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## Impact of motor fluctuations on real-life gait in Parkinson's patients

## Impact of motor fluctuations on real-life gait in Parkinson's patients

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### Highlights

- Parkinson's patients were more active between 8am and 1pm;
- Patients summed  $72 \pm 39$  (mean  $\pm$  standard deviation) minutes of walking per day.
- The severity of motor fluctuations did not correlate with time spent walking.
- Higher age and greater disease severity correlated with less time spent walking.
- The severity of motor fluctuations did not impact time spent walking after levodopa.

## Abstract

**Background:** people with PD (PWP) have an increased risk of becoming inactive. Wearable sensors can provide insights into daily physical activity and walking patterns.

**Research questions:** (1) is the severity of motor fluctuations associated with sensor-derived average daily walking quantity? (2) is the severity of motor fluctuations associated with the amount of change in sensor-derived walking quantity after levodopa intake?

**Methods:** 304 Dutch PWP from the Parkinson@Home study were included. At baseline, all participants received a clinical examination. During the follow-up period (median: 97 days; 25-Interquartile range-IQR: 91 days, 75-IQR: 188 days), participants used the Fox Wearable Companion app and streamed smartwatch accelerometer data to a cloud platform. The first research question was assessed by linear regression on the sensor-derived mean time spent walking/day with the severity of fluctuations (MDS-UPDRS item 4.4) as independent variable, controlled for age and MDS-UPDRS part-III score. The second research question was assessed by linear regression on the sensor-derived mean post-levodopa walking quantity, with the sensor-derived mean pre-levodopa walking quantity and severity of fluctuations as independent variables, controlled for mean time spent walking per day, age and MDS-UPDRS part-III score.

**Results:** PWP spent most time walking between 8am and 1pm, summing up to  $72 \pm 39$  (mean  $\pm$  standard deviation) minutes of walking/day. The severity of motor fluctuations did not influence the mean time spent walking ( $B=2.4 \pm 1.9$ ,  $p=0.20$ ), but higher age ( $B=-1.3 \pm 0.3$ ,  $p<0.001$ ) and greater severity of motor symptoms ( $B=-0.6 \pm 0.2$ ,  $p<0.001$ ) was associated with less time spent walking ( $F(3,216) = 14.6$ ,  $p<0.001$ ,  $R^2 = .17$ ). The severity of fluctuations was not associated with the amount of change in time spent walking in relation to levodopa intake in any part of the day.

**Significance:** Analysis of sensor-derived gait quantity suggests that the severity of motor fluctuations is not associated with changes in real-life walking patterns in mildly to moderate affected PWP.

**Keywords:** Parkinson's disease; Ambulatory monitoring; Gait quantity; Wearable devices; Motor fluctuations

## 1. Introduction

People with Parkinson's disease (PWP) are at risk of developing an inactive lifestyle[1]. The reason for this is multifactorial, with involvement of both physical and psychological factors. Some of these risk factors are non-specific, such as older age and fear of falling[2, 3], while others are more specific to PD, such as reduced physical capacity or gait and balance problems[4, 5]. Being physically inactive is generally undesirable, particularly for PWP. Traditionally, self-reported diaries and questionnaires are used to assess daily physical activity. These instruments have dubious reliability and validity, in particular for people with cognitive impairments[6]. To overcome limitations related to self-reported activity, wearable sensors may provide more objective and continuous measurements, with the potential to generate novel insights into real-life activity patterns in PWP. Early studies that used wearable sensors to quantify physical activity in PD showed that greater disease severity correlates with less ambulatory activity[2, 7, 8]. These studies typically had small sample sizes, with the exception of one (n=586)[2], and had short follow-up periods (maximum 7 days).

In addition to assessing the overall amount of ambulatory activity, wearable sensors offer the possibility to study activity patterns throughout the day in detail. This is particularly relevant for PWP who experience motor fluctuations, i.e. periods with either a good levodopa therapy response ("ON" state) or periods when the medication effects wear off and motor symptoms re-emerge ("OFF" state)[9]. The presence of OFF periods has a large limiting impact on mobility and quality of life in PD[10, 11]. It is known that gait patterns change in response to levodopa intake in PWP with motor fluctuations [12] and small-scale studies demonstrated that wearable sensors can capture the effects of levodopa on gait quality[13-15]. However, the impact of levodopa intake on gait quantity, as a measure of physical activity, is largely unknown and has never been studied in a large population followed for a long period of time.

Therefore, the aim of this study is to investigate whether the severity of motor fluctuations is associated with changes in physical activity patterns in a large cohort of PWP, who used wearable sensors for a prolonged period of time (up to 665 days). As walking is the most common activity for older adults, the mean time spent walking in minutes per day – labeled as "gait quantity" in this study – is used as a proxy measure of physical activity.

## 2. Methodology

### *2.1 Participants*

Patients included in this study participated in the Dutch cohort of the Parkinson@Home study. The Parkinson@Home study was an observational, two-cohort (North America and The Netherlands) study aiming to investigate the feasibility of large-scale deployment and the compliance with wearable sensor usage over a long follow-up time. The recruitment process and study design were previously described in detail[16]. In summary, in the Dutch cohort, 304 participants were recruited from support groups, internet communities, and through physiotherapists specialized in treating PWP. Inclusion criteria were: 30 years of age or older; possession of a smartphone with Android OS version  $\geq 4.2$ ; and self-reported diagnosis of PD. No exclusion criteria were applied. Participants used the Fox Wearable Companion app developed by Intel® Pharma Analytics Platform team[17]. The application was installed on the participants own Android smartphone and on a Pebble smartwatch provided by the research team. Participants were asked to wear the smartwatch and keep their smartphone with them as much as possible on a 24/7 basis for 13-weeks. At the end of the 13-weeks study period, participants had the option to continue using the system, if they wished. The Parkinson@Home study showed that compliance of PWP with the wearable system was high[16].

This study was conducted in compliance with the Ethical Principles for Medical Research Involving Human Subjects, as defined in the Declaration of Helsinki. The study protocol was approved by the local ethics committee (CMO Arnhem-Nijmegen; NL53034.091.15).

### *2.2 Data collection*

Data used in this study were collected during the Parkinson@Home study and obtained from a database curated by the Michael J. Fox Foundation. The Fox Wearable Companion app platform used in that study enables raw smartwatch accelerometer data capture (average 50 Hz sampling rate) streaming via Bluetooth radio to a complementary smartphone Android app. Next, the smartphone app transfers data via Wi-Fi or mobile data to the Intel® Pharma Analytics cloud platform, which uses machine learning to estimate objective measures of participants behavior. Among these objective measures is a gait detection algorithm, which estimates whether or not a person was walking during a specific time interval. For the detection of gait episodes, an algorithm was trained on 10 hours of walking and non-walking episodes collected from PD (N=19) and non PD (N=12) participants wearing a smartwatch. Raw accelerometer data were segmented into 5 second interval and transformed into aggregate features in the time and frequency domains. Then, a decision tree model was used to classify every 5-second interval as either walking or non-walking.

The algorithm accuracy was 98.5% (precision 98.9%, recall 96%) on the training data[17] (see Appendix A for algorithm details). The objective measures are presented to participants using graphs and summary reports within the app. In addition to using the smartwatch and smartphone app, users were asked to set medication reminders and report their daily actual medication intake within the app (Figure 1). Finally, all enrolled participants received a single medical examination, based on the “Parkinson's Progression Markers Initiative” (PPMI) protocol. The medical examination collected information such as time since diagnosis and the full MDS-UPDRS[18]. The medical examination was performed in the ON state by specially trained physiotherapists who are members of ParkinsonNet, a Dutch network of health professionals specialized in PD management.

### *2.3 Outcomes and statistical analysis*

Two statistical analyses were performed. The first analysis aimed to assess whether a higher severity of motor fluctuations is associated with a smaller mean time spent walking per day. Only participants that contributed at least 7 days of accelerometer data during the follow-up period were included. The mean time spent walking per day was calculated by first dividing the total number of minutes identified as walking by the total number of minutes of accelerometer data. Next, this ratio was multiplied by 1440, i.e. the number of minutes in a day, to obtain the daily mean expressed in minutes. The severity of fluctuations was determined by the score of item 4.4 of the MDS-UPDRS Part IV (question: “4.4 Functional impact of fluctuations”) and the severity of motor symptoms was expressed as the sum score of the MDS-UPDRS Part III. Both outcomes were treated as scale variables in the analyses. Linear regression analysis was performed on the mean time spent walking per day, with the severity of fluctuations as independent variable. To control for potential confounders, age and MDS-UPDRS part III scores were included in the model using a backward stepwise input selection (criterion of removal: probability of  $F > 0.10$ ).

The second analysis aimed to investigate whether a higher severity of motor fluctuations is associated with a higher change in time spent walking after levodopa intake. Only levodopa intakes were considered because this drug has the strongest association with occurrence of fluctuations[19]. The analysis was performed separately for the morning (between 6:00 and 12:00), afternoon (between 12:00 and 18:00), evening (between 18:00 and 0:00) and night (between 0:00 and 6:00), because both the amount of walking[20] and the responsiveness to levodopa may vary across the day[21]. To account for possible participants errors while reporting medication intake, e.g. reporting

the same medication intake time point multiple times, only the first report within a certain hour was considered as the actual time of medication intake.

To assess the change in time spent walking, we calculated both the mean time spent walking in the *second hour after* levodopa intake (post-levodopa activity) and the mean time spent walking in the *last hour before* levodopa intake (pre-levodopa activity) per individual (Figure 2). Only pairs of pre-levodopa and post-levodopa activity consisting of at least 115 minutes of data, out of a possible total of 120 minutes during those two hours, were included. Moreover, participants needed to have at least a total of 10 unique levodopa reports in the part of the day being analyzed. Linear regression was performed on the mean post-levodopa activity, with the mean pre-levodopa activity and the severity of fluctuations as independent variables. To control for potential confounders, the mean time spent walking per day, age and MDS-UPDRS part III score were included as inputs to the model using backward stepwise selection (criterion of removal: probability of  $F > 0.10$ ).

For the coefficients, a critical p-value of 0.05 was applied. All analyses were performed using the Statistical Package for the Social Sciences (SPSS®) Version 22.

### 3. Results

The cohort consisted of 304 mostly mildly to moderately affected PWP (Table 1).

#### 3.1 Impact of motor fluctuations on daily time spent walking

220 participants were included in analysis 1. They contributed a median of 78 complete days of usable accelerometer data (25 Interquartile range-IQR: 60 days, 75 Interquartile range-IQR: 110 days), during a median of 97 days of follow-up period (25-IQR of 91 days and 75-IQR of 188 days). On average, participants walked  $72 \pm 39$  minutes per day, with the largest number of minutes walked occurring between 8 am and 1 pm (Figure 3). The severity of motor fluctuations did not influence the mean time spent walking ( $B = 2.4 \pm 1.9$ ,  $p = 0.20$ ), whereas higher age ( $B = -1.3 \pm 0.3$ ,  $p < 0.001$ ) and higher severity of motor symptoms ( $B = -0.6 \pm 0.2$ ,  $p < 0.001$ ) was associated with less time spent walking (model  $F(3,216) = 14.6$ ,  $p < .001$ ,  $R^2 = .17$ ).

#### 3.2 Impact of fluctuations on the change in time spent walking after levodopa intake

The post-levodopa activity was on average higher than the pre-levodopa activity in the morning and night, while in the afternoon and evening the post-levodopa activity was lower. The pattern of post-levodopa activity did not differ between week or weekend days (Figure 4a/b). The severity of

fluctuations was not significantly associated with the difference between pre- and post-levodopa activity (i.e. the amount of change in walking quantity) in any part of the day (Table 2).

#### 4. Discussion

This study presents data from the first large-scale cohort study using wrist-worn accelerometry in which sensor-based passive monitoring was combined with daily reports of levodopa intake. The much longer follow-up time here (up to 665 days, with a median follow-up of 97 days) contrasts markedly with previous studies using wearable sensors, where follow-up was typically limited to one week[8, 13, 22, 23]. Our sample size was also large. Using this sizeable dataset, we demonstrated that the severity of motor fluctuations did not lead to a smaller mean amount of daily walking quantity. Also, higher severity of motor fluctuations did not cause a higher mean change in walking quantity in relation to levodopa intake. These findings contradict our hypothesis that PWP with more severe motor fluctuations would be more inactive before intake of levodopa, as a result of wearing off. Studies in controlled settings showed that motor performance, which includes gait and postural transitions, is worse during off periods[12]. Thus, it seems reasonable that this could affect the amount of real-life walking quantity, both through physical limitations and through a patient's confidence in being active. Therefore, a careful interpretation of possible explanations for our present results is needed.

Our findings highlight the complexity of studying physical activity in a free-living environment, where little or no contextual information about participants behavior is known. As a reflection of this, large variation in the amount of activity is present both between patients and within patients on different days. Our study showed that the severity of potential fluctuations around the time of levodopa intake does not explain a substantial proportion of this already large variation in walking quantity. On the one hand, this may be explained by the fact that a patient's activity pattern is highly influenced by behavioral factors that are not related to the severity of symptoms. For example, the influence of participants' behavior most likely explains the large increase in the time spent walking after levodopa intake during the night presented in Figure 4. As the majority of the levodopa reports at night took place around 5 a.m., the comparison includes a part of the morning, with a higher number of minutes walked. On the other hand, our results indicate that the severity of fluctuations does not have a detectable or consistent influence on activities around the time of levodopa intake. This is supported by the fact that patients in our study were on average still active before levodopa administration, regardless of the severity of their fluctuations. It should be emphasized that we



investigated a relatively mildly to moderately affected PD population, hence the generalizability to later stage PWP, who typically have more disabling fluctuations[24], remains to be addressed.

Some limitations of this approach need to be discussed. First, the severity of fluctuations was based on item 4.4 from the MDS-UPDRS part IV, which may be susceptible to inter-rater variability. However, it is a valid scale[25] and all assessors involved in this study received additional training for conducting the MDS-UPDRS. Using alternative approaches to evaluate motor fluctuations, such as the Hauser diary [26], might allow for a more accurate comparison of the amount of activity between OFF and ON periods, particularly if fluctuations are characterized by unpredictable OFF periods, dose failures or delayed ON periods. However, it is unlikely that these phenomena were important in our study sample, as these typically occur in people with more advanced PD [27].

Second, limitations related to compliance may have influenced the results. Because data related to actual wear time were not available, we cannot guarantee that all sensor data were collected while the participants were in fact wearing the smartwatch. To minimize this risk and filter out highly non-compliant participants, we have only including participants with a minimum amount of streamed data. In addition, we have no reason to believe that the proportion of non-wear data correlates with our main variable of interest, namely the severity of fluctuations. Although the gait detection algorithm was only validated in a lab-based setting [17], the outcomes of both the mean walking quantity and the daily pattern are similar to what has been reported earlier [2, 20, 28]. Moreover, we were also able to reproduce earlier findings that age and MDS-UPDRS part III are determinants for the amount of activity[1, 8]. These findings give us some confidence that the gait measurements from the smartwatch data are reasonably reliable. Lastly, although we have no data on the accuracy or compliance with medication reports through the app, we believe that the medication reminders and the high compliance with the system usage increased the accuracy of medication reports.

Despite the fact that our findings contradict those of a small study with a short follow-up [29], we posit that limitations in their data analysis (e.g. only comparing post- and pre-levodopa activity without assessing the influence of the severity/presence of fluctuations on this difference, producing a result that is highly influenced by general behavioral factors) explain the divergence in conclusions.

A clinically relevant conclusion of our findings is that gait quantity is not a suitable way to capture wearing off in mild to moderately affected PWP. Instead, the use of gait quality features that are more responsive to levodopa[9], reflect changes over time[30], and are likely less affected by behavior, appears as a more adequate approach to monitor changes in gait due to motor fluctuations in a real-life environment. Together with the role of gait quality analysis, determining

optimal sensor type, sensor location and feature extraction for home-based monitoring still remains to be addressed. Lastly, in addition to exploring the role of gait quality to capture the influence of fluctuations on walking patterns, future research into activity patterns of PWP would benefit from a more heterogeneous PWP group and age-matched healthy controls, to be able to better discriminate between PD-specific and behavioral influences in activity patterns. Hopefully, this will lead to a better understanding of the underlying factors that have an impact on physical activity in PD, and generate useful knowledge that can further contribute to the promotion of an active life-style among PWP.

In conclusion, this study showed that the severity of motor fluctuations was not associated with the mean amount of walking quantity in PWP. Similarly, the severity of motor fluctuations was not associated with the mean change in walking quantity in relation to levodopa intake. Finally, our study does not support the assessment of gait quantity as a suitable method to investigate the influence of motor fluctuations on walking activity in real-life.

#### **Author's contribution**

Ana Lígia Silva de Lima, Luc JW Evers and Tim Hahn: design of the study; acquisition, analysis and interpretation of the data; drafting and revision the manuscript for important intellectual content; final approval to the version submitted.

Nienke M de Vries and Margaret Daeschler: interpretation of the data; revision the manuscript for important intellectual content; final approval to the version submitted.

Max A. Little: interpretation of the data; revision the manuscript for important intellectual content; final approval to the version submitted.

Babak Boroojerdi, Dolors Terricabras: interpretation of the data; revision the manuscript for important intellectual content; final approval to the version submitted.

Bastiaan R Bloem and Marjan J Faber: concept and design of the study; acquisition, analysis and interpretation of the data; drafting and revision the manuscript for important intellectual content; final approval to the version submitted.

#### **Competing Interest statement**

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Margaret Daeschler are supported by the Michael J. Fox Foundation.

Babak Boroojerdi and Dolores Terricabras are employed by UCB.

Max A Little received research funding support from the Michael J Fox Foundation and UCB.

Bastiaan R Bloem has previously served as an editorial board member of Movement Disorders, currently serves as Associate Editor for the Journal of Parkinson's disease, received honoraria from serving on the scientific advisory board for Zambon, has received fees for speaking at conferences from AbbVie and Teva, and received research support from the Netherlands Organization for Scientific Research, the Michael J Fox Foundation, the Prinses Beatrix Foundation, the Stichting Parkinson Fonds, the National Parkinson Foundation and the Parkinson Vereniging.

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The Fox Companion App and the cloud platform used in this study were developed by Intel® Pharma Analytics team.

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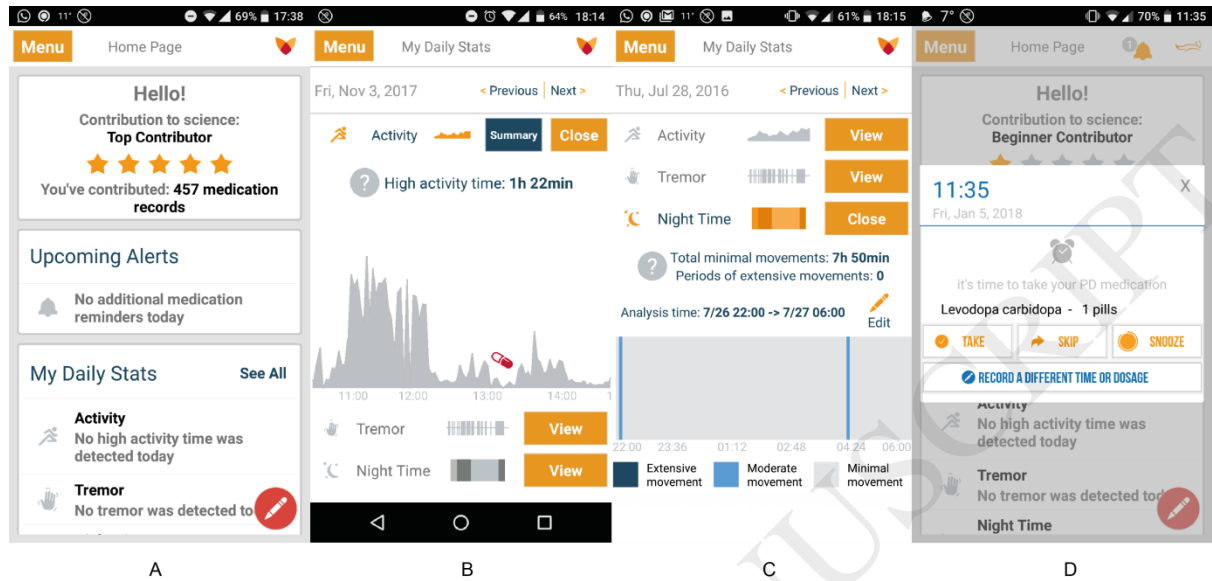
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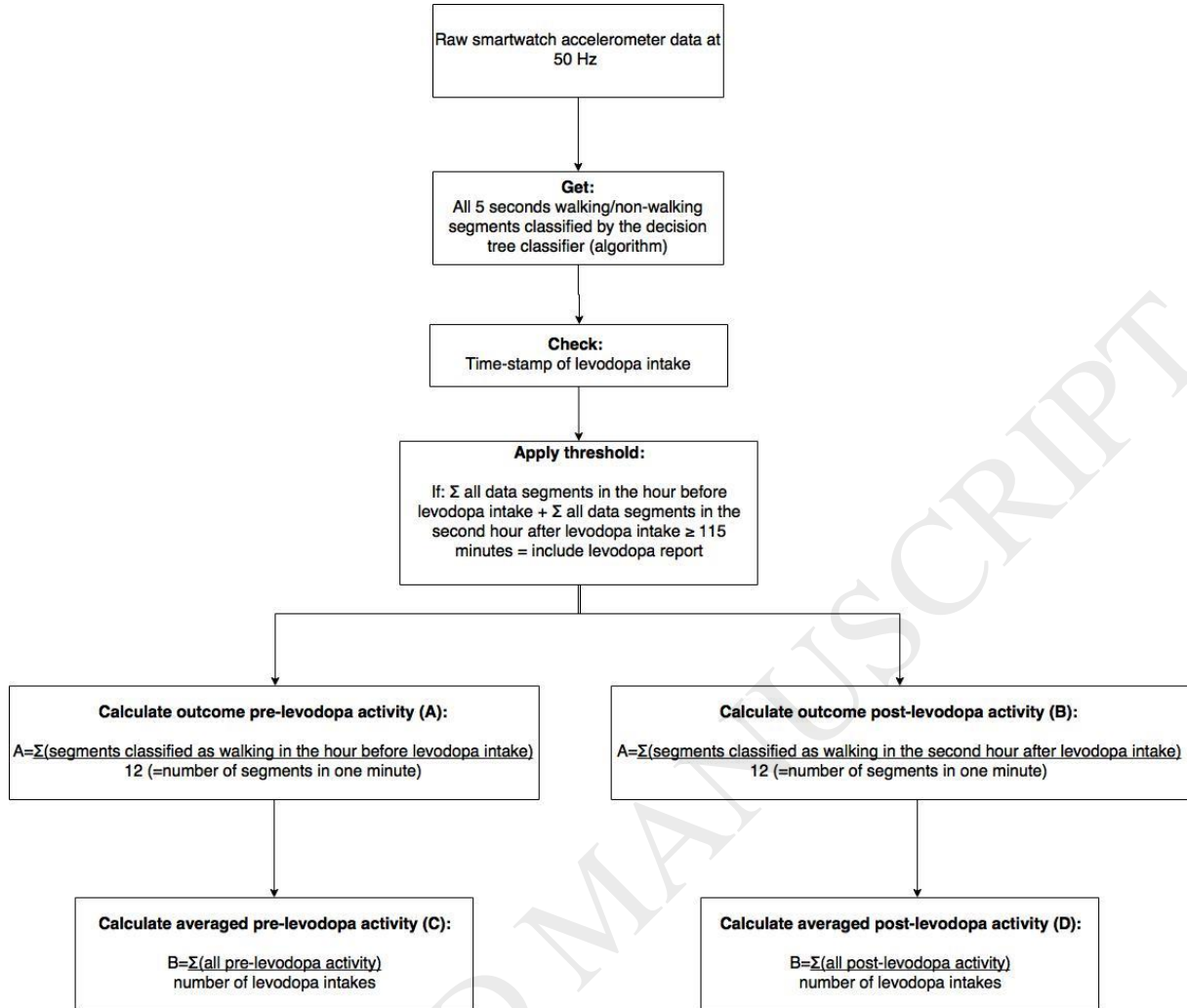
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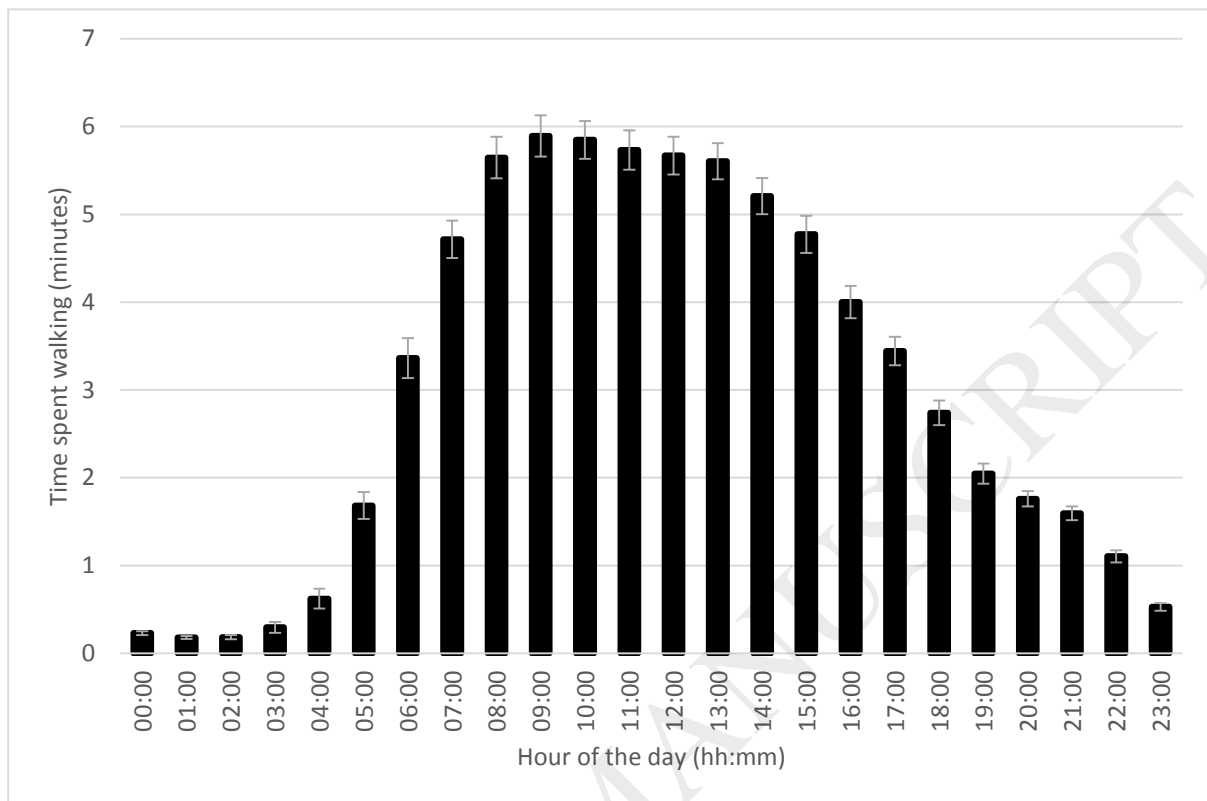
**Figure 1:** screenshots of the Fox Wearable Companion app: (A) main screen; (B) activity graph; (C) movement during sleep graph; (D) medication reminder.



**Figure 2:** Data reduction and pre/post-levodopa activity calculation per participant.

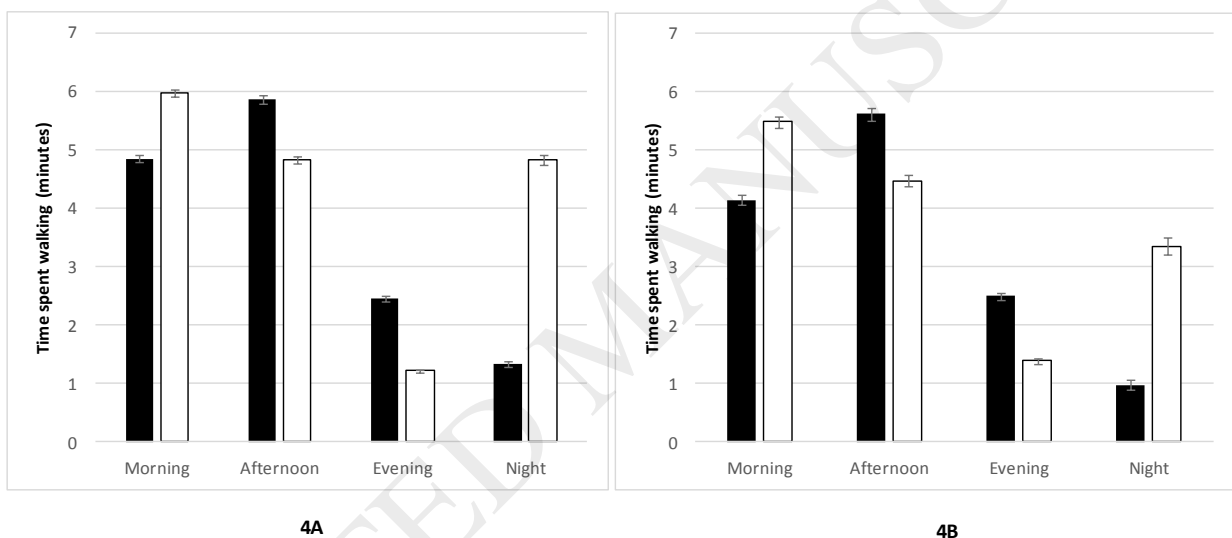


**Figure 3:** Mean time spent walking during each hour of the day (n=220). Error bars indicate standard error of the mean.





**Figure 4: 4A** - Mean time spent walking per hour before (black) and after levodopa intake (white) on week days, presented separately for the morning (n=182, number of levodopa reports per person ranging from 11 to 429), afternoon (n=175, number of levodopa reports ranging from 11 to 323), evening (n=140, number of levodopa reports ranging from 11 to 467) and night (n=99, number of levodopa reports ranging from 11 to 197). **4B** - Mean time spent walking per hour before (black) and after levodopa intake (white) on weekend days, presented separately for the morning (n=134, number of levodopa reports per person ranging from 11 to 170), afternoon (n=129, number of levodopa reports ranging from 11 to 129), evening (n=100, number of levodopa reports ranging from 11 to 180) and night (n=61, number of levodopa reports ranging from 11 to 72). Error bars indicate standard error of the mean.



**Table 1:** Demographic and clinical characteristic of the study participants (n=304).

Characteristic		n (%)	Mean±SD
Gender	Men	163 (66%)	-
Age (years)		-	63.1±8.5
Time since diagnose (years)		-	6.1±4.3
Disease stage <sup>1</sup>	0	6 (3%)	-
	1	68 (28%)	-
	2	127 (53%)	-
	3	34 (14%)	-
	4	5 (2%)	-
	5	1 (0.4%)	-
Cognitive impairment <sup>2</sup>		-	25.4±3.0
Severity of motor symptoms <sup>3</sup>		-	28±14.5
Independency level <sup>4</sup>	≤70	36 (15%)	-
	71-80	51 (21%)	-
	81-90	110 (46%)	-
	≥91	41 (17%)	-
Severity of fluctuations <sup>5</sup>	None	120 (50%)	-
	Slight	42 (17%)	-
	Mild	21 (9%)	-
	Moderate	47 (20%)	-
	Severe	11 (5%)	-

\*Number of missing values differed across variables; only valid percentages are reported. 1-Disease stage: Hoehn and Yahr stage (0-5 point scale); 2-Cognitive impairment: Montreal Cognitive Assessment (0-30); 3- Severity of motor symptoms: sum of Movement Disorders Society – Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part III (0-132); 4-Independency level: Schwab and England scale (0-100), 5-Impact of motor fluctuations: item 4.4 from MDS-UPDRS part IV (0-4 point scale).

**Table 2:** Adjusted impact of the severity of motor fluctuations on post-levodopa activity (in minutes).

	n	B ± SE	β	p-value	ΔR <sup>2</sup>
Morning	166	.004 ± .104	.002	.97	<.001
Afternoon	162	.156 ± .082	.074	.06	.005
Evening	134	.082 ± .044	.122	.07	.015
Night	95	.124 ± .203	.044	.54	.002

Confounders and R<sup>2</sup> per model:

Morning: pre-levodopa activity (p = .43), mean time spent walking (p < .001); R<sup>2</sup> = .72.

Afternoon: pre-levodopa activity (p < .001), mean time spent walking (p < .001); R<sup>2</sup> = .77.

Evening: pre-levodopa activity (p < .001); R<sup>2</sup> = .44.

Night: pre-levodopa activity (p = .002), mean time spent walking (p < .001), age (p=.03); R<sup>2</sup> = .54.

ACCEPTED MANUSCRIPT