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Gait characteristics track biological disease stages in Parkinson's disease

Chiara Pirini
Translational and Clinical Research Institute, Faculty of Medical Sciences
Lisa Alcock
Translational and Clinical Research Institute, Faculty of Medical Sciences
Cameron Kirk
Translational and Clinical Research Institute, Faculty of Medical Sciences
Rachael A. Lawson
Translational and Clinical Research Institute, Faculty of Medical Sciences
Camille Carroll
Translational and Clinical Research Institute, Faculty of Medical Sciences
Lynn Rochester
Translational and Clinical Research Institute, Faculty of Medical Sciences
Silvia Del Din
Translational and Clinical Research Institute, Faculty of Medical Sciences
Alison J. Yarnall
alison.yarnall@newcastle.ac.uk

Translational and Clinical Research Institute, Faculty of Medical Sciences

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Abstract

Parkinson's disease (PD) exhibits a heterogeneous course, posing challenges for accurate trajectory prediction. The Neuronal Alpha-Synuclein Disease-Integrated Staging System (NSD-ISS) provides a biological framework for staging from at risk to advanced disease. Within this framework, gait characteristics hold promise as quantitative digital markers, as they are sensitive to motor severity. However, their role within the NSD-ISS remains unclear. Using data from the ICICLE-GAIT study, we investigated whether quantitative gait characteristics derived from an instrumented walkway and an accelerometer-based body-worn monitor (BWM) during laboratory assessment differ between stages of the clinically manifest component of the NSD-ISS. Participants with PD were classified as Stage 3 (walkway: n = 40; BWM: n = 35) or Stage 4 (walkway: n = 36; BWM: n = 28). Significant ($p < 0.05$) differences between stages were observed in gait characteristics across the domains of pace, rhythm, and variability for both systems, whereas postural control differed significantly only for the instrumented walkway. These findings provide proof of concept for the potential role of gait characteristics as objective digital measures within the clinically manifest component of the NSD-ISS. Further research is needed to evaluate the full NSD-ISS and to validate these findings longitudinally and in real-world settings.

Introduction

Parkinson's disease (PD) is one of the fastest growing neurological diseases worldwide [1]. Although common, PD progression is heterogeneous, posing challenges for accurately predicting disease trajectory [2]. A biologically grounded staging framework of PD has been recently proposed as a departure from prior staging systems (e.g., Hoehn & Yahr (HY) staging system [3]), which are based solely on clinical features. With a biological staging system in PD, the disease is defined by the presence of α-synuclein (α-syn) pathology and dopaminergic neuronal loss, with clinical features defining a specific syndrome driven by the unifying biology [2].

Against this background, the Neuronal Alpha-Synuclein Disease-Integrated Staging System (NSD-ISS) relies on the presence of an in vivo biomarker of neuronal α-syn (n-α-syn) pathology; it divides the continuum of PD into 7 discrete stages (0–6), by leveraging the presence of fully penetrant genetic variants (e.g., *SNCA* gene), biomarker evidence of n-α-syn pathology (S biomarker) and dopaminergic dysfunction (D biomarker) in the earliest non-manifesting stages (0–1), and incorporating manifesting clinical signs and symptoms (stage 2) and levels of functional impairment (stages 3–6) [4, 5]. To date, the NSD-ISS has been operationalised by defining specific biological and clinical anchors for each stage [4, 6]. NSD-ISS stages 3–6, defined according to increasing levels of functional impairment, were operationalised using clinical measures such as the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II [4, 6]. Hereafter, we refer to the stages 3–6 with the expression "clinically manifest portion" of the NSD-ISS continuum. However, clinical measures can be influenced by factors such as medications, day-to-day variability, and the timing of assessment, such that changes in clinical measures may not necessarily reflect changes in the underlying disease biology.

Moreover, the biological markers of stages 0–1, being binary, simply denote the presence or absence of genetic variants, n-α-syn pathology, and dopaminergic dysfunction. Together, these considerations highlight the potential value of complementary measures that can provide continuous or high-frequency data able to detect meaningful change across the NSD-ISS continuum.

Gait characteristics may represent promising digital measures within the NSD-ISS. Gait is a particularly relevant domain for investigating quantitative markers of motor severity in PD, as gait alterations can emerge early in the disease course and change with disease progression [7]. In fact, a growing body of evidence indicates that gait characteristics are sensitive to motor severity and reflective of functional decline across the PD continuum [8–12]. Measures including gait variability and asymmetry have been associated with a shorter time to PD diagnosis in at-risk individuals [8], whereas step length was found to be a promising marker of disease progression [9]. Longitudinal studies further demonstrate progressive deterioration in gait characteristics, such as step length and swing time, over periods of 18[12] to 72[11] months. These findings suggest that gait provides quantitative measures, which may be integrated within the NSD-ISS continuum. However, despite this accumulating evidence, gait characteristics have not yet been formally incorporated into biological staging frameworks such as the NSD-ISS, because robust empirical evidence linking gait alterations to the underlying biological stages of PD remains limited.

We therefore conducted an exploratory analysis integrating quantitative gait characteristics within the clinically manifest portion of the NSD-ISS, which comprises stages 3–6. We did not consider prior stages (0–2) because no data were available for three of the main (and biological) anchors (n-α-syn pathology: S biomarker, dopaminergic pathology: D biomarker, genetic variants: G biomarker).

The primary aim of this study was to investigate whether quantitative gait characteristics obtained from laboratory-based, active gait assessments, could serve as candidate staging markers by distinguishing between two or more disease stages. Specifically, we aimed to: (i) apply the clinically manifest portion of the NSD-ISS to an existing cohort of individuals with PD to assign stages 3–6; and (ii) assess whether gait characteristics are significantly different across these stages, adding proof of principle for their role as digital markers in the NSD-ISS. We hypothesised that: (i) individuals with PD could be classified into clinically operationalised NSD-ISS stages [5, 6]; and (ii) selected gait characteristics, such as step length, would differ across stages, reflecting their sensitivity to motor severity in PD.

Results

ICICLE-GAIT participants and assignment of NSD-ISS stages

The same participants (N = 119) underwent simultaneous assessments with the instrumented walkway and the body-worn monitor (BWM). Of these, 43 participants were excluded from the instrumented walkway analysis and 56 from the BWM analysis due to missing data. Consequently, 76 participants

were included in the final instrumented walkway analysis (Fig. 1, Supplementary Table 1). The mean age of participants was 69.2 ± 10.0 years, 68.4% were males, the mean MDS-UPDRS Part III was 16.9 ± 11.4, and the mean BMI 27.4 ± 5.3 kg/m^2. From the BWM data, 63 participants were considered, with a mean age 69.9 ± 9.7 years, 68.3% male, a mean MDS-UPDRS Part III 37.0 ± 11.9, and a mean BMI 27.1 ± 5.0 kg/m^2. The results of the selection bias risk assessment are reported in the Additional Information (Supplementary Table 2).

Participants were assigned to NSD-ISS stages 3 and 4 (Fig. 1), as they did not exhibit MDS-UPDRS Part II scores high enough to correspond to stages 5 or 6. Moreover, prior stages (0–2) were not defined as biological markers were not consistently available within the ICICLE-GAIT study.

Participant demographic, clinical and cognitive descriptors are shown in Table 1 (instrumented walkway) and Table 2 (BWM). Participants were comparable for all demographic characteristics between stages 3 and 4. Participants in stage 4 had significantly higher MDS-UPDRS Parts II and III, in addition to significantly lower total MoCA scores, compared to participants in stage 3 at both assessments (Table 1, Table 2).

Table 1
Demographic and clinical variables of PD participants in NSD-ISS stages 3 and 4 for the instrumented walkway.

Instrumented walkway				
Variable	Stage 3 (n = 40)	Stage 4 (n = 36)	*p*	Effect size
Demographic				
Sex (m, f)	m 26, f 14	m 26, f 10	0.499	0.08
Age (years)	68.4 (9.9)	70.0 (10.0)	0.503	0.16
Height (m)	1.70 (0.09)	1.68 (0.08)	0.379	0.20
Weight (kg)	76.5 (67.0-83.4)	81.6 (69.0-88.5)	0.156	0.16
BMI (kg/m^2)	26.2 (23.2–27.8)	28.1 (24.8–32.9)	0.050	0.22
Clinical				
MDS-UPDRS Part II	10.0 (7.0-12.8)	17.0 (15.0–19.0)	**< 0.001****	0.86
MDS-UPDRS Part III	31.0 (8.9)	43.5 (10.4)	**< 0.001****	1.30
HY	HY I 1, HY II 38, HY III 1	HY II 30, HY III 6	**0.048***	0.26
MoCA	28.0 (26.3–29.8)	25.0 (23.0–28.0)	**< 0.001****	0.40

MDS-UPDRS Part II/III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part II/III; HY: Hoehn and Yahr scale; MoCA: Montreal Cognitive Assessment

Data are reported as mean (SD) or median (IQR Q1-Q3).

**p < 0.05, **p < 0.01*

Table 2
Demographic and clinical variables of PD participants in NSD-ISS stages 3 and 4 for the BWM.

BWM				
Variable	Stage 3 (n = 35)	Stage 4 (n = 28)	*p*	Effect size
Demographic				
Sex (m, f)	m 23, f 12	m 20, f 8	0.628	0.06
Age (years)	68.7 (9.9)	71.3 (9.5)	0.282	0.28
Height (m)	1.70 (0.09)	1.68 (0.08)	0.240	0.30
Weight (kg)	75.9 (13.3)	79.3 (67.0-85.2)	0.529	0.08
BMI (kg/m^2)	26.1 (3.8)	27.7 (24.0-31.7)	0.224	0.15
Clinical				
MDS-UPDRS Part II	10.0 (7.0–12.0)	17.0 (16.0–19.0)	**< 0.001****	0.86
MDS-UPDRS Part III	30.7 (9.1)	44.8 (10.4)	**< 0.001****	1.46
HY	HY I 1, HY II 33, HY III 1	HY II 23, HY III 5	0.080	0.27
MoCA	28.0 (26.0–30.0)	25.0 (23.0–28.0)	**0.004****	0.37

MDS-UPDRS Part II/III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part II/III; HY: Hoehn and Yahr scale; MoCA: Montreal Cognitive Assessment

Data are reported as mean (SD) or median (IQR Q1-Q3).

**p < 0.05, **p < 0.01*

Gait differentiates between clinically operationalised NSD-ISS stages

Instrumented walkway. Between-group (stage 3 vs 4) significant ($p < 0.05$) differences were found in the micro domains of pace (step length: $p < 0.001$, $\eta_p^2 = 0.223$; step velocity: $p < 0.001$, $\eta_p^2 = 0.213$; swing time variability: $p = 0.013$, $\eta_p^2 = 0.083$), rhythm (stance time: $p = 0.008$, $\eta_p^2 = 0.095$), variability (step time variability: $p = 0.009$, $\eta_p^2 = 0.092$; stance time variability: $p = 0.009$, $\eta_p^2 = 0.091$; step length variability: $p = 0.025$, $\eta_p^2 = 0.069$), and postural control (step width: $p = 0.031$, $\eta_p^2 = 0.064$; step width variability: $p = 0.037$, $\eta_p^2 = 0.060$) after controlling for age, sex, and BMI (Table 3). The highest effect sizes were observed in the pace domain ($\eta_p^2 = 0.223$).

Table 3

Gait characteristics distributions in the NSD-ISS stages 3 and 4.

Gait characteristic	Instrumented walkway				BWM			
	Stage 3 (n = 40)	**Stage 4 (n = 36)**	***p***	η_p^2	**Stage 3 (n = 35)**	**Stage 4 (n = 28)**	***p***	η_p^2
Pace								
Step Length (m)	0.652 [0.627–0.677]	0.568 [0542-0.595]	**< 0.001****	0.223	0.537 [0.514–0.561]	0.517 [0.493–0.543]	0.272	0.021
Step Velocity (m/s)	1.217 [1.158–1.276]	1.025 [0.963–1.087]	**< 0.001****	0.213	0.979 [0.931-0,971]	0.903 [0.853–0.955]	**0.040***	0.071
Swing Time Variability (s)	0.015 [0.013–0.017]	0.019 [0.017–0.021]	**0.013***	0.083	0.043 [0.033–0.056]	0.058 [0.043–0.078]	0.128	0.040
Rhythm								
Step Time (s)	0.541 [0.528–0.554]	0.559 [0.546–0.573]	0.059	0.049	0.554 [0.537–0.571]	0.581 [0.561-0.600]	**0.048***	0.066
Stance Time (s)	0.695 [0.674–0.715]	0.736 [0.714–0.757]	**0.008****	0.095	0.711 [0.692–0.730]	0.734 [0.713–0.756]	0.110	0.043
Swing Time (s)	0.386 [0.378–0.396]	0.382 [0,373-0,392]	0.539	0.005	0.397 [0.379–0.416]	0.427 [0.406–0.448]	**0.046***	0.067
Variability								
Step Time Variability (s)	0.016 [0.014–0.018]	0.020 [0.018–0.023]	**0.009****	0.092	0.042 [0.032–0.055]	0.057 [0.042–0.077]	0.136	0.038
Stance Time Variability (s)	0.019 [0.016–0.021]	0.024 [0.021–0.028]	**0.009****	0.091	0.044 [0.034–0.057]	0.058 [0.044–0.078]	0.154	0.035
Step Length Variability (m)	0.021 [0.019–0.024]	0.026 [0.021–0.028]	**0.025***	0.069	0.063 [0.053–0.075]	0.086 [0.071–0.104]	**0.020***	0.090
Step Velocity Variability (m/s)	0.052 [0.047–0.057]	0.055 [0.050–0.061]	0.343	0.013	0.130 [0.114–0.149]	0.153 [0.132–0.177]	0.119	0.041
Asymmetry								
Step Time Asymmetry	0.018 [0.013–	0.017 [0.012–	0.691	0.002	0.023 [0.016–	0.015 [0.010–	0.124	0.040

Gait characteristic	Instrumented walkway				BWM			
	Stage 3 (n = 40)	Stage 4 (n = 36)	*p*	η_p^2	Stage 3 (n = 35)	Stage 4 (n = 28)	*p*	η_p^2
(s)	0.024]	0.023]			0.032]	0.022]		
Stance Time Asymmetry (s)	0.014 [0.010–0.018]	0.010 [0.007–0.015]	0.241	0.019	0.020 [0.014–0.029]	0.014 [0.009–0.021]	0.175	0.032
Swing Time Asymmetry (s)	0.013 [0.009–0.017]	0.011 [0.008–0.016]	0.633	0.003	0.021 [0.015–0.030]	0.014 [0.009–0.020]	0.112	0.043
Postural Control								
Step Length Asymmetry (m)	0.026 [0.020–0.033]	0.023 [0.017–0.030]	0.523	0.006	0.069 [0.048–0.092]	0.070 [0.047–0.097]	0.948	0.000
Step Width (m)	0.087 [0.078–0.095]	0.101 [0.091–0.110]	**0.031***	0.064	-	-	-	-
Step Width Variability (m)	0.084 [0.076–0.089]	0.098 [0.093–0.108]	**0.037***	0.060	-	-	-	-

Data are reported as adjusted mean (95% confidence interval [CI]). Step width (variability) is not reported for the BWM as the processing pipeline of BWM data did not enable the extraction of this measure.

*ANCOVA. Covariates: age, sex, BMI. Fixed factor: stage. Dependent variable: gait characteristic. *p < 0.05, **p < 0.01, η_p^2 = partial eta squared*

BWM. The domains of pace (step velocity: $p = 0.040$, $\eta_p^2 = 0.071$), rhythm (step time: $p = 0.048$, $\eta_p^2 = 0.066$; swing time: $p = 0.046$, $\eta_p^2 = 0.067$), and variability (step length variability: $p = 0.020$, $\eta_p^2 = 0.090$) were significantly ($p < 0.05$) different between the stages 3 and 4, after controlling for age, sex, and BMI (Table 3). The highest effect size was found in variability ($\eta_p^2 = 0.090$).

The complete results are reported in Table 3. To facilitate a comprehensive comparison across all gait domains, the results are visually summarised using two separate radar plots for the instrumented walkway and the BWM assessments, respectively, in Fig. 2 and Fig. 3. Gait characteristics were standardised using Z-scores derived from NSD-ISS stage 3 as the reference baseline to illustrate the magnitude and direction of measure change in stage 4 relative to stage 3.

Discussion

This study provides proof of concept that gait characteristics may serve as objective digital markers aligned with the clinically manifest portion of the NSD-ISS, representing an initial step toward the integration of continuous, quantitative assessments within this framework. We demonstrated that selected gait characteristics differed significantly between two clinically operationalised NSD-ISS stages, supporting their potential utility as objective indicators of disease stage. To our knowledge, this is the first study to investigate digital gait measures as quantitative markers within a biologically grounded staging system for PD, although the NSD-ISS was operationalised using clinical, rather than biological, criteria.

Our results support the feasibility of classifying an existing cohort of PD individuals into clinically defined NSD-ISS stages. The application of the NSD-ISS in this context represents an important step toward the implementation of a multidimensional staging system that may provide complementary information to widely adopted clinical staging systems, such as the Hoehn and Yahr (HY) system. Using the clinical operationalisation criteria [6], the NSD-ISS stages were assigned to participants in the ICICLE-GAIT cohort at the 36-month assessment, supporting the practical implementation of this novel staging framework in clinical research. As disease duration was relatively short, participants were only assigned to stages 3 and 4. Moreover, we did not consider the components of the staging system that are biologically based, limiting the assessment of the full NSD-ISS framework. This was primarily due to the absence of biological markers (α-synuclein seed amplification assay, α-syn SAA, predated by the ICICLE study, or universal use of dopamine transporter (DAT) imaging across the participants), necessary to define the disease from a purely biological perspective.

Future studies should evaluate the full NSD-ISS framework and identify objective measures that could complement current staging anchors—an area where gait characteristics may hold promise.

Findings from our PD cohort support the hypothesis that selective gait characteristics, sensitive to motor severity, differ between clinically defined NSD-ISS stages. Specifically, gait characteristics within the pace, rhythm, and variability domains showed significant differences between stages 3 and 4 across both assessment modalities. These domains have been widely reported in the literature as commonly affected in PD [13–17]. In contrast, gait characteristics related to postural control differed between stages only for the instrumented walkway, likely reflecting differences in measurement technology, data volume, and the number of derived metrics between the two instrumentations. Importantly, as the clinically manifest component of the NSD-ISS was operationalised using the MDS-UPDRS Part II, the observed differences in gait between stages likely reflect the greater functional impairment associated with higher NSD-ISS stages [6]. These findings suggest that gait characteristics are sensitive to the functional impairment represented by the NSD-ISS. This interpretation is also consistent with previous literature, which found significant associations between gait measures and MDS-UPDRS Part II scores, supporting the relevance of gait as an objective marker of functional motor impairment in PD [18, 19]. For example, gait characteristics such as step length and gait speed, which reflect overall gait quality, have been reported to be significantly associated with MDS-UPDRS part II, with feature selection score of 10.53 and 9.11, respectively, highlighting their potential relevance to functional impairment in PD [18].

Moreover, digital measures obtained from standardised tests (e.g., instrumented Timed-Up-and-Go, iTUG) were used to predict PD severity scales, such as the MDS-UPDRS Part II [19].

Our work represents a first attempt toward integrating laboratory-based digital gait measures into a biologically grounded staging framework for PD. Moreover, quantitative gait assessment enables the objective evaluation of mobility and the extraction of specific gait characteristics across multiple domains. In this context, gait characteristics may provide sensitive markers of functional impairment within the NSD-ISS and may complement established clinical measures.

Both the instrumented walkway and the BWM assessments provided gait measures capable of differentiating NSD-ISS stages, supporting the feasibility of performing measurements using controlled or active gait testing protocols. Several questions, however, remain unanswered: Do gait characteristics differentiate all NSD-ISS stages—from 1 to 6? Can the findings be reproduced in data from real-world capture? How do gait measures contribute to our understanding of biologically grounded stages, and how do they relate to emerging biomarkers such as imaging markers and bio samples? Addressing these questions will require further investigation.

Overall, this work provides proof of concept that gait characteristics derived during supervised gait tests using either an instrumented walkway or a BWM hold potential as digital markers by providing objective, quantitative information on the clinically manifest component of the NSD-ISS.

This study has several limitations. Firstly, the sample size was relatively small in both the instrumented walkway (N = 76) and BWM (N = 63) assessments, with participants being newly diagnosed with PD at recruitment. This may not have enabled patient classification in other NSD-ISS stages. Another limitation regards the extraction of gait characteristics: for the instrumented walkway, data was available only when the participant was walking over the mat, in contrast to the BWM, where data were available for the entire task duration, including wide turns on the circuit. The differences in the technology used, the volume of data collected, and the processing pipelines could have affected gait characteristics estimation. In addition, the ICICLE-GAIT cohort lacks biological data (SAAs or universal evidence of dopaminergic neuron dysfunction, such as DAT imaging), which is required to diagnose PD from a purely biological perspective. For this reason, the analysis was limited to the clinically manifest portion of the NSD-ISS. However, all participants were diagnosed with idiopathic PD according to the UK Parkinson's Disease Brain Bank criteria by a movement disorder specialist, and diagnosis was confirmed at each follow-up visit. Moreover, the results of this exploratory analysis were not directly compared with literature using the NSD-ISS, as no previous work has explored the role of gait characteristics with this staging framework. However, the findings from the NSD-ISS were considered in relation to the MDS-UPDRS Part II, which was used to operationalise stages. Finally, gait characteristics were derived exclusively from supervised gait tests, limiting the validity of the results to the laboratory setting. Initiatives such as the Mobilise-D [20–23] consortium have developed more advanced, standardised, and sensitive approaches in real-world settings, which may further extend and strengthen the findings of the present study.

In conclusion, this exploratory analysis provides proof of concept for the potential role of gait characteristics as objective markers within the NSD-ISS framework. Specifically, we observed that selected gait measures within the domains of pace, rhythm, variability, and postural control significantly differ between stages 3 and 4. Further studies should expand our work, by exploring whether gait characteristics can differentiate other stages or by validating our results longitudinally, and possibly in real-world settings.

Methods

Participants

This was a cross-sectional study utilising data collected as part of the ICICLE-GAIT, a nested study within the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-PD (ICICLE-PD) [11,16,24–26]. Full methodology has been previously described [11,24,26]. Briefly, participants were recruited from community and outpatient clinics in Newcastle upon Tyne/Gateshead and Cambridgeshire, UK between June 2009 and December 2011 [25,26]. PD diagnosis was made according to the UK Parkinson's disease Brain Bank criteria by a movement disorder specialist and confirmed at each follow-up visit [27]. Baseline exclusion criteria of the ICICLE-GAIT comprised: significant memory impairment (Mini-Mental State Exam (MMSE) < 24) or a diagnosis of Parkinson's disease dementia [28]; dementia with Lewy bodies; drug-induced parkinsonism; "vascular" parkinsonism; atypical parkinsonian disorders; poor command of English; or presence of any neurological (other than idiopathic PD), orthopaedic, or cardiovascular conditions that severely impacted mobility [26]. Participants of the ICICLE-GAIT study were assessed at 18-, 36-, 54-, and 72-months following baseline visit. For our cross-sectional study, we selected data from the 36-month visit for several reasons. Firstly, this time point provided the largest sample size [26]. In addition, given the exploratory nature of this analysis, a single time-point cross-sectional approach was prioritised over a longitudinal or repeated-measures design. This strategy was implemented to establish a proof of concept of the potential alignment between the NSD-ISS and gait before introducing the complexities associated with longitudinal analysis.

At 36-month assessment, we included all PD participants for whom complete data was available.

Ethical considerations

ICICLE-GAIT was conducted in accordance with the Declaration of Helsinki, and ethical approval was granted by the Newcastle and North Tyneside Research Ethics Committee (REC reference: 09/H0906/82). All participants provided informed consent prior to assessment.

Demographic and clinical measures

Demographic and clinical data were extracted from within the ICICLE-GAIT dataset. Demographic variables included age, sex, height (m), weight (kg), and body mass index (BMI, kg/m^2). Clinical data comprised the MDS-UPDRS Parts II and III [29], the Hoehn and Yahr (HY) scale [3], and the Montreal Cognitive Assessment (MoCA) scale [30].

Application of the clinically operationalised NSD-ISS to the ICICLE-GAIT cohort

As outlined above, this analysis focused solely on the clinically manifest portion of the NSD-ISS continuum (stages 3-6) because biological markers required for earlier stages were not consistently available in the ICICLE-GAIT. PD participants from the 36-month assessment were classified into the NSD-ISS stages 3-6, as operationalised by MDS-UPDRS Part II scores: Stage 3: $3 \leq$ MDS-UPDRS Part II ≤ 13; Stage 4: $14 \leq$ MDS-UPDRS Part II ≤ 26; Stage 5: $27 \leq$ MDS-UPDRS Part II ≤ 39; Stage 6: MDS-UPDRS Part II ≥ 40 [5,6,29]. However, the final analysis was restricted to stages 3 and 4, as participants did not exhibit MDS-UPDRS Part II scores high enough to correspond to stages 5 or 6.

Gait assessment

Within the ICICLE-GAIT, gait was measured during a two-minute walk at a comfortable pace around a 25-m oval circuit using a 7-metre-long instrumented walkway (Platinum model GAITRite, CIR systems Inc, USA; sampling frequency 240 Hz). At the same time, the participants wore a tri-axial accelerometer-based body worn monitor (BWM) (Axivity AX3, York, UK; dimensions 23.0×32.5×7.6 mm; weight: 11 grams; triaxial accelerometer range: ±8 g, sampling frequency: 100 Hz) on the lower back (fifth lumbar vertebra, L5) during the entire walking trial, including turns [31]. Gait data were recorded only during the 7-metre straight walkway for the instrumented walkway, instead of the entire two-minute continuous gait recording for the BWM. These diverse assessment modalities may result in different estimations of quantitative gait characteristics, as the walkway measured exclusively straight walking sections and, consequently a lower volume of gait cycles if compared to the BWM. However, given the exploratory nature of this work, both the walkway and the BWM assessments were retained for further investigation and the corresponding data were analysed separately.

Gait data processing

Gait signals acquired during the two-minute continuous walking task were processed and analysed independently for each assessment modality. To extract the quantitative gait characteristics, established data processing pipelines were implemented; these workflows were derived from previously validated protocols applied within the ICICLE-GAIT or in studies leveraging identical instrumentation [11,31].

1. Instrumented walkway. Gait measures were derived and quantified according to an *a priori* model developed in older adults [32] and validated in PD [33]. This model describes 16 discrete gait characteristics representing the microstructural (micro) domains of pace, rhythm, variability, asymmetry, and postural control (see Table 2 for the list of characteristics).
2. BWM. BWM data were downloaded to a computer and analysed by a MATLAB program. Firstly, accelerometer raw signals were converted into a horizontal-vertical coordinate system [34] and filtered with a fourth order Butterworth filter at 20 Hz [35–37]. Fourteen gait characteristics, representing five microstructural gait domains (pace, variability, rhythm, asymmetry, and postural control; see Table 2 for the list of characteristics) were extracted according to a methodology fully detailed in [31,38]. Briefly, the initial contact (IC, heel strike) and final contact (FC, toe-off) events within the gait cycle were recognized from the Gaussian continuous wavelet transform of the vertical acceleration. ICs and FCs events enabled the estimation of step, stance, and swing time [31]. ICs were also used to obtain step length from the inverted pendulum model [37]. Step length was obtained using the equation *step length* = $2\sqrt{2lh - h^2}$, where *h* is equal to the change in height of the centre of mass (CoM), and *l* is the pendulum length [37]. Step velocity was computed as the ratio between step length and step time [31]. From this, 14 gait characteristics of the gait model comprising the five domains were determined as detailed previously [31,32,38]. To obtain step variability, the standard deviation (SD) from all steps (left and right combined) was calculated. Asymmetry was computed as the absolute difference between left and right steps (alternating) for each walking pass, averaged across all passes [12,31].

Conceptual models of gait were utilised in this analysis because they provide a simplified framework, minimising dimensionality while preserving clinical interpretability [33].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (version 24.0). Identical statistical workflows were executed independently for the instrumented walkway and the BWM data. To minimise the risk of selection bias, the demographic and clinical characteristics of participants included in and excluded from the analyses were compared for both the instrumented walkway and BWM assessments (Supplementary Table 2). Normality was assessed using the Shapiro-Wilk test (non-normal: $p < 0.05$). Accordingly, descriptive statistics were reported as means $\pm$ standard deviations (SD) for normally distributed data, or as medians and interquartile ranges (IQR: Q1-Q3) for non-normally distributed continuous variables (Table 1, Table 2, Supplementary Table 1).

Unadjusted between-group differences in demographic, and clinical characteristics between the identified NSD-ISS stages were evaluated using independent t-tests for normally distributed continuous data, Mann-Whitney U tests for non-normal continuous distributions, and Chi-square (χ^2) tests for categorical variables. To quantify the magnitude of these unadjusted differences, effect sizes (Cohen's *d* for t-tests and $r=Z/\sqrt{N}$ for Mann-Whitney U tests) were calculated.

To control for potential confounding factors, between-group differences in quantitative gait characteristics were further evaluated using an analysis of covariance (ANCOVA). Variables were transformed where necessary to meet assumptions for parametric tests [39]. Discrete gait characteristics were defined as dependent variables, the NSD-ISS stage was entered as the fixed factor, and age, sex, and BMI were incorporated as standard covariates [39–41]. For the ANCOVA models, effect sizes were estimated using partial eta-squared (η_p^2), and the estimated marginal means for each stage were reported alongside their 95% confidence interval (CI) (Table 3). Given the exploratory nature of this analysis, we used $p < 0.05$ to guide statistical interpretation and did not adjust for multiple comparisons [41]. We also provided $p < 0.01$ to help the reader assess the statistical strength of the results [6,41].

Declarations

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Authors contributions

A.J.Y., S.D.D., L.R., L.A., and C.P. conceptualised and designed the study. L.A. and C.P. performed data curation. C.P. conducted the data analysis. C.P., A.J.Y., S.D.D., L.R., and C.C. contributed to the interpretation of the data analysis. C.P. wrote the main manuscript text. All authors edited and reviewed the manuscript. All authors approved the final manuscript for submission.

Data availability statement

The datasets analysed during this study are not publicly available due to institutional and/or ethical restrictions. Request for data access should be directed to the corresponding author's email alison.yarnall@newcastle.ac.uk. All data supporting the findings of this study are available in the paper and in Supplementary Information.

Competing interests

AJY has received research support from the NIHR BRC: Newcastle, Dunhill Medical Trust, EU IMI, NIHR, Parkinson's UK, Michael J Fox Foundation, Weston Brain Institute, Lewy Body Society, Intercept Pharmaceuticals, Electrocore; and has received funding and/or honoraria from Britannia, UCB, Abbvie, GSK, Teva-Lundbeck, GE Healthcare and Genus for attending or speaking at educational events. She declares no financial or non-financial competing interests.

SDD is a shareholder in Enoda Health Ltd. This shareholding has no financial or non-financial competing interests. SDD reports consultancy activity with Grasshopper Health, Inc. outside of this study. CC receives salary from Newcastle University and Parkinson's UK. She has received advisory, consulting or lecture fees from AbbVie, Bial, Britannia, inMuneBio, Mission Therapeutics, Merz and Roche, and research funding from Parkinson's UK, Edmond J Safra Foundation, John Black Charitable Foundation, Gatsby Charitable Foundation, van Andel Institute, Michael J Fox Foundation, National Institute of Health and Care Research and Cure Parkinson's. She financial or non-financial competing interests.

LR has received research support from the NIHR Newcastle Biomedical Research Centre, Dunhill Medical Trust, EU IMI, NIHR, Parkinson's UK, Michael J Fox Foundation, MRC, EPSRC and is a shareholder in Enoda Health Ltd. This shareholding has no financial or non-financial competing interests.

All other authors declare no financial or non-financial competing interests.

References

1. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. *The Lancet* vol. 397 2284–2303 Preprint at (2021). https://doi.org/10.1016/S0140-6736(21)00218-X
2. Chahine, L. M. et al. Proposal for a Biologic Staging System of Parkinson's Disease. *Journal of Parkinson's disease* vol. 13 297–309 Preprint at (2023). https://doi.org/10.3233/JPD-225111
3. Hoehn, M. M. & Yahr, M. D. Parkinsonism: onset, progression and mortality. *Neurology* **17**, 427 (1967).
4. Simuni, T. et al. Neuronal α-Synuclein Disease Stage Progression over 5 Years. *Mov. Disord.* https://doi.org/10.1002/mds.30191 (2025).
5. Simuni, T. *et al. Position Paper A Biological Definition of Neuronal α-Synuclein Disease: Towards an Integrated Staging System for Research*. vol. 23 (2024).
6. Dam, T. et al. Neuronal alpha-Synuclein Disease integrated staging system performance in PPMI, PASADENA, and SPARK baseline cohorts. *NPJ Parkinsons Dis* **10**, (2024).
7. Mancini, M. et al. Digital gait biomarkers in Parkinson's disease: susceptibility/risk, progression, response to exercise, and prognosis. *npj Parkinson's Disease* vol. 11 Preprint at (2025). https://doi.org/10.1038/s41531-025-00897-1
8. Del Din, S. et al. Gait analysis with wearables predicts conversion to parkinson disease. *Ann. Neurol.* **86**, 357–367 (2019).

9. Welzel, J. et al. Step length is a promising progression marker in parkinson's disease. *Sensors* **21**, (2021).
10. Morris, R. et al. Gait Rather Than Cognition Predicts Decline in Specific Cognitive Domains in Early Parkinson's Disease. *Journals Gerontol. - Ser. Biol. Sci. Med. Sci.* **72**, 1656–1662 (2017).
11. Wilson, J. et al. Gait Progression Over 6 Years in Parkinson's Disease: Effects of Age, Medication, and Pathology. *Front Aging Neurosci* **12**, (2020).
12. Galna, B., Lord, S., Burn, D. J. & Rochester, L. Progression of gait dysfunction in incident Parkinson's disease: Impact of medication and phenotype. *Mov. Disord.* **30**, 359–367 (2015).
13. Grajić, M., Stanković, I., Radovanović, S. & Kostić, V. Gait in drug naïve patients with de novo parkinson's disease – altered but symmetric. *Neurol. Res.* **37**, 712–716 (2015).
14. Wu, Z. et al. Mild Gait Impairment and Its Potential Diagnostic Value in Patients with Early-Stage Parkinson's Disease. *Behavioural Neurology* (2021). (2021).
15. Zhang, X. et al. Single- and dual-task gait performance and their diagnostic value in early-stage Parkinson's disease. *Front Neurol* **13**, (2022).
16. Rehman, R. Z. U. et al. Selecting Clinically Relevant Gait Characteristics for Classification of Early Parkinson's Disease: A Comprehensive Machine Learning Approach. *Sci Rep* **9**, (2019).
17. Del Din, S., Godfrey, A., Galna, B., Lord, S. & Rochester, L. Free-living gait characteristics in ageing and Parkinson's disease: Impact of environment and ambulatory bout length. *J Neuroeng. Rehabil* **13**, (2016).
18. Mirelman, A. et al. Digital Mobility Measures: A Window into Real-World Severity and Progression of Parkinson's Disease. *Mov. Disord.* **39**, 328–338 (2024).
19. Dewey, D. C. et al. Automated gait and balance parameters diagnose and correlate with severity in Parkinson disease. *J. Neurol. Sci.* **345**, 131–138 (2014).
20. Micó-Amigo, M. E. et al. Assessing real-world gait with digital technology? Validation, insights and recommendations from the Mobilise-D consortium. *J Neuroeng. Rehabil* **20**, (2023).
21. Mazzà, C. et al. Technical validation of real-world monitoring of gait: A multicentric observational study. *BMJ Open* **11**, (2021).
22. Mikolaizak, A. S. et al. Connecting real-world digital mobility assessment to clinical outcomes for regulatory and clinical endorsement–the Mobilise-D study protocol. *PLoS One* **17**, (2022).
23. Yarnall, A. J. et al. The future of clinical trials? Monitoring mobility as an outcome measure in Parkinson's disease: The mobilise-D study. *J. Parkinsons Dis.* **16**, 110–124 (2026).
24. Del Din, S., Godfrey, A., Galna, B., Lord, S. & Rochester, L. Free-living gait characteristics in ageing and Parkinson's disease: Impact of environment and ambulatory bout length. *J Neuroeng. Rehabil* **13**, (2016).
25. Yarnall, A. J. et al. Characterizing Mild Cognitive Impairment in Incident Parkinson Disease The ICICLE-PD Study. www.neurology.org (2014).

26. Kirk, C. et al. Can Digital Mobility Assessment Enhance the Clinical Assessment of Disease Severity in Parkinson's Disease? *J. Parkinsons Dis.* **13**, 1001–1011 (2023).
27. Hughes, A. J., Daniel, S. E., Kilford, L. & Lees, A. J. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatry*. **55**, 181–184 (1992).
28. Emre, M. et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Movement Disorders* vol. 22 1689–1707 Preprint at (2007). https://doi.org/10.1002/mds.21507
29. Goetz, C. G. et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov. Disord.* **23**, 2129–2170 (2008).
30. Nasreddine, Z. S. et al. The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* **53**, 695–699 (2005).
31. Del Din, S., Godfrey, A. & Rochester, L. Validation of an Accelerometer to Quantify a Comprehensive Battery of Gait Characteristics in Healthy Older Adults and Parkinson's Disease: Toward Clinical and at Home Use. *IEEE J. Biomed. Health Inf.* **20**, 838–847 (2016).
32. Lord, S. et al. Independent domains of gait in older adults and associated motor and nonmotor attributes: Validation of a factor analysis approach. *Journals Gerontol. - Ser. Biol. Sci. Med. Sci.* **68**, 820–827 (2013).
33. Lord, S., Galna, B. & Rochester, L. Moving forward on gait measurement: Toward a more refined approach. *Movement Disorders* vol. 28 1534–1543 Preprint at (2013). https://doi.org/10.1002/mds.25545
34. Moe-Nilssen, R. *A New Method for Evaluating Motor Control in Gait under Real-Life Environmental Conditions. Part 1: The Instrument*. *Clinical Biomechanics* vol. 13 (1998).
35. McCamley, J., Donati, M., Grimpampi, E. & Mazzà, C. An enhanced estimate of initial contact and final contact instants of time using lower trunk inertial sensor data. *Gait Posture*. **36**, 316–318 (2012).
36. González, R. C., López, A. M., Rodriguez-Uría, J., Álvarez, D. & Alvarez, J. C. Real-time gait event detection for normal subjects from lower trunk accelerations. *Gait Posture*. **31**, 322–325 (2010).
37. Zijlstra, W. & Hof, A. L. *Assessment of Spatio-Temporal Gait Parameters from Trunk Accelerations during Human Walking*.
38. Godfrey, A., Del Din, S., Barry, G., Mathers, J. C. & Rochester, L. Instrumenting gait with an accelerometer: A system and algorithm examination. *Med. Eng. Phys.* **37**, 400–407 (2015).
39. Lord, S. et al. Ambulatory activity in incident Parkinson's: More than meets the eye? *J. Neurol.* **260**, 2964–2972 (2013).
40. Morris, R. et al. Cognitive function in people with and without freezing of gait in Parkinson's disease. *NPJ Parkinsons Dis* **6**, (2020).

41. Del Din, S. et al. Continuous Real-World Gait Monitoring in Idiopathic REM Sleep Behavior Disorder. *J. Parkinsons Dis.* **10**, 283–299 (2020).

Figures

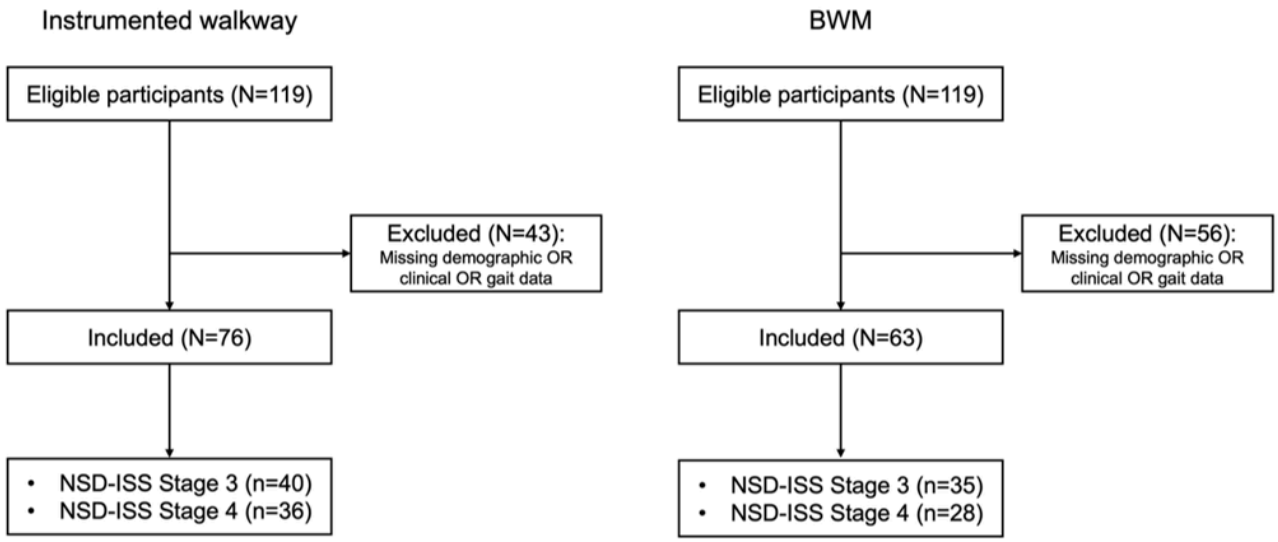


Figure 1

Flow charts of participants included in instrumented walkway and BWM assessments, with NSD-ISS stage assignment.

Abbreviations: BWM - body-worn monitor, NSD-ISS - Neuronal alpha-synuclein disease-integrated staging system

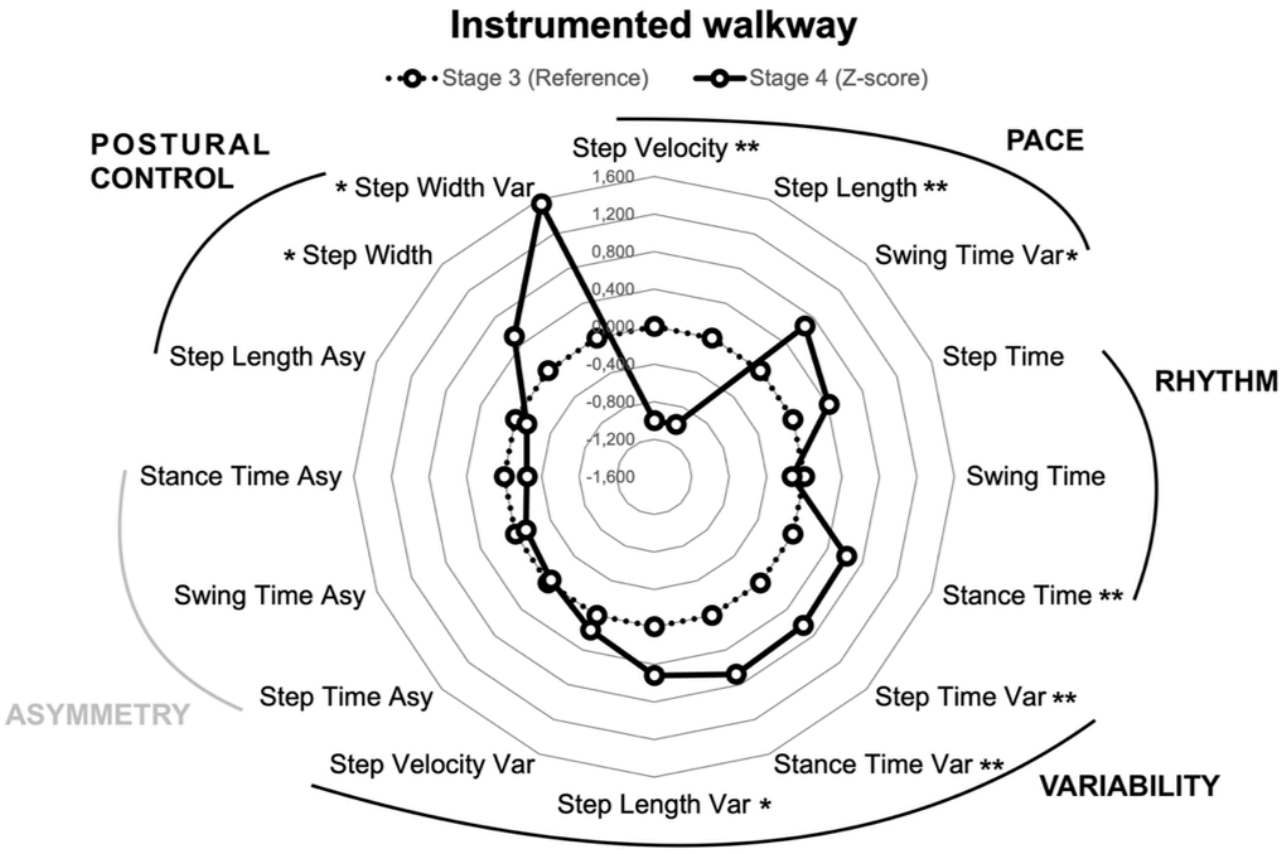


Figure 2

Radar plot illustrating the gait characteristics in the NSD-ISS stages 3 and 4 for the instrumented walkway. Stage 3 is the zero (Reference) line, stage 4 is the Z-score line, obtained as $Z\text{-score}_{Xstage4}$ = (mean (X_{stage4}) - mean (X_{stage3})) / std (X_{stage3}), where X is the gait characteristic considered. Significant differences: *p < 0.05, **p < 0.01. Abbreviations used: Asy = asymmetry, Var = variability.

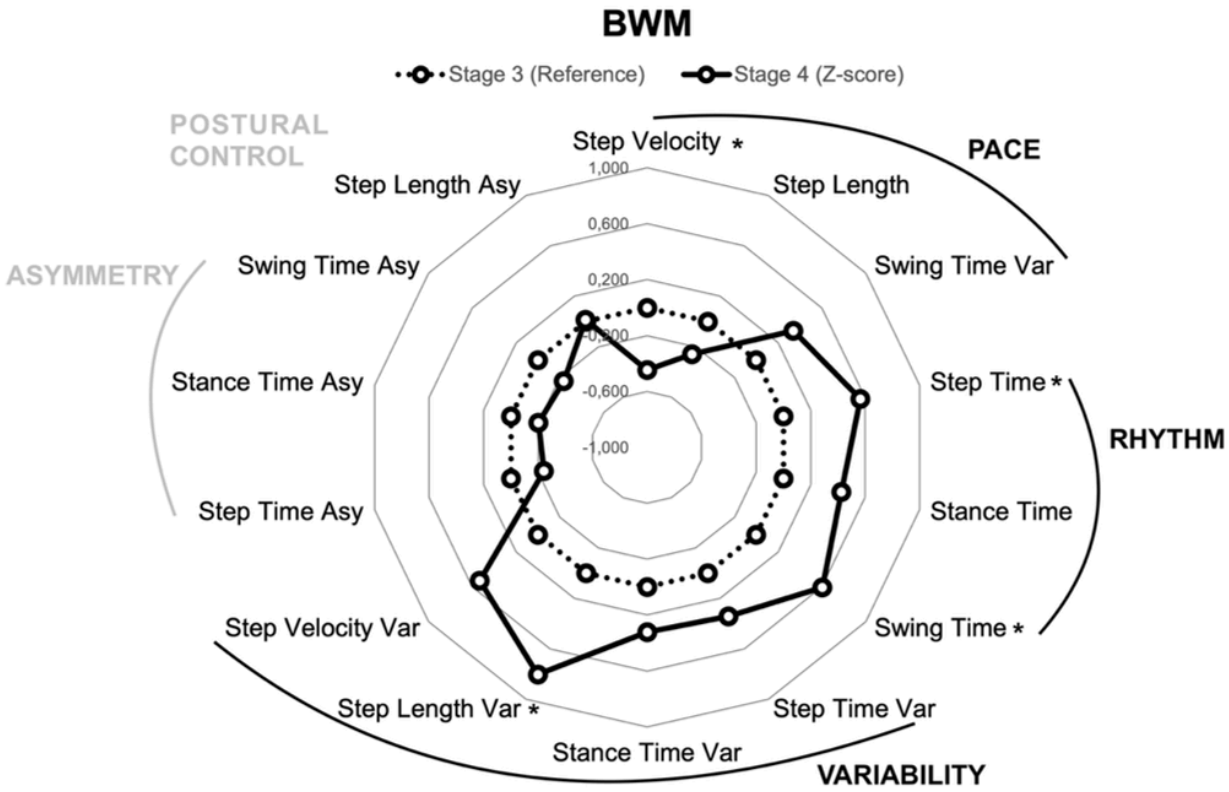


Figure 3

Radar plot illustrating the gait characteristics in the NSD-ISS stages 3 and 4 for the BWM. Stage 3 is the zero (Reference) line, stage 4 is the Z-score line, obtained as $Z\text{-score}_{Xstage4}$ = (mean (X_{stage4}) - mean (X_{stage3})) / std (X_{stage3}), where X is the gait characteristic considered. Significant differences: *p < 0.05, **p < 0.01. Abbreviations used: Asy = asymmetry, Var = variability.

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