A Multifactorial Model of Multiple Sclerosis Gait and its Changes Across Different Disability Levels

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***Abstract*— *Objective:* Mobility assessment is critical in the clinical management of people with Multiple Sclerosis (pwMS). Instrumented gait analysis provides a plethora of metrics for quantifying concurrent factors contributing to gait deterioration. However, a gait model discriminating underlying features contributing to this deterioration is lacking in pwMS. This study aimed at developing and validating such a model. *Methods:* The gait of 24 healthy controls and 114 pwMS with mild, moderate, or severe disability was measured with inertial sensors on the shanks and lower trunk while walking for 6 minutes along a hospital corridor. Twenty out of thirty-six initially explored metrics computed from the sensor data met the quality criteria for exploratory factor analysis. This analysis provided the sought model, which underwent a confirmatory factor analysis before being used to characterize gait impairment across the three disability groups. *Results:* A gait model consisting of five domains (rhythm/variability, pace, asymmetry, and forward and lateral dynamic balance) was revealed by the factor analysis, which was able to highlight gait abnormalities across the disability groups: significant alterations in rhythm/variability-, asymmetry-, and pace-based features were present in the mild group, but these were more profound in the moderate and severe groups. Deterioration in dynamic balance-based features was only noted in pwMS with a moderate and severe disability. *Conclusion:* A conceptual model of gait for disease-specific mobility assessment in pwMS was successfully developed and tested. *Significance:* The new model, built with metrics that represent gait impairment in pwMS, highlighted clinically relevant changes across different disability levels, including those with no clinically observable walking disability. This shows the clear potential as a monitoring biomarker in pwMS.**

***Index Terms*—Accelerometry, gait monitoring, six-minute walk, wearable sensors.**

I. Introduction

MULTIPLE sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system [1], typically characterized by gait impairment, poor balance, and loss of coordination [2], [3], which all lead to an increased risk of falling [4]–[6].

Assessment of gait and mobility is clearly of interest for the clinical management of this disease. As such, this forms a critical component of the Expanded Disability Status Scale (EDSS) [7], one of the most widely used outcome measures in clinical trials of MS. The EDSS ranges from 0 (normal status) to 10 (death from MS) in 0.5-unit increments, each representing a worsening disability. EDSS scores are calculated based on the findings of a neurological examination, which determines the scores of seven Functional Systems and the ability of the people with MS (pwMS) to walk up to 500 meters. EDSS scores up to 3.5 are given to those who have no apparent gait impairment, whereas scores of 4.0 to 6.5 are largely informed by the maximum distance walked and the level of assistance needed for walking. Higher scores relate to more severe levels of disability and affecting bulbar and upper limb, as well as lower limb function. However, many pwMS suffer from gait alterations that are too subtle to be captured by a standard neurological examination but could be reliably quantified using instrumented gait analysis. This approach could also help assess concurrent motor and balance difficulties and provide clinicians with information about subtle changes in the pyramidal or cerebellar domains not captured by the EDSS system.

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TABLE I
DEMOGRAPHIC CHARACTERISTICS OF PEOPLE WITH MULTIPLE SCLEROSIS AND HEALTHY CONTROLS

	Age	**Gender**	**MS subtypes**			**Walking assistive devices**		
	Mean (SD)	*N male*	*PP*	*RR*	*SP*	*None*	*Unilateral*	*Bilateral*
Healthy controls *n = 24*	49.9 (8.3) [a]	8	–	–	–	24	0	0
MSmild *n = 25* *EDSS ≤ 3.5*	43.6 (10.5) [b]	8	1	21	3	25	0	0
MSmod *n = 48* *4.0 ≤ EDSS ≤ 5.5*	53.8 (11.7)	21	1	13	34	44	4	0
MSsev *n = 41* *EDSS ≥ 6.0*	54.1 (10.6)	14	1	7	33	7	18	16

[a]Denotes significant difference in age as compared to MSmild ($t(47) = 2.3$; p-value = 0.023).
[b]Denotes significant difference in age as compared to MSmod ($t(71) = -3.7$; p-value < 0.001) and to MSsev ($t(64) = -3.9$; p-value < 0.001).
SD: standard deviation; EDSS: Expanded Disability Status Scale; MSmild: people with a mild MS disability; MSmod: people with a moderate MS disability; MSsev: people with a severe MS disability.

Changes in gait characteristics across different disability levels have been previously assessed in pwMS with moderate or severe disability by measuring spatiotemporal and kinematics metrics [8]–[15] and/or by investigating metrics more related to the overall quality and energetic efficiency of gait, such as regularity among steps and strides, symmetry, and gait intensity [11], [16]–[21]. Compared to healthy controls, pwMS with moderate or severe walking disability show reduced gait speed, shorter stride length, and prolonged swing phase, double limb support time, and stride time [22]. Moreover, greater step time variability has been observed in pwMS than in controls, which has also been associated with impaired balance and increased risk of falls [23], [24]. Few studies, however, have focused on identifying pathology specific characteristics of gait in pwMS with mild disability [5], [8], [10], [12], [19], [23], [25]–[27]. While all these studies reported some impairments in spatiotemporal and kinematic gait parameters, they failed to provide consistent results, likely due to the limited number of participants and the differences in the chosen EDSS cut-offs. For example, some studies showed a significant decrease in walking speed, shorter strides, and a prolonged double limb support phase [5], [23], [25], while others did not find any significant differences in those metrics when compared to healthy controls [8], [10], [27]. However, in all these studies, gait limitations resulting from poor balance control and/or altered coordination and tremor were not investigated, although these factors have been cited as mechanisms contributing to gait dysfunction in pwMS [2].

While the integration between spatiotemporal and gait quality metrics seems the ideal goal to pursue to thoroughly assess gait in pwMS [21], high potential covariance among these metrics may compromise their clinical interpretation. The need to reduce the number of gait metrics to a more manageable size, while retaining as much of the original information as possible has previously led to the development of several conceptual gait models. In particular, these models have been proposed for community-dwelling older adults [28]–[30], older adults with mild cognitive impairment syndromes [31], people with dementia [32], people with Parkinson's disease (PD) [33]–[36], people with early-stage neurological (peripheral vestibular, cerebellar, hypokinetic, vascular or functional) gait disorders [37], and people with hip fracture [38]. Overall, these studies showed that gait characteristics of different cohorts do not consistently load onto identical domains. Therefore, if a non-disease specific conceptual gait model is used, this might create ambiguity and limit gait metrics' interpretation. To the best of our knowledge, a gait model of this kind is currently lacking for pwMS. This hinders the identification of the gait metrics best suited to act as biomarkers for disease progression or efficacy of an intervention in this cohort. The aims of this study were to a) propose a conceptual domain model of gait that is specific for pwMS; and b) test the model's ability to detect and quantify gait and balance impairment across different levels of disability, including also those pwMS with mild disease severity, for whom these are not yet clinically detectable.

II. MATERIALS AND METHODS

A. Participants

This study was approved by the NRES Committee Yorkshire & The Humber-Bradford Leeds (Ref: 15/YH/0300) and by the North of Scotland Research Ethics Committee (Ref: 17/NS/0020). Following routine clinic appointments, 114 pwMS provided written informed consent before entering the study (Table I). Of these, 32 pwMS were taking part in an observational study (STH18829; IRAS-183915), 31 pwMS in a double-blinded Investigational Medicinal Product clinical trial (CTIMP) attended for their baseline assessment (STH17249; IRAS-115286), while 51 pwMS participated in a double-blinded, intervention-based, and non-CTIMP (STH19739; IRAS-224422). Post-intervention gait data from the subset enrolled in the latter trial were used to test the robustness of the proposed gait model.

People with neurological conditions other than MS, coexisting cardiovascular disease, orthopedic pathologies causing lower limb disability, significant visual impairment, excessive alcohol consumption, or those taking vestibular sedatives were excluded from this study. People with relapsing-

remitting MS were only included if no relapse had occurred for 30 days prior to testing and were on stable treatments for the past three months. A group of 24 healthy controls (Ctrl) with no history of musculoskeletal or neurological disorders that might influence their balance or mobility also took part in the study.

The level of disability in pwMS was scored according to the EDSS by a neurologist with experience in MS. Those pwMS who were able to walk independently and had EDSS scores of 3.5 and below were classified as mild (MSmild), those who were able to walk limited distances independently and had EDSS scores ranging between 4.0 and 5.5 were classified as moderate (MSmod), and those who were only able to walk using a unilateral or bilateral assistive device with EDSS score of 6 and above were classified as severe (MSsev). Demographic data from the four groups were compared using the independent Mann-Whitney U for ordinal variables (e.g., age and EDSS scores) and the Pearson's chi-square test for categorical variables (e.g., gender).

B. Gait assessment

Participants were instrumented with three tri-axial inertial measurement units (IMU; OPAL, APDM Inc., Portland, OR, USA, sampling frequency 128 Hz, accelerometer range ± 6 g) fixed through elastic bands on the anterior aspect of both lower shanks and at the lower back (L4-L5). Sensing axes were aligned approximately along the anatomical antero-posterior (AP), medio-lateral (ML), and vertical (V) directions. Participants were asked to walk for 6 minutes along a 10-m hospital corridor, going back and forth at their comfortable, self-preferred pace, and could rest if needed. Walking assistive devices such as canes or tripods were permitted if used in daily life.

C. Gait metrics

IMU signals were pre-processed using in-house developed routines (MATLAB R2019a, MathWorks, Inc., Natick, MA, USA). Acceleration raw data from the lumbar IMU were first reoriented to a horizontal-vertical coordinate system [39] and then filtered with a 10 Hz cut-off, zero phase, low-pass Butterworth filter. Resting breaks and turns were automatically removed [20], and only isolated bouts of steady-state walking were used for further analysis. Turns were detected by searching for steep positive or negative gradients in the trunk rotation angle (obtained as the integral of the lumbar IMU angular velocity around the V axis, filtered with a 1.5 Hz cut-off frequency low-pass Butterworth filter), which exceeded a threshold of 115°. Resting breaks were identified by checking in non-overlapping 2 s windows if more than 50% of the samples had both the norm of the lumbar IMU angular velocity and the norm of the lumbar IMU acceleration lower than 0.5 rad/s and within ± 10% of 9.81 m/s², respectively [40].

An initial set of gait metrics to undergo the factor analysis was selected based on previous relevant literature on healthy older adults [28], [31], pwMS [16], [18]–[21], and people with PD [30], [36]. These led to the identification of 36 metrics (Table I-supplementary material). Of these, 23 described spatiotemporal gait features and were calculated from the gait events detected from shank angular velocity signals. The remaining 13, referred to as gait quality metrics, were extracted by processing in the time and frequency domain the resultant lumbar filtered accelerations and their AP, ML, and V components.

Initial and final contacts were detected from the ML angular velocity of the right and left shank sensors [41] and used to isolate individual steps. The average spatiotemporal gait features were calculated over the total walking bouts: stride time, step time, stance time, swing time, single support time, double support time, swing phase, double support phase, and gait speed (determined as the ratio between the distance covered during testing and the ambulation time, excluding breaks and turns). Variability in stride time, step time, stance time, and swing time was also quantified across at least 50 steps [42] using both the coefficient of variance (CV) and the combined within-person standard deviation (SD). Asymmetry of the metrics was defined both as the absolute difference between the mean values for the right and left limbs [43] and as the natural logarithm of the absolute ratio of the shorter to the longer mean value of the metric [44]. The 13 gait quality metrics were computed using the first five strides of each walking bout and then averaged over the total walking bouts recorded over the 6 minutes. These included: root mean square (RMS), RMS ratio, jerk, jerk ratio, step regularity, stride regularity, gait symmetry, and harmonic ratio. Details for each metric are reported in Table I-supplementary material.

D. Factor analysis

All statistical analyses were carried out in R (R Core Team, 2017). A factor analysis, including Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA), was performed to identify which factors, referred to as domains, best describe MS gait in the investigated sample. EFA, based on the analysis of covariance, was chosen over similar techniques (e.g., Principal Component Analysis) to reach a theoretical solution that is minimally affected by error variability and to explain the underlying constructs of the metrics of interest.

Our sample of 114 pwMS was large enough to achieve convergent and admissible solutions [45] (ratio of the number of metrics to the number of factors equal to 20:5 and mean level of communalities of 0.82 (0.65-0.92)).

The suitability of the chosen EFA analysis was firstly ensured by inspecting the Pearson's correlation matrix (R) and including only the gait metrics for which at least one correlation coefficient (r) exceeded 0.3. Secondly, if two metrics presented multicollinearity (i.e., a variable is explained by other variables in the analysis having $r \geq 0.9$) or singularity (i.e., perfect correlation, $r = 1$), one of them was removed before further analysis [46]. This step was taken to avoid redundancy and duplication in the model while ensuring that the gait metrics accurately characterized the underlying construct in pwMS. Thirdly, the factorability of R and the appropriateness of EFA were tested by performing Kaiser-Meyer-Olkin (KMO)

statistics of sampling adequacy [47]. According to these criteria, if the overall and the individual KMO measures, calculated for all metrics combined and for each one separately, were lower than 0.7 and 0.5, respectively [48], the metrics were removed from the EFA analysis. Finally, Bartlett's test of sphericity was used to verify the null hypothesis that R is an identity matrix (p-value < 0.05). Principal axis factoring was chosen as the extraction method, retaining only factors: (1) with eigenvalues above 1 [49]; (2) explaining at least 5% of the total variance; (3) with eigenvalues higher than those obtained for a randomly generated dataset having the same number of metrics and participants [50]; (4) satisfying the scree test criterion [51] (based on which the number of factors to retain is indicated by the number of eigenvalues above the point of inflection of the eigenvalues vs the number of factors curve). With the aim of improving the interpretability of the factor solution, a rotational method was then employed. This method allows for a simpler and theoretically more meaningful structure with minimal cross-loading of metrics. Since the retained factors were expected to be correlated to each other, an oblique rotation was selected. Specifically, promax was applied because of its computational speed [46]. To the best of the authors' knowledge, no empirically based rules are currently available to guide the decision regarding the power (k) to which the loadings are raised in a promax rotation. Values between 2 and 4 allow to stably reduce error and bias of the sample factor pattern [52]. We opted for k = 4, as previously suggested ([53], [54]). A threshold value of 0.45 was set as a minimum significant factor loading [55], which corresponds to a 20% overlapping variance.

The robustness of the generated EFA model was finally tested, repeating the CFA using data collected in the post-intervention gait test from the 51 participants enrolled in the non-CTIMP study.

E. Group analysis

The gait model resulting from the EFA analysis was applied to investigate changes in gait features across the Ctrl, MSsev, MSmod, and MSmild groups. Minimum, 25th percentile, median, 75th percentile, and maximum values were calculated for the identified gait metrics. Shapiro-Wilk test highlighted that most of the gait metrics were not normally distributed. Differences between Ctrl, MSsev, MSmod, and MSmild groups on gait performance in pwMS were evaluated with one-way non-parametric multivariate analysis of variance (PERMANOVA, [56]). Since one-way PERMANOVA was statistically significant, non-parametric Kruskal-Wallis tests were run to identify which specific metrics contributed to the significant global effect. Statistical significance was accepted at a Bonferroni-adjusted alpha level of 0.003, which corresponds to 0.05 divided by the number of statistical tests conducted (i.e., 20 tests). Independent Mann-Whitney U tests were then used for post-hoc comparisons between groups (Ctrl vs MSmild; Ctrl vs MSmod; Ctrl vs MSsev; MSmild vs MSmod; MSmild vs MSsev; MSmod vs MSsev), with a Bonferroni correction applied to compensate for the use of multiple comparisons (p-value < 0.05/6). Type II error was evaluated by calculating the effect size (d) for non-parametric tests as $d = z/\sqrt{N}$ (where z is the z-score, and N is the number of total observations) and values of 0.1, 0.3, and 0.5 were set as thresholds, defining small, medium, and large effect sizes, respectively [57].

The gait metrics for pwMS were normalized to those calculated for the healthy controls by computing the robust z-scores, z_R, as described in Iglewicz and Hoaglin [58]. This statistical metric is more robust to single outliers and computed by replacing the sample mean with the median and the sample standard deviation with the median absolute deviation (i.e., MAD) multiplied by a constant of 1.4826. Z_R values were then reported in a radar plot, where the central line corresponds to controls (z_R equal to 0), and radial deviations from this line indicate how pwMS with different levels of disability vary from controls.

III. Results

A. Factor Analysis

Fifteen of the initial 36 gait metrics were excluded from the EFA analysis (Fig. 1) since inspection of the correlation matrix (Fig. 1-supplementary material) highlighted that they had correlation coefficients lower than 0.3 or higher than 0.9. The correlation matrix was likely factorizable, with an overall KMO = 0.728, and gait symmetry was the only variable that had to be

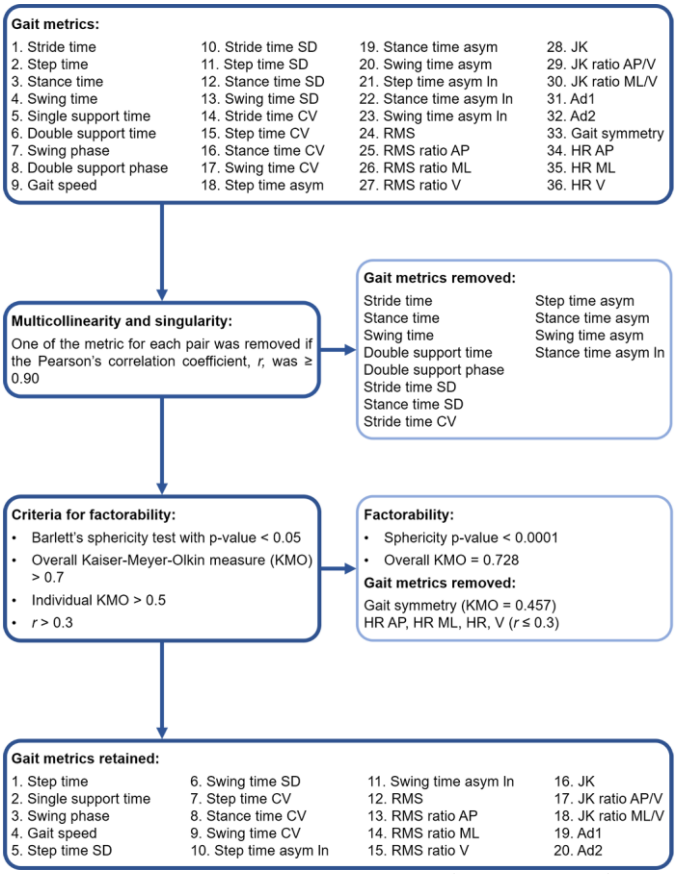

Fig. 1. Flow-chart describing the initial selection of the gait metrics for EFA analysis. SD: standard deviation; CV: coefficient of variation; RMS: root mean square; JK: jerk; Ad1: step regularity; Ad2: stride regularity; HR: harmonic ratio; AP: antero-posterior; ML: medio-lateral; V: vertical.

eliminated for having an individual KMO < 0.5. Bartlett's test of sphericity showed a statistically significant correlation between the tested metrics ($\chi^2(190) = 3061$, p-value < 0.0005).

The EFA analysis carried out on the remaining 20 gait metrics yielded five correlated domains (Fig. 2a), which explained 82.9% of the total variance in gait performance. According to the characteristics of the metrics that they included, and to terminology proposed in similar studies, these domains were labeled as (1) rhythm/variability (accounting for 47.6% of total variance), (2) asymmetry (13.0% of total variance), (3) pace (9.3% of total variance), (4) forward dynamic balance (7.7% of total variance), and (5) lateral dynamic balance (5.2% of total variance). All metrics except for stance time CV and RMS ratio in V direction showed no cross-loadings. The absolute values of r between rhythm/variability, asymmetry, pace, and lateral balance domains exceeded 0.32 (representing about 10% overlap in variance), which as a rule of thumb, necessitates the use of oblique rotation rather than orthogonal rotation (Fig. 2a, [46]). According to the results of EFA, our new model was built with structural equation modeling and reached convergence when examined using CFA. Factor loadings (i.e., regression weights) and correlations among the five domains obtained from EFA and CFA analysis were similar, as evident in Fig. 2.

B. Model ability to discriminate across disability levels

Significant alterations in gait dynamics were observed in MSmod and MSsev groups when compared to Ctrl (Fig. 3 and Table II). Some of these abnormalities were also evident in the MSmild group, with significant changes in rhythm/variability (step time, swing phase, and stride regularity with p-value$_{\text{Ctrl-MSmild}} \leq 0.01$ and moderate effect size), asymmetry (step regularity with p-value$_{\text{Ctrl-MSmild}} = 0.02$ and moderate effect size), and pace (jerk with p-value$_{\text{Ctrl-MSmild}} = 0.03$ and moderate effect size) domains. Significant changes in these domains were also found in the MSmild compared to MSmod and MSsev groups. On the contrary, dynamic balance was only significantly deteriorated in pwMS with higher degrees of disability (RMS ratio AP, RMS ratio ML, and RMS ratio V with p-value$_{\text{MSmild-MSsev}} \leq 0.04$ and moderate effect size; RMS ratio ML with p-value$_{\text{Ctrl-MSmod}} \leq 0.03$ and moderate effect size; RMS ratio AP, RMS ratio ML, and RMS ratio V with p-value$_{\text{Ctrl-MSsev}} \leq 0.004$ and moderate or large effect size). MSmod and MSsev also walked at a slower pace with longer step and single limb support durations and more variable and asymmetric gait pattern than Ctrl (Fig. 3 and Table II). These abnormalities across all domains were exacerbated in the MSsev compared with the MSmod group (p-value$_{\text{MSmod-MSsev}} \leq 0.01$ with moderate or large effect size).

IV. Discussion

This study aimed to propose a conceptual model of gait specific for pwMS and identify the key gait metrics which could act as biomarkers of disease progression or intervention in these patients by detecting those that best discriminate between different levels of disability in pwMS.

In a previous paper [21], we identified reliable metrics for assessing gait in pwMS and grouped them into domains that were inspired by literature from other disease populations. Conceptual models of gait have, in fact, already been proposed for older adults [28]–[30]. Most of these models were built with only spatiotemporal metrics and consisted of three domains (rhythm, pace, and variability). When additional metrics were

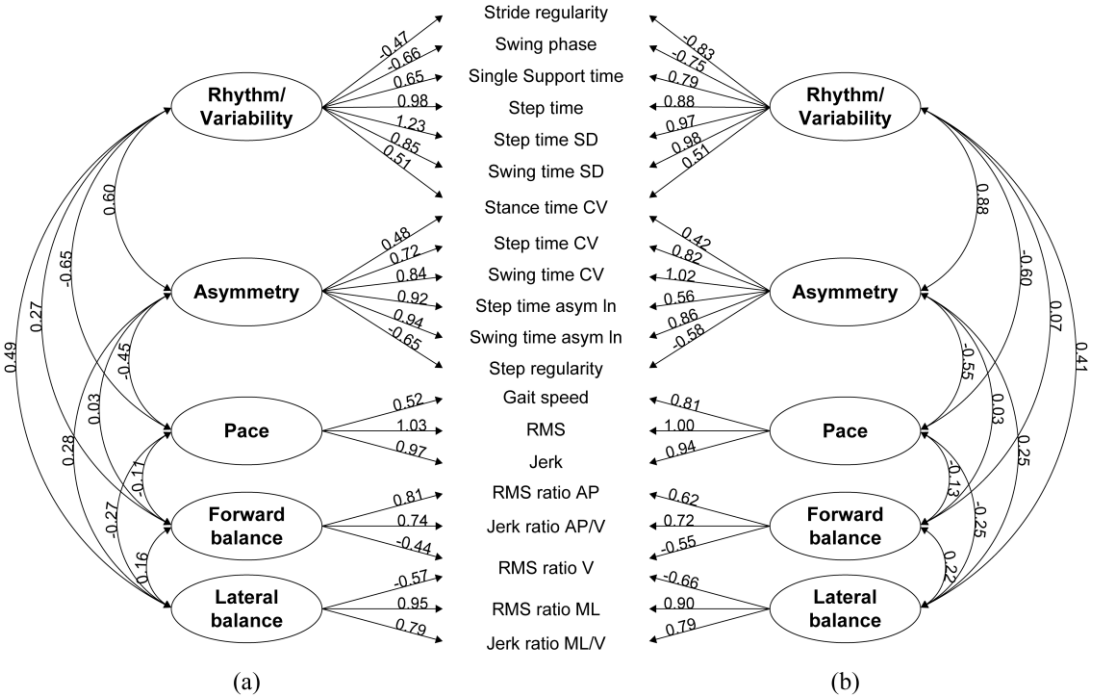

Fig. 2. (a) Exploratory factor analysis. (b) The standardized solution of confirmatory factor analysis. One-headed arrows represent factor loadings while two-headed arrows represent covariance.
SD: standard deviation; CV: coefficient of variation; RMS: root mean square; AP: antero-posterior; ML: medio-lateral; V: vertical.

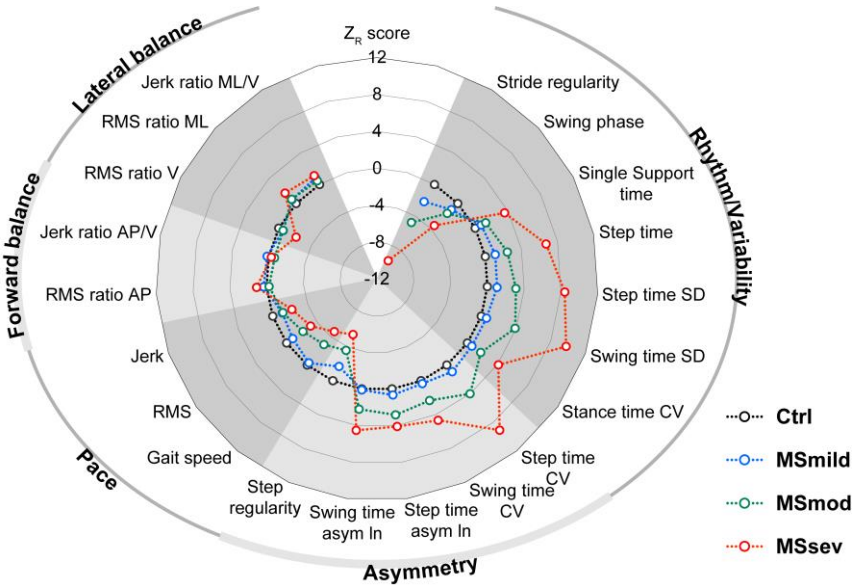

Fig. 3. Gait metrics representative of rhythm/variability, asymmetry, pace, forward dynamic balance, and lateral dynamic balance domains with z_R score indicating change compared to Ctrl cohort.
Ctrl: healthy controls; MSmild: people with a mild MS disability; MSmod: people with a moderate MS disability; MSsev: people with a severe MS disability; SD: standard deviation; CV: coefficient of variation; RMS: root mean square; AP: antero-posterior; ML: medio-lateral; V: vertical.

integrated into the model, the number of domains increased to four or five and included asymmetry and/or postural control. Similar observations were reported for people with PD, where three-factor (pace/rhythm, variability, and asymmetry) [36] or five-factor models (pace, rhythm, variability, asymmetry, and postural control) [33], [35] were proposed depending on the inclusion of metrics related to postural control. The five-factor models were able to account for about 80% of gait variance in both lab-based [33] and real-world observations [35]. Interestingly, when additional motor tasks and metrics associated with static postural balance were introduced, six domains were reported as being of relevance in PD [34]. The results reported here for pwMS reflect the same pattern. The selected metrics, including both spatiotemporal and acceleration-related metrics, were represented by five independent domains (Fig. 2a), accounting for 82.9% of the total gait variance. In contrast to the mostly pace-based models proposed for PD gait, the domain that explained most of the variance in pwMS was rhythm/variability (i.e., 47.6% of total variance), thus confirming the increasing evidence that MS negatively impacts both temporal gait metrics [8]–[15] and their fluctuations between steps (i.e., gait variability, [24], [26], [59]–[62].

The five domains identified in this paper reflect clinically distinctive characteristics of MS, such as poor balance control, altered movement coordination, and greater movement variability [3], [24]. Particularly, gait variability has been previously recognized as a clinical predictor of gait impairment

TABLE II
DESCRIPTIVE STATISTICS FOR THE INVESTIGATED GAIT METRICS, TOGETHER WITH P-VALUES FOR THE INDEPENDENT MANN-WHITNEY U TESTS WITH BONFERRONI CORRECTION AND ASSOCIATED EFFECT SIZES

	Ctrl	**MSmild**	**MSmod**	**MSsev**	**Ctrl vs MSmild**	**Ctrl vs MSmod**	**Ctrl vs MSsev**	**MSmild vs MSmod**	**MSmild vs MSsev**	**MSmod vs MSsev**
Rhythm/Variability	*Median (min, 25th percentile, 75th percentiles, max)*				*p-value (d)*					
Stride regularity (–)	0.87 (0.80, 0.84, 0.90, 0.93)	0.79 (0.45, 0.64, 0.87, 0.92)	0.70 (0.28, 0.59, 0.75, 0.90)	0.52 (0.14, 0.41, 0.59, 0.76)	**0.01** (0.4)	**<0.001** (0.7)	**<0.001** (0.8)	**0.03** (0.3)	**<0.001** (0.6)	**<0.001** (0.5)
Swing phase (%)	40 (30, 39, 41, 43)	38 (30, 37, 39, 42)	37 (24, 36, 38, 44)	33 (20, 28, 36, 42)	**0.005** (0.4)	**<0.001** (0.5)	**<0.001** (0.7)	0.08 (0.2)	**<0.001** (0.6)	**<0.001** (0.5)
Single support time (s)	0.79 (0.70, 0.76, 0.84, 0.96)	0.84 (0.75, 0.79, 0.87, 1.04)	0.87 (0.70, 0.82, 0.94, 1.10)	1.01 (0.45, 0.94, 1.15, 1.72)	0.17 (0.2)	**<0.001** (0.4)	**<0.001** (0.6)	0.52 (0.1)	**<0.001** (0.6)	**<0.001** (0.5)
Step time (s)	0.49 (0.44, 0.47, 0.52, 0.64)	0.54 (0.49, 0.51, 0.59, 0.70)	0.59 (0.49, 0.54, 0.65, 0.75)	0.76 (0.50, 0.67, 0.94, 1.98)	**0.003** (0.4)	**<0.001** (0.6)	**<0.001** (0.7)	0.06 (0.2)	**<0.001** (0.7)	**<0.001** (0.6)
Step time SD (ms)	14 (10, 12, 20, 30)	20 (10, 13, 27, 65)	31 (13, 24, 43, 138)	58 (21, 44, 101, 394)	0.53 (0.1)	**<0.001** (0.6)	**<0.001** (0.8)	**0.003** (0.3)	**<0.001** (0.7)	**<0.001** (0.6)

Swing time SD (ms)	13 (8, 11, 15, 23)	15 (7, 12, 23, 43)	25 (10, 19, 31, 60)	42 (19, 31, 53, 124)	0.75 (0.0)	**<0.001** (0.7)	**<0.001** (0.8)	**0.001** (0.4)	**<0.001** (0.7)	**<0.001** (0.5)
Stance time CV (%)	3 (2, 3, 4, 5)	4 (2, 3, 6, 11)	6 (3, 5, 9, 18)	10 (6, 8, 14, 30)	0.54 (0.1)	**<0.001** (0.7)	**<0.001** (0.8)	**<0.001** (0.4)	**<0.001** (0.7)	**<0.001** (0.5)
Asymmetry										
Step time CV (%)	3 (2, 3, 4, 7)	4 (2, 3, 6, 10)	6 (2, 5, 9, 27)	10 (4, 7, 15, 29)	0.71 (0.1)	**<0.001** (0.6)	**<0.001** (0.8)	**0.003** (0.4)	**<0.001** (0.6)	**<0.001** (0.4)
Swing time CV (%)	4 (2, 3, 4, 5)	4 (2, 3, 7, 12)	7 (2, 6, 9, 19)	11 (4, 9, 15, 26)	1.00 (0.0)	**<0.001** (0.7)	**<0.001** (0.8)	**<0.001** (0.4)	**<0.001** (0.7)	**<0.001** (0.4)
Step time asym ln (%)	2 (0, 1, 4, 8)	3 (0, 1, 5, 15)	6 (0, 2, 12, 40)	8 (0, 4, 15, 43)	1.00 (0.0)	**0.002** (0.4)	**<0.001** (0.5)	0.08 (0.2)	**0.003** (0.4)	0.67 (0.0)
Swing time asym ln (%)	3 (0, 1, 4, 6)	3 (0, 1, 7, 14)	7 (1, 3, 13, 26)	13 (0, 4, 19, 39)	1.00 (0.0)	**<0.001** (0.4)	**<0.001** (0.6)	**0.02** (0.3)	**<0.001** (0.5)	0.25 (0.1)
Step regularity (–)	0.79 (0.46, 0.73, 0.85, 0.93)	0.65 (0.30, 0.47, 0.80, 0.89)	0.50 (0.06, 0.31, 0.63, 0.88)	0.34 (0.05, 0.17, 0.44, 0.64)	**0.02** (0.3)	**<0.001** (0.6)	**<0.001** (0.8)	**0.02** (0.3)	**<0.001** (0.6)	**0.003** (0.3)
Pace										
Gait speed (m/s)	1.59 (1.21, 1.42, 1.73, 2.07)	1.53 (0.68, 1.18, 1.62, 1.87)	1.00 (0.46, 0.83, 1.22, 2.17)	0.63 (0.23, 0.52, 0.80, 1.10)	0.30 (0.1)	**<0.001** (0.7)	**<0.001** (0.8)	**<0.001** (0.5)	**<0.001** (0.8)	**<0.001** (0.6)
RMS (m/s^2)	3.84 (2.37, 3.43, 4.25, 5.31)	3.38 (1.79, 2.70, 4.02, 4.64)	2.63 (1.69, 2.24, 3.28, 5.41)	2.06 (1.08, 1.65, 2.47, 3.75)	0.25 (0.2)	**<0.001** (0.5)	**<0.001** (0.7)	**0.04** (0.2)	**<0.001** (0.6)	**<0.001** (0.4)
Jerk (m/s^3)	44.62 (20.57, 36.36, 50.75, 80.04)	32.69 (18.01, 26.92, 42.87, 56.74)	31.92 (14.95, 23.77, 37.02, 63.89)	20.64 (7.33, 14.96, 26.08, 47.72)	**0.03** (0.3)	**<0.001** (0.4)	**<0.001** (0.7)	0.99 (0.0)	**<0.001** (0.5)	**<0.001** (0.4)
Forward dynamic balance										
RMS ratio AP (–)	0.46 (0.34, 0.40, 0.51, 0.57)	0.49 (0.38, 0.44, 0.52, 0.67)	0.43 (0.27, 0.40, 0.50, 0.58)	0.55 (0.32, 0.46, 0.64, 0.75)	1.00 (0.0)	1.00 (0.0)	**0.003** (0.4)	0.38 (0.1)	**0.04** (0.3)	**<0.001** (0.4)
Jerk ratio AP/V (–)	−1.34 (−2.67, −2.00, −0.38, 1.25)	−1.15 (−3.77, −2.06, −0.31, 0.76)	−2.03 (−4.23, −2.80, −0.93, −0.03)	−1.64 (−3.48, −2.37, −1.04, 2.49)				–*		
Lateral dynamic balance										
RMS ratio V (–)	0.70 (0.46, 0.65, 0.74, 0.84)	0.66 (0.51, 0.58, 0.70, 0.73)	0.66 (0.49, 0.61, 0.68, 0.82)	0.55 (0.20, 0.48, 0.63, 0.74)	0.19 (0.2)	0.10 (0.2)	**<0.001** (0.5)	1.00 (0.0)	**0.01** (0.3)	**<0.001** (0.4)
RMS ratio ML (–)	0.36 (0.24, 0.30, 0.42, 0.48)	0.41 (0.25, 0.36, 0.51, 0.55)	0.42 (0.31, 0.37, 0.50, 0.66)	0.50 (0.29, 0.43, 0.55, 0.81)	0.10 (0.2)	**0.01** (0.3)	**<0.001** (0.6)	1.00 (0.0)	**0.02** (0.3)	**0.01** (0.3)
Jerk ratio ML/V (–)	−1.74 (−4.88, −2.69, −0.65, 1.27)	−0.59 (−4.85, −1.84, 0.14, 1.81)	−1.10 (−3.79, −2.28, −0.05, 3.25)	−0.20 (−3.81, −1.09, 0.60, 2.08)				–*		

k*p*-value < 0.05 (k = number of multiple comparisons, equal to 6) are in bold.

*Note that Kruskal-Wallis tests for Jerk ratio AP/V and Jerk ratio ML/V were not statistically significant. Therefore, independent Mann-Whitney U tests were not performed.

Ctrl: healthy controls MSmild: people with a mild MS disability MSmod: people with a moderate MS disability MSsev: people with a severe MS disability; SD: standard deviation; CV: coefficient of variation; RMS: root mean square; AP: antero-posterior; ML: medio-lateral; V: vertical

and falls in pwMS [6], [24], [59], [61], and it has been shown to be more sensitive than walking speed in the identification of gait dysfunction in this cohort [63]. Gait variability has also been associated with relevant neurological clinical features, such as spasticity, muscle weakness, and impaired proprioception and balance [62]. Greater gait variability has further been linked to other clinically significant factors such as reduced motor control function [64], a higher energetic cost of walking [65], and fatigue [6].

Step and swing time variability metrics loaded onto two different domains when quantified using the CV (asymmetry domain) as opposed to the SD (variability domain). This

confirms previous reports that the combined within-person SD reflects step-to-step variability, while the CV is associated with the variation originating from the asymmetry between the left and right steps [42]. Similarly, step regularity, which compares the acceleration signals between the left and right feet, loaded onto the asymmetry domain, whereas stride regularity loaded onto the variability domain [19], [66], [67]. It has previously been shown that in patients post-stroke, step regularity in AP and V directions is strongly correlated with asymmetry in step time and in swing time [66], with similar results also seen in people with PD [67]. Not surprisingly, both jerk and RMS metrics loaded onto the pace domain. In fact, jerk-based measures are highly sensitive to movement amplitude and duration, with smaller values being associated with increased movement durations [68]. Acceleration is also strongly correlated to gait speed in older adults [69]. Indeed, both jerk and RMS are also strongly correlated with other pace variables in people with PD [67].

The goodness of the overall content structure of the five-factor model of gait in pwMS here proposed was confirmed by the preliminary CFA data analysis (Fig. 2b). This led to very similar loading factors and correlation results when the model was run on a new data set. However, caution is required before the model can be considered fully validated for a generic MS population since the small sample size used for CFA did not allow for a sound calculation of goodness-of-fit indexes. Further studies involving a larger cohort are needed for this purpose.

Testing of the identified conceptual gait model across data from pwMS with different levels of disability showed that wearable sensor-based gait analysis can detect gait alterations not only in pwMS with higher disability levels, as confirmed in previous literature [10], [13], [19], [21], [24], but also in people who are still fully ambulatory and generally have gait impairment that is too subtle to be captured by a standard neurological examination. At present, there are no clinical tools that can predict the progression of disease in pwMS with mild disability. Our study addressed this issue and demonstrated a reliable method of capturing subclinical impairments in the early stage of MS disease.

The MSmod and MSsev groups showed a lower ability to control dynamic stability and to regulate their walking pattern, which was more variable, less rhythmic, and more asymmetrical compared to Ctrl. The MSmild cohort also exhibited unique patterns of gait deterioration (Fig. 3 and Table II), emphasized by significant changes in rhythm/variability, asymmetry, and pace domains. Specifically, minimally disabled pwMS walked with prolonged steps and spent a smaller percentage of their gait cycle with a single foot on the ground, as partially found before [5], [25]. Furthermore, when looking at the gait quality metrics, the jerk value was significantly lower, as reflected in the reduced self-selected gait speed. Gait quality metrics also highlighted a reduced gait coordination ability, which to our knowledge, has not been reported before in the MSmild group. This is demonstrated by an increased variability between steps (i.e., step regularity) and a greater asymmetry between the two limbs (i.e., stride regularity). On the contrary, dynamic balance did not seem to be affected in the early stage of MS but was significantly compromised in people with greater disability. This is partly in contrast with an earlier study, which suggested that some degree of forward and lateral instability exists in pwMS with a mild disability [5]. However, the authors based their observation on postural tasks rather than on walking gait tasks and only found significance for those pwMS with pyramidal signs on clinical examination. Further studies are needed to understand the reasons for these contrasting results.

This study has several limitations that should be acknowledged. Patients were recruited after their scheduled clinic appointments, and an effect of fatigue on gait and balance performance cannot be excluded [19]. However, this was mitigated by asking all subjects to sit and rest before undergoing further assessments and by asking them to walk at their self-selected speed without any specific encouragement. Other environmental factors such as obstructions from other patients or hospital personnel who were nearby at the time of testing or the short walking pathway of 10-m used for the walking test might have also affected the subject's performance and the reliability of the gait metrics investigated. Nonetheless, differences in testing site characteristics were previously noted to influence only marginally the proposed gait metrics [20]. Another limitation of this study relates to the inclusion of patients with a different clinical course of MS. Further investigations are needed to establish whether this factor could have affected the reported results.

V. Conclusions

A new conceptual gait model has been proposed, which describes the essential features that contribute to gait dysfunction in pwMS. A comprehensive description of changes in the gait patterns across groups of pwMS with different levels of disability was also provided. Alterations in selected gait domains were detected in pwMS with no clinically observable walking disability and were significantly worsened in pwMS with higher degrees of disability. As such, the suggested quantitative approach to gait analysis has clear potential as a biomarker for disease progression and as a tool for patient stratification in clinical trials. While the data presented here were recorded within a clinical setting and represent quantification of mobility capacity, the applicability of the proposed approach might also be tested on data continuously acquired during daily life to include an assessment of mobility performance.

Appendix

This article has supplementary material.

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REFERENCES

[1] D. M. Wingerchuk *et al.*, "Multiple Sclerosis: Current Pathophysiological Concepts," *Laboratory Investigation,* vol. 81, pp. 263–281, 2001.

[2] M. H. Cameron, and J. M. Wagner, "Gait Abnormalities in Multiple Sclerosis: Pathogenesis, Evaluation, and Advances in Treatment," *Current Neurology and Neuroscience Reports,* vol. 11, no. 5, pp. 507, 2011.

[3] M. H. Cameron, and Y. Nilsagard, "Chapter 15 - Balance, gait, and falls in multiple sclerosis," *Handbook of Clinical Neurology*, B. L. Day and S. R. Lord, eds., pp. 237–250: Elsevier, 2018.

[4] Y. E. Nilsagård *et al.*, "Balance Exercise Program Reduced Falls in People With Multiple Sclerosis: A Single-Group, Pretest-Posttest Trial," *Archives of Physical Medicine and Rehabilitation,* vol. 95, no. 12, pp. 2428–2434, 2014.

[5] C. L. Martin *et al.*, "Gait and balance impairment in early multiple sclerosis in the absence of clinical disability," *Mult Scler,* vol. 12, no. 5, pp. 620–8, 2006.

[6] J. J. Sosnoff *et al.*, "Mobility, Balance and Falls in Persons with Multiple Sclerosis," *PLOS One,* vol. 6, no. 11, 2011, Art no. e28021.

[7] J. F. Kurtzke, "Rating neurologic impairment in multiple sclerosis," *Neurology,* vol. 33, no. 11, pp. 1444, 1983.

[8] M. Liparoti *et al.*, "Gait abnormalities in minimally disabled people with Multiple Sclerosis: A 3D-motion analysis study," *Multiple Sclerosis and Related Disorders,* vol. 29, pp. 100–107, 2019.

[9] L. E. Cofré Lizama *et al.*, "The use of laboratory gait analysis for understanding gait deterioration in people with multiple sclerosis," *Multiple Sclerosis Journal,* vol. 22, no. 14, pp. 1768–1776, 2016.

[10] M. Pau *et al.*, "Clinical assessment of gait in individuals with multiple sclerosis using wearable inertial sensors: Comparison with patient-based measure," *Multiple Sclerosis and Related Disorders,* vol. 10, pp. 187–191, 2016.

[11] R. I. Spain *et al.*, "Body-worn motion sensors detect balance and gait deficits in people with multiple sclerosis who have normal walking speed," *Gait & Posture,* vol. 35, no. 4, pp. 573–578, 2012.

[12] R. I. Spain *et al.*, "Body-worn sensors capture variability, but not decline, of gait and balance measures in multiple sclerosis over 18 months," *Gait & Posture,* vol. 39, no. 3, pp. 958–964, 2014.

[13] Y. Moon *et al.*, "Monitoring gait in multiple sclerosis with novel wearable motion sensors," *PLOS One,* vol. 12, no. 2, 2017.

[14] I. Dujmovic *et al.*, "Gait pattern in patients with different multiple sclerosis phenotypes," *Multiple Sclerosis and Related Disorders,* vol. 13, pp. 13–20, 2017.

[15] F. A. Storm *et al.*, "Free-living and laboratory gait characteristics in patients with multiple sclerosis," *PLOS One,* vol. 13, no. 5, 2018.

[16] J. M. Huisinga *et al.*, "Accelerometry reveals differences in gait variability between patients with multiple sclerosis and healthy controls," *Annals of biomedical engineering,* vol. 41, no. 8, pp. 1670–1679, 2013.

[17] M. Pau *et al.*, "Smoothness of gait detects early alterations of walking in persons with multiple sclerosis without disability," *Gait & Posture,* vol. 58, pp. 307–309, 2017.

[18] J. J. Craig *et al.*, "Instrumented balance and walking assessments in persons with multiple sclerosis show strong test-retest reliability," *J Neuroeng Rehabil,* vol. 14, no. 1, 2017.

[19] S. Shema-Shiratzky *et al.*, "Deterioration of specific aspects of gait during the instrumented 6-min walk test among people with multiple sclerosis," *Journal of Neurology*, vol. 266, no. 12, pp. 3022–3030, 2019.

[20] L. Angelini *et al.*, "Is a Wearable Sensor-Based Characterisation of Gait Robust Enough to Overcome Differences Between Measurement Protocols? A Multi-Centric Pragmatic Study in Patients with Multiple Sclerosis," *Sensors,* vol. 20, no. 1, pp. 79, 2020.

[21] L. Angelini *et al.*, "Wearable sensors can reliably quantify gait alterations associated with disability in people with progressive multiple sclerosis in a clinical setting," *Journal of Neurology,* 2020.

[22] L. Comber *et al.*, "Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis," *Gait & Posture,* vol. 51, pp. 25–35, 2017.

[23] J. J. Sosnoff *et al.*, "Quantifying gait abnormalities in persons with multiple sclerosis with minimal disability," *Gait & Posture,* vol. 36, no. 1, pp. 154–156, 2012.

[24] M. J. Socie *et al.*, "Gait variability and disability in multiple sclerosis," *Gait & Posture,* vol. 38, no. 1, pp. 51–55, 2013.

[25] M. G. Benedetti *et al.*, "Gait abnormalities in minimally impaired multiple sclerosis patients," *Multiple Sclerosis Journal,* vol. 5, no. 5, pp. 363–368, 1999.

[26] J. P. Kaipust *et al.*, "Gait variability measures reveal differences between multiple sclerosis patients and healthy controls," *Motor Control,* vol. 16, no. 2, pp. 229–44, 2012.

[27] L. A. C. Nogueira *et al.*, "Gait characteristics of multiple sclerosis patients in the absence of clinical disability," *Disability and Rehabilitation,* vol. 35, no. 17, pp. 1472–1478, 2013.

[28] J. Verghese *et al.*, "Quantitative Gait Markers and Incident Fall Risk in Older Adults," *The Journals of Gerontology: Series A,* vol. 64A, no. 8, pp. 896–901, 2009.

[29] J. H. Hollman *et al.*, "Normative spatiotemporal gait parameters in older adults," *Gait & Posture,* vol. 34, no. 1, pp. 111–118, 2011.

[30] S. Lord *et al.*, "Independent Domains of Gait in Older Adults and Associated Motor and Nonmotor Attributes: Validation of a Factor Analysis Approach," *The Journals of Gerontology: Series A,* vol. 68, no. 7, pp. 820–827, 2012.

[31] J. Verghese *et al.*, "Gait Dysfunction in Mild Cognitive Impairment Syndromes," *Journal of the American Geriatrics Society,* vol. 56, no. 7, pp. 1244–1251, 2008.

[32] J. Verghese *et al.*, "Quantitative gait dysfunction and risk of cognitive decline and dementia," *Journal of Neurology, Neurosurgery & amp; Psychiatry*, vol. 78, no. 9, pp. 929–935, 2007.

[33] S. Lord *et al.*, "Moving forward on gait measurement: toward a more refined approach," *Mov Disord,* vol. 28, no. 11, pp. 1534–1543, 2013.

[34] F. B. Horak *et al.*, "Balance and Gait Represent Independent Domains of Mobility in Parkinson Disease," *Physical Therapy,* vol. 96, no. 9, pp. 1364–1371, 2016.

[35] R. Morris *et al.*, "A model of free-living gait: A factor analysis in Parkinson's disease," *Gait & Posture,* vol. 52, pp. 68–71, 2017.

[36] I. Arcolin *et al.*, "Proposal of a new conceptual gait model for patients with Parkinson's disease based on factor analysis," *BioMedical Engineering OnLine,* vol. 18, no. 1, pp. 70, 2019.

[37] M. Wuehr *et al.*, "Independent domains of daily mobility in patients with neurological gait disorders," *Journal of Neurology,* 2020.

[38] P. Thingstad *et al.*, "Identification of gait domains and key gait variables following hip fracture," *BMC Geriatrics,* vol. 15, no. 1, pp. 150, 2015.

[39] R. Moe-Nilssen, "A new method for evaluating motor control in gait under real-life environmental conditions. Part 2: Gait analysis," *Clinical Biomechanics,* vol. 13, no. 4, pp. 328–335, 1998.

[40] L. Palmerini *et al.*, "Identification of Characteristic Motor Patterns Preceding Freezing of Gait in Parkinson's Disease Using Wearable Sensors," *Frontiers in Neurology,* vol. 8, no. 394, 2017.

[41] A. Salarian *et al.*, "Gait assessment in Parkinson's disease: toward an ambulatory system for long-term monitoring," *IEEE Trans Biomed Eng,* vol. 51, pp. 1434–1443, 2004.

[42] B. Galna *et al.*, "Is gait variability reliable in older adults and Parkinson's disease? Towards an optimal testing protocol," *Gait & Posture,* vol. 37, no. 4, pp. 580–585, 2013.

[43] A. Godfrey *et al.*, "Instrumenting gait with an accelerometer: a system and algorithm examination," *Medical engineering & physics,* vol. 37, no. 4, pp. 400–407, 2015.

[44] G. Yogev *et al.*, "Gait asymmetry in patients with Parkinson's disease and elderly fallers: when does the bilateral coordination of gait require attention?" *Experimental brain research,* vol. 177, no. 3, pp. 336–346, 2007.

[45] R. C. MacCallum *et al.*, "Sample size in factor analysis," *Psychological Methods,* vol. 4, no. 1, pp. 84–99, 1999.

[46] B. G. Tabachnick *et al.*, *Using multivariate statistics*: Pearson Boston, MA, 2007.

[47] H. F. Kaiser, "An index of factorial simplicity," *Psychometrika,* vol. 39, no. 1, pp. 31–36, 1974.

[48] G. R. Norman, and D. L. Streiner, *Biostatistics: the bare essentials*: PMPH USA, 2008.

[49] H. F. Kaiser, "The Application of Electronic Computers to Factor Analysis," *Educational and Psychological Measurement,* vol. 20, no. 1, pp. 141–151, 1960.

[50] J. L. Horn, "A rationale and test for the number of factors in factor analysis," *Psychometrika,* vol. 30, no. 2, pp. 179–185, 1965.

[51] R. B. Cattell, "The Scree Test For The Number Of Factors," *Multivariate Behavioral Research,* vol. 1, no. 2, pp. 245–276, 1966.

[52] D. J. Tataryn *et al.*, "Setting the value of k in promax: A Monte Carlo study," *Educational and Psychological Measurement,* vol 59, no. 3, pp. 384-391, 1999.

[53] A. E. Hendrickson, and P. O. White, "Promax: A quick method for rotation to oblique simple structure," *British journal of statistical psychology,* vol. 17, no. 1, pp. 65–70, 1964.

[54] E. E. Cureton, "Studies of the Promax and Optres rotations," *Multivariate Behavioral Research*, 1976.
[55] A. L. Comrey, and H. B. Lee, *A first course in factor analysis*, Hillsdale, N.J.: L. Erlbaum Associates, 1992.
[56] M. J. Anderson, "A new method for non-parametric multivariate analysis of variance," *Austral ecology*, vol. 26, no. 1, pp. 32–46, 2001.
[57] J. Cohen, "CHAPTER 3 - The Significance of a Product Moment rs," *Statistical Power Analysis for the Behavioral Sciences*, J. Cohen, ed., pp. 75–107: Academic Press, 1977.
[58] B. Iglewicz, and D. C. Hoaglin, *How to Detect and Handle Outliers*: ASQC Quality Press, 1993.
[59] G. Allali *et al.*, "Gait variability in multiple sclerosis: a better falls predictor than EDSS in patients with low disability," *Journal of neural transmission*, vol. 123, no. 4, pp. 447–450, 2016.
[60] Y. Moon *et al.*, "Gait variability in people with neurological disorders: a systematic review and meta-analysis," *Human movement science*, vol. 47, pp. 197–208, 2016.
[61] Y. Moon *et al.*, "Stride-Time Variability and Fall Risk in Persons with Multiple Sclerosis," *Mult Scler Int*, vol. 964790, no. 10, pp. 30, 2015.
[62] M. J. Socie, and J. J. Sosnoff, "Gait variability and multiple sclerosis," *Multiple sclerosis international*, vol. 2013, 2013.
[63] M. Flegel *et al.*, "Step-length variability in minimally disabled women with multiple sclerosis or clinically isolated syndrome," *International Journal of MS Care*, vol. 14, no. 1, pp. 26–30, 2012.
[64] N. Stergiou *et al.*, "Optimal movement variability: a new theoretical perspective for neurologic physical therapy," *Journal of Neurologic Physical Therapy*, vol. 30, no. 3, pp. 120–129, 2006.
[65] S. M. O'Connor *et al.*, "Energetic cost of walking with increased step variability," *Gait & Posture*, vol. 36, no. 1, pp. 102–107, 2012.
[66] C. Buckley *et al.*, "Gait Asymmetry Post-Stroke: Determining Valid and Reliable Methods Using a Single Accelerometer Located on the Trunk," *Sensors*, vol. 20, no. 1, pp. 37, 2019.
[67] C. Buckley *et al.*, "Upper body accelerations as a biomarker of gait impairment in the early stages of Parkinson's disease," *Gait & Posture*, vol. 71, pp. 289–295, 2019.
[68] N. Hogan, and D. Sternad, "Sensitivity of smoothness measures to movement duration, amplitude, and arrests," *Journal of motor behavior*, vol. 41, no. 6, pp. 529–534, 2009.
[69] H. B. Menz *et al.*, "Acceleration patterns of the head and pelvis when walking on level and irregular surfaces," *Gait & Posture*, vol. 18, no. 1, pp. 35–46, 2003.
[70] M. Sekine *et al.*, "A gait abnormality measure based on root mean square of trunk acceleration," *Journal of NeuroEngineering and Rehabilitation*, vol. 10, no. 1, pp. 118, 2013.
[71] P. Fazio *et al.*, "Gait measures with a triaxial accelerometer among patients with neurological impairment," *Neurological Sciences*, vol. 34, no. 4, pp. 435–440, 2013.
[72] R. P. Young and R. G. Marteniuk, "Acquisition of a multi-articular kicking task: Jerk analysis demonstrates movements do not become smoother with learning," *Human Movement Science*, vol. 16, no. 5, pp. 677–701, 1997.
[73] M. A. D. Brodie *et al.*, "Age-associated changes in head jerk while walking reveal altered dynamic stability in older people," *Experimental Brain Research*, vol. 232, no. 1, pp. 51–60, 2014.
[74] R. Moe-Nilssen and J. L. Helbostad, "Estimation of gait cycle characteristics by trunk accelerometry," *J. of Biomechanics*, vol. 37, no. 1, pp. 121–126, 2004.
[75] D. Kobsar *et al.*, "Evaluation of age-related differences in the stride-to-stride fluctuations, regularity and symmetry of gait using a waist-mounted tri-axial accelerometer," *Gait & Posture*, vol. 39, no. 1, pp. 553–557, 2014.
[76] G. L. Smidt *et al.*, "Accelerographic analysis of several types of walking," *American Journal of Physical Medicine*, vol. 50, no. 6, pp. 285–300, 1971.
[77] S. H. Gage, "Microscopy in America (1830-1945)," *Transactions of the American Microscopical Society*, vol. 83, no. 4, pp. 1–125, 1964.