

Supplementary Material

Gait Declines Differentially in, and Improves Prediction of, People with Parkinson’s Disease Converting to a Freezing of Gait Phenotype

Supplementary Table 1. Summary of FOG criteria and study assessments used in published FOG prediction studies.

Study	Initial noFOG	Final FOGConv	maximum duration monitored (y)	Monitoring Interval	best estimated conversion rate	FOG criteria used	Levodopa state
Giladi 2001	743	193	2	Every 3 months	13.0%	UPDRS 2.14	OFF
Forsaa 2015	169	82	12	At 4 years, 8 years, then annually	12.4%	UPDRS 2.14	
Zhang 2016	248	128	3	Annually	17.2%	self-assessment or exam	pre-levodopa->some on levodopa?
Veervoort 2016 ⁺	59	5	1	At 1 year	8.5%	N-FOG-Q	OFF
Ou 2017	225	85	3	At 3 years	12.6%	FOG-Q 3	OFF
Ehgoetz-Martens 2018	129	41	2	variable, at least 2 visits 6-24 months apart	15.9%	FOG-Q item 3	not reported
D'Cruz 2020 ⁺	60	12	2	annually	11.8%	N-FOG-Q	OFF
D'Cruz 2021 ⁺	45	9	2	At 2 years	20.0%	N-FOG-Q	OFF
Gallea 2021	25	17	5	At 5 years	13.6%	GABS	OFF/ON
Xu 2021	967	255	1	At 1 year	26.4%	UPDRS 2.14, NFOGQ	OFF
Jeong JPD 2021	329	52	2	Every 3-6 months	7.9%	subjective+objective?	pre-levodopa
Zhao 2022	350	132	2	At 2 years	18.9%	N-FOG-Q, or self-report, or exam	not reported
PPMI Database							
Kim 2019	393	136	3	Every 3 months first year, then every 6 months	11.5%	MDS UPDRS, either 2.13 or 3.11	pre-levodopa-> OFF/ON
Kim 2018							pre-levodopa-> OFF/ON
Banks 2019	100	50	4	Every 3 months first year, then every 6 months	12.5%	MDS UPDRS 2.13	pre-levodopa-> OFF/ON

Wang 2022	183	68	5	Every 3months first year, then every 6 months	7.4%	ADLs or exam	pre-levodopa-> OFF/ON
Retrospective studies							
Herman 2018	57	26	5	At 5 years	9.1%	N-FOG-Q + clinical observation	OFF/ON
Jung 2020	433	44	5	Every 3-6 months, retrospective chart review	2.0%	self report or exam	not reported

Study cont.	Gait	balance	cognition	Psychiatric	Non-motor	Sleep	olfaction	imaging	other
Giladi 2001									
Forsaa 2015			MMSE	UPDRS 1.2					
H Zhang 2016				HAMD, HAMA	NMSS				
Veervoort 2016 ⁺	spatiotemporal	MiniBEST, fall history							
Ou 2017		falls history	MoCA, FAB	HAMD, HAMA	NMSS				
Ehgoets Martens 2018			Digit span, MMSE, logical memory, TMT A, B	HADSA/D		RBDSQ4			
D'Cruz 2020 ⁺	spatiotemporal	Falls efficacy scale, miniBEST,	MMSE, MoCA, SCOPA-Cog, FAB, Alternate Naming Test, Alternate intake test, Rey- Osterrieth, trial making test	Hospital Anxiety and depression scale					objective finger/foot tapping
D'Cruz 2021	spatiotemporal							MRI	
Gallea 2021	GABS	GABS							antisaccade task, SWJ frequency
Xu 2021			MMSE	HAMD	NMSS, ROME III constipation criteria, PD Fatigue scale	RBD-Q, ESS	Hyposmia rating scale		PDQ-39

Jeong JPD 2021			K-MMSA	K-NPI				DAT, FP-PET	
Zhao 2022		Berg-balance	MoCA	HAMD, HAMA					
PPMI Database									
Kim 2019			MoCA	GDS, state trait anxiety inventory	SCOPA-Aut	RBD-Q, ESS	UPSIT	DAT	CSF A β 42
Kim 2018	Same as Kim 2019 above								
Banks 2019			MoCA, phonemic fluency, semantic fluency, letter no. seq, Judge line orient., symbol digit mod, Hopkins verbal learn test, total learning task	GDS, state trait anxiety inventory	MDS-UPDRS part 2	RBD-Q, ESS			
Wang 2022			MoCA, phonemic fluency, semantic fluency, letter no. seq, Judge line orient., symbol digit mod, hopkin verbal learn test, total learning task	GDS, state trait anxiety inventory, Q for imp do (QUIP)	SCOPA-Aut	RBD-Q, ESS	UPSIT	DAT, FP-PET	CSF A β 42, total tau, α -syn; Genetics MAPT, APOE4, SNCA
Retrospective studies									
Herman 2018	spatiotemporal	fall risk, Berg balance scale, ABC	MMSE, MoCA, TMT A and B	GDS, UPDRS 1 subscore	NMS scale, SCOPA-Aut	PSQi			PDQ-39
Jung 2020			Korean-MMSE	BDI			CCSIT	MRI, FP-PET	

Supplementary Table 2. Univariate predictive analysis

Feature	No. of studies	Study
LEDD*	4	Forsaa 2015, Zhang 2016, Ou 2017, Ehgoetz-Martens 2018
lower TD/non-TD or greater non-TD	4	Ehgoetz-Martens 2018, Xu 2021, PPMI (Kim 2018, Wang 2022)
NMSS scales (total, item), SCOPA-Aut	4	Zhang 2016, Ou 2017, Xu 2021, Wang 2022
Depression (HAM-D, HADs D)	4	Zhang 2016, Ou 2017, Ehgoetz-Martens 2018, Xu 2021
Age*	3	Zhang 2016, Xu 2021, Wang 2022
lower cognition scores	3	Xu 2021, PPMI (Kim 2018, Wang 2022)
Anxiety (HAM-A, HADs A)	3	Zhang 2016, Ou 2017, Ehgoetz-Martens 2018
MDS III total	2	Ou 2017, Kim 2018
MDS III subscores	2	Giladi 2001, Xu 2021
Hoehn & Yahr scale	2	Ou 2017, Xu 2021
Male sex	2	Xu 2021, Kim 2018
lower education level	2	Zhang 2016, Xu 2021
Disease duration	2	Giladi 2001, Xu 2021
early amantadine use	2	Zhang 2016, Xu 2021
DAT (lower caudate and putamen uptake)	2	PPMI (Kim 2018, Wang 2022)
MRI (thalamic inflation, cerebellar connectivity)	2	D'cruz 2021, Jung 2020)
lower A β 42	2	PPMI (Kim 2018, Wang 2022)
Single task gait asymmetry	1	D'cruz 2020
dual task gait asymmetry	1	D'cruz 2020
swing time CV	1	D'cruz 2020
finger tap ampl CV	1	D'cruz 2020
finger tap phase inconsistency	1	D'cruz 2020
finger tap amplitude	1	D'cruz 2020
toe tap phase inconsistency	1	D'cruz 2020
MDS non-motor subscale cognition	1	D'cruz 2020
MDS non-motor subscale pain	1	D'cruz 2020
MDS II	1	Wang 2022
MDS I	1	Wang 2022
miniBEST	1	Veervort 2016
rural residence location	1	Zhang 2016
motor fluctuations	1	Forsaa 2015
dyskinesias	1	Forsaa 2015
FOG-Q*	1	Ehgoetz-Martens 2018
falls	1	Ou 2017
increased anti-saccade latency	1	Gallea 2021
PDQ-39	1	Xu 2021
*Significant in our study		

Supplementary Table 3. Multivariable analysis features reported to be predictive of FOG conversion

Feature	No. of studies	Study
disease duration	4	Ou 2017, Ehgoetz-Martens 2018, Gallea 2021, Zhao 2022
depression scores	4	Ehgoetz-Martens 2018, D'Cruz 2020, Zhao 2022, Herman 2018
lower TD/non-TD or greater non-TD	3	Ehgoetz-Martens 2018, Xu 2021, PPMI (Kim 2018 PRD, Kim 2018, Wang 2022)
age	2	Ehgoetz-Martens 2018, Xu 2021
LEDD	2	D'cruz 2021, Zhao 2022
gait speed	2	D'cruz 2020, Herman 2018
DAT (lower caudate, caudate and putamen)	1	PPMI (Kim 2018, Kim 2018 PRD)
A β 42	1	PPMI (Kim 2018, Wang 2022)
SDMT	1	PPMI (Banks 2019, Wang 2022)
MDS UPDRS II and III axial	1	D'cruz 2020
MDS UPDRS II hand function	1	D'cruz 2020
MDS UPDRS I	1	D'cruz 2020
MDS UPDRS I fatigue score	1	Wang 2022
UPDRS III ON vs OFF scores	1	Herman 2018
MDS UPDRS III	1	Ou 2017
MDS UPDRS III Item 30	1	Xu 2021
delta UPDRS III	1	Ou 2017
delta MoCA visuospatial-executive function	1	Ou 2017
gender	1	D'cruz 2021
festination	1	Ou 2017
falls	1	Ou 2017
hallucinations	1	Ou 2017
FOG-Q	1	Ehgoetz-Martens 2018
fatigue on PFS score	1	Xu 2021
NMSS	1	Xu 2021
PDQ-39	1	Xu 2021
lower limb motor onset	1	Ou 2017
finger tap amplitude, rhythm inconsistency relative phase inconsistency, frequency, amplitude	1	D'cruz 2020
gait variability	1	D'cruz 2020
Dual-task gait asymmetry	1	D'cruz 2020
Dual-task step width	1	D'cruz 2020
toe tap amplitude	1	D'cruz 2020
Stroop response time while walking	1	D'cruz 2020

motor upper limb + axial	1	D'cruz 2020
anxiety	1	Ehgoetz-Martens 2018
HVLT-L	1	Banks 2019
ESS	1	Banks 2019
NPI total score	1	Jeong 2021
increased anti-saccade latency	1	Gallea 2021
left thalamic inflation	1	D'cruz 2021

Supplementary Table 4. Spatiotemporal gait parameter definitions.

Measure	Definition
Integrated-pressure (pressure x s)	the sum of pressure applied by a footstep at each sampling time (120 Hz sampling rate) in the area of its contact with the ground.
Foot-strike-length (cm)	length of the major axis of the ellipse enclosing each footstep; PKMAS creates an ellipse around each footstep during footstep identification.
Stride-length (cm)	the distance between heel strikes of two consecutive footsteps of the same foot, i.e., two right or two left heel strikes.
Stride-width (cm)	the distance between heel strikes of two consecutive footsteps of the same foot, i.e., two right or two left heel strikes, perpendicular to the direction of travel (y-axis)
Stride-time (s) also known as gait cycle time	the time difference (s) between the initial heel contacts with the mat of two consecutive footsteps of the same foot, i.e., two right or two left.
Stride-velocity (cm/s)	the stride length divided by stride time, calculated for each gait cycle.
Swing-percent	a percentage measure of time spent in swing phase of the gait cycle and calculated as stance time/gait cycle time.
Total-double-support-percent	a percentage measure of the total time spent in total-double-support phase of the gait cycle and calculated as total double support time/gait cycle time.
Stance-COP-distance (cm)	stance Center of Pressure distance; the Pythagorean distance between the first and last contact points of the center of pressure (COP) waveform trail for a footstep in stance phase, based on X and Y coordinates corresponding to first and last contact times of a foot during stance.

¹All calculations were auto-generated by the PKMAS software and definitions are based on the PKMAS Measurements and Definitions manual provided by Protokinetics with their software.

Supplementary Table 5. Area under the curve (AUC) values for classification of noFOG and FOGConv groups based on initial visit pre-conversion.

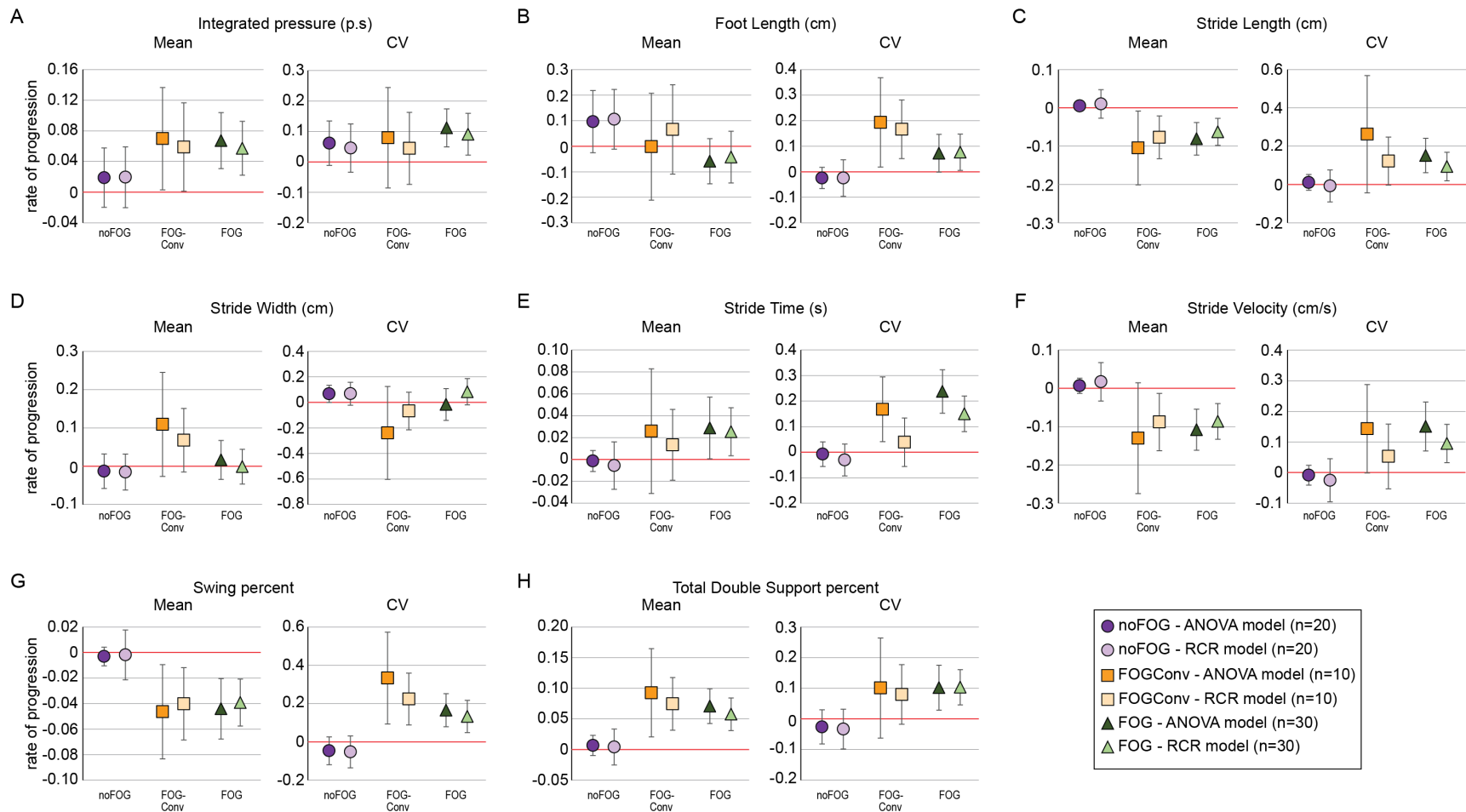
		AUC	<i>p</i>	Confidence Interval	
				Upper	Lower
Age at onset (y)		0.735	0.039	0.544	0.926
Age at enrollment (y)		0.500	1.000	0.266	0.734
Disease duration (y)		0.685	0.104	0.485	0.885
<u>General motor function</u>					
ON Motor UPDRS		0.608	0.344	0.388	0.827
ON Total UPDRS		0.693	0.090	0.503	0.882
Hoehn & Yahr stage		0.635	0.235	0.430	0.840
FOG-Q		0.788	0.011	0.606	0.969
<u>Non-motor disease features</u>					
MoCA		0.585	0.455	0.349	0.821
SCOPA-Cog		0.533	0.775	0.306	0.759
FAB		0.505	0.965	0.272	0.738
HAM-D		0.663	0.153	0.448	0.877
HAM-A		0.663	0.153	0.452	0.873
AES		0.623	0.281	0.405	0.840
ESS		0.325	0.124	0.129	0.521
RBD-Q		0.525	0.826	0.299	0.751
PDQ-39		0.638	0.226	0.414	0.861
<u>Parkinson's Medications</u>					
Daily levodopa dose (mg)		0.753	0.026	0.555	0.950
Duration on levodopa (y)		0.775	0.016	0.579	0.971
LEDD (mg)		0.815	0.006	0.653	0.977
<u>Initial Spatiotemporal Gait Measures</u>					
Integrated pressure	mean	0.640	0.218	0.430	0.850
	CV	0.595	0.403	0.388	0.802
Foot-strike length (cm)	mean	0.640	0.218	0.429	0.851
	CV	0.630	0.253	0.409	0.851
Stride length (cm)	mean	0.650	0.187	0.440	0.860
	CV	0.575	0.509	0.346	0.804
Stride width (cm)	mean	0.690	0.095	0.480	0.900
	CV	0.755	0.025	0.550	0.960
Stride time (s)	mean	0.558	0.613	0.329	0.786
	CV	0.710	0.065	0.511	0.909
Stride velocity (cm/s)	mean	0.645	0.202	0.448	0.842
	CV	0.650	0.187	0.444	0.856
Swing-phase percent	mean	0.610	0.333	0.384	0.836
	CV	0.515	0.895	0.281	0.749
Total-double-support-phase percent	mean	0.595	0.403	0.366	0.824
	CV	0.460	0.725	0.229	0.691

¹Items in **bold** are significant.

Supplementary Table 6. For distinguishing FOGConv from noFOG based on progression rates¹, cutoff points² that optimize the Youden's index are provided.

		FOGConv pre-conversion observations (n=9)		FOGConv all observations (n=10)	
		Youden's Index	Cutoff point	Youden's Index	Cutoff point
Integrated-pressure	mean	0.398	0.074	0.250	0.042
	CV	0.301	-0.121	0.086	0.042
Foot-strike-length (cm)	mean	0.399	-0.013	0.210	-0.013
	CV	0.434	0.105	0.484	0.085
Stride-length (cm)	mean	0.614	-0.040	0.602	-0.036
	CV	0.354	0.153	0.401	0.117
Stride-width (cm)	mean	0.431	0.082	0.449	0.062
	CV	0.488	-0.185	0.366	-0.012
Stride-time (s)	mean	0.225	0.016	0.233	0.015
	CV	0.360	-0.181	0.433	0.108
Stride-velocity (cm/s)	mean	0.530	-0.051	0.551	-0.046
	CV	0.402	0.141	0.428	0.084
Swing-phase %	mean	0.625	-0.022	0.569	-0.019
	CV	0.624	0.188	0.692	0.142
Total-double-support-phase %	mean	0.588	0.045	0.517	0.043
	CV	0.411	0.127	0.464	0.101

¹ The progression rate is the linear slope of the log₂-transformed spatiotemporal gait parameter over time for a single patient. ² Cutoff points were estimated with the kernel smoothing method recommended in Fluss et al. (2005).



Supplementary Figure 1. Comparison of ANOVA and RCR models. A-H) The rate of progression (slope) in the log₂-transformed mean (left panels) and coefficient of variability (CV, right panels) are shown for 8 spatiotemporal gait parameters for both the ANOVA (dark colored symbols) and RCR models (light colored symbols). Values are plotted as means with 95% confidence intervals. Groups with confidence intervals not crossing 0 are significantly declining over time. Estimates from the ANOVA model are similar to those from the most complicated RCR model.