 7 days. Participants were asked to keep a wear-time diary to determine compliance as well as to verify algorithm-derived wake and sleep bouts. Mild AD participants had study partners (required for recruitment) to help with completing study logs and ensuring compliance.

2.4 | Gait feature extraction

Protocols for extracting gait features have been described in detail previously.[19,6] Walking, lying, standing, and sitting were identified automatically using an algorithm. Walking bouts of at least 60 seconds were evaluated to generate 55 gait variables within five domains: amplitude, pace, rhythm, symmetry, and variability. The amplitude domain includes measures related to amplitude of gait function. The pace domain includes measures related to walking speed as well as stride and step length.[27] The rhythm domain includes cadence and parameters related to stride and step time.[28] The symmetry domain includes spatiotemporal measures related to differences between the right and left lower limbs.[27] The variability domain includes measures related to stride-to-stride fluctuations.[27] Table S2 contains complete descriptions of each of the domain and associated gait variables.

2.5 | Cognitive status and psychometric test battery

Diagnosis of cognitive status was determined through consensus diagnosis by trained clinicians using comprehensive clinical research evaluations and a review of medical records following the NINCDS-ADRDA criteria.[29] Cognitive testing was completed within a mean of 40.64 days of the measurement of accelerometer data, with all but three cases occurring within 1 year of the accelerometry collection. Cognitive tests were administered by a trained psychometrician; The cognitive test battery included tests of verbal memory (Wechsler Memory Scale [WMS]–Revised Logical Memory I and II, Free, and Cued Selective Reminding Task), attention (Digits Forward and Backward, Wechsler Adult Intelligence Scale [WAIS] subscale Letter–Number Sequencing) and executive function (Digit Symbol Substitution Test, and Stroop Color–Word Test [interference score], Trail Making Test Part B, and Category Fluency).

Composite scores for each domain (verbal memory [VM], attention [ATTN], and executive function [EF]) were derived using confirmatory factor analysis (CFA). CFA is an advantageous method of summarizing multiple cognitive scores into empirically and theoretically justified components. Scores were standardized to the mean performance of CNC participants. Additional information on the CFA derived factor scores are in Table S3.

2.6 | Statistical analysis

The primary goal of this study was to determine whether gait features derived from continuous, in-community ambulatory assessment could differentiate between mild AD and CNC.

Our analytic plan first explored different aggregation or summary approaches—mean or variability—that may be most appropriate for gait metrics collected continuously (ie, 24 hours a day) over 7 days. Second, we determined whether those summary gait metrics discriminated between AD and CNC participants using a two-stage,

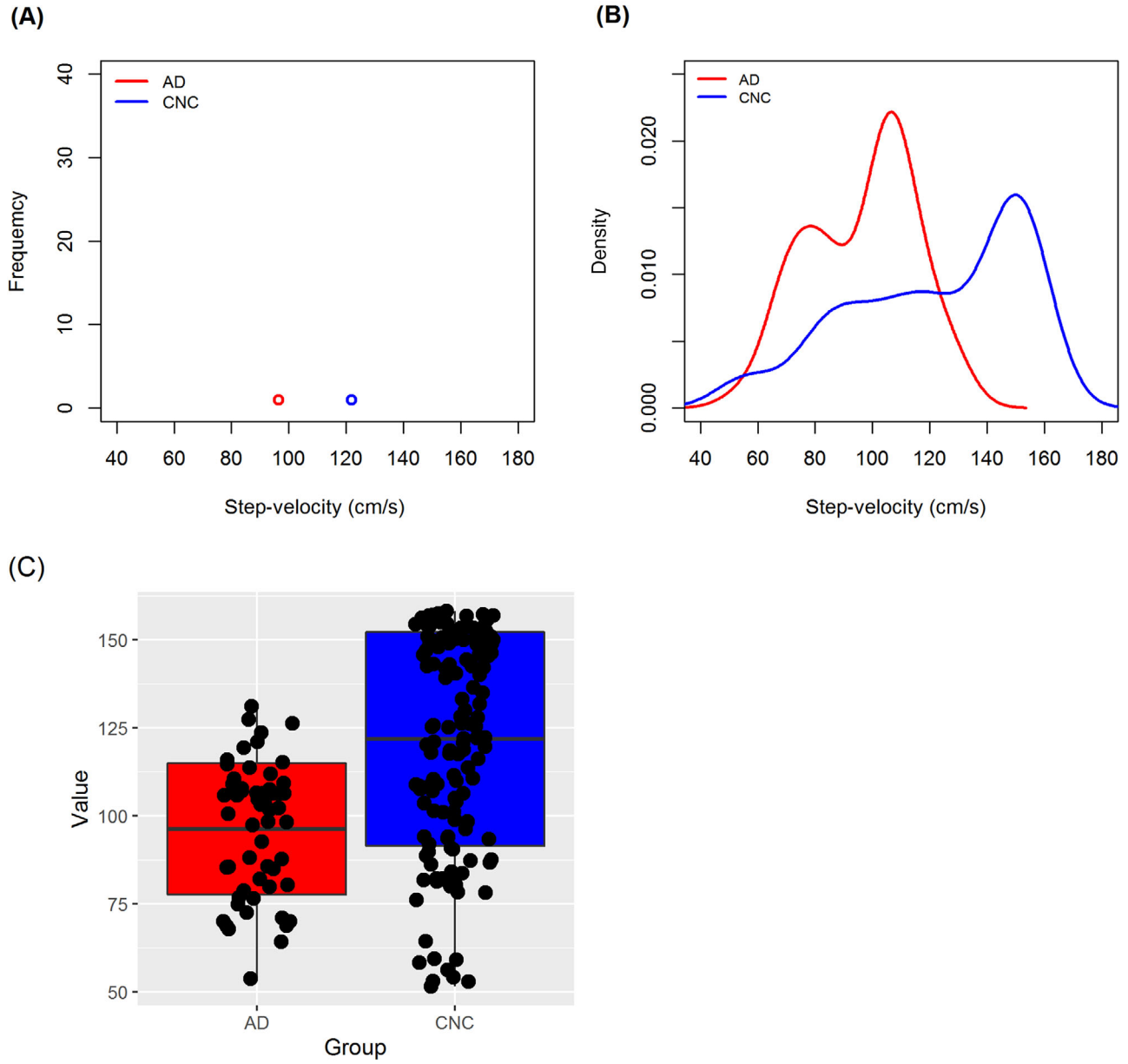

FIGURE 1 Step-velocity comparisons for two study participants, mild AD (red) and CNC (blue). (A) A single, hypothetical performance-based evaluation in the laboratory (single evaluation and one value). (B) Density plots from continuous free-living gait data collected over 7 days, providing multiple evaluations and a distribution of values. (C) Side-by-side boxplots for values of step-velocity-cm-sec data over 24 hours across 7 days of data collection. Participants in (B) and (C) were the same, and were chosen to clearly visualize differences between CNC and AD groups. Abbreviations: AD, Alzheimer's disease; CNC, cognitively normal control; step-velocity-cm-sec, mean step length/mean step time

data-driven approach. Third, we explored whether the most discriminatory metrics from the two-stage approach were associated with cognitive scores.

I. Exploring aggregation approaches for continuous gait metrics

Because we had multiple observations per gait metric per subject generated from valid (at least 60 seconds long) walking bouts over the course of 7 days, it was possible to aggregate each metric into a single summary using either the central tendency of the metric (mean) or its variability (standard deviation; SD). Similar to Figure 2 in Warmerdam et al ,[16] in Figure 1A,B compares hypothetical performance-based gait metrics collected in-lab (ie, single evaluation and one value) versus continuous free-living gait data collected over 7 days that provides multiple evaluations and a distribution of values. We display data from two subjects (mild AD vs CNC) for one of the gait metrics—step-velocity-cm-sec (defined as mean step length/mean step time)—assessed during valid walking bouts (>60 seconds) over 7 days.

Figure 1C displays the boxplots for values of step-velocity-cm-sec for the same two participants. While the mild AD participant had a lower median and lower variability compared to the CNC participant, it is not immediately clear which summary is more likely to discriminate between them. Because both tendency and variability measures likely contain relevant and potentially unique information,[30] we

explored and compared both in the discrimination models described below.

II. Two-stage approach to identify metrics that discriminate between AD and CNC

We followed a two stage, data-driven approach to select gait metrics that identify significant differences between the two groups. In the first stage, we performed variable selection using penalized logistic regression to identify the important gait metrics associated with cognitive status (AD vs CNC), after adjusting for age and sex. Specifically, we used a bi-level selection penalty "Group Exponential Lasso" (GEL)[31] to simultaneously identify both the informative domains and the important gait metrics. This model includes a penalty that induces sparsity at both the group (domain) and individual (metrics) levels.

We used repeated five-fold cross-validation with 100 times repeated Monte-Carlo resampling[32] on data and noted the selection percentages of each of the domains and gait metrics. A variable is selected for an iteration if it is identified to be important in at least one of the folds of cross-validation. In particular, the selection percentage of a metric G is given by $P_G = 1/100 \sum_{I=1}^{100} I_{\{\cup^5_{k=1} s_{ik}\}}(G)$, where $I_{\{\cup^5_{k=1} s_{ik}\}} = 1$ if G is a selected feature for iteration i in any of the fold k (k = 1,2,…,5). This helped us rank the gait metrics and domains according to importance defined via selection percentages.

In the second stage, we used the five top performing gait metrics identified in the first stage in age and sex adjusted logistic regression (unpenalized) models to study their association with AD status as the main outcome. A conservative Bonferroni corrected *P*-value (significance) threshold of .01 (= 0.05/5) was applied to account for multiple comparisons. We explored correlations across gait metrics and decided to use each gait metric separately in marginal models due to high correlation and a relatively small sample size. For the evaluation of predictive performance of the models, we performed repeated cross-validation and reported the average cross-validated area under the curve (cvAUC) of the receiver operating characteristic (ROC) curve for each of the five logistic regression models. We then reported any increased cvAUC comparing each model to the age and sex only benchmark logistic regression model. In an exploratory analysis to identify the predictive value of combining multiple gait metrics in a joint model, we fit a multiple regression model with two gait metrics (ie, step-velocity-cm-sec, and width of the dominant frequency in the power spectrum frequency domain, mediolateral direction [wdML]; SD) that were minimally correlated (r ~ 0.1).

III. Associations between discriminatory gait metrics and cognition

Using multivariate linear regression models, we explored whether the two most discriminatory gait metrics identified in the two stage model were associated with cognitive scores of VM, ATTN, and EF, after adjusting for age, sex, and years of education. Adjusted R-square values of the models were used to assess performance compared to the age, sex, and education only benchmark model.

Because of the important associations between sex and gait[33] as well as significant sex imbalance between the AD and CNC samples in this study, we explored the effect of sex in models described above by adding a sex-interaction term.

3 | RESULTS

Table S1 displays sample characteristics for the total, AD, and CNC participants. On average, respondents were 73.2 years of age (SD = 7.1 years) with 16.6 years of education (SD = 3.2). Half (50%) of the total sample was female. No statistical differences between the AD and CNC groups were observed across age, BMI, or $V0_2$ max. Compared to the CNC group, the AD group had a significantly smaller percentage of females (26.3 vs 68.8) and lower education (15.6 years vs 17.4 years).

In the first stage of our two-stage approach to identify metrics that discriminate between AD and CNC, we used variable selection and repeated cross validation to identify the most predictive domains (Figure 2A,B) and the top five most predictive gait metrics (Figure 2C,D) according to selection percentages for both mean and SD. The top five most predictive gait metrics were then used in the second stage to explore discriminative predictive performance.

Predictive domains and the top five gait metrics varied between mean and SD. Among domains, pace had the highest selection percentage for both the mean and SD. For mean, pace was followed by amplitude and then symmetry and variability; rhythm was not selected in repeated cross-validations. For SD, pace was followed by rhythm, variability, and then symmetry; amplitude was not selected in repeated cross-validations. Among gait metrics, step velocity (pace domain) had the highest selection percentage for both mean and SD. For mean, step velocity was followed by activity level (amplitude domain); step length (pace domain); acceleration range, vertical direction (rngV; amplitude domain); and the wdML (variability domain). For SD, step velocity (pace domain) was followed by distance (pace domain), cadence (rhythm domain), step length (pace domain), and then wdML (variability domain). The selection percentages of gait metrics were higher among the SD metrics compared to mean, suggesting that SD aggregation may be more predictive than mean aggregation.

In the second stage of our two-stage approach, we used the top five selected gait metrics for both mean and SD in age and sex adjusted logistic regression models. The selected gait measures were generally moderately to highly correlated for both mean (Figure 3A) and SD (Figure 3B) aggregations. In particular, among the top five selected SD metrics the pace domain measures (step velocity, distance-m, mean step length) were highly intercorrelated and correlated with cadence-V-time-domain (rhythm domain) (r = 0.5 to 1.0). Therefore, each gait metric was used in a separate logistic regression model along with age and sex as covariates. Step velocity and wdML (SD) were both identified as important gait metrics (ie, selected in the top five) and had the lowest correlation (r ~ 0.1), and therefore were used in the exploratory joint models described below.

Tables 1 (for mean) and 2 (for SD) indicate the predictive performance of the top five gait metrics in terms of cvAUC and provide comparison to the benchmark logistic model including only age and sex with cvAUC = 0.705. In the mean model, higher mean of step-velocity-cm-sec and mean-step-length were significantly (alpha = 0.01) associated with a lower odds of AD. Increased predictive performance compared to the benchmark model ranged from 9% to 14%.

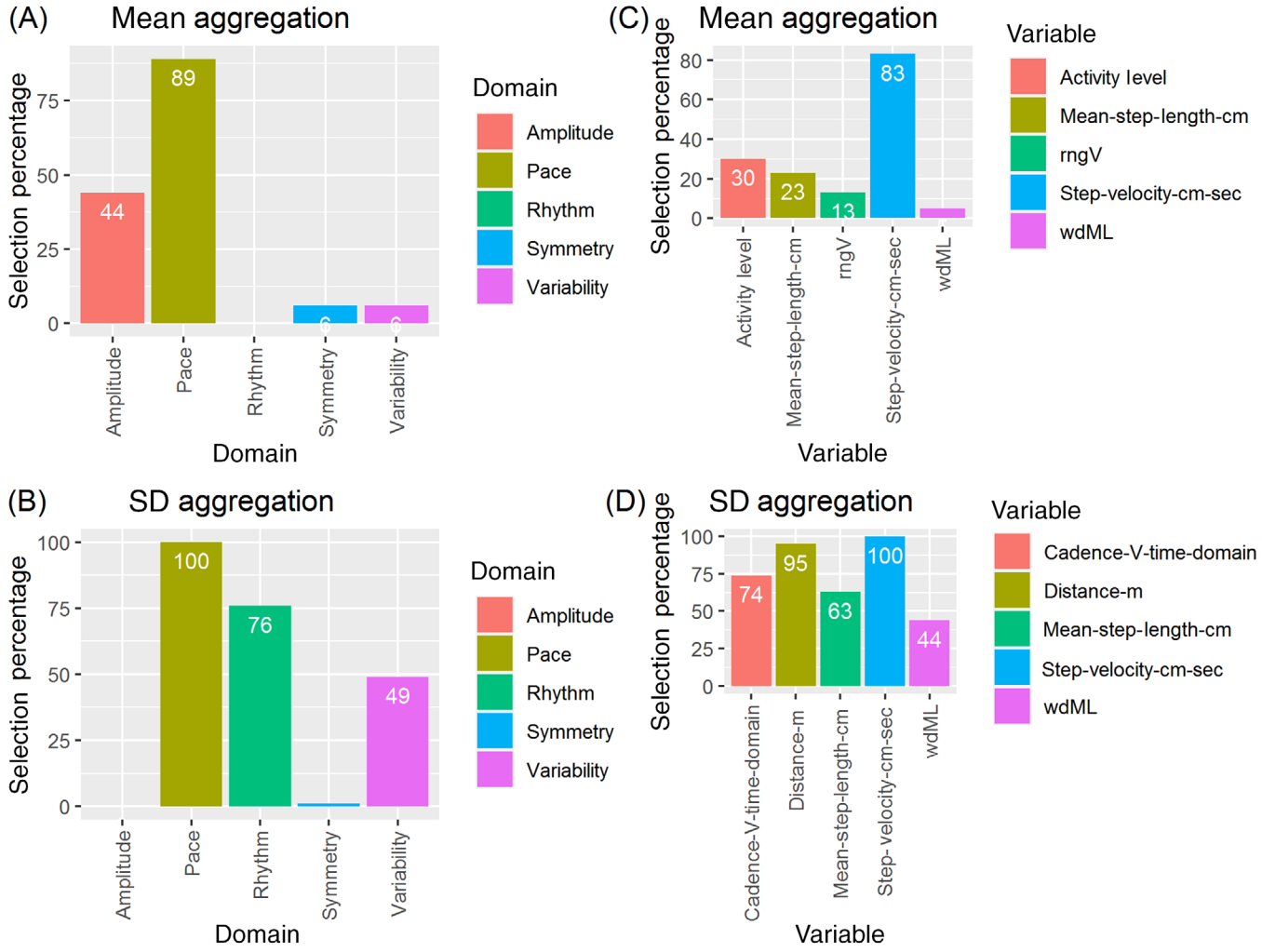

FIGURE 2 Selection percentages of the most predictive domains and gait metrics from variable selection for discriminating between mild Alzheimer's disease (AD) and cognitively normal control (CNC) participants, for means and standard deviations (SD) of measured values calculated continuously (ie, 24 hours a day) over 7 days. (A) Mean aggregation for domains. (B) SD aggregation for domains. (C) Mean aggregation for gait metrics. (D) SD aggregation for gait metrics. Selection was performed using penalized logistic regression (bi-level selection penalty Group Exponential Lasso [GEL]). Selection percentages from the model for the five domains and the top five most predictive gait metrics are indicated. Abbreviations: activity level (amplitude domain), mean signal vector magnitude; cadence-V-time-domain (rhythm domain), number of steps per minute (calculated from the vertical axis); distance-m (pace domain), sum of step length; mean-step-length-cm (pace domain), mean step length calculated using the inverted pendulum model; rngV (amplitude domain), acceleration range, vertical direction; step-velocity-cm-sec (pace domain), mean step length/mean step time; wdML (variability domain), width of the dominant frequency in the power spectrum frequency domain, mediolateral direction

In the SD model, the gain in the overall predictive performance was approximately two times higher than that of the mean model. Greater variability of step-velocity-cm-sec, distance-m, cadence-V-time-domain and wdML were significantly (alpha = 0.01) associated with a lower odds of AD. Increase in the predictive performance compared to the benchmark model ranged from 9% to 26%.

Models including interactions between sex and each gait metric were not significant and did not improve predictive performance in logistic regression models.

In Figure 4, we have included a violin plot displaying a side-by-side comparison (AD vs CNC) of the two SD gait metrics with the highest predictive performance: step-velocity-cm-sec (pace domain) (Figure 4A) and cadence (cadence-V-time-domain; rhythm domain) (Figure 4B). The AD samples have distinctly lower adjusted residuals (after adjusting for sex and age) compared to CNC.

In exploratory analyses, we fit a joint SD model including step-velocity-cm-sec and wdML, two metrics with minimal correlation (~0.1). As indicated in Table S4, both gait metrics significantly increased predictive performance compared to the benchmark model by around 30%.

Finally, we used the two most discriminatory metrics from the second stage of analysis described above—step-velocity-cm-sec (SD) (pace domain) and cadence-V-time-domain (SD) (rhythm domain)—in models exploring associations with cognitive performance. Model results are included in Table S5. Both step-velocity-cm-sec and

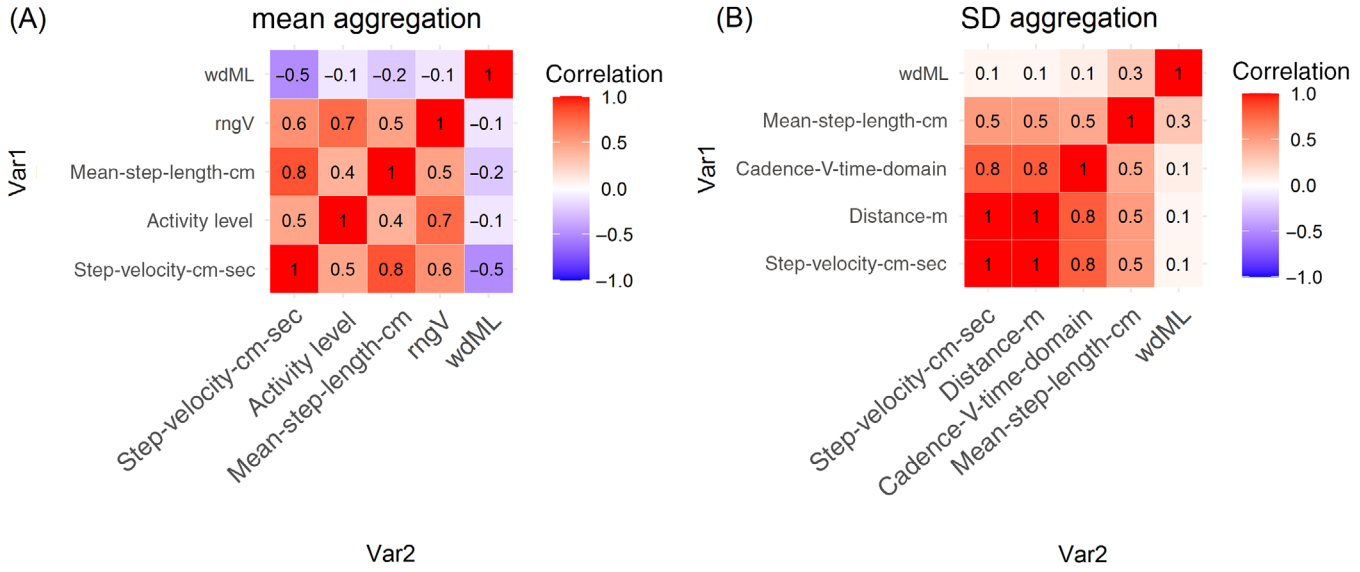

FIGURE 3 Heatmaps of correlations between the top gait metrics. (A) Mean aggregation. (B) SD aggregation. Abbreviations: activity level (amplitude domain), mean signal vector magnitude; cadence-V-time-domain (rhythm domain), number of steps per minute (calculated from the vertical axis); distance-m (pace domain), sum of step length; mean-step-length-cm (pace domain), mean step length calculated using the inverted pendulum model; rngV (amplitude domain), acceleration range, vertical direction; SD, standard deviation; step-velocity-cm-sec (pace domain), mean step length/mean step time; wdML (variability domain), width of the dominant frequency in the power spectrum frequency domain, mediolateral direction

TABLE 1 Mean results from logistic regression of cognitive status (AD, CNC) on gait metrics

Gait measure	Beta	*P*	cvAUC	% gain cvAUC
Step-velocity-cm-sec	−0.043	.00201	0.801	13.62
Activity level	−43.514	.01104	0.767	8.79
Mean-step-length-cm	−0.090	.00352	0.790	12.06
rngV	−2.044	.0116	0.770	9.22
wdML	−0.138	.88897	0.680	−3.55

Each gait measure was used separately along with age and sex as the predictor. We indicated the percentage gains using each gait metric compared to the benchmark cvAUC of 0.705 (age+sex logistic regression model). Bonferroni corrected P-value threshold of .01 was applied to identify significant associations.

Abbreviations: activity level, mean signal vector magnitude; AD, Alzheimer's disease; CNC, cognitive normal controls; cvAUC, average cross-validated area under the curve; mean-step-length-cm, mean step length calculated using the inverted pendulum model; rngV, acceleration range, vertical direction; step-velocity-cm-sec, mean step length/mean step time; wdML, width of the dominant frequency in the power spectrum frequency domain, mediolateral direction.

cadence-V-time-domain were significantly associated with cognitive scores of ATTN, VM, and EF after adjusting for age, sex, and education. The increase in the adjusted R-square value for step-velocity-cm-sec was 33% for ATTN, 44% for VM, and 40% for EF. The increase in the adjusted R-square value for cadence-V-time-domain was 24% for ATTN, 40% for VM, and 33% for EF. Similar to the direction in the logistic regression models, greater variability of the SD gait metrics was associated with higher cognitive scores.

Models exploring interaction between sex and each gait metric did not result in improved predictive performance in linear regression models.

4 | DISCUSSION

Low-cost, biologically relevant biomarkers are essential for improving diagnosis of AD and screening large, community-based samples to identify individuals at the earliest stage of dementia for targeted interventions. This study is the first to measure gait continuously in a free-living community setting and identify gait metrics that can differentiate between individuals with mild AD and CNC.

We found that the variability in gait metrics (ie, SD aggregation), features that are intrinsic to 24-hour, continuous and near real-time gait assessment, may be more sensitive measures of AD-related gait impairment than mean measures. Specifically, variability in step velocity and cadence, gait metrics in the pace and rhythm domains respectively, provided a significant gain in predictive utility beyond a benchmark model and were significantly associated with cognitive status and additionally explained a large percent of variability in cognition impacted in early AD.

Specific gait metrics may be sensitive to changes in specific disease pathology and cognitive decline. Prior work has shown that changes in pace and rhythm may be specific to AD pathology (compared to Lewy Body disease pathology)[15] and pace (including step velocity) is associated with memory decline while rhythm (including cadence) is associated with executive function decline.[34] Our findings suggest that step velocity and cadence (ie, the pace and rhythm domains) are the most discriminative between mild AD and CNC and are strongly associated

TABLE 2 SD results from logistic regression of cognitive status (AD, CNC) on gait metrics

Gait measure	Beta	*P*	cvAUC	% gain cvAUC
Step-velocity-cm-sec	−0.249	.00019	0.887	25.82
Distance-m	−0.431	.00019	0.886	25.67
Cadence-V-time-domain	−0.587	$2.9 * 10^{-5}$	0.889	26.1
Mean-step-length-cm	−0.142	.0378	0.774	9.79
wdML	−5.164	.00912	0.771	9.36

Each gait measure was used separately along with age and sex as the predictor. We indicated the percentage gains using each gait metric compared to the benchmark cvAUC of 0.705 (age+sex logistic regression model). Bonferroni corrected *P*-value threshold of .01 was applied to identify significant associations. Abbreviations: AD, Alzheimer's disease; cadence-V-time-domain: number of steps per minute (calculated from the vertical axis); CNC, cognitive normal controls; cvAUC, average cross-validated area under the curve; distance-m, sum of step length; mean-step-length-cm, mean step length calculated using the inverted pendulum model; SD, standard deviation; step-velocity-cm-sec: mean step length/mean step time; wdML, width of the dominant frequency in the power spectrum frequency domain, mediolateral direction.

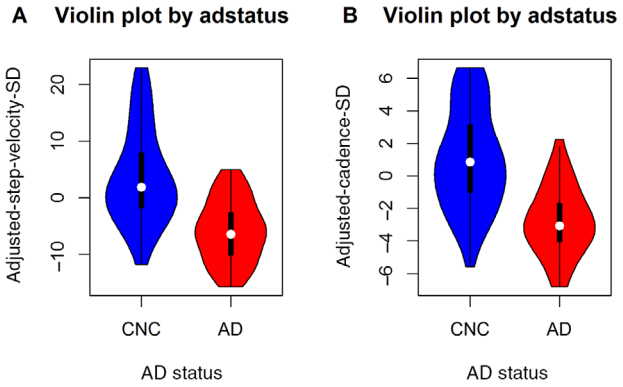

FIGURE 4 Violin plots indicating the distribution of the residual associations between cognitive status (AD, CNC) and SD values of gait metrics, after adjusting for sex and age. (A) Step-velocity. (B) Cadence. Abbreviations: AD, Alzheimer's disease; cadence (cadence-V-time-domain), dominant frequency of the power spectrum in the rhythm domain * 60; CNC, cognitive normal control; SD, standard deviation

with cognitive domains that change early in disease progression. This suggests that both metrics may be sensitive to cognitive change prior to disease onset and diagnosis, and may be useful for monitoring cognitive change and estimating disease progression in the prodromal or preclinical stages of AD.

Our study results suggest that unsupervised, 24-7 gait monitoring may be a feasible, low-cost, and scalable method to identify individuals at the earliest stage of dementia and can potentially be used to identify individuals at risk of progressing to dementia. While there are important differences between gait measured in free-living versus lab settings, there is considerable interest in real-time measurements of risk factors and the use of technology for diagnostic support, for example, teleneurology.[18] Our findings are among the first to suggest the benefits of diagnosis using remote, real-time gait assessments. They pave the way for generating gait metrics from accelerometer data collected in large, community-based studies to determine whether these digital biomarkers may predict dementia onset and progression.

Rather than simply being a motor control activity, gait is a complex function that involves coordination across multiple cognitive domains and is likely a main feature of many neurodegenerative diseases.[35] Early gait dysfunction, a feature of motoric cognitive risk syndrome, has been shown to be highly prevalent among individuals with preclinical AD.[36,37] Prior studies using laboratory or performance-based gait measures have shown that gait dysfunction across multiple domains, including pace, rhythm, and variability, are associated with cognitive decline, incident dementia, and MCI subtypes compared to normal controls.[38,39] Numerous papers have identified specific, lab-based quantitative gait metrics that can differentiate between disease groups. Variability of walking quality (ie, SD of stride regularity and SD of peak amplitude), velocity, stride length, and stride time are different between MCI and healthy controls.[13,40] Gait speed, symmetry, and regularity are lower in MCI individuals who progressed to AD versus those who did not;[30] gait speed, step length, and double support declined in AD;[41] and variability is likely more sensitive than mean among individuals with dementia.[42] Step time variability has been shown to be a stronger predictor of risk of MCI among cognitive normal individuals compared to gait speed.[43]

Our results, which indicate specific domains (pace, rhythm, amplitude, and variability) and gait metrics (cadence and step velocity) discriminate between AD and CNC, are broadly consistent with prior findings. As illustrated in Figure 1, gait measures collected continuously in the community over a 7-day period produce a significant amount of information that likely better represents subtle differences in gait between mild AD and CNC compared to both averaged data and single point gait measures recorded in lab or structured settings. Significant associations between variability in step velocity and cadence, and cognitive measures of EF, ATTN, and VM, are consistent with the close relationship between higher order cognitive functions and gait,[35,5] as well as prior studies indicating that gait measures among individuals with MCI or AD are significantly associated with EF, ATTN, and memory.[35,34,44]

The novelty of this study is in the use of 24-7 gait monitoring in a community-based population to identify gait metrics that can discriminate between AD and CNC. The use of small, nonintrusive devices

to measure gait continuously while individuals are "in the wild" have recently been used in fall prevention and Parkinson's research.[19] Additionally, accelerometers and wearable sensors have been used in structured settings to measure gait using performance-based tests (ie,[45]). While one study has described the feasibility of 24-7 gait monitoring using accelerometers[20] and another study used a gait specific sensor to record gait during usual daily activities,[46] our study is the first to use a standard accelerometer commonly used across multiple large, population-based studies. Gait variability measured over long periods of time when environmental and external conditions are not fixed is a novel and likely sensitive biomarker for AD.

This study has a number of important implications with regard to AD treatment. First, our results suggest that continuous gait monitoring may be a scalable method to identify at-risk individuals within large, population-based studies. As an early screener, continuous gait monitoring holds promise as a cost-effective "first gate" that does not require the use of invasive procedures or significant resources to assess cognition.[47] Additionally, continuous gait monitoring may provide metrics that are sensitive to changes in cognitive impairment prior to the onset of dementia as well as disease progression.[48]

There are limitations to this study. First, we have a relatively small sample size that is not balanced for sex. While we considered these limitations when designing appropriate statistical analyses, our results will need to be validated in larger studies and with longitudinal measures of AD phenotypes. Second, this study is cross-sectional and does not measure whether gait metrics measured using 24-7 gait monitoring may predict AD or identify risk for AD during the preclinical stage. Third, placement of the accelerometer on the dominant hip is likely not the optimal location to measure gait. However, this placement, compared to lower back placement, is more typical of large population-based studies. Our future goal is to scale this work to large, prospective studies that include both accelerometer data collection and dementia outcomes in order to further explore whether sensor-generated gait biomarkers can predict whether individuals will progress to AD.

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CONFLICT OF INTERESTS

Authors have no competing interests to declare.

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SUPPORTING INFORMATION

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

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