The validity of the Gait Variability Index for individuals with mild to moderate Parkinson's disease.

Linda Rennie,[1] Espen Dietrichs,[2] Rolf Moe-Nilssen,[3] Arve Opheim,[1,4] Erika Franzén,[1,5,6]

[1]Research Department, Sunnaas Rehabilitation Hospital, Nesodden, Norway

[2]Department of Neurology, Oslo University Hospital and Faculty of Medicine, University of Oslo, Norway.

[3]Physiotherapy Research Group, Department of Global Public Health and Primary Health Care, University of Bergen, Norway.

[4]Rehabilitation Medicine, Institute of Neuro Science and Physiology, University of Gothenberg, Sweden.

[5]Karolinska Institutet, Department of Neurobiology, Care Sciences and Society, Division of Physiotherapy, Stockholm, Sweden.

[6]Functional Area Occupational Therapy & Physiotherapy, Allied Health Professionals Function, Karolinska University Hospital, Stockholm, Sweden.

Corresponding author:

Linda Rennie

Sunnaas Rehabilitation Hospital, Research Department, Bjørnemyrveien 11, 1450 Nesoddtangen, Norway. Tel: +47 928 48 853

E-mail: linda.rennie@sunnaas.no

E-mail addresses of co-authors:

espen.dietrichs@medisin.uio.no

Arve.Opheim@sunnaas.no

Rolf.Moe-Nilssen@uib.no

Erika.franzen@ki.se

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Abstract

Increased step-to-step variability is a feature of gait in individuals with Parkinson's disease (PD) and is associated with increased disease severity and reductions in balance and mobility. The Gait Variability Index (GVI) quantifies gait variability in spatiotemporal variables where a score ≥ 100 indicates a similar level of gait variability as the control group, and lower scores denote increased gait variability. The study aim was to explore mean GVI score and investigate construct validity of the index for individuals with mild to moderate PD. 100 (57 males) subjects with idiopathic PD, Hoehn &Yahr 2 (n=44) and 3, and ≥ 60 years were included. Data on disease severity, dynamic balance, mobility and spatiotemporal gait parameters at self-selected speed (GAITRite) was collected. The results showed a mean overall GVI: 97.5 (SD 11.7) and mean GVI for the most affected side: 94.5 (SD 10.6). The associations between the GVI and Mini- BESTest and TUG were low (r = 0.33 and 0.42) and the GVI could not distinguish between Hoehn &Yahr 2 and 3 (AUC = 0.529, SE=0.058, p=0.622). The mean GVI was similar to previously reported values for older adults, contrary to consistent reports of increased gait variability in PD compared to healthy peers. Therefore, the validity of the GVI could not be confirmed for individuals with mild to moderate PD in its current form due to low associations with validated tests for functional balance and mobility and poor discriminatory ability. Future work should aim to establish which spatiotemporal variables are most informative regarding gait variability in individuals with PD.

Keywords: Parkinson's disease, gait variability index, construct validity, walking, balance

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with common features such as hypokinesia, resting tremor, rigidity and postural instability [1]. Disturbances of gait are apparent in almost all cases of PD and become more pronounced as the disease progresses [2].

A feature of gait in individuals with PD is a decreased ability to produce a steady gait rhythm, resulting in higher step-to-step variability during walking [3]. Increased variability, thought to reflect reduced motor control, has been demonstrated for multiple spatiotemporal variables (STVs) in individuals with PD when performing level ground walking, treadmill walking, walking backwards and walking while undertaking a cognitive task [4-6]. Increased gait variability has been identified in newly diagnosed individuals [7] and was found to increase with disease severity [8]. Further, declining balance and mobility were associated with increased gait variability, which also has been shown to distinguish fallers from non-fallers [9, 10].

However, when identifying gait variability it is unclear which single variable, or combination of several STVs, are most informative for any given neurological diagnosis or disease severity [11]. The Gait Variability Index (GVI) was recently developed as a potential standardized tool for quantifying gait variability in STVs [12]. The GVI was intended to be generic and therefore applicable to different diagnostic groups and disease severities. It was constructed as a conglomerate measure of nine weighted STVs seen in relation to a reference population. A GVI $\geq$ 100 indicates a similar level of gait variability as the reference population, and each 10 point reduction in the score corresponds to one standard deviation from the reference mean

where lower scores denote increased gait variability. The GVI has previously been validated for individuals with Friedrich's Ataxia [13] and for healthy elderly [13].

The study aim was to explore mean GVI score and investigate construct validity of the index for individuals with mild to moderate PD. To do so, the association between the GVI score and scores on dynamic balance and mobility tests was examined. A moderate to high correlation was postulated to signify that functional balance and mobility does not entirely reflect the same construct as gait variability, though closely related. Further, the discriminatory ability of the GVI was evaluated by investigating how well the index distinguishes mild from moderate disease severity. It was hypothesized that individuals with moderate disease severity would have significantly lower GVI scores than those classified as mild.

2. Methods

2.1 Participants

Data for this cross sectional study was extracted from a larger randomized control trial (trial number: NCT01417598) [14]. 100 individuals (57 males) with mild to moderate PD were included based on the following criteria; having a clinical diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank criteria [15], be in Hohen & Yahr (H&Y) stage 2 (n=44) or 3 (n=56) which is characterized by bilateral or midline involvement of symptoms, with (H&Y 3) or without (H&Y 2) postural instability [16], and be 60 years or older. Participants were excluded if they had a history suggesting atypical PD symptoms as defined by Hughes et al [15], a Mini-Mental State Examination (MMSE) score ≤

24 [17], or other existing neuromuscular disorders or medical conditions that influenced their gait and balance performance. Recruitment was done via advertisements in local newspapers, from Karolinska University Hospital and outpatient neurological clinics in Stockholm County, Sweden. Ethical approval was given by the Regional board of ethics in Stockholm, and all participants gave their informed consent.

2.2 Control group

The already existing control group values embedded in the GVI and made available by Gouelle et al. [12] was used. This control group represents normative variability values for matured adult gait and not age matched older adults. However, adding to, or replacing, these reference values would change the basis for the estimated mean gait variability representing a GVI of 100 and the following GVI calculations. This would make direct comparison with previously published GVI estimates invalid. Additionally, it was considered important to evaluate the index in its current form from a clinical application point of view. The control group gait variability values are presented in the supplementary excel macro file supplied by Gouelle et al [13] and displayed as 18 absolute difference values (v_n) in percentage points for each control (see section 2.4).

2.3 Procedures

Participants used their regular medication during the study and those with motor fluctuations were tested in their medication "on" phase. Subjects were interviewed regarding their current

health status and general activity level, before their UPDRS motor examination score and H&Y score were determined. Following this, participants were instructed to walk back and forth on a pressure sensor mat (GAITRite, CIR Systems Inc., Franklin, NJ, USA). Balance was tested with the Mini Balance Evaluation Systems Test (Mini-BESTest) [18] and mobility with the Timed Up and Go (TUG) [19]. This was done in a randomized order.

Spatiotemporal gait variables were collected on a GAITRite mat (active zone 8.3 meters) at their self-selected walking speed. To facilitate a steady pace, a distance of 2.5 meters was available on each side of the mat for acceleration and deceleration. The possibility of resting was given between walks. Up to six valid trials for each subject were included in the analysis.

The Mini-BESTest is a 14 item test that focuses on dynamic balance, specifically anticipatory postural adjustments, postural responses, sensory orientation and dynamic gait. Each item is scored from 0-2 (0=unable, 2=normal) [18], with a maximum score of 28 points [20].

Testing general mobility the TUG requires the subject to rise from an arm chair, walk 3 meters, turn, walk back, and sit down again at his or hers self-selected speed, while being timed. The subject wears shoes and uses his or hers walking aid [19]. Participants made a practice run prior to testing, and one valid attempt of the TUG was recorded.

2.4 GVI calculations

The calculations were based on nine specified STVs (Table 3). These were generated using the GAITRite software (version 4.7). The GVI scores were calculated using the Excel macro (Excel®, Microsoft, USA) which is available as supplemental material provided by Gouelle et al [12].

For any given STV *i*, within any given trial *j* (STV_{ij}) the left and right foot falls were considered separately. The STV_{ij} trial mean was given the dimensionless value of 100 percent, and the intra trial STV_{ij} foot falls were expressed in percentage points in relation to its trial mean. The percentage point difference between foot falls within a trial were calculated over all trials, giving an absolute difference mean and SD of STV_i foot falls. The mean evaluates the magnitude of the variability and the SD provides an additional measure of its consistency [12]. This procedure gave 18 alternative variables (v_n) for each lower limb. These were adjusted in relation to weighting coefficients c_n determined by Gouelle et al [12] through a principal component analysis, and for a subject (α) the sum of the products was calculated:

$$s^{\alpha} = \sum_{1}^{18} (v_n \,.\, c_n) \qquad (1)$$

The distance between a subject sum score and the mean sum score of the control group (σ) was determined:

$$d^{\alpha,\sigma} = \|s^{\alpha} - s^{\sigma}\| \qquad (2)$$

The natural logarithm of this difference was computed to give a raw index score:

$$GVI_{raw}^{\alpha} = ln(d^{\alpha,\sigma}) \quad (3)$$

The subject's z-score was then determined:

$$zGVI_{raw}^{\alpha} = \frac{GVI_{\alpha}^{raw} - Mean(GVI_{\sigma}^{raw})}{SD(GVI_{\sigma}^{raw})} \quad (4)$$

The z-score was used to determine the GVI score as follows:

$$GVI^{\alpha} = 100 - 10\ x\ zGVI_{raw}^{\alpha} \quad (5)$$

The overall GVI is the mean of right and left side.

2.5 Statistical analysis

To explore the variability in the raw spatiotemporal variables used in the GVI the within-subject SD was calculated based on < 30 steps. Also, the extracted 18 absolute difference values for the control group was compared to the equivalent values from the PD cohort to further evaluate to what extent the groups differed. Despite bilateral involvement of symptoms in H&Y stage 2 and 3, there is in most cases substantial asymmetry of clinical symptoms from disease onset [21]. Therefore both the overall GVI and the GVI score for the most affected side (mean, SD) were calculated both for the total group and for the sub-groups H&Y 2 and 3. Independent samples t-test and Cohen's d effects size was used to investigate significance and magnitude of differences between the PD cohort and control group, and further for sub-groups H&Y 2 and 3. Paired samples t-test was used to determine if there was a significant difference between the overall and most affected side GVI scores. The following

categorization was used to interpret the Cohn's d effect sizes (ES): small=0.2; medium =0.5; and large =0.8 [22]. The Pearson's correlation coefficient was used to investigate the association between GVI and the Mini-BESTest and the TUG. Due to a heteroscedastic distribution in the data, an inverse transformation was performed on the TUG scores (1/TUG). The strength of all correlations where interpreted according to Munro (p. 358 [23]); <0.25= little if any correlation; 0.25=low correlation; 0.50= moderate correlation; 0.70=high correlation; 0.90=very high correlation. The discriminatory ability of the GVI, with regards to the ability to distinguish between H&Y 2 and 3, was investigated using ROC curve analysis. The strength of discrimination was interpreted according to Hosmer and Lemeshow (p. 473 [24]); 0.5=no discrimination; 0.7=acceptable; 0.8=excellent; 0.9=outstanding. Significance level was set to $p<0.05$ and data was analyzed using SPSS 21.0 (IBM).

3. Results

Demographic description of the participants is shown in Table 1. The within-person SD for the 9 raw spatiotemporal variables is shown in Table 2.

3.1 Comparing the PD cohort to the control group

The 18 absolute difference values in percentage points for the PD cohort and the control group are shown in Table 3. The PD cohort showed higher gait variability in 15 of the 18 variables and 14 of the 18 were significantly different. In 7 of the variables these differences were considered large (ES>0.8). The largest differences were seen in step length, swing time

and single support time where individuals with PD had approximately 1.5 percentage points larger mean gait variability compared to controls ($p<0.01$, ES=0.93-1.19).

3.2 GVI values for individuals with PD

The mean overall GVI was 97.5 (SD 11.7) and 94.5 (SD 10.6) for the most affected side. This is significantly different from the reported reference group mean of 100.3 (SD 7.6) [12] for both overall GVI (mean difference: 2.8, 95% CI [0.2-5.4], $p= 0.04$) and most affected side (mean difference: 5.8, 95% CI [3.4-8.2], $p<0.001$). Further, the GVI of the most affected side was significantly lower as compared to the overall GVI (mean difference: 3.0, 95% CI [2.4-3.5], $p< 0.001$).

3.3 Associations between GVI and dynamic balance and mobility

A low correlation was found between the Mini-BESTest and GVI (overall GVI: $r= 0.33$, $p<0.001$; GVI most affected side: $r= 0.29$, $p=0.004$) as well as between the 1/TUG and GVI (overall GVI: $r= 0.42$, $p< 0.001$, GVI most affected side: $r= 0.42$, $p< 0.001$) (Figure 1).

3.4 Ability of the GVI to discriminate mild from moderate disease severity in PD

The within-person SD for H&Y 2 and 3 showed that there were significant differences in variability between the sub-groups in 4 out of the 9 raw STVs used in the GVI, and two additional variables were close to significance (SD swing time and SD double support time). However, there was no significant difference between the mean GVI for H&Y 2 and 3, either for the overall GVI (mean difference: -0.9, $p=0.6$) or the most affected side (mean difference:

-0.9, p=0.6) (Table 2). Further, the ROC curve analysis showed low discriminatory ability both for overall GVI (AUC = 0.529, SE=0.058, p=0.622) and GVI most affected side (AUC = 0.533, SE=0.058, p=0.569) (Figure 2).

4. Discussion

The main finding of this study was that the mean GVI in a population of individuals with mild to moderate PD was close to normal (97.5), indicating only a small increase in gait variability, even when only considering the most affected side (94.5). Further, the GVI scores correlated poorly with dynamic balance and mobility scores, and lastly, the index showed poor ability in discriminating mild from moderate disease severity with no significant difference in the GVI between groups.

Despite the GVIs being significantly lower than the control group mean of 100.3, both scores were within ½ SD, indicating only a small increase in gait variability for this group. Also, the GVIs found in this study were slightly higher, or equal too, previously reported GVIs for elderly people, where the mean overall GVI was 91.9, ranging from 89.3 to 94.3 in healthy older adults, and 96.4 for high functioning older adults [13]. This suggests that gait variability in individuals with PD in these stages is comparable to healthy peers. As no other study to our knowledge has investigated GVI values in the PD population, we deemed it reasonable to view our results in relation to other reports on gait variability in separate STVs for individuals with PD. Other investigations show higher gait variability in mild to moderate PD compared to healthy controls, such as for stride time, stride length, step time, swing time, double support time and stride velocity [4, 8, 25, 26]. These are all variables included in the GVI, and

importantly, the levels of gait variability reported in these studies are similar to those found in our results (Table 2). Additionally, when comparing the gait variability in the PD cohort against the control group, the PD cohort showed significantly higher variability in 14 of the 18 variables that go into the GVI calculations, and in 7 of the variables these differences were deemed large (ES>0.8) (Table 3). One must therefore consider that the reported increase in gait variability in separate STVs for individuals with PD was not reflected in the sum score of the GVI, leading to the contradictory results of equal, or even higher, GVI scores in individuals with PD compared to those reported for healthy older adults.

Previous studies have shown associations between increased gait variability in individual STVs and reduced balance and mobility [9, 10, 27, 28]. Also, higher gait variability has been found in those with moderate compared to mild PD severity [8, 29]. These findings were not verified by our results where the index scores showed low correlation with dynamic balance and mobility scores, and further, poor ability to distinguish the moderate from the mild cases. Interestingly, the discriminatory ability of the GVI has been demonstrated for other groups, such as level of Friedrich's Ataxia classified by the International Cooperative Ataxia Rating Scale [12], and higher functioning older adults as opposed to those with reduced mobility [13]. Certainly, the mean GVI differences were more distinct in these groups compared to those found for H&Y 2 and 3 in this study, suggesting that the GVI performs better in these diagnostic groups as opposed to PD. On the other hand, a previous report utilizing a similar cohort as this study, showed that the Mini-BESTest had acceptable ability to distinguish H&Y 2 from 3 [30]. The argument can be made that the GVI was not sensitive enough to detect known group differences in individuals with PD, a difference which has been detected by a validated dynamic balance test. This, together with the fact that the mean values of the GVI in this cohort were equal to those of healthy peers, and the low correlation found between the

GVI and dynamic balance and mobility scores, we consider the GVI to exhibit poor construct validity for individuals with PD.

There may be several reasons for why the GVI does not reflect the expected gait variability in individuals with PD. Firstly, as many as 44 % of the cohort had GVI values of 100 or above for the overall GVI, and 28 % for the most affected side. All values over 100 are regarded as normal levels of gait variability [12, 13] regardless if the GVI is 101 or 130. The reason for these higher values is seen in equation 3. When the difference between the subject and control group is small the natural log of values approaching zero will tend toward infinity resulting in an exponential distribution in GVI values well above 100. Although there is no interpretational difference between a GVI of 101 or 130, it is clear that the more extreme values will elevate the group mean and give a misleading result. It was therefore appealing to explore median GVI when all values over 100 were scored as 100. This resulted in little change from the initial group mean GVIs, where the median overall GVI was 97.9 and the median GVI most affected side was 95.2.

Secondly, higher values can also result in masking of unilateral increase in gait variability in the overall GVI calculation. If one side has normal gait variability with a GVI of 120, whereas the most affected side has an increased variability with a GVI of 80, this would give an overall GVI of 100 and wrongly be assessed as normal. The reduction in values of 100 or higher from 44% for overall GVI to 28% for most affected side indicates that a unilateral increase in gait variability has been equaled out by the closer to normal contralateral side. This warrants caution when using the overall GVI for individuals with PD.

Thirdly, the GVI has an exponential distribution rather than a linear one, inferring that changes in GVI scores relative to the underlying gait variability is not evenly distributed across the continuum of the index. Individuals with a high GVI could see relatively large changes in the score with only small changes in variability, whereas in those with low GVI, the same changes in gait variability would show minimal changes in the GVI score. This implies that using the index to monitor change over time in an individual or group, or comparing different groups, is problematic both clinically and statistically.

Lastly, the seemingly low sensitivity of the GVI to display increased gait variability in individuals with PD, and further distinguish between mild and moderate disease severity, may reflect the inclusion of multiple STVs. Considering the differences found in the gait variability in the PD cohort compared to the control group (Table 3), could indicate that key variables becomes leveled out by those less important, leading to an under-representation in the GVI sum score. There is to date no consensus in the literature which STVs best represent gait variability in individuals with PD, though swing time has been reported to display the highest CV value differences from healthy peers in multiple studies of approximately 1.5 percentage points, [4, 7, 26, 31] and is supported by our results where step length, swing time and single support time showed the largest differences from the control group. It is important to note that single support time and swing time are highly correlated due to the combined values for the left and right side. The two events happen simultaneously but on opposite legs interchangeably, and the norm is to report one of the two variables. Conversely, Lord et al [11] identified in their gait model a cluster of STVs found to be most informative of variability in the gait of individuals with PD. These were step and stance time variability, step length and step velocity variability. However, with regards to the GVI it could be argued that the weighting coefficients used in the calculation ensures that the variability for each

parameter is appropriately expressed in the total summation. However, one must consider that these weights were based on combined data from healthy individuals and varied pathologies, and therefore question if the coefficients are representative for other groups such as individuals with PD. The model proposed by Lord et al [11] is perhaps one way forward, where clusters of variables that explain most of the underlying construct of gait variability are identified using rigorous statistical methodology and is tested over time.

Limitations

It is important to highlight that the control group used was not collected as part of this study and represent variability found in matured adult gait, rather than gait variability in age matched older adults. Also, potential differences in testing protocols between the two studies could have influenced our results. The control group data was collected at two different sites using slightly shorter GAITRite mats than the one used in this study. However, similar distances were used before and after the mat to ensure steady state walking, and similar amount of steps were analysed in this study as was done by Gouelle et al [12] making it unlikely that that these differences have influenced the result to a large extent.

Further, our results are only applicable to gait variability measured for individuals with PD in their medication "on" phase. Literature indicates that improvements in straight walking as a result of dopaminergic treatment are mainly seen in spatial parameters such as stride/ step length and is related to improvements of bradykinesia. However, temporal variables and gait variability does not appear to be improved significantly by levodopa [32]. As the majority of the variables included in the GVI are temporal, the argument can be made that testing the participants in the "on" phase would not have influenced our results greatly. However,

contradicting this, Bryant et al. [25] showed improved variability in step time, swing time, stride length and stride velocity when investigating the effects of levodopa on gait in Parkinson's disease. It seems that further research is warranted to investigate these contradictory results, and our results should be interpreted accordingly.

Conclusion

The mean GVI scores for individuals with mild to moderate PD were found to be relatively high, within ½ SD of the reference population mean, and similar to reported GVI values for older adults. This is contrary to consistent accounts of increased gait variability in individuals with PD compared to healthy peers. The GVI displayed low correlation with validated tests for functional mobility and balance, and poor discriminatory ability in identifying level of disease severity. This was contrary to previous findings showing that increased gait variability was associated with disease severity and decreased balance and mobility capabilities. Therefore, the validity of the GVI could not be confirmed for individuals with mild to moderate PD in its current form.

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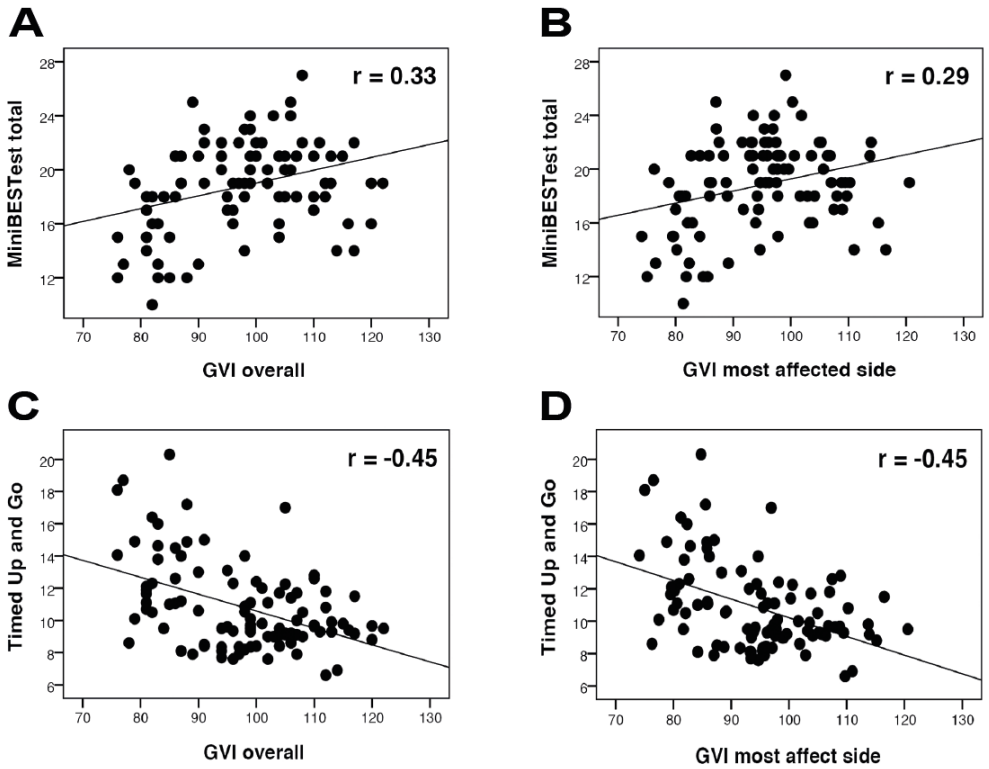

Fig 1. The correlation between the Mini Balance Evaluation Systems Test and the Gait Variability Index (GVI), and the inverse transformed Timed Up and Go and the GVI. The association between GVI and dynamic balance were found to be low both for the overall GVI (A) and the GVI most affected side (B). The same was true for functional mobility (C and D).

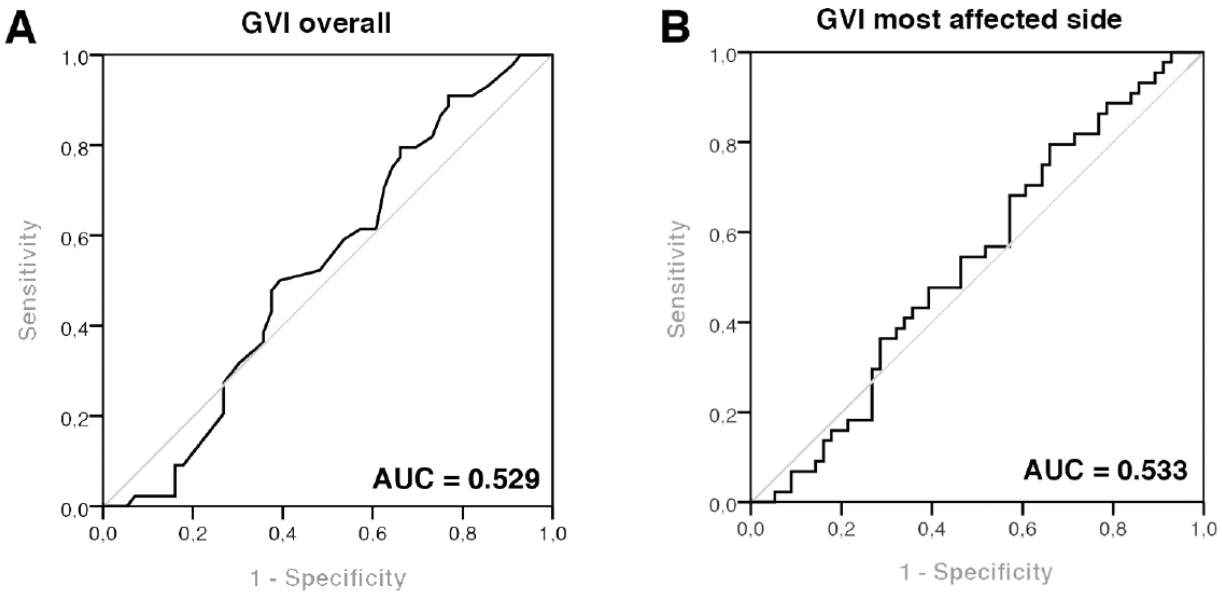

Fig 2. The ability of the overall Gait Variability Index (GVI) (A) and the GVI most affected side (B) to distinguish mild from moderate disease severity in individuals with Parkinson's disease. The GVI showed low discriminatory ability for both conditions.

Table 1

Participant Characteristics (means and standard deviations).

	PD cohort total	Hoehn & Yahr 2	Hoehn & Yahr 3
Number of participants	100	44	56
Sex (male/ female)	57/ 43	25/19	32/ 24
Age (years)	73.2 (5.6)	72.7 (5.7)	73.5 (5.6)
Height (cm)	171.0 (8.9)	172.0 (7.8)	170.0 (9,6)
Body Mass Index (kg/m^2)	22.0 (3.4)	22.0 (3.3)	21.8 (3.5)
Years since diagnosis	5.8 (5.0)	4.0 (2.9)	7.0 (5.7)
UPDRS subscale III (0-108 points)	36.6 (10.5)	34.4 (9.5)	38.5 (10.7)

Abbreviations: UPDRS=Unified Parkinson's Disease Rating Scale

Table 2

PD Cohort Gait Variability Characteristics (within-person SD and GVI values included).

Variables	**PD cohort total**	**H&Y 2 (n=44)**	**H&Y 3 (n=56)**	**p-value**
SD Step length (cm)	2.48	2.52	2.46	0.66
SD Stride length (cm)	3.82	3.86	3.79	0.78
SD Step time (ms)	18.6	16.8	20.0	0.04*
SD Stride time (ms)	26.8	23.9	29.1	0.03*
SD Swing time (ms)	17.1	15.7	18.2	0.06
SD Stance time (ms)	21.3	19.0	23.2	0.01*
SD Single support time (ms)	16.9	14.9	18.4	0.01*
SD Double support time (ms)	20.6	19.4	21.6	0.08
SD Stride Velocity (cm/s)	4.67	4.56	4.74	0.53
GVI overall	97.5	98.1	97.1	0.66
GVI most affected side	94.5	95.1	94.1	0.67

Abbreviations: SD=standard deviation; PD=Parkinson's disease: H&Y=Hoehn and Yahr scale; GVI= gait variability index; *=significantly different.The calculations are for left side only and are based on < 30 steps.

Table 3.
Within-subject gait variability expressed as absolute difference values in percentage points (mean and SD) for the PD cohort and GVI control group (combined left and right side).

	Var. mean PD	Var. mean control	Mean Diff.	p-value	Effect size	Var. SD PD	Var. SD control	Mean Diff.	p-value	Effect size
Step length	3.62	2.15	1.47	< 0.01*	1.19	2.92	1.72	1.20	< 0.01*	1.92
Stride length	2.61	1.72	0.89	< 0.01*	0.99	2.06	1.27	0.79	< 0.01*	1.06
Step time	3.23	2.73	0.50	< 0.01*	0.47	2.55	2.11	0.44	< 0.01*	0.50
Stride time	2.26	1.94	0.32	< 0.01*	0.38	1.76	1.48	0.28	<0.01*	0.38
Swing time	4.67	3.21	1.46	< 0.01*	0.93	3.58	2.52	1.06	< 0.01*	0.85
Stance time	2.56	2.41	0.15	0.19	0.15	2.01	1.93	0.08	0.41	0.09
Single sup. Time	4.68	3.04	1.54	< 0.01*	1.06	3.58	2.68	0.90	< 0.01*	0.70
Double sup. Time	5.97	6.22	-0.25	0.30	0.13	4.54	5.40	-0.85	< 0.01*	0.44
Stride velocity	2.59	2.87	-0.28	0.04*	0.27	2.00	1.86	0.14	0.13	0.18

Abbreviations: SD = standard deviation; PD = Parkinson's disease; GVI = Gait Variability Index; Var = variability; Diff = difference; sup = support. Effect size=Cohen's d. The control group data is extracted from Gouelle et al (2013).