Parkinsonism and Related Disorders 65 (2019) 190–196

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Quantitative mobility metrics from a wearable sensor predict incident parkinsonism in older adults

Rainer von Coelln[a,*], Robert J. Dawe[b,c], Sue E. Leurgans[b,d], Thomas A. Curran[b], Timothy Truty[b], Lei Yu[b], Lisa L. Barnes[b], Joshua M. Shulman[e,f], Lisa M. Shulman[a], David A. Bennett[b,d], Jeffrey M. Hausdorff[b,g,h,i,j], Aron S. Buchman[b,d]

[a] Department of Neurology, University of Maryland School of Medicine, Baltimore, MD, USA
[b] Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA
[c] Department of Diagnostic Radiology and Nuclear Medicine, Rush University Medical Center, Chicago, IL, USA
[d] Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA
[e] Departments of Neurology, Neuroscience, and Molecular & Human Genetics, Baylor College of Medicine, Houston, TX, 77030, USA
[f] Jan and Dan Duncan Neurologic Research Institute, Texas Children's Hospital, Houston, TX, 77030, USA
[g] Center for the Study of Movement, Cognition, and Mobility, Neurological Institute, Tel Aviv Medical Center, Tel-Aviv, Israel
[h] Department of Physical Therapy, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[i] Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel
[j] Department of Orthopedic Surgery, Rush University Medical Center, Chicago, IL, USA

ARTICLE INFO

Keywords:
Parkinsonism
Gait testing
Biosensor
Accelerometry
Longitudinal

ABSTRACT

Introduction: Mobility metrics derived from wearable sensor recordings are associated with parkinsonism in older adults. We examined if these metrics predict incident parkinsonism.

Methods: Parkinsonism was assessed annually in 683 ambulatory, community-dwelling older adults without parkinsonism at baseline. Four parkinsonian signs were derived from a modified Unified Parkinson's Disease Rating Scale (UPDRS). Parkinsonism was based on the presence of 2 or more signs. Participants wore a sensor on their back while performing a 32 foot walk, standing posture, and Timed Up and Go (TUG) tasks. 12 mobility scores were extracted. Cox proportional hazards models with backward elimination were used to identify combinations of mobility scores independently associated with incident parkinsonism.

Results: During follow-up of 2.5 years (SD = 1.28), 139 individuals developed parkinsonism (20.4%). In separate models, 6 of 12 mobility scores were individually associated with incident parkinsonism, including: Speed and Regularity (from 32 ft walk), Sway (from standing posture), and 3 scores from TUG subtasks (Posterior sit to stand transition, Range stand to sit transition, and Yaw, a measure of turning efficiency). When all mobility scores were analyzed together in a single model, 2 TUG subtask scores, Range from stand to sit transition (HR, 1.42, 95%CI, 1.09, 1.82) and Yaw from turning (HR, 0.56, 95%CI, 0.42, 0.73) were independently associated with incident parkinsonism. These results were unchanged when controlling for chronic health covariates.

Conclusion: Mobility metrics derived from a wearable sensor complement conventional gait testing and have potential to enhance risk stratification of older adults who may develop parkinsonism.

1. Introduction

Parkinsonism, including bradykinesia, tremor, rigidity and gait impairment, is common in older adults without Parkinson disease (PD) and as it increases with age it may affect 50% or more of the population by age 85 [1]. Parkinsonism is a heterogeneous syndrome, which is not limited to PD, but can be caused by diverse etiologies, some of which are amenable to treatment [2]. Furthermore, parkinsonism is associated with adverse health outcomes including death, disability, and cognitive impairment [3]. Given the magnitude and consequence of parkinsonism in our aging population, identification of at-risk individuals offers the potential for early interventions that which may prevent the development of parkinsonism [4].

Conventional mobility metrics, such as gait speed, are sensitive but non-specific predictors of parkinsonism [5,6]. Mobility is a multi-dimensional trait derived from dissociable neural control systems within

* Corresponding author.
E-mail address: RvonCoelln@som.umaryland.edu (R. von Coelln).

https://doi.org/10.1016/j.parkreldis.2019.06.012
Received 22 February 2019; Received in revised form 19 May 2019; Accepted 18 June 2019
1353-8020/ © 2019 Elsevier Ltd. All rights reserved.

the central nervous system [7,8]. Investigations in gait laboratories have quantified additional facets of mobility necessary for successful locomotion [9,10]. Emerging technologies including wearable sensors show promise for extending these advances beyond the lab or hospital setting to varied venues including outpatient clinics and community studies of aging [11,12].

In a prior cross-sectional study, we found that sensor-derived mobility metrics were related to the severity of parkinsonian signs in older adults [13–15]. However, it is not known if these sensor-derived mobility metrics are associated with incident parkinsonism. To address this question, we used clinical data from older adults, participating in two community-based longitudinal cohort studies, who undergo annual motor testing for parkinsonian signs, as well as mobility testing with a wearable sensor.

2. Methods

2.1. Participants

Participants were from two ongoing longitudinal cohort studies, recruited from retirement communities and subsidized housing facilities in the Chicago metropolitan area, the Rush Memory and Aging Project (MAP) and the Minority Aging Research Study (MARS) [16,17].

All procedures in both studies were approved by the Institutional Review Board of Rush University Medical Center and were conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

There were 815 participants (MAP: N = 619; MARS: N = 196) who did not have clinical parkinsonism at their first visit with instrumented gait testing, which served as baseline visit for this study. Since these analyses focused on the association of mobility metrics with incident parkinsonism, we excluded participants who did not have a follow-up assessment (n = 132), because they either died before the second assessment or had not yet reached their first follow-up visit. The characteristics of the remaining 683 individuals at their baseline visit (MAP: N = 500; MARS: N = 183) are summarized in Table 1.

2.2. Demographics and other chronic health covariates

Demographics covariates were obtained at study entry (Table 1). Chronic health conditions included the number out of 3 vascular risk factors (diabetes, hypertension, smoking [median = 0; Q1,0, Q3,3]) and the number out of 4 vascular diseases (claudication, congestive heart failure, myocardial infarction, stroke [median = 0; Q1,1, Q3,4]). BMI was calculated from measured height and weight.

Table 1
Characteristics at baseline, N = 683.

Variable	Mean (SD) or N (%)
Demographics	
Age (years)	80.7 (7.7)
Sex (females)	535 (78)
Education (years)	15.2 (3.0)
Race (Black)	199 (29.1)
BMI (kg/m^2)	28.2 (5.9)
MMSE (0–30)	27.9 (2.5)
Vascular Risk Factors	
Diabetes mellitus	143 (20.9)
Hypertension	450 (65.9)
Smoker (ever)	303 (44.4)
Vascular Diseases	
Claudication	80 (11.7)
Congestive heart failure	39 (5.7)
Myocardial Infarction	66 (9.7)
Stroke	46 (7.0)

BMI: Body mass index; MMSE: Mini-Mental State Examination.

2.3. Assessment and categorization of individuals with parkinsonism and PD

Global Parkinsonism Score: The annual evaluation includes a modified version of the Unified Parkinson's Disease Rating Scale (UPDRS) [18] administered by trained nurse clinicians [19]. 26 items which assess 4 parkinsonian signs (parkinsonian gait, bradykinesia, rigidity, and tremor, including rest tremor and action tremor) were summarized as continuous *global parkinsonism score*, as previously described [19]. This *global parkinsonism score* allows for the assessment of the severity of parkinsonian signs in all individuals, including those with mild signs not meeting criteria for parkinsonism (described below).

Categorization of Parkinsonism: Previously validated categories of parkinsonism were based on the number of parkinsonian signs present. A sign was present if 2 or more of their respective items had at least a score of 1 indicating mild abnormality. *Parkinsonism* was present if 2 or more signs were documented. *Possible parkinsonism* was present if there was 1 sign, and *No parkinsonism* if there were none [3]. Prior publications have established interrater reliability between nurse clinicians and a movement disorder specialist for both the global parkinsonism score and categorization of parkinsonism [3,19].

Diagnosis of PD: A diagnosis of PD was based on the self-reported history of PD for which the participant was treated by a physician with levodopa or other dopamine agonists [20].

2.4. Assessment of mobility

Wearable Sensor: Mobility testing with a wearable sensor (Dynaport MT, McRoberts B·V., The Netherlands) positioned on the lower back with a neoprene belt was performed at the participant's residence. This device consists of three orthogonally oriented piezoelectric accelerometers and three gyroscopic sensors for 100 Hz sampling of three-dimensional acceleration and rotation rate of the lower trunk.

Mobility Performances: Three performances were recorded. A) 32 ft *walk*: Participants walked at their self-selected speed on a marked 8 ft course back and forth twice without stopping. The length of the course was limited to 8 ft, in order to ensure that the task could be performed in participants' homes [15]. B) *Modified TUG:* Participants were instructed to stand up from a chair, walk 8 ft at a comfortable self-selected speed, turn and walk back to the chair and sit down again. C) *Standing Posture*: Participants were asked to stand for 20 s in a comfortable position with their eyes closed.

Extraction of Mobility Measures: All three performances were recorded in a single file, with markers embedded in the file to identify the beginning and the end of each performance. Before automated processing of the segmented files, a research assistant confirmed correct marker locations in the segmented performances, using a custom Matlab-based graphical user interface. The single file is then segmented into separate files for each performance tested, based on the embedded markers.

Mobility measures were extracted from each of the performances using previously described formulas [21–23]. The TUG is composed of 4 different movements or subtasks [21,22]. This study examined 3 TUG subtasks including: 1) *transition from sit to stand* (S1), 2) *transition from stand to sit (S2)*, and 3) *turning subtasks* and did not include the walk components. The TUG walk subtasks were not included so as not to duplicate the walk measures obtained from the 32 ft walk.

Mobility Scores: In a previous study we used available literature and principal component analyses to guide our construction of 12 mobility scores, which summarize the 26 measures extracted from the 5 mobility subtasks [15]. Table 2 shows the relationship between the mobility subtasks, measures and scores. Each mobility score had a standard deviation equal to 1, and higher values corresponded to more movement. These 12 mobility scores were used in the analyses described below.

Table 2
Baseline mobility measures derived from a wearable sensor.

Performance Tests	Mobility Subtasks	Mobility Measures			Mobility Scores
		Measure (units)	Mean (SD)/median	Q1, Q3	
32 ft Walk	Walk	Speed (ft/s)	2.52 (0.31)	2.33, 2.73	Speed
		Stride length (ft)	3.03 (0.96)	2.46, 3.56	
		Cadence (steps/min)	56.6 (11.4)	49.8, 63.6	Cadence
		Stride time CV (%)	3.89 (1.75)	2.67, 4.58	Variability
		Stride regularity (g^2)	0.30 (0.10)	0.23, 0.36	Regularity
		Step symmetry	1.37 (1.75)	1.14, 1.55	
Timed Up and Go (TUG)	TUG Sit to Stand (S1)	AP Duration (s)	0.85 (0.55)	0.51, 1,02	Anterior-Posterior
		AP Jerk (g/s)	−1.43 (1.09)	−1.85, −0.76	
		AP range (g)	1.04 (0.37)	0.81, 1.19	Range
		AP Acc SD (g)	0.29 (0.08)	0.23, 0.35	
		Pitch range (deg/s)	171.7 (51.1)	138.4, 197.9	
		Pitch jerk (deg/s^2)	210.9 (99.6)	138.5, 268.5	Posterior
		Pitch duration (s)	0.84 (0.29)	0.63, 0.99	
	TUG Stand to Sit (S2)	Pitch jerk (deg/s^2)	160.5 (93.2)	101.2, 197.1	Jerk
		AP duration (s)	0.97 (0.12)	0.63, 1.19	
		Pitch duration (s)	1.04 (0.42)	0.74, 1.23	
		AP jerk (g/s)	1.38 (3.64)	0.72, 1.46	
		AP range (g)	1.05 (0.33)	0.83, 1.18	Range
		Pitch range (deg/s)	161.6 (50.3)	129.6, 184.5	
		AP Acc. SD (g)	0.29 (0.08)	0.24, 0.34	
	TUG Turning	Yaw, Turn 1 (deg/s)	150.8 (38.2)	123.2, 178.1	Yaw
		Yaw, Turn 2 (deg/s)	152.4 (41.9)	120.9, 182.5	
		Duration, Turn 1 (s)	2.15 (0.62)	1.76, 2.42	
		Duration, Turn 2 (s)	2.02 (0.60)	1.61, 2.35	
		Frequency, Turn 1 (Hz)	1.81 (0.39)	1.56, 1.95	Frequency
		Frequency, Turn 2 (Hz)	1.66 (0.65)	1.17, 1.95	
Standing Posture Eyes Closed	Standing Posture	Jerk (g/s)	0.05 (0.21)	0.01.0.03	Sway
		RMS distance (g)	0.15 (0.12)	0.09, 0.17	
		Total power (psd)	0.30*	0.16, 0.32	

Mobility measures extracted from each mobility subtask, and mobility scores summarizing respective measures, as previously described.[23] * median.

2.5. Statistical analysis

The goal of this multi-stage analysis is to identify a group of mobility scores independently associated with incident parkinsonism. *Stage 1* determined which of the scores were individually associated with incident parkinsonism by examining each of the 12 scores in a separate Cox proportional hazards model. *Stage 2* determined which scores from each of the five mobility subtasks were independently associated with incident parkinsonism. We included all mobility scores of the respective subtask together in a single Cox proportional hazards model and employed backward elimination. To ensure that we did not exclude a potential significant association in this stage, we chose $p < 0.1$ as cutoff to carry forward mobility scores to Stage 3. Stages 1 and 3 employed a conventional nominal significance of $p < 0.05$. The Stage 2 analysis cannot be performed for the Sway mobility score, as there is only one mobility score summarizing the standing posture subtask. *Stage 3* determined which mobility scores from all 5 subtasks were independently associated with incident parkinsonism when analyzed together in a Cox proportional hazards model with backward elimination with the Sway score and all mobility scores which survived Stage 2 for the other four subtasks.

The same 3-stage approach was used to determine which mobility scores independently predicted incident possible parkinsonism, in persons with no parkinsonian signs at baseline. In order to be able to compare across subtasks, the demographic variables (age, sex, education and race) were included in all models and only the mobility scores varied with backward elimination.

In further analyses, we examined if the addition of terms for chronic health conditions or a term for the clinical severity of parkinsonism at baseline, which are known to predict parkinsonism, attenuated the association of the final combinations of mobility scores from Stage 3 with incident parkinsonism. We then employed c-statistics to evaluate the value added of these different terms for predicting incident parkinsonism [24]. A higher c-statistic suggests a better predictive model. Models were examined graphically and analytically and assumptions were judged to be adequately met. Programming was done in SAS version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

We included 683 participants in our longitudinal analysis. Clinical characteristics at baseline are summarized in Table 1 and the individual mobility measures in Table 2.

3.1. Association of sensor-derived mobility scores with incident parkinsonism

During an average 2.5 years of follow-up (SD = 1.3, range 1–6 years), 139 out of 683 (20.4%) participants developed parkinsonism. In Stage 1 we found that six out of 12 mobility scores were associated with incident parkinsonism (Table 3, Stage 1).

Stage 2 examined combinations of mobility scores within each of the 4 mobility subtasks that were summarized by 2 or more mobility scores. Following stepwise backward elimination, 5 mobility scores remained associated with incident parkinsonism (Table 3, Stage 2).

In Stage 3, we included the independently associated mobility scores for all 5 mobility subtasks (5 mobility scores which remained significant after Stage 2, plus Sway) in a single model, to determine which mobility scores were independently associated with incident parkinsonism. Two mobility scores (which did not include gait speed) remained associated with incident parkinsonism: Range from TUG stand to sit (S2) transition, and Yaw (as a measure of turning efficiency) from TUG turning (Table 3, Stage 3). These results were unchanged when we excluded 4 individuals with a clinical diagnosis of PD (data not shown).

Chronic health conditions can contribute to parkinsonian signs in

Table 3
Association of mobility scores with incident parkinsonism.

Mobility subtasks and their constituent mobility scores	Stage 1 Associations of individual mobility scores with incident parkinsonism			Stage 2 Mobility scores within subtasks independently related to incident parkinsonism			Stage 3 Mobility scores from 5 subtasks independently related to incident parkinsonism		
	HR	CI	p-value	HR	CI	p-value	HR	CI	p-value
32 ft Walk									
Speed	0.59	0.44, 0.79	< 0.001	0.59	0.44, 0.79	< 0.001			
Cadence	0.95	0.80, 1.13	0.575						
Regularity	0.77	0.61, 0.97	0.027						
Stride Variability	0.85	0.70, 1.04	0.109						
TUG Sit to Stand (S1)									
Anterior-Posterior	0.93	0.75, 1.17	0.551						
Range	1.04	0.81, 1.33	0.770						
Posterior	0.69	0.55, 0.87	0.001	0.69	0.56, 0.87	0.001			
TUG Stand to Sit (S2)									
Jerk	0.87	0.68, 1.11	0.251	0.73	0.56, 0.96	0.022			
Range	1.33	1.04, 1.69	0.024	1.52	1.16, 1.98	0.002	1.49	1.15, 1.92	0.003
TUG Turning									
Yaw	0.58	0.44, 0.76	< 0.001	0.62	0.47, 0.81	< 0.001	0.58	0.43, 0.77	< 0.001
Frequency	0.98	0.79, 1.23	0.89						
Standing Posture									
Sway	1.28	1.06, 1.55	**0.011**						

Final models for each of the three stages of analyses to identify the combination of mobility scores independently related to incident parkinsonism. **HR**: hazard ratio; **CI**: confidence interval.

older adults [25]. We therefore repeated the final model including the two mobility scores and added terms to control for BMI, four chronic vascular diseases and three vascular risk factors. TUG stand to sit Range and TUG turning Yaw mobility scores remained associated with incident parkinsonism (Table e1, Model 2).

To show that the sensor-derived mobility scores add to the previously established association of a global parkinsonian score with incident parkinsonism [25], we repeated the previous model, but added a term for the global parkinsonism score obtained during the same annual testing cycle as the mobility scores. In this model, both Range from TUG stand to sit (HR, 1.37, 95%CI, 1.07, 1.75) and the global parkinsonism score (HR, 2.31, 95%CI, 1.74, 3.08) were independently associated with incident parkinsonism, but Yaw from TUG turning was no longer associated (Table e1, Model 3).

To quantify the value added of sensor-derived mobility metrics, we calculated c-statistics for the previous models and compared them to a reference model with terms for demographic covariates. The model c-statistic increased as we sequentially added terms for chronic health conditions (Table e1, Model 1), sensor-derived mobility metrics, (Table e1, Model, 2) and global parkinsonism (Table e1, Model 3) suggesting that adding terms for each of these covariates improved the model prediction of incident parkinsonism.

3.2. Association of wearable sensor mobility scores with incident possible parkinsonism

Many older adults with possible parkinsonism (i.e., only 1 parkinsonian sign) progress to parkinsonism and have an increased risk of adverse health outcomes [3]. Therefore, we restricted our analyses to individuals without any signs of parkinsonism at baseline by excluding 237 of 683 (35%) subjects with 1 parkinsonian sign at baseline. We repeated the three stages of analyses described above to determine which combinations of mobility scores predict the development of possible parkinsonism.

During 2.2 years (SD = 1.2, range 1–6 years) of follow-up, 181 out of 446 (40.6%) participants developed possible parkinsonism. In separate models, 6 out of 12 mobility scores were associated with incident possible parkinsonism (Table 4, Stage 1). Next, following backward elimination within each mobility subtask (Table 4, Stage 2), 8 mobility scores were associated with incident possible parkinsonism. Lastly (Table 4, Stage 3), we identified 4 mobility scores which were independently associated with incident possible These results were unchanged when we excluded individuals with a history of PD (data not shown).

We again repeated the Cox model including the four mobility scores related to incident possible parkinsonism and additionally included terms to control for chronic health conditions. Three mobility scores, including TUG sit to stand Posterior, TUG stand to sit Range, and TUG turning Yaw, remained associated with incident possible parkinsonism (Table e2, Model 2). These results were unchanged when we added terms for the severity of parkinsonism at baseline to the previous model (Table e2, Model 3).

To quantify the value added of sensor-derived mobility metrics, we calculated c-statistics for the previous models and compared them to a reference model with terms for demographic covariates. The model c-statistic increased as we sequentially added terms for chronic health conditions (Table e2, Model 1), sensor-derived mobility metrics, (Table e2, Model, 2) and global parkinsonism (Table e2, Model 3) suggesting that adding terms for each of these covariates improved the model prediction of incident possible parkinsonism.

4. Discussion

This large longitudinal study shows that sensor-derived mobility metrics recorded outside of the lab setting in the homes of older individuals predict incident parkinsonism. Further analyses of these diverse measures together in a single analytic framework identified a parsimonious combination of metrics that were independently associated with incident parkinsonism. Although gait speed, a sensitive but non-specific predictor of many adverse health outcomes [6,26] was one of the metrics we extracted, it did not survive backward elimination and was not included in the final combination of metrics associated with incident parkinsonism. The sensor-derived mobility metrics improved the prediction of incident parkinsonism in a model which included terms for chronic health conditions and clinical severity of parkinsonism based on a modified UPDRS. These data suggest that sensor-derived mobility metrics complement conventional gait speed and clinical assessments of parkinsonism and offer the potential for identifying older adults at risk for parkinsonism to facilitate early interventions.

Parkinsonism in older adults is not synonymous with PD, but may be caused by diverse etiologies including medications, chronic medical

Table 4
Association of mobility scores with incident possible parkinsonism.

Mobility subtasks and their constituent mobility scores	Stage 1 Associations of individual mobility scores with incident possible parkinsonism			Stage 2 Mobility scores within subtasks independently related to incident possible parkinsonism			Stage 3 Mobility scores from 5 subtasks independently related to incident possible parkinsonism		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
32 ft Walk									
Speed	0.72	0.53, 0.98	**0.037**	0.65	0.48, 0.88	0.005			
Cadence	0.82	0.68, 0.98	**0.025**	0.77	0.64, 0.93	0.005			
Regularity	1.13	0.89, 1.44	0.315	1.38	1.06, 1.78	0.015	1.32	1.01, 1.73	0.047
Stride Variability	1.08	0.90, 1.29	0.425						
TUG Sit to Stand (S1)									
Anterior-Posterior	0.91	0.74, 1.11	0.347						
Range	1.26	1.00, 1.58	0.051	1.34	1.06, 1.68	0.015			
Posterior	0.60	0.48, 0.75	< **0.001**	0.59	0.47, 0.73	< 0.001	0.65	0.51, 0.82	< 0.001
TUG Stand to Sit (S2)									
Jerk	0.92	0.74, 1.14	0.457	0.79	0.62, 1.01	0.057			
Range	1.28	1.02, 1.62	**0.036**	1.45	1.11, 1.89	0.006	1.50	1.16, 1.93	0.002
TUG Turning									
Yaw	0.48	0.36, 0.64	< **0.001**	0.49	0.36, 0.66	< 0.001	0.56	0.41, 0.76	< 0.001
Frequency	0.96	0.77, 1.21	0.737						
Standing Posture									
Sway	1.28	1.05, 1.56	**0.013**						

Final models for each of the three stages of analyses to identify the combination of mobility scores independently related to incident possible parkinsonism. **HR**: hazard ratio; **CI**: confidence interval.

conditions, and other neurodegenerative disorders [2]. Recent work has shown that the accumulation of diverse neurodegenerative and cerebrovascular disease pathologies are related to the severity of parkinsonism in adults without overt neurologic disease and that only a minority show evidence of PD pathology [20,27,28]. Regardless of its underlying causes, the societal costs and its increasing magnitude with age make the prevention of parkinsonism a public health priority. Developing clinical biomarkers which can facilitate early interventions for specific etiologies or brain pathologies to maintain ambulation in older adults is a health priority in our aging population.

In a prior cross-sectional study, we showed that the sensor-derived mobility metrics examined in this study were related to the severity of parkinsonian gait in older adults. This study extends these cross-sectional findings by showing that these metrics may identify older adults who do not currently have parkinsonism, but have an increased risk of its subsequent development. As in our prior study, some but not all of the mobility scores measured were associated with incident parkinsonism. This suggests that there may be distinct facets of mobility in older adults which are particularly salient for the development of parkinsonism. Metrics from the wearable sensor also predicted possible parkinsonism, which is an intermediate state in many adults who may transition to parkinsonism [25]. Importantly, the combinations of mobility scores at baseline which predicted possible parkinsonism and parkinsonism differed, underscoring their heterogeneity. This heterogeneity may also explain why some but not all individuals progress from possible parkinsonism to parkinsonism. Further work is needed to determine to what extent these differences in mobility score combinations might be specific to distinct underlying mechanisms of disease and how they change over time.

The results of our analyses highlight features of gait that were independently associated with incident parkinsonism. Specifically, we identified 2 mobility scores from TUG (Yaw and Range) that make significant contributions to incident parkinsonism in a joint model. These mobility scores are derived from 2 distinct motor subtasks of the TUG, highlighting these specific aspects of mobility (turning and the transition from standing to sitting) as predictors of incident parkinsonism. Interestingly, turning has long been clinically recognized as a challenging task for patients with PD and other forms parkinsonism [29]; yet, assessment of turning is not well reflected in standard clinical scales. The Yaw metric in the current study provides a quantitative measure of trunk angular velocity. The Range score of the stand to sit transition subtask was independently associated with incident parkinsonism even when controlling for the clinical severity of parkinsonism. Difficulty with initiating movements as well as smooth transitions during rapid sequential movements are both known to be particularly problematic for adults with parkinsonism due to PD or other causes [30]. Further work is needed to determine if the difficulty in transition from standing to sitting is due to difficulty in initiating movement or because of the difficulties associated with sequential movements.

This study has several limitations. Participants were selected by their willingness to participate in a clinical autopsy study. They are more highly educated and older than the general populations, making it important to replicate our findings in more diverse cohorts. It will be important to include older adults with clinical PD in further studies to determine if combinations of mobility metrics differ in parkinsonism and PD. Among the notable strengths of our study, the cohorts tested in this study provide a relatively large sample of community-dwelling older subjects with prospective data collection and uniform clinical assessments with a previously validated modified UPDRS. These encouraging results highlight the need for further work to determine whether extracting additional mobility metrics will increase the specificity of this approach, to identify older adults at risk for specific etiologies of parkinsonism and especially those who will develop PD and other synucleinopathies.

Financial disclosure/conflict of interest

The authors declare no conflict of interest concerning the research related to this manuscript.

Funding sources

This work was supported by the NIA (R01AG17917 [DAB, LY], RF1AG22018 [LLB, SL], R01AG56352 [ASB]), the NINDS (R01NS78009 [ASB]), the Illinois Department of Public Health (DAB, SL); and the Robert C. Borwell Endowment Fund (DAB).

Authors' roles

Rainer von Coelln: Statistical analysis (review and critique), manuscript (first draft, revisions).

Robert J. Dawe: Project (organization, design and execution),

software generation (design, execution); statistical analysis (review and critique), manuscript (review and critique).

Sue E. Leurgans: Statistical analysis (design, execution), manuscript (revisions, review and critique).

Thomas A. Curran: Project (execution), software generation (design, execution); Statistical analysis (review and critique), manuscript (review, critique, revision).

Timothy Truty: Project (execution), Software generation (design, execution); manuscript (review and critique).

Lei Yu: Statistical analysis (design, review and critique), manuscript (revisions, review and critique).

Lisa L. Barnes: Project (organization), manuscript (review and critique).

Joshua M. Shulman: Statistical analysis (review and critique), manuscript (revisions, review and critique).

Lisa M. Shulman: Statistical analysis (review and critique), manuscript (review and critique).

David A. Bennett: Project (design, organization, execution, funding), manuscript (review and critique)Jeffrey M. Hausdorff: Project (execution); Software generation (design, execution), statistical analysis (review and critique), manuscript (review and critique).

Aron S. Buchman: Project (design, conception, organization, execution, funding), Software generation (review, critique, execution), statistical analysis (design, review and critique), manuscript (revisions, review and critique).

Financial disclosures

Full Financial Disclosures of all Authors for the Past Year:

Stock Ownership in medically-related fields: none.

Intellectual Property Rights: Jeffrey Hausdorff has submitted a patent application on the use of body fixed sensors for assessing symptoms in Parkinson disease, the intellectual property rights for which are held by the Tel Aviv Medical Center.

Consultancies: Jeffrey Hausdorff serves on the Movement Disorders Society Technology Task Force and on the Michael J Fox Foundation task force on gait.

Expert Testimony: none.

Advisory Boards: Jeffrey M. Hausdorff serves on advisory boards for Sanofi and Biogen.

Employment: Rainer von Coelln is employed by University of Maryland School of Medicine and University of Maryland Faculty Physicians, Inc, Baltimore, MD. Robert Dawe is employed by Rush University Medical Center, Chicago, IL. Sue Leurgans is employed by Rush University Medical Center, Chicago, IL. Thomas Curran is employed by Rush University Medical Center, Chicago, IL. Timothy Truty is employed by Rush University Medical Center, Chicago, IL. Lei Yu is employed by Rush University Medical Center, Chicago, IL. Lisa Barnes is employed by Rush University Medical Center, Chicago, IL. Joshua Shulman is employed by Baylor College of Medicine, Houston, TX. Lisa Shulman is employed by University of Maryland School of Medicine and University of Maryland Faculty Physicians, Inc., Baltimore, MD. David Bennett is employed by Rush University Medical Center, Chicago, IL. Jeffrey Hausdorff is employed by Tel Aviv University, Tel Aviv, Israel, and Rush University Medical Center, Chicago, IL. Aron Buchman is employed by Rush University Medical Center, Chicago, IL.

Partnerships: none.

Contracts: none.

Honoraria: none.

Royalties: none.

Grants: Rainer von Coelln is supported by the NIH and a Claude D. Pepper University of Maryland Older Americans Independence Center Junior Faculty Scholar award. Robert Dawe is supported by the NIH. Sue Leurgans is supported by the NIH and by the Illinois Department of Public Health. Lisa Barnes is supported by the NIH. Joshua Shulman is supported by the NIH, as well as by grants from the Huffington Foundation, Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, and a Career Award for Medical Scientists from the Burroughs Wellcome Fund. Lisa Shulman is supported by The Rosalyn Newman Foundation and Eugenia and Michael Brin. David Bennett is supported by the NIH. Jeffrey Hausdorff receives grant support from the Michael J Fox Foundation, the National Multiple Sclerosis Society, the Israel Science Foundation, the US-Israel Bi-National Science Foundation, and the NIH. Aron Buchman is supported by the NIH grants.

Acknowledgement

We thank all the participants in the Rush Memory and Aging Project and Minority Aging Research Study. We also thank the staff of the Rush Alzheimer's Disease Center. More information regarding obtaining RADC clinical and postmortem data for research use can be found at the RADC Research Resource Sharing Hub (www.radc.rush.edu).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.06.012.

References

[1] E.D. Louis, D.A. Bennett, Mild Parkinsonian signs: an overview of an emerging concept, Mov. Disord. 22 (12) (2007) 1681–1688.
[2] A.M. Keener, Y.M. Bordelon, Parkinsonism, Semin Neurol 36 (4) (2016) 330–334.
[3] A.S. Buchman, R.S. Wilson, J.M. Shulman, S.E. Leurgans, J.A. Schneider, D.A. Bennett, Parkinsonism in older adults and its association with adverse health outcomes and neuropathology, J Gerontol A Biol Sci Med Sci 71 (4) (2016) 549–556.
[4] D. Berg, A.E. Lang, R.B. Postuma, W. Maetzler, G. Deuschl, T. Gasser, A. Siderowf, A.H. Schapira, W. Oertel, J.A. Obeso, C.W. Olanow, W. Poewe, M. Stern, Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities, Lancet Neurol. 12 (5) (2013) 514–524.
[5] N. Paker, D. Bugdayci, G. Goksenoglu, D.T. Demircioglu, N. Kesiktas, N. Ince, Gait speed and related factors in Parkinson's disease, J. Phys. Ther. Sci. 27 (12) (2015) 3675–3679.
[6] G. Abellan van Kan, Y. Rolland, S. Andrieu, J. Bauer, O. Beauchet, M. Bonnefoy, M. Cesari, L.M. Donini, S. Gillette Guyonnet, M. Inzitari, F. Nourhashemi, G. Onder, P. Ritz, A. Salva, M. Visser, B. Vellas, Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force, J. Nutr. Health Aging 13 (10) (2009) 881–889.
[7] S. Grillner, P. Wallén, K. Saitoh, A. Kozlov, B. Robertson, Neural bases of goal-directed locomotion in vertebrates–An overview, Brain Res. Rev. 57 (1) (2008) 2–12.
[8] L. Ferrucci, R. Cooper, M. Shardell, E.M. Simonsick, J.A. Schrack, D. Kuh, Age-related change in mobility: perspectives from life course epidemiology and geroscience, J Gerontol A Biol Sci Med Sci 71 (9) (2016) 1184–1194.
[9] B. Najafi, K. Aminian, F. Loew, Y. Blanc, P.A. Robert, Measurement of stand-sit and sit-stand transitions using a miniature gyroscope and its application in fall risk evaluation in the elderly, IEEE Trans. Biomed. Eng. 49 (8) (2002) 843–851.
[10] A. Salarian, C. Zampieri, F.B. Horak, P. Carlson-Kuhta, J.G. Nutt, K. Aminian, Analyzing 180 degrees turns using an inertial system reveals early signs of progression of Parkinson's disease, Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference 2009, 2009, pp. 224–227.
[11] D. Johansson, K. Malmgren, M. Alt Murphy, Wearable sensors for clinical applications in epilepsy, Parkinson's disease, and stroke: a mixed-methods systematic review, J. Neurol. 265 (8) (2018) 1740–1752.
[12] A.J. Espay, P. Bonato, F.B. Nahab, W. Maetzler, J.M. Dean, J. Klucken, B.M. Eskofier, A. Merola, F. Horak, A.E. Lang, R. Reilmann, J. Giuffrida, A. Nieuwboer, M. Horne, M.A. Little, I. Litvan, T. Simuni, E.R. Dorsey, M.A. Burack, K. Kubota, A. Kamondi, C. Godinho, J.F. Daneault, G. Mitsi, L. Krinke, J.M. Hausdorff, B.R. Bloem, S. Papapetropoulos, T. Movement disorders society task force on, Technology in Parkinson's disease: challenges and opportunities, Mov. Disord. 31 (9) (2016) 1272–1282.
[13] A. Weiss, A. Mirelman, A.S. Buchman, D.A. Bennett, J.M. Hausdorff, Using a body-fixed sensor to identify subclinical gait difficulties in older adults with IADL disability: maximizing the output of the timed up and go, PLoS One 8 (7) (2013) e68885.
[14] R.J. Dawe, S.E. Leurgans, J. Yang, J.M. Bennett, J.M. Hausdorff, A.S. Lim, C. Gaiteri, D.A. Bennett, A.S. Buchman, Association between quantitative gait and balance measures and total daily physical activity in community-dwelling older adults, J Gerontol A Biol Sci Med Sci 73 (5) (2018) 636–642.
[15] A.S. Buchman, S.E. Leurgans, A. Weiss, V. VanderHorst, A. Mirelman, R. Dawe,

L.L. Barnes, R.S. Wilson, J.M. Hausdorff, D.A. Bennett, Associations between quantitative mobility measures derived from components of conventional mobility testing and parkinsonian gait in older adults, PLoS One 9 (1) (2014) e86262.
[16] L.L. Barnes, R.C. Shah, N.T. Aggarwal, D.A. Bennett, J.A. Schneider, The Minority Aging Research Study: ongoing efforts to obtain brain donation in African Americans without dementia, Curr. Alzheimer Res. 9 (6) (2012) 734–745.
[17] D.A. Bennett, A.S. Buchman, P.A. Boyle, L.L. Barnes, R.S. Wilson, J.A. Schneider, Religious orders study and Rush memory and aging Project, J. Alzheimer's Dis. : JAD 64 (2018) S161–S189.
[18] S. Fahn, E. R.L., UPDRS Program Members, Unified Parkinson's disease rating scale, in: S. Fahn, C.D. Marsden, M. Goldstein, C.B. Calne (Eds.), Recent Developments in Parkinson's Disease, Macmillan Healthcare Information, Florham Park, NJ, 1987, pp. 153–163.
[19] D.A. Bennett, K.M. Shannon, L.A. Beckett, C.G. Goetz, R.S. Wilson, Metric properties of nurses' ratings of parkinsonian signs with a modified Unified Parkinson's Disease Rating Scale, Neurology 49 (6) (1997) 1580–1587.
[20] A.S. Buchman, J.M. Shulman, S. Nag, S.E. Leurgans, S.E. Arnold, M.C. Morris, J.A. Schneider, D.A. Bennett, Nigral pathology and parkinsonian signs in elders without Parkinson disease, Ann. Neurol. 71 (2) (2012) 258–266.
[21] A. Weiss, T. Herman, M. Plotnik, M. Brozgol, I. Maidan, N. Giladi, T. Gurevich, J.M. Hausdorff, Can an accelerometer enhance the utility of the Timed up & Go Test when evaluating patients with Parkinson's disease? Med. Eng. Phys. 32 (2) (2010) 119–125.
[22] A. Weiss, T. Herman, M. Plotnik, M. Brozgol, N. Giladi, J.M. Hausdorff, An instrumented timed up and go: the added value of an accelerometer for identifying fall risk in idiopathic fallers, Physiol. Meas. 32 (12) (2011) 2003–2018.
[23] M. Matinolli, J.T. Korpelainen, R. Korpelainen, K.A. Sotaniemi, M. Virranniemi, V.V. Myllyla, Postural sway and falls in Parkinson's disease: a regression approach, Mov. Disord. 22 (13) (2007) 1927–1935.
[24] H. Uno, T. Cai, M.J. Pencina, R.B. D'Agostino, L.J. Wei, On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data, Stat. Med. 30 (10) (2011) 1105–1117.
[25] A.S. Buchman, S.E. Leurgans, L. Yu, R.S. Wilson, A.S. Lim, B.D. James, J.M. Shulman, D.A. Bennett, Incident parkinsonism in older adults without Parkinson disease, Neurology 87 (10) (2016) 1036–1044.
[26] S. Studenski, S. Perera, K. Patel, C. Rosano, K. Faulkner, M. Inzitari, J. Brach, J. Chandler, P. Cawthon, E.B. Connor, M. Nevitt, M. Visser, S. Kritchevsky, S. Badinelli, T. Harris, A.B. Newman, J. Cauley, L. Ferrucci, J. Guralnik, Gait speed and survival in older adults, J. Am. Med. Assoc. 305 (1) (2011) 50–58.
[27] A.S. Buchman, S.E. Leurgans, S. Nag, D.A. Bennett, J.A. Schneider, Cerebrovascular disease pathology and parkinsonian signs in old age, Stroke 42 (11) (2011) 3183–3189.
[28] A.S. Buchman, L. Yu, R.S. Wilson, S.E. Leurgans, S. Nag, J.L. Shulman, L.L. Barnes, J.A. Schneider, D.A. Bennett, Progressive Parkinsonism in Older Adults Is Related to the Burden of Mixed-Brain Pathologies, Neurology in Press, (2019).
[29] E. Stack, A. Ashburn, Dysfunctional turning in Parkinson's disease, Disabil. Rehabil. 30 (16) (2008) 1222–1229.
[30] A. Zijlstra, M. Mancini, U. Lindemann, L. Chiari, W. Zijlstra, Sit-stand and stand-sit transitions in older adults and patients with Parkinson's disease: event detection based on motion sensors versus force plates, J. NeuroEng. Rehabil. 9 (2012) 75.