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Spatio-temporal gait signatures across prodromal and early Parkinson's disease in two independent cohorts

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Gait abnormalities are key features of Parkinson's disease (PD) and might be present in isolated REM Sleep Behavior Disorder (iRBD), a prodromal marker of alpha-synucleinopathy. To assess spatio-temporal gait parameters from prodromal (iRBD) to early/moderate PD stages in normal, fast and dual-task conditions. This prospective multicenter study included two independent cohorts with Polysomnography-confirmed iRBD, drug-naïve PD (naïve-PD), early and moderate treated PD (early-PD, mid-PD), and age-matched healthy controls (HC). Gait was assessed using mobile health technology. A total of 324 participants were enrolled: 194 in the Digital Neurological Assessment (DNA) cohort (23 iRBD, 57 naïve-PD, 49 mid-PD, 65 HC) and 130 in the TPA cohort (28 iRBD, 34 early-PD, 68 HC) composed from TREND, PASS-PD and ABCPD cohorts. In the two independent cohorts, iRBD and early PD (treated and non-treated) showed higher step time compared to HC, especially during dual-task gait. In fast walking, all patient groups had longer step time than HC. Step length was control-like in iRBD and early treated PD, whereas it was lower in both naïve and moderate stages PD in all different task conditions. Temporal gait parameters, especially during dual task walking, are sensitive markers of prodromal PD whereas reduced step length is occurring only in phases when PD diagnosis is already possible. These cross-sectional data need a further validation on ongoing longitudinal studies in prodromal and early stages PD.

Keywords Gait, Mobile health technology, REM sleep behavior disorder, Prodromal Parkinson's disease

Parkinson disease (PD) is a neurodegenerative disease diagnosed when bradykinesia occurs along with rigidity or tremor, with consideration of additional supporting and exclusionary features[1]. Neuropathological evidence indicates that by the time PD is clinically diagnosed, substantial neuronal loss has already occurred in the substantia nigra, and within a few years, dopamine terminals in the dorsal putamen are almost completely depleted[2,3]. These findings suggest that the neurodegenerative process begins 5 to 10 years before diagnosis, highlighting a long prodromal phase preceding motor symptom onset[4].

This prodromal phase represents an opportunity of early recognition enabling better prognostic counselling, but also initiation of possible modifying therapies at a stage when therapies might be most effective[5].

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REM sleep behaviour disorder (RBD) is a REM sleep parasomnia characterized by the loss of REM physiological muscle atonia and by the presence of abnormal motor activity often related to dream content[6].

Isolated RBD (iRBD) is the condition associated with the highest risk of developing an alpha-synucleinopathy, specifically Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA)[7–12] representing a unique window on the prodromal phase of alpha-synucleinopathies.

Previous longitudinal studies have identified several clinical, neurophysiological, and imaging markers associated with an increased risk of conversion in REM sleep behavior disorder (RBD), including older age, hyposmia, impaired color vision, subtle parkinsonian signs, mild cognitive impairment, autonomic dysfunction, nigrostriatal dopaminergic deficits, and REM sleep without atonia (RSWA) severity[13–15].

However, often these markers have been studied in small or retrospective cohorts, or in multicentre studies lacking standardized data collection. In addition, many of the most informative assessments—such as dopaminergic imaging or polysomnography—are costly, time-consuming, and not widely accessible[16,17].

Gait alterations are a common feature during the course of PD and the development of mobile health technology (MHT) for gait assessment enables the quantification of specific parameters, that are expected to differ within various stages of the disease. According to the literature, step time and step time variability are expected to be increased in PD, while step length is shortened, but their trends at different stages and in different gait conditions (i.e. normal gait, fast gait and dual-task gait) remain elusive[18].

Also, only few data on gait alterations in prodromal stages of PD are available so far[10,19–23]. Early work by McDade and colleagues found that patients with iRBD already display reduced walking speed and increased variability[10]. Building on this, Del Din et al. used wearable technology to monitor gait over time in healthy controls and found that higher step time variability and asymmetry were associated with a shorter time to PD diagnosis[19]. Maetzler et al. emphasized that impaired balance, decreased coordination, and slowed fine motor movements are key indicators of an underlying neurodegenerative process in its earliest stages[24]. Similarly, Mirelman and colleagues applied machine learning to mobility data, identifying sensitive motor features capable of differentiating between early disease stages and healthy aging[21]. In a related study, Mirelman, Siderowf and Chahine discussed how both clinical and digital mobility metrics can serve as reliable outcome measures in PD prevention trials[22]. Finally, Schalkamp et al. provided evidence that the use of machine learning on wearable data may reveal PD several years before diagnosis[23].

Defining the specific digital measures altered in earliest PD phases is of particular importance, as there is no international consensus on which digital parameter(s) should be used for (a) screening persons at risk for PD and (b) track disease progression and/or detect the transition from the prodromal to the clinical phases of the disease[18,20,22]. Moreover, characterizing gait alterations across PD stages may provide valuable insights into underlying pathological mechanisms. Previous studies have often been limited by small sample sizes and/or retrospective designs. Also, few studies have systematically evaluated gait across multiple task conditions or validated findings in independent cohorts.

In this multi-centre cross-sectional study, we evaluated temporal and spatial parameters of gait across the PD spectrum from prodromal to early clinical stages during normal, fast and dual-task conditions in two independent cohorts. The objective of the study was to evaluate the spatio-temporal gait characteristics in the different groups in order to (a) identify the gait parameter(s) most sensitive to prodromal and early phases of the disease, and (b) evaluate the relationship between spatio-temporal gait parameters and dopaminergic treatment during different gait conditions (normal pace, fast pace, and dual-task setting).

Results

The Digital Neurological Assessment (DNA) cohort included 23 iRBD, 83% male with a mean age of 72 ± 6 years,, 57 drug-naïve PD patients, 54% male, with a mean age of 68 ± 7 years, a group of 49 stable mid-stage treated PD patients, 51% male, with a mean age of 70 ± 8 years, and 65 HCs, 40% male, with a mean age of 69 ± 5 years (Table 1). Naïve and treated PD showed similar MDS-UPDRS-III values, in both cases significantly higher than iRBD and HC. iRBD did not show any clinically relevant motor impairment, as indicated by total MDS-UPDRS-III (mean score 2 ± 2 points, Table 1).

	HC	iRBD	Naïve-PD	Mid-PD	*p*-value
Numbers [*n*]	65	23	57	49	
Age [y]	69 ± 5	71 ± 6	68 ± 7	70 ± 8	0.090[a]
Sex M/F	26/39	19/4*	31/26#	25/24#	**0.003**[b]
Disease Duration [y]	–	-	1 ± 1	10 ± 6§	**< 0.001**[a]
MDS-UPDRS-III [pts]	2 ± 3	2 ± 2	16 ± 10*#	23 ± 12*#§	**< 0.001**[a]
H&Y [pts]	–	0 ± 0	1 ± 0.5	2 ± 1	**< 0.001**[a]
MoCA [pts]	27 ± 2	25 ± 3	25 ± 2	25 ± 1	**< 0.001**[a]
LEDD [mg]	0 ± 0	0 ± 0	0 ± 0	770 ± 450*#§	**< 0.001**[a]

Table 1. Demographics and clinical characteristics of DNA cohort. [a]Parametric ANOVA. [b]Chi square test. *Against HC; #, against iRBD; §, against naïve-PD; HC, healthy controls; iRBD, idiopathic REM sleep behavior disorder; DNA, digital neurological assessment; LEDD, Levodopa equivalent daily dose; mid-PD, moderate treated PD participants; MDS-UPDRS-III, MDS-Unified Parkinson's Disease Rating Scale part III ; naïve-PD, drug naïve PD participants. Statistically significant p-values ($p<0.05$) are highlighted in bold.

	HC	iRBD	early-PD	*p*-value
Numbers [*n*]	68	28	34	
Age [y]	67 ± 7	66 ± 10	67 ± 8	0.892
Sex M/F	50/18	25/3	25/9	0.215
Disease Duration [y]			1 ± 1	–
MDS-UPDRS-III [pts]	1 ± 3	3 ± 4	21 ± 7*#	**< 0.001**[a]
H&Y [pts]	–	0 ± 0	2 ± 0.5	**< 0.001**[a]
MoCA [pts]	27 ± 1	26 ± 3	26 ± 3	**0.892**
LEDD [mg]	0 ± 0	0 ± 0	350 ± 220*#	**< 0.001**[a]

Table 2. Demographics and clinical characteristics of TPA cohort. [a]Parametric ANOVA. [b]Chi square test. *Against HC; #, against iRBD; early-PD, early treated PD participants; HC, healthy controls; iRBD, idiopathic REM sleep behavior disorder; LEDD, Levodopa equivalent daily dose; MDS-UPDRS-III, MDS-Unified Parkinson's Disease Rating Scale part III; TPA, TREND-PASSPD-ABCPD. Statistically significant p-values ($p<0.05$) are highlighted in bold.

	HC	iRBD	naïve-PD	mid-PD	*p*-value
Straight walk normal pace					
StepTime [s]	0.51 ± 0.04	0.55 ± 0.03*	0.54 ± 0.05*	0.53 ± 0.06	**0.008**[a]
StepTimeVariability	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	0.407
StepLength [m]	0.62 ± 0.06	0.59 ± 0.07	0.56 ± 0.06*#	0.50 ± 0.10*#	**< 0.001**[a]
Straight walk fast pace					
StepTime [s]	0.45 ± 0.04	0.49 ± 0.04*	0.49 ± 0.04*	0.49 ± 0.05*	**< 0.001**[a]
StepTimeVariability	0.04 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.02*	**0.002**[a]
StepLength [m]	0.65 ± 0.06	0.62 ± 0.06	0.6 ± 0.07*	0.53 ± 0.11*#	**< 0.001**[a]
Dual task straight walk checking boxes					
StepTime [s]	0.49 ± 0.06	0.56 ± 0.07*	0.55 ± 0.07*	0.57 ± 0.1*	**< 0.001**[a]
StepTimeVariability	0.05 ± 0.02	0.05 ± 0.03	0.05 ± 0.02	0.07 ± 0.03*#§	**0.002**[a]
StepLength [m]	0.61 ± 0.07	0.57 ± 0.08	0.54 ± 0.07*	0.48 ± 0.11*#	**< 0.001**[a]
Dual task straight walk serial subtraction					
StepTime [s]	0.50 ± 0.05	0.58 ± 0.06*	0.55 ± 0.06*	0.56 ± 0.09*	**< 0.001**[a]
StepTimeVariability	0.04 ± 0.01	0.06 ± 0.02	0.05 ± 0.02	0.07 ± 0.02*	**< 0.001**[a]
StepLength [m]	0.63 ± 0.07	0.58 ± 0.08	0.54 ± 0.08*#	0.49 ± 0.1*#	**< 0.001**[a]

Table 3. Gait parameters in HC, iRBD, naïve-PD and mid-PD in DNA Cohort. [a]Univariate analysis corrected for age and sex. [b]Pairwise with Tukey correction. *Against HC; #, against iRBD; §, against naïve-PD; HC, healthy controls; iRBD, idiopathic REM sleep behavior disorder; DNA, digital neurological assessment LEDD, Levodopa equivalent daily dose; mid-PD, moderate treated PD participants; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III ; m, meters; naïve-PD, Drug Naïve PD participants; s, seconds. TPA, TREND-PASSPD-ABCPD. Statistically Significant p-values ($p<0.05$) are highlighted inbold.

The TREND-PASSPD-ABCPD (TPA) cohort included 28 persons with PSG-confirmed iRBD, 89% male, with a mean age of 66 ± 10 years, 34 early treated PD patients, 74% male, with a mean age of 67 ± 8 years and a duration of 1 ± 1 year, and 68 HCs, 74% male, with a mean age of 67 ± 7 years. The demographic and clinical characteristics of the participants are shown in Table 2. Early treated PD showed MDS-UPDRS-III values significantly higher than iRBD and HC. iRBD showed minimal motor impairment (mean total MDS-UPDRS-III score 3 ± 4 points, Table 2).

Tables 3 and 4, and Figs. 1 and 2 show the digital parameters associated with the gait analyses respectively in cohort 1 and 2.

Normal pace

In cohort 1, both iRBD and naïve PD showed longer step time compared to healthy controls (iRBD 0.55 ± 0.03; naïve PD 0.54 ± 0.05 vs. HC 0.51 ± 0.04; $p = 0.034$ and $p = 0.018$), while no differences were observed between mid-stage PD and controls. Conversely, step length was shorter in naïve and mid-stage PD (0.56 ± 0.06 and 0.50 ± 0.10) compared to both HC (0.62 ± 0.06) and iRBD (0.59 ± 0.07; $p < 0.001$). Step time variability did not differ between groups.

	HC	iRBD	ePD	*p*-value
Straight walk normal pace				
StepTime [s]	0.52 ± 0.03	0.56 ± 0.05*	0.56 ± 0.05*	**0.001**[a]
StepTimeVariability	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.02*#	**< 0.001**[a]
StepLength [m]	0.60 ± 0.05	0.60 ± 0.07	0.60 ± 0.07	0.807
Straight walk fast pace				
StepTime [s]	0.45 ± 0.04	0.50 ± 0.04*	0.50 ± 0.05*	**< 0.001**[a]
StepTimeVariability	0.01 ± 0.02	0.02 ± 0.01	0.04 ± 0.04*#	**< 0.001**[a]
StepLength [m]	0.66 ± 0.07	0.64 ± 0.08	0.63 ± 0.08*	**0.016**[a]
Dual Task straight walk checking boxes				
StepTime [s]	0.50 ± 0.05	0.56 ± 0.09*	0.56 ± 0.07*	**< 0.001**[a]
StepTimeVariability	0.02 ± 0.01	0.04 ± 0.06*	0.06 ± 0.08*#	**< 0.001**[a]
StepLength [m]	0.60 ± 0.06	0.57 ± 0.08	0.59 ± 0.07	0.210
Dual task straight walk serial subtraction				
StepTime [s]	0.50 ± 0.04	0.59 ± 0.12*	0.59 ± 0.11*	**< 0.001**[a]
StepTimeVariability	0.02 ± 0.01	0.05 ± 0.06*	0.08 ± 0.12*#	**< 0.001**[a]
StepLength [m]	0.62 ± 0.07	0.61 ± 0.09	0.60 ± 0.08	0.114

Table 4. Gait parameters in HC, iRBD and early-PD in TPA Cohort. [a]Univariate analysis corrected for age and sex. [b]Pairwise with Tukey correction. *Against HC; #, against iRBD; §, against naïve-PD; HC, healthy controls; iRBD, idiopathic REM sleep behavior disorder; LEDD, Levodopa equivalent daily dose; mid-PD, moderate treated PD participants; MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III ; m, meters; naïve-PD, Drug Naïve PD participants; s, seconds. Statistically significant p-values (p<0.05) are highlighted in bold.

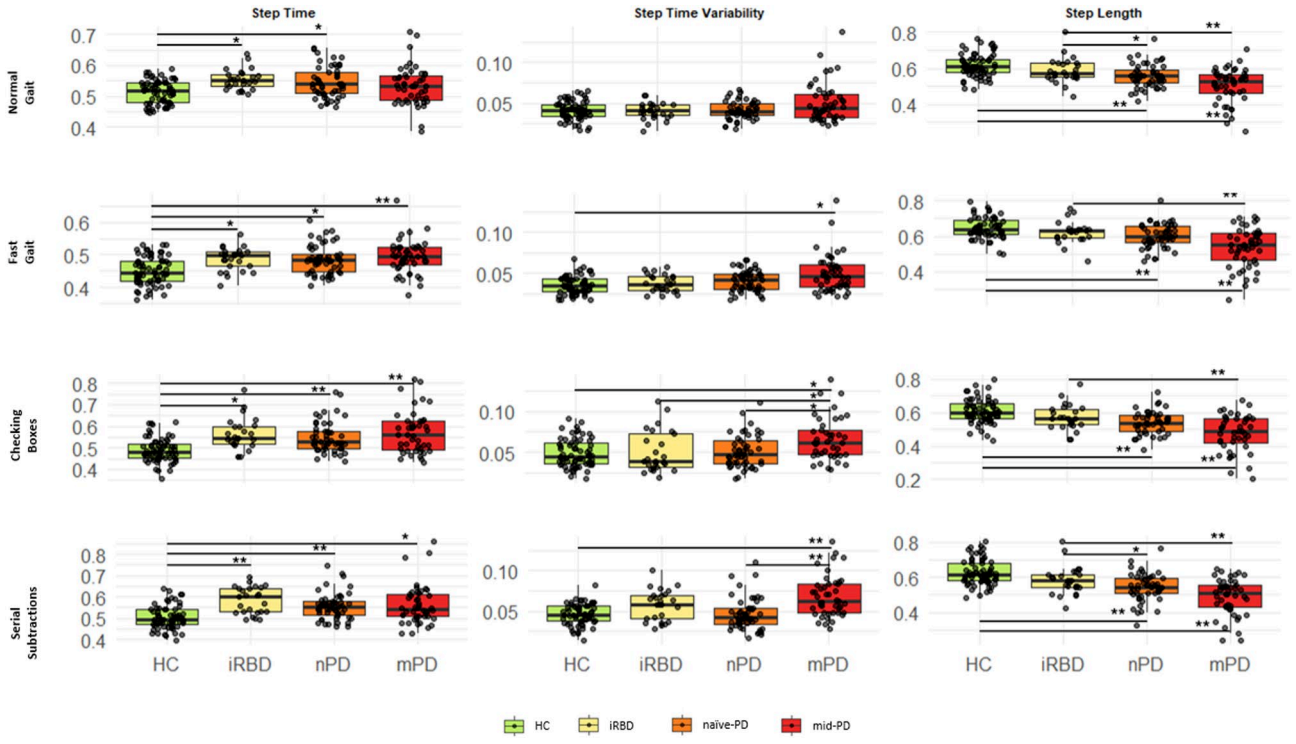

Fig. 1. Gait parameters in HC, iRBD, naïve-PD and mid-PD in DNA Cohort. Abbreviations: HC, healthy controls; iRBD, isolated REM sleep behavioural disorders; naïve-PD, Parkinson's disease patients without any dopaminergic treatment at the time of assessment; mPD (mid-PD), Parkinson's disease patients under dopaminergic treatment and disease duration > 3 years. *p-value < 0.05, **p-value < 0.001.

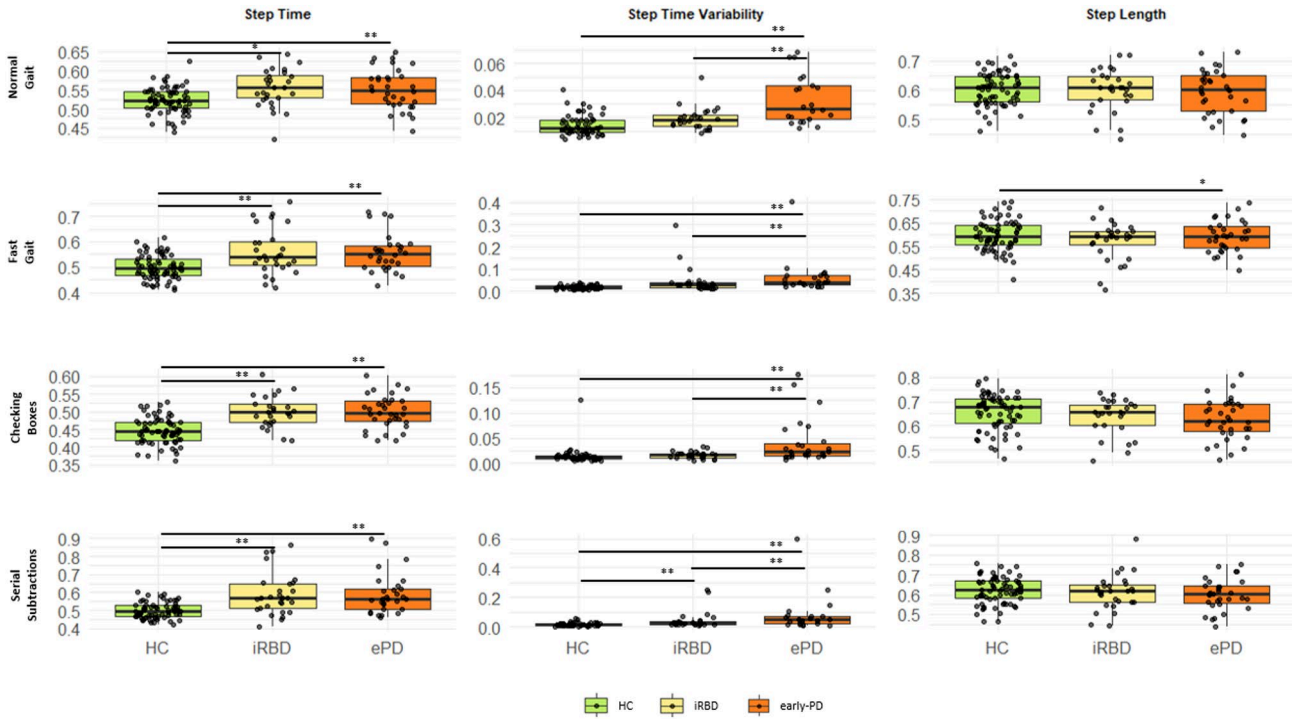

Fig. 2. Gait parameters in HC, iRBD and early-PD in TPA cohort. Abbreviations: HC, healthy controls; iRBD isolated REM sleep behavioural disorders; ePD (early-PD): Parkinson's disease patients under dopaminergic treatment and disease duration < 3 years. *p-value < 0.05, **p-value < 0.001.

In cohort 2, iRBD and early PD similarly showed longer step time (0.56 ± 0.05 for both) compared to controls (0.52 ± 0.03; $p = 0.005$ and $p < 0.001$). Only early PD exhibited increased step time variability (0.03 ± 0.02 vs. HC 0.01 ± 0.01 and iRBD 0.02 ± 0.01; $p < 0.001$), while step length did not differ across groups.

Fast pace

In cohort 1, naïve and mid-stage PD showed longer step time than controls (0.49 ± 0.04 and 0.49 ± 0.05 vs. 0.45 ± 0.04; $p < 0.001$), along with shorter step length (0.60 ± 0.07 and 0.53 ± 0.11 vs. 0.65 ± 0.06; $p < 0.001$). iRBD also showed slightly higher step time (0.49 ± 0.04; $p = 0.049$), but preserved step length comparable to controls and higher than mid-PD (0.62 ± 0.06; $p < 0.001$). Step time variability was higher only in mid-PD (0.05 ± 0.02 vs. 0.04 ± 0.01; $p = 0.001$).

In cohort 2, both iRBD and early PD showed longer step time compared to controls (0.50 ± 0.04 and 0.50 ± 0.05 vs. 0.46 ± 0.04; $p < 0.001$). Step length was shorter only in early PD (0.63 ± 0.08 vs. 0.66 ± 0.07; $p = 0.036$), while step time variability was higher in early PD compared to both HC and iRBD (0.04 ± 0.04 vs. 0.01 ± 0.02 and 0.02 ± 0.01; $p < 0.001$ and $p = 0.002$).

Motor dual-task pace

During the checking boxes task in cohort 1, step time was higher in all patient groups compared to controls (iRBD 0.56 ± 0.07, naïve PD 0.55 ± 0.07, mid-PD 0.57 ± 0.10 vs. HC 0.49 ± 0.06; $p < 0.001$). Step length was shorter in PD (0.54 ± 0.07 and 0.48 ± 0.11 vs. 0.61 ± 0.07; $p < 0.001$), while iRBD showed preserved values similar to controls and higher than mid-PD (0.57 ± 0.08; $p < 0.001$). Step time variability was higher only in mid-PD compared to all other groups.

In cohort 2, iRBD and early PD again showed longer step time than controls (0.56 ± 0.09 and 0.56 ± 0.07 vs. 0.50 ± 0.05; $p < 0.001$), while higher variability was observed only in early PD (0.06 ± 0.08 vs. 0.02 ± 0.01 and 0.04 ± 0.06; $p < 0.001$ and $p = 0.007$). No differences emerged in step length.

Cognitive dual task pace

During serial subtraction, cohort 1 showed higher step time across all patient groups (iRBD 0.58 ± 0.06, naïve PD 0.55 ± 0.06, mid-PD 0.56 ± 0.09 vs. HC 0.50 ± 0.05; $p < 0.001$), with shorter step length in PD only. Step time variability was higher in mid-PD compared to HC and naïve PD.

In cohort 2, both iRBD and early PD showed higher step time and variability compared to controls ($p < 0.001$), with no differences in step length.

Discussion

The results of this multicentre study encompassing two independent cohorts suggest that an increase of step time is a sensitive marker of prodromal PD, especially in gait performed under dual-tasking conditions. In

contrast, step length remains preserved in the prodromal stage (iRBD), and obviously starts to shorten when PD is diagnosed. Notably, the data also confirm that the dopaminergic treatments—while potentially impacting step length, at least in early stages—did not normalize temporal gait alterations, specifically not step time.

Different studies and reviews explored gait alterations in PD[25–27], however, the distribution of spatio-temporal gait characteristics under various conditions across different stages of PD remains an unresolved issue in clinical research[18,20]. In prodromal PD, the data are even more contentious, as at-risk populations exhibit varying levels of risk for developing PD and differ substantially in their time to conversion to clinical PD[11,20]. One of the few longitudinal studies published so far has assessed the walking characteristics of 680 healthy older adults under supervised conditions using a wearable sensor positioned on the lower back[19]. The study uncovered that individuals who developed PD during the follow-up had longer step time, higher variability and higher asymmetry of steps which started about 4.5 years before diagnosis[19]. These findings align with another study that evaluated patients with genetically increased risk for PD (LRRK2-G2019S mutation carriers). That study showed that carriers had increased stride time variability when compared to age-matched non-carriers[28]. The baseline gait data were comparable between the two studies[19,28].

These findings are in line with the results presented here. This case-control study applied MHT during different walking trials under different supervised conditions in two large and well-characterized cohorts of PSG-confirmed iRBD patients—currently the most reliable prodromal marker of PD[18,20], and treated and untreated PD.

In normal gait, both iRBD and PD groups (naïve and treated) showed significantly longer step times compared to HC, confirming that alterations in temporal parameters emerge early in the disease course, even before the onset of overt motor symptoms. This pattern was consistently observed across both cohorts and task conditions, including walking during cognitive and motor secondary tasks, reinforcing the notion that step time is a robust and sensitive marker of prodromal alpha-synuclein pathology. Of note, the temporal step time values are highly similar to those presented by Del Din and colleagues in participants who converted to PD in longitudinally follow-up[19].

Notably, step time alterations appeared largely independent of dopaminergic treatment, as they were observed in both naive and early-treated PD patients. This suggests that step time reflects dysfunction in non-dopaminergic pathways, potentially involving cortico-cerebellar circuits, frontostriatal loops, and brainstem timing networks[29–31].

Our results showed that step length changes in later PD stages compared to step time.

These findings are consistent with a study by Welzel et al. (2021), which claimed that step length varies significantly along with PD progression, while temporal parameters remain relatively stable[32]. The preservation of step length in iRBD—even under fast gait and dual-tasking—indicates that spatial gait components are maintained until the disease is so far developed that clinical diagnosis is possible (therefore, that at least two disease-specific motor symptoms are present), possibly reflecting relatively intact basal ganglia output and/or effective cortical compensation in this prodromal state[33], as recently suggested also for turning performances in iRBD[34].

Of note, step time variability is altered only in treated PD subjects, both in early and mid-stage of PD, but not in drug-naïve persons with (very early) PD[19,21].

The study examined gait differences in various stages of PD by utilizing both a motor (checking boxes) and cognitive secondary task (serial subtractions) during the walking trial. Results showed that the motor secondary task increased gait alterations, thereby magnifying the discrepancy between PD and iRBD on one hand and HC on the other. This result suggests that the implementation of such challenging walking trials could increase the sensitivity of an assessment panel for the detection of very early PD phases[35].

This study has several strengths, including the systematic assessment of gait across multiple conditions and disease stages, and the inclusion of naïve and treated PD patients, allowing us to disentangle the effects of disease progression and dopaminergic therapy. Still, several limitations should be acknowledged. The cross-sectional design, the absence of unsupervised data - which, notably, has shown potential to detect PD years before clinical conversion[23]- and the relatively small iRBD sample limit the generalizability of the results. Furthermore, the use of different wearable systems (RehaGait and OPAL) across cohorts represents an additional limitation inherent to multicentre digital biomarker studies. However, as each system was used exclusively within its respective cohort and no direct cross-cohort comparisons of raw gait data were performed, inter-system variability is unlikely to substantially affect our findings. Moreover, both systems have been independently validated for gait assessment in Parkinson's disease populations[36–38].

Moreover, to our best knowledge, this study presents the largest PSG-confirmed cohort of iRBD evaluated with supervised single and dual task setting so far. The inclusion of two independent cohorts did enable the evaluation of consistencies across studies independently from devices used and cohorts, which is still a major issue in prodromal PD and digital motor testing worldwide[20,22,35].

In conclusion, our findings provide compelling evidence that step time is increasing very early in the trajectory of alpha-synucleinopathies in general and PD in particular. Therefore, it may offer a reliable digital marker of early motor impairment due to neurodegeneration, which might in the future help to predict conversion to the clinical phase of the disease. Step length is also associated with PD stages, but (changes) decreases later during the course of the disease.

These results may aid to the definition of promising digital gait biomarkers capable of capturing both early changes and treatment effects in PD, supporting clinical-based recommendation for precision monitoring and intervention in the earliest phases of the disease and clinical trials[8,39].

Methods

Participants' selection and clinical assessment

This prospective study enrolled two independent cohorts, the Digital Neurological Assessment (DNA) and the TREND-PASSPD-ABCPD (TPA) cohorts.

The DNA cohort included consecutive patients with a diagnosis of early-PD or Polysomnography (PSG)-confirmed isolated REM sleep behaviour disorder who underwent a diagnostic work-up at the Movement Disorder outpatient clinic and the sleep Disorder Centre, Neurology Unit of the ASST Spedali CIvili University Hospital of Brescia, at the Parkinson's disease Rehabilitation Centre of Trescore Balneario, and the Sleep disorders Centre of San Raffaele University of Milan from April 2018 to November 2023. The research protocol was approved by the Ethics Committee of the Hospital of Brescia, Brescia, Italy (DMA study, NP 1471, 26th April 2022). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

The second cohort (TPA) is built from data derived from three subcohorts from northern and southern Germany:

- The TREND (Tübinger Erhebung von Risikofaktoren zur Erkennung von Neurodegeneration) Cohort includes healthy older adults collected at the University of Tuebingen between 2015 and 2020 and assessed longitudinally every 2 years (www.trend-studie.de)[40];
- The ABC-PD (Amyloid-Beta incerebrospinal spinal fluid as a risk factor for cognitive dysfunction in Parkinson's Disease) cohort included treated PD collected between 2015 and 2020 at the University of Tubingen who underwent an extensive motor and cognitive assessment[41];
- The PASS-PD (Prodromal Alpha-Synuclein Screening in Parkinson's Disease) cohort comprises individuals with PSG-confirmed iRBD who were enrolled between 2022 and 2024 in a longitudinal study in Kiel and underwent comprehensive diagnostic evaluation at the Department of Neurology, University Hospital of Kiel, Germany.

Persons with iRBD were included based on the following criteria: (i) history of dream-enacting behaviour; (ii) Polysomnography (PSG) proven REM sleep with sustained electromyographic (EMG) activity[42]; (iii) absence of any other known pathological neurological condition; iv) absence of motor or cognitive complaints, v) normal magnetic resonance imaging (MRI) and vi) absence of any other sleep disorder, medical condition or medication affecting gait, or substance abuse[13]; vii) absence of gait abnormalities at standard neurological examination;

Drug-naïve patients with clinically evident PD symptoms and early treated PD patients with a disease duration of up to 2 year and no motor fluctuations (defined by a MDS-UPDRS-IV of 0, which assesses motor complications including fluctuations and dyskinesias[1] were included in cohort 1 and 2 respectively. The following exclusion criteria were applied: (i) symptoms or features suggestive of atypical parkinsonism[1]; (ii) dementia[1,43]; (iii) other neurological disorders or medical conditions potentially associated with gait changes; (iv) abnormal MRI (v) need for walking aids; (vi) normal nigrostriatal dopaminergic imaging; (vii) bipolar disorder, schizophrenia, history of drug or alcohol abuse or impulse control disorder.

Treated PD without motor fluctuations were included and divided based on disease duration in early (< 3 years) and mid-stage (> 3 years) PD. Patients' caregivers and healthy volunteers served as HCs.

Each patient underwent a standard medical and neurological assessment, including the Movement Disorder Society- Unified Parkinson Disease Rating Scale (MDS-UPDRS) with Part III evaluating motor signs through clinical examination[1] and Hoehn and Yahr staging (H&Y)[44], and the Montreal Cognitive Assessment (MoCA)[45].

Mobile health technology-instrumented gait analysis

Each participant underwent gait assessment under supervised conditions[46]. They were asked to perform straight-line walking trials over a 20 m walkway at their normal (usual) speed and at fast speed. Each participant was also asked to perform two dual-task trials, the first one consisting on walking as fast as possible while checking boxes, the second one consisting on walking as fast as possible while performing serial subtractions[47,48]. The tests were performed in the ON medication state in treated participants.

The assessment of the first cohort was integrated into the mobile health technology assessment using Rehagait® (Hasomed, Germany). Briefly, three triaxial gyroscopes were placed on the lateral side of each shoe and at the level of the fifth lumbar spine segment near the centre of mass[25]. The assessment of the second cohort was performed using the APDM Mobility Lab Opal system® (APDM Wearable Technologies, Portland, Oregon). For both cohorts triaxial acceleration signals were downloaded to a computer, segmented into individual walking trials using time stamps, and analysed by a bespoke MATLAB (R2021a) program.

Statistical analyses

Between-groups differences in demographic and clinical characteristics were separately evaluated for the two different cohorts. The variables were tested for normality distribution using Shapiro-Wilk test. As the assumption of normality was met for these variables, parametric analyses were performed using ANOVA for continuous variables and the chi-squared test for categorical variables.

Gait variables were tested for normality distribution using Shapiro-Wilk test. As these variables significantly deviated from normality ($p \leq 0.05$), non-parametric analyses were applied for between-group comparisons, adjusting for age, sex, and height. Post-hoc pairwise comparisons were conducted using Tukey-type multiple comparisons on ranked data.

All analyses were 2-tailed, and $p < 0.05$ was considered as statistically significant. Statistical analyses were performed with IBM SPSS Statistics version 26.

Data availability

Data are located in controlled access data storage at University of Brescia. They are available from the corresponding author upon completion of a specific request form (including data needed, objectives of the study/analyses and a specific data sharing agreement- provided by the corresponding author andrea.pilotto@unibs.it).

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Author contributions

A.Pi., C.Z., W.M. and A.Pa. contributed to the conception and design of the study; A.Pi, A.R., C.Z., M.C., L.P., A.G., L.FS.,MP.P., I.L.S, A-K.V.T., C.H., R.R., MC.R., I.L-S., U.S., B.A., J.G., W.M and A.Pa. contributed to the acquisition and analyses of data; A.Pi., C.Z., A.R., C.H., R.R., D.B.,E.S., A.G., W.M. and A.Pa, contributed to drafting the text; A.Pi., C.Z., A.R., C.H. and R.R contributed to statistical analyses. All authors read and approved the final manuscript.

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Declarations

Competing interests

C.Hansen, A. Rizzardi, M. Catania, R. Romijnders, L. Purin, MP. Pasolini, (A) Galbiati, I. Liepelt, U. Sunkel, (B) Anton, J.Geritz and A-K. Von Thaler report no conflict of interest. (C) Zatti received grant support from Fondazione LIMPE per il Parkinson Onlus – 2024 Young Researchers Award. (D) Berg received grant support from Deutsche Forschungsgemeinschaft, German Parkinson's Disease Association, BMBF, Parkinson Fonds

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Additional information

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