UNIVERSIDADE DE LISBOA

Faculdade de Medicina de Lisboa

FUNCTIONAL MOBILITY IN PARKINSON'S DISEASE

Raquel de Queirós Bouça Ribeirinho Machado

Orientador: Prof. Doutor Joaquim Ferreira

Coorientador: Prof. Doutor Ricardo Matias

Tese especialmente elaborada para obtenção do grau de Doutor em Neurociências

2021

UNIVERSIDADE DE LISBOA

Faculdade de Medicina de Lisboa

FUNCTIONAL MOBILITY IN PARKINSON'S DISEASE

Raquel de Queirós Bouça Ribeirinho Machado

Orientador: Prof. Doutor Joaquim Ferreira

Coorientador: Prof. Doutor Ricardo Matias

Tese especialmente elaborada para obtenção do grau de Doutor em Neurociências

Júri:

Presidente: Doutor José Augusto Gamito Melo Cristino, Professor Catedrático e Presidente do Conselho Científico da Faculdade de Medicina da Universidade de Lisboa

Vogais:

- Doutor Tiago Alexandre Mestre, Professor Associado da Faculty of Medicine, University of Ottawa;
- Doutora Patrícia Duarte de Almeida, Professora Adjunta da Escola Superior de Saúde de Alcoitão;
- Doutor Miguel Albino Silva Fernandes Gago, Especialista de Reconhecido Mérito e Competência e Médico Assistente Hospitalar Graduado de Neurologia do Hospital da Senhora da Oliveira-Guimarães, E.P.E;
- Doutor Joaquim José Coutinho Ferreira, Professor Associado da Faculdade de Medicina da Universidade de Lisboa;
- Doutora Ana Catarina Gaspar Fonseca, Professora Auxiliar Convidada da Faculdade de Medicina da Universidade de Lisboa;
- Doutora Sofia Cristina Pereira Coutinho Reimão, Professora Auxiliar Convidada da Faculdade de Medicina da Universidade de Lisboa.

Instituição financiadora: Bolsa de doutoramento da FCT - Fundação para a Ciência e a Tecnologia (SFRH/BD/120773/2016)

2021

A impressão desta tese foi aprovada pelo Conselho Científico a Faculdade de Medicina da Universidade de Lisboa em reunião de 28 de Janeiro de 2021.

As opiniões expressas nesta publicação são da exclusiva responsabilidade do autor.

TABLE OF CONTENTS

ABSTRACT

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1% of the world population over the age of 60. The presence of a large and heterogeneous spectrum of motor and non-motor symptoms, some resistant to levodopa therapy, is usually a major source of disability that affects patients' daily activities and social participation. Functional mobility (FM) is an outcome that merges the concepts of function with mobility, autonomy, and the accomplishment of daily tasks in different environments. Its use in PD studies is common. However, several aspects associated with its application in PD remain to be defined, hampering a wider use of the concept in clinical practice and the comparison of clinical study results.

Aim: This thesis aimed to provide evidence on the appropriateness of the concept of FM in the PD field. A two-fold approach was used to this end: 1) To investigate the clinical and research applicability of the concept of FM in PD; 2) To identify the most suitable clinical and technological outcome measures for evaluating the response of PD patients' FM to a therapeutic intervention.

Methods: A narrative review using the framework of the International Classification of Functioning, Disability, and Health (ICF) was performed to explore the concept of FM when applied to PD. This first study aimed to provide a better understanding of the interaction between PD symptoms, FM, and patients' daily activities and social participation.

To identify and recommend the most suitable outcome measures to assess FM in PD, a systematic review was conducted using the CENTRAL, MEDLINE, Embase, and PEDro databases, from their inception to January 2019. During this review, we also explored the different definitions of FM present in the literature, proposing the one we believed should be established as the definition of FM in the PD field. We then conducted a focus group to explore PD patients' and health professionals' perspectives on the proposed definition. Part of the scope of the focus group was also to investigate the impact of FM problems on patients' daily living and the strategies used to deal with this. The study included four focus groups, two with patients (early and advanced disease stages), and two with health professionals (neurologists and physiotherapists).

A second systematic review using the CENTRAL, MEDLINE, Embase, and PEDro databases, from their inception to September 2019, was performed to summarize and critically appraise the published evidence on PD spatiotemporal gait parameters. Finally, a pragmatic clinical study was

conducted to identify the clinical and technological outcome measures that better predict changes in FM, when patients are submitted to a specialized multidisciplinary program for PD.

Results: All the definitions found in an open search of the literature on the FM concept included three key aspects: gait, balance, and transfers. All participants in the focus group study were able to present a spontaneous definition of FM that matched the one used by the authors. All also agreed that FM reflects the difficulties of PD patients in daily life activities. Early-stage PD patients mentioned needing more time to complete their usual tasks, while advanced-stage PD patients considered FM limitations as the main limiting factor of daily activities, especially in medication "OFF" periods. Physiotherapists maintained that the management of PD FM limitations should be a joint work of the multidisciplinary team. For neurologists, FM may better express patients' perception of their overall health status and may help to adopt a more patient-centered approach. Of the 95 studies included in the systematic review aiming to appraise the outcome measures that have been used to assess FM in PD patients, only one defined the concept of FM. The most frequent terms used as synonyms of FM were mobility, mobility in association with functional activities/performance, motor function, gait-related activity, or balance. In the literature, the Timed Up and Go (TUG) test was the most frequently reported tool used as a single instrument to assess FM in PD. The changes from baseline in the TUG Cognitive test, step length, and free-living step time asymmetry were identified as the best predictors of TUG changes.

Conclusion: The information generated by the different studies included in this thesis revealed FM as a useful concept to be adopted in the PD field. FM was shown to be a meaningful outcome (for patients and health professionals), easy to measure, and able to provide more global and ecological information on patients' daily living performances. Our results support the use of FM for PD assessment and free-living monitoring, as a way to better understand and address patients' needs. The changes in the TUG Cognitive test, the supervised step length, and the free-living step time asymmetry seem the most suitable outcomes to measure an effect in FM. Future research should focus on determining the severity cut-off for FM changes, the minimal clinical important difference (MCID) for each of these outcome measures and resolve the current obstacles to the widespread use of technological assessments in PD clinical practice and research.

Keywords: Functional Mobility, Parkinson's disease, Outcome measures, Technology, sensors

RESUMO

Introdução: A doença de Parkinson (DP) afeta 1% da população mundial acima de 60 anos de idade, sendo a segunda doença neurodegenerativa mais comum. É caracterizada pela presença de um amplo e heterogéneo espectro de sintomas motores e não motores, alguns com uma baixa resposta às intervenções farmacológicas, responsáveis por um importante grau de incapacidade nas atividades da vida diária e na participação social dos doentes. A mobilidade funcional (MF) é um conceito que congrega as noções de função, mobilidade, autonomia e a realização de tarefas diárias em diferentes ambientes. A sua utilização é frequente em estudos clínicos em DP. No entanto, vários aspetos associados à sua aplicação na DP continuam por definir, interferindo com uma utilização mais alargada do conceito na prática clínica e com a possibilidade de comparar os resultados de diferentes estudos clínicos.

Objetivo: A presente tese tem como objetivo explorar a potencial aplicabilidade e benefício da utilização do conceito de MF no campo da DP. Para tal foram adotadas duas abordagens: 1) Investigar a aplicabilidade na prática clínica e investigação do conceito de MF na DP; 2) Identificar os instrumentos de medida clínicos e tecnológicos mais adequados para avaliar a resposta da MF a uma intervenção terapêutica.

Métodos: Foi realizada uma revisão narrativa, seguindo a abordagem da Classificação Internacional de Funcionalidade, Incapacidade e Saúde (CIF), para explorar o conceito de MF quando aplicado à DP. Este primeiro estudo teve como objetivo clarificar a interação entre os sintomas da DP, a MF e a vida diária e participação social dos doentes. De forma a clarificar e fazer recomendações sobre os instrumentos de medida mais adequados para a avaliar MF em pessoas com DP, foi realizada uma revisão sistemática utilizando as bases de dados CENTRAL, MEDLINE, Embase e PEDro, desde a sua criação até Janeiro de 2019. Como preparação para este estudo, realizamos uma pesquisa aberta sobre a definição de MF e propusemos uma para ser utilizada quando aplicado à DP. Posteriormente, utilizamos a metodologia de grupos de foco para explorar a perspetiva de pessoas com DP e profissionais de saúde sobre o conceito proposto de MF, estudando também o seu impacto na vida diária dos doentes e as estratégias adotadas para lidar com suas limitações. Foram realizados quatro grupos de foco, que incluíram doentes em fase inicial de doença, doentes em fase avançada, neurologistas e fisioterapeutas. De forma a resumir e avaliar criticamente a evidência publicada sobre a análises cinemáticas da marcha na DP,

realizámos uma segunda revisão sistemática, usando para a pesquisa de artigos as bases de dados CENTRAL, MEDLINE, Embase e PEDro, desde o início até setembro de 2019. Por último, conduzimos um estudo clínico com o objetivo de identificar os instrumentos de medida, clínicos e tecnológicos, que ao avaliados no início e fim de um programa multidisciplinar para DP têm melhor capacidade de predizer alterações da FM.

Resultados: As definições de MF encontradas na literatura coincidiram em quatro aspetos chave: marcha, equilíbrio, transferências e a execução de uma tarefa funcional. Todos os participantes do grupo de foco foram capazes de apresentar uma definição espontânea de MF compatível com aquela proposta pelos autores do estudo. Foi transversal a todos os grupos a ideia de que a MF é um conceito útil para informar sobre as limitações crescentes na vida diária dos doentes. Os participantes com DP em fase inicial referiram que as alterações na MF apenas se traduziam na necessidade de mais tempo para realizar suas tarefas habituais. Para os participantes em fase avançada de doença as limitações da MF eram o principal fator de limitação nas atividades diárias, especialmente nos períodos "OFF" de medicação. Para os doentes em fase inicial de doença as limitações na MF apenas são percebidas pelos familiares diretos e amigos próximos. Os doentes em fase avançada de doença referem que este tipo de limitação frequentemente atrai a atenção dos outros, gerando uma sensação de embaraço. Para estes doentes, a família e os amigos mais próximos costumam ser um apoio. No entanto, referem que amigos mais distantes e colegas têm habitualmente mais dificuldade em compreender as flutuações da doença, o que geralmente contribui para o isolamento social e para a sobrecarga dos familiares. Segundo a opinião dos fisioterapeutas a abordagem às limitações da MF na DP deve ser um trabalho conjunto da equipa multidisciplinar. Para os neurologistas, a MF pode representar um meio eficaz para obter uma melhor perceção do estado geral de saúde dos doentes, ajudando assim a adotar uma abordagem mais centrada no doente. Dos 95 estudos incluídos na revisão sobre os instrumentos utilizados para avaliar MF na DP, apenas um definiu o conceito de MF. O termo mais usado como sinónimo foi mobilidade, isolado ou associado aos conceitos de atividade, desempenho funcional, função motora, atividade relacionada à marcha ou equilíbrio. O teste *Timed Up and Go* (TUG) foi, de acordo com os resultados da pesquisa da literatura, o instrumento de medida mais frequentemente utilizado como instrumento único para avaliação da MF na DP. Segundo os resultados da revisão sistemática sobre as análises cinemáticas da marcha na DP, os parâmetros mais frequentemente relatados nos estudos foram a velocidade da marcha, o comprimento da passada e do passo e a

cadência. Os acelerómetros foram o tipo de sensor mais utilizado, sendo o local mais comum de utilização a região lombar (L2-L5). Não foi encontrada nenhuma diferença estatisticamente significativa no valor médio dos parâmetros ao comparar sensores *wearable* e não *wearable*, diferentes tipos de sensores *wearable* e diferentes localizações dos sensores. Segundo os resultados do estudo clínico, o TUG Cognitivo, o comprimento do passo numa avaliação supervisionada e a assimetria do tempo do passo avaliado em *free-living* (FL) foram identificados, quando avaliados na admissão e alta de um programa multidisciplinar para DP, como os melhores preditores de mudanças no TUG. O comprimento do passo numa avaliação supervisionada e a assimetria do tempo do passo avaliado FL foram capazes de detectar um efeito da intervenção com valores de *d de Cohen* entre os -0,26 e os 0,42.

Conclusão: As informações geradas pelos diferentes estudos incluídos nesta tese indicam a MF como um conceito útil a ser adotado na área de DP. Como instrumento de medida, a MF demonstrou ser compreensível e com significado para doentes e profissionais de saúde, fácil de medir em diferentes contextos de avaliação e oferecer dados mais globais e ecológicos (i.e., mais próximos da realidade do doente no seu ambiente) sobre o desempenho dos doentes nas atividades da vida diária. Desta forma, os nossos resultados apoiam a adoção do conceito de MF na avaliação e monitorização à distância da DP. Antecipamos que a sua utilização contribua para uma melhor compreensão e resposta às necessidades reais do doente, no seu ambiente. As diferenças no teste TUG Cognitivo, no comprimento do passo e na assimetria do tempo do passo medido em FL são, segundo os resultados obtidos, a melhor forma de avaliar mudanças na MF dos doentes de DP. A definição de pontos de corte de severidade das alterações da MF e a diferença mínima com relevância clínica para doentes e clínicos deve ser definida para cada um dos instrumentos de medida apresentados. Adicionalmente, são necessários estudos para solucionar os atuais obstáculos ao uso disseminado, na prática clínica e na investigação em DP, de avaliações com base em instrumentos tecnológicas.

Palavras-chave: Mobilidade Funcional, Doença de Parkinson, Instrumentos de Medida, Tecnologia, sensores

ABREVIATIONS

ADL	Activities of daily living
BBS	Berg Balance Scale
CGI	Clinical Global Impression
CV	Coefficient of Variation
FC	Final Contact
FTSTS	Five-time sit-to-stand test
FM	Functional mobility
FRT	Functional reach test
HC	Healthy controls
HrQoL	Health-related quality of life
HY	Hoehn and Yahr scale
ICF	International Classification of Functioning, Disability, and Health
IC	Initial Contact
ICC	Intraclass correlation coefficients
LPA	Lindop Parkinson's Disease Mobility Assessment
MCID	Minimal clinical important difference
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
mPAS	The Modified Parkinson Activity Scale
NA	Not applicable
NWS	Non-wearable sensors
PD	Parkinson's disease
PGI	Patient Global Impression
SD	Standard Deviation
SPPB	The Short Physical Performance Battery
TOM	Technology-based objective measures
TUG	Timed up-and-go test
TUG DT	Dual-task Time Up and Go Test
Unk	Unknown

WS	Wearable sensors
WHO	World Health Organization
6-MWT	6-Minute Walk Test
10-MWT	10-Meters Walk Test

CHAPTER 1

Introduction

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide[1,2]. Due to the increased life expectancy and because PD incidence is associated with aging, the prevalence is expected to increase considerably over the next decades[3].

PD diagnosis is focused on specific motor symptoms, namely the presence of bradykinesia plus rest tremor, muscle rigidity, or both[1,2]. At the beginning, symptoms are unilateral and mild, with an excellent response to treatment and without a major impact on patients' functionality. However, some slowness in daily tasks and slight changes in gait (e.g. reduced arm swing, shortened stride) are already present[1,2,4].

Over time, the majority of patients start to experience a decline in the duration of levodopa action with alternating phases of good and poor response to medication[1,2]. In addition, symptoms worsen, specifically bradykinesia and axial symptoms, which contribute to the occurrence of frequent falls and cause limitations in the functionality and autonomy of patients.[1,5,6] At this point, the OFF-periods (i.e. the time when medication is not working optimally) are associated with high disability and dependency on caregivers. However, the impact on the quality of life is lower since patients are also unwell during ON-periods.[5,6]

PD management is largely based on pharmacological interventions, with dopamine replacement therapies the mainstay of treatment. [7] Despite the advances in many different treatments, there are still no drugs able to halt or even slow down disease progression, and so PD care is restricted to symptomatic control.[7] Due to the large spectrum of motor and non-motor symptoms that a PD patient can experience and because of symptoms that respond poorly to pharmacological interventions (e.g. axial symptoms), a comprehensive multidisciplinary approach seems crucial in providing more effective management of the disease.[8,9]

Outcome Measures in Parkinson's Disease

The use of standardized outcome measures for quantifying patients' health status and symptoms changes is vital to monitor disease progression, clarify treatment effects, and assist communication between health professionals.[10] Outcome measures are also crucial in clinical trials for evaluating

the efficacy of interventions and to enable the interpretation and comparison of study results. The more multidimensional the disease, the more difficult it is to identify the most appropriate outcome measures. An ideal outcome measure is one that is accurate and meaningful to patients. [10,11]

Because of its heterogeneity and diverse spectrum of symptoms, PD requires close monitoring to optimize patient care and improve disease knowledge.

The diagnosis of PD continues to be based on clinical judgment and in a set of predefined criteria, created by a group of experts from the International Parkinson and Movement Disorder Society.[12] The gold standard for evaluating PD-related symptoms and disease progression is the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), an adaption, published in 2008, of the UPDRS scale.[13] This is a very comprehensive scale, divided into four sections: non-motor experiences of daily living, motor experiences of daily living, motor examination, and motor complications.[13]

Although this and other conventional clinical scales and tests provide an overall notion of disease severity without the need for specialized equipment and with the added value of having been validated and used in large clinical trials, they present some constraints. These include: (1) only providing brief "snapshots" of a patient's condition, limited in the ability to capture symptom fluctuations and episodic events; (2) prone to intra- and inter-rater variability; (3) requiring an in-person supervised assessment; and (4) are usually time-consuming.[10,14]

Technology-based Objective Measures in Parkinson's Disease

With technological advances and widespread usage in health care, a multitude of new and improved technology-based objective measures (TOMs) were developed to overcome the limitations of the traditional clinical scales.[14–16] In particular, these have the added value of: 1) capturing, with higher sensitivity and accuracy, the full complexity and diversity of PD symptoms; 2) providing a more realistic portrayal of patients' functionality; and 3) enabling closer monitoring of response to therapy. In the research field, they also allow a reduction in in-person office assessments and thereby patients from geographically remote locations to be assessed.[14–16] Although very promising, there are some aspects of TOMs that need to be improved. [14]

To truly address patients' needs and optimize patient adherence, the development of new technological devices should be driven by burning questions from the clinical field.[14] Unfortunately, it is still common to create new devices without prospectively defining their clinical usefulness and without engaging a collaboration among technologists, health professionals, and patients throughout the entire process.[14]

Despite the large and fast advances in the characteristics of devices, the development of algorithms did not follow the same pace. Currently, issues such as the ability to algorithmically analyze the captured data, defining the truly relevant clinical information, and displaying them synthetically and intuitively still need to be improved. [14–16]

Additionally, patient and caregiver engagement with wearable and mobile technology is presently modest, resulting in a high dropout rate after a few uses.[14] According to the literature, adherence problems can be minimized by: (1) including meaningful outcome measures for patients and displaying them in a user-friendly format; (2) developing continuously sensing minimally intrusive systems, with the capacity to record multiple motor and nonmotor behaviors; (3) improving the communication between the patient and the clinical team. [14–16]

Functional Mobility

Functional mobility (FM) incorporates the capacity of a person to move independently and safely to accomplish tasks.[17,18]

In the pediatric field, where the concept is more developed, FM is operationalized through tasks like walking to pick up an object, sitting at the table to eat, getting in and out of a car or a chair, walking on uneven surfaces, or climbing stairs. [17,18] A broader version of the concept is also used, including the use of walking aids, as another way for children to interact with the world around them. Based on this, children's FM is classified as (1) walking without limitations; (2) walking with limitations; (3) walking using manual device mobility; (4) auto-mobility with limitations; (5) transported in a manual wheelchair.[17,18]

In 2013, Forhan & Gill published a review on the impact of obesity on FM and quality of life[19], in which they present a clearer definition of FM. Accordingly, FM is a person's physiological ability

to move independently and safely in a variety of environments, to accomplish functional activities or tasks, and to participate in the activities of daily living, at home, at work, and in the community. They also state that FM includes movements like standing, bending, walking, and climbing.[19]

As a more global and ecological concept (i.e., most suggestive of the patient's true health status in daily life), this may be an interesting and useful outcome to apply in a complex and fluctuating disease like PD.

AIM OF THE THESIS

This thesis aimed to provide evidence on the appropriateness of the concept of FM in the PD field. A two-fold approach was used to achieve this goal:

1. To investigate the clinical and research applicability of the concept of FM in PD;

2. To identify the most suitable clinical and technological outcome measures for assessing the response of FM to a therapeutic intervention.

Thesis Outline

In chapter 2, we use the International Classification of Functioning, Disability, and Health (ICF) to approach the FM concept in the PD field. This first literature review aims to provide a better understanding of how PD symptoms can contribute to the presence of FM problems and how, according to the literature, these can be addressed.

In chapter 3, we appraise the measurement instruments that have been used to assess FM in the PD field and make recommendations on those that are the most appropriate. In this study, we also propose a definition of FM to be used in the PD field.

In chapter 4, we use a focus group methodology, to explore PD patients' and health professionals' perspectives on the proposed concept of FM (chapter 3), investigating also its impact on patients' daily life and the strategies to deal with its limitations.

Since kinematic gait analysis started recently being used to study PD patients' FM, in chapter 5, we summarize and critically appraise the published evidence on PD spatiotemporal gait parameters, providing reference values for each.

Finally, in chapter 6, we sought to identify the best kinematic and clinical outcome measures to evaluate the effect of a multidisciplinary intervention on PD FM.

CHAPTER 2

What is Functional Mobility applied to Parkinson's disease?

What is Functional Mobility applied to Parkinson's disease?

Raquel Bouça-Machado[a,b], Walter Maetzler[c], Joaquim J. Ferreira[a,b,d]

a - Instituto de Medicina Molecular, Lisbon, Portugal

b- CNS-Campus Neurológico Sénior, Torres Vedras, Portugal

c - Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany.

d - Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Portugal

Contents of this chapter were extracted from the peer-reviewed publication with the following reference: **Bouça-Machado R**, Maetzler W, Ferreira JJ. What is Functional Mobility applied to Parkinson's Disease? J Parkinsons Dis. 2018;8(1):121-130.

Raquel Bouça-Machado conceptualized the review, conducted data collection, and drafted the manuscript.

Abstract

Although yet poorly defined and often misused, the concept of functional mobility (FM) has been used in research studies as a more global and ecological outcome of patients' health status. FM is a person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living, at home, work and in the community. Parkinson's disease (PD) has a direct impact on patients' motor control and on mobility in general. Even with optimal medical management, the progression of PD is associated with mounting impairments at different levels of body function, causing marked limitations in a wide variety of activities, as well as a severe disability and loss of autonomy. Despite this, for everyday functioning PD patients need to have a good FM that allow them to get around effortlessly in a reasonable amount of time to access to the same environments as others. This paper reviewed the concept of FM applied to PD. This was done through an International Classification of Functioning and Disability (ICF) perspective. Recommendations to address the known factors that contribute to a poor FM were outlined while suggestions for clinical practice and research were made.

Key Words: Functional mobility, Parkinson's disease, International Classification of Functioning, Disability and Health

What is functional mobility? Is there a difference in the functional mobility (FM) of two Parkinson's disease (PD) patients with similar gait disturbance, one using an assistive mobility device, the other not? How do health professionals account for these differences?

This paper reviewed the FM concept and its implications for PD patients' everyday functioning. It followed the International Classification of Functioning, Disability and Health (ICF) model. The ICF model goes beyond the usual focus on a diagnosis, incorporating detailed information on how functional, societal aspects, and contextual factors contribute to a patient's health condition. Therefore, it allows to better understand and describe health and health-related problems and to improve communication between patients, health professionals, researchers, and policy makers. [20–2223–25] This model have been previously used for studying PD patients' disability [20,26–2829] and quality-of-life [19,3012,22,31,32].

A PubMed search, from inception to June 2017, was made using the following search terms were: "Functional mobility", "Mobility", "Disability", "Participation restrictions" and "Parkinson's disease". Language and publication restrictions were not applied. Being a narrative review, a systematic selection of the included studies was also not performed. In order to fully address the opening question, the concept of FM was introduced and, through the ICF model, the factors related with PD body functions impairments and activity limitations that could affect FM were presented. It was also discussed how FM limitation may restrict patients' everyday functioning and the potential impact of contextual factors. Additionally, in the end of the review, the most suitable outcome tools and interventions to address PD FM limitations were appraised.

1) Functional mobility

FM is increasingly used as an outcome in clinical studies as it may provide a more global and functional perspective of patients' health conditions. However, it is still a poorly defined concept, being commonly equated with mobility or functionality (Fig. 1). According to Forhan & Gill in a review on obesity [2222,33], FM is the physiological ability of people to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living (ADL), at home, work and in the community. It includes movements like standing, bending, walking and climbing, which are the building blocks of ADL,

and hence crucial to an individual's independent living and global health status. [3422,35] Impaired FM has been found to be associated with a greater risk of falls, loss of independence, and institutionalization. [19,21,25,28,36–3831]

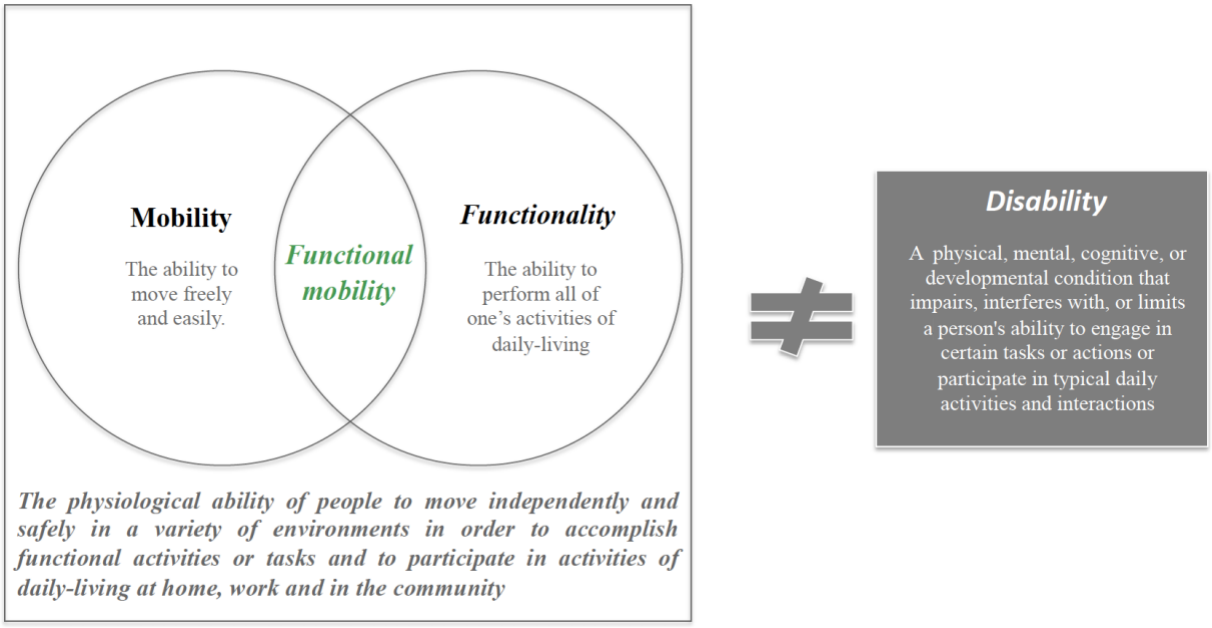


Figure 1 – Functional mobility concept

2) International Classification of Functioning and Disability (ICF)

As formulated by the World Health Organization (WHO) in 2001, the ICF is conceptualized as a universal framework focused on the description of how people live with a health condition (Fig. 2). [22,25,39,40] Three levels of human functioning are classified: 1) body functions and structures as physiological and psychological functions, as well as body impairments, and anatomical deficiencies; 2) limitations in performing tasks or actions; and 3) participation restrictions in daily life. Contextual factors can be either personal, such as age, gender, experiences, and interests; or environmental like physical, social, and attitudinal environment. This model assumes that all levels of human functioning and contextual factors are interconnected, i.e., impairments in body functions and structures may induce problems in activities that leads to participation restrictions, which can be facilitated or hindered by environmental or personal factors. [25,3925,41]

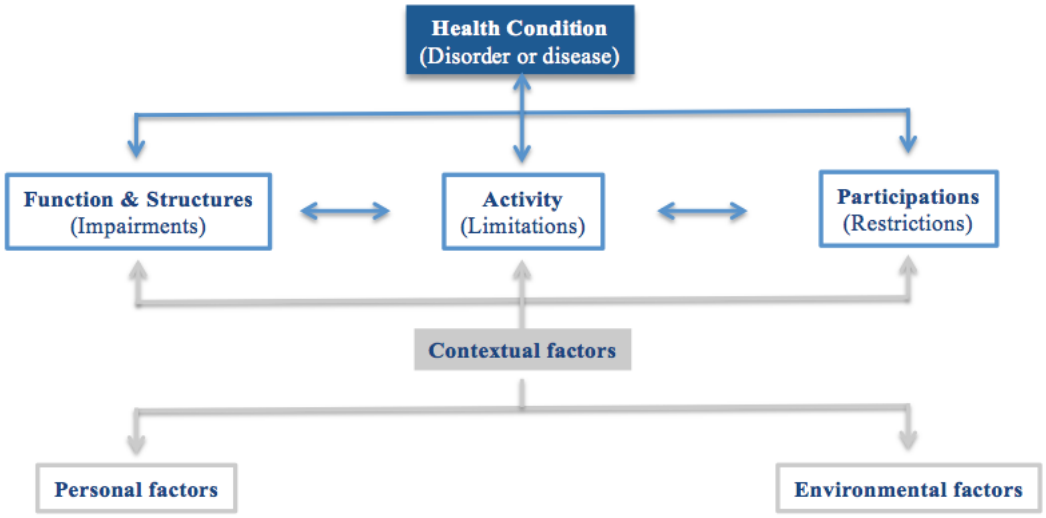


Figure 2 - ICF framework. Adapted from World Health Organization. Towards a Common Language for Functioning, Disability and Health: The International Classification of Functioning, Disability and Health. Int. Classif. 2002;1149:1–22.

3) Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease. [4241] It is characterized by its motor (bradykinesia, associated with rest tremor and rigidity) and non-motor problems. [25,41,4325,44]

Despite the variety of therapeutic options, disease progression usually leads to impairments at different levels of body function, limitations in a wide variety of ADL, and in severe disability, social embarrassment and increasing dependence. Gradually, it reduces health-related quality of life (HrQoL) and increases the burden of patients and caregivers. [19,4519,25,27]

4) Functional mobility in PD: ICF-based methodology

In order to improve patients' global health status and reduce disease burden associated with functional immobility, it is important to understand a patient's personal needs, activity and environment. [19,25,2737] In this section, we present the three levels of human functioning included in

the ICF framework: 1) the impairments to body structures and functions relevant to PD patients' FM; 2) how the activities that compose FM are compromised by these impairments, in a functional perspective; 3) participation restrictions that PD patients may encountered, induced by functional mobility limitations; 4) lastly, some examples of frequent personal and environmental factors that influence the first three domains are presented (Fig. 3 and 4).

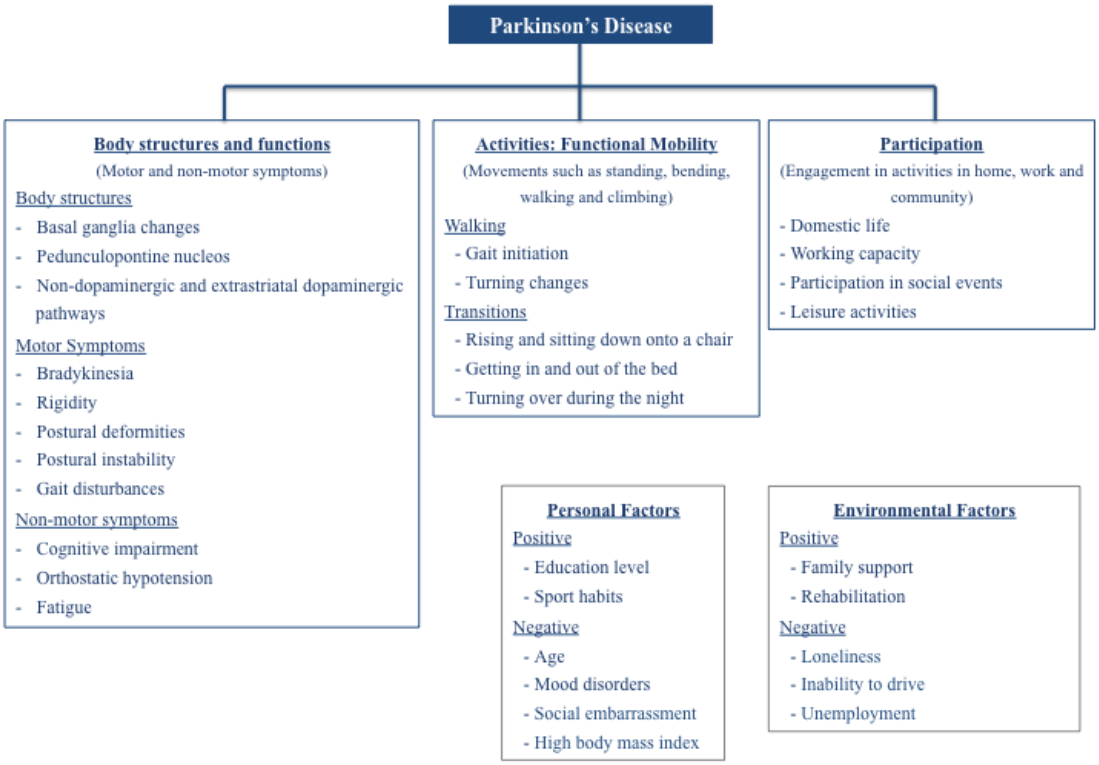


Figure 3 – The concept of FM applied to PD in an ICF perspective

4.1) Body functions and structures domain

FM requires dynamic neural control to quickly and effectively adapt locomotion, balance, and postural transitions to changing environmental and task conditions. This in turn requires sensorimotor agility that involves: 1) coordination of complex sequences of movements, 2) on-going evaluation of environmental cues and contexts, 3) the ability to quickly switch motor programs with environmental changes, and 4) the ability to maintain safe mobility during multiple motor and cognitive tasks. [2,24,31,37,46,4738]

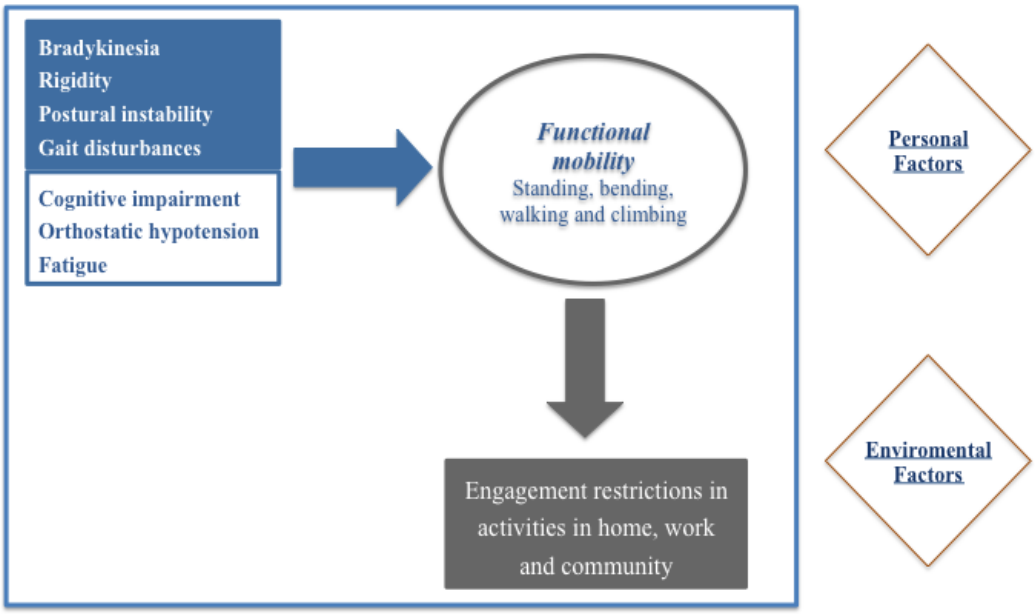


Figure 4 - Human domains and contextual factors contribution to PD FM

Motor symptoms

Motor symptoms may contribute to FM impairments directly, through gait impairments cause by non-dopaminergic pathways degeneration and indirectly due to bradykinesia and rigidity, which affect PD patients gait, balance and transitions. [1548–50]

Gait impairments are complex to characterize because of the difficulty in distinguishing between the specific contribution of sensory, motor, and cognitive deficits and other factors like fear, muscle weakness or misjudgment of hazard risk. Evidence suggests that in later stage cholinergic dysfunction in the pedunculopontine nucleus has a key role in gait disturbance. [5152]

With disease progression, severe and disabling postural deformities are usually present (e.g., camptocormia, antecollis, pisa syndrome or scoliosis). These interfere with daily living activities, often leading to falls. Although still not well understood, a series of central and peripheral causes have been proposed to explain the complex and multifaceted underlying pathophysiology of these deformities. [1439]

Non-motor symptoms

FM is also affected by PD non-motor symptoms.

The inability to simultaneously carry out a cognitive and a motor task is a predictor of falls and a critical element to FM. This has been found to be more difficult for PD patients than healthy controls, especially when walking is one of the tasks.

Dysautonomia seems also to play an important role in PD FM. In concrete, orthostatic hypotension symptoms are a frequent complaint, associated to a higher prevalence of falls and a more rapid PD progression. It also affects mobility in general, patients' confidence in their own abilities and may undermine an active style of life. [30,3830,38]

Additionally, patients have frequently fatigue complaints, which has physical and psychological repercussions in PD FM. The feeling of being tired all day and of not knowing how to get through the day makes fatigue, in patients perspective one of the symptoms most difficult to cope with. [3038]

4.2) Activity domain

In PD, activity limitations range from minor difficulties (e.g., fine motor coordination tasks) to more serious problems (e.g., skilled ADL motor tasks). Patients generally experience a loss of FM resulting from the neurodegenerative effects of the disease in posture, balance, postural stability, and gait. Loss of independence in performing activities arises in the transition between Hoehn and Yahr (H&Y) stages III and IV, and activities such as walking, housework, dressing and transfers are the most affected. [3053]

Walking

Patients describe gait disorders as a loss of confidence in walking, a feeling of imbalance or reduced ability to negotiate uneven terrain or stairs. A slower walking speed is often the first noticeable sign of parkinsonism. [5353,54]

Gait is defined as the forward propulsion of the body with rhythmical coordination of all four limbs combined with control of dynamic equilibrium of the body's center of mass. It is also a complex

sensorimotor activity that involves spatial-temporal coordination of the legs, trunk and arms, as well as dynamic equilibrium.

Gait of PD patients have been shown to be: 1) significantly slower (typically 40-60m/min rather than 75-90/min in age-matched controls), 2) with less foot clearance (foot's height during the swing phase) and an increased double phase support in the gait cycle (from the usual 20-30% of the gait cycle to over 35%), 3) with smaller step lengths (0.4-0.9m for PD patients after withdrawal of medication or 0.8-1.0m for those at the end-of-dose compared with 1.2-1.5m for healthy older people), 4) narrow based, 5) asymmetrically reduced or absent arm swing 6) and stooped posture. Small shuffling steps (resulting from the reduced ground clearance and increased double phase support in gait cycle), a bilaterally reduced arm swing and slow, en bloc turns are also common. [53,5553]

Walking problems are usually more pronounced during gait initiation, turning, walking through doorways and when performing simultaneous motor or cognitive tasks. These relates with the triggering of festination and freezing episodes, characterize by the sudden inability to generate effective stepping movements. [5356] During festination episodes, the feet are behind the center of gravity, which causes rapid small steps. Freezing episodes are described by patients as having the feet "glued to the floor", which usually does not present as complete akinesia, but rather as shuffling with small steps or trembling of the legs.

Transitions

Throughout the course of disease, transitions become truly affected and predict risk of falls. Are particularly problematic: rising from, and sitting down on a chair, getting in or out and turning over in bed. [56–5859] Sitting-to-standing is a complex component of some everyday functional tasks that requires the body to accelerate forward and then upward, and to transfer from a large to a small base of support to achieve an upright stance. [6019,41] PD patients exhibit a general slowness when compared to control subjects in performing this tasks with a spatiotemporal pattern preserved. [19,2819,20,61] This indicates that PD patients' problems are not related with the selection, but in initiating and sequencing the appropriate motor program. Additionally, task analysis has shown that PD patients take a significantly longer time to complete each individual phase and a

have a significantly smaller peak hip extension and ankle dorsiflexion torque when compared with control subjects. [5937,60] The likely responsible factors are weak limb support against gravity (particularly reduced muscle power of the hip extensors), the difficulty in muscle activation and the inability to counteract unexpected external forces, vestibular impairment, and orthostatic hypotension. [19,39,4312,22,31,32]

PD patients seem also to have less body position changes during the night compared to the general population, which may affect sleep quality. Impaired bed mobility is often attributed to nocturnal hypokinesia, yet pain and overall muscle weakness and external factors such as bedcovers or reduced levels of levodopa at night, may also contribute to difficulty turning over in bed. The precise causal mechanism is still not clear. [2222,33]

4.3) Participation domain

Participation problems are aspects of life as a member of society hindered by activity limitations. (11) Impairments in PD patients' FM may compromise involvement in leisure, work or social aspects of life in both household and community settings.

Working capacity, often affected in PD patients, is a concrete example of an important participation restriction related with FM, not only because of work role in active fighting against exclusion from social and occupational environments, but also as livelihood. [3425,47]

4.4) Contextual factors

Contextual factor could be personal or environmental and have a positive or negative effect.

Age, a high body mass index, feeling disabled and social embarrassed represent some examples of personal factors with potential negative influence on PD patients' FM. In contrast, high education levels and sport habits are examples of factors with a positive influence. [20,28,2962]

Similarly, unemployment, loneliness and the inability to drive, are examples of possible environmental negative factors. The existence of family caregivers is the most valued environmental positive factor, once PD patients rely on them for most of their ADL needs. [2925,47]

Within personal factors, perceived control (i.e., the person's belief of controlling the situations and act in accordance to that) is a prime candidate and a powerful predictor of active life and FM. [20,28,2962] PD clearly affects patients' perceived control, not only because of the impact of motor and non-motor symptoms on daily FM, but also because of the unpredictability and social embarrassment frequently associated. This has multiple manifestations in patients' life, such as: to avoid walking on the street or in less familiar places due to fear of falling, concerns scheduling appointments because of not being sure of being able to get through it or to stay away from public places or social events to prevent feeling embarrassed with disease limitations. [19,30,38,49,61]

5) Functional mobility: Scales and tools available

FM is a global disease-related feature that may provide adequate information about treatment responses and disease course, as it may encompasses one of the outcomes most relevant to patients' daily lives. [29,4919,29,63]

Due to the heterogeneity and complexity of PD, its fluctuating nature and unpredictable medication response in advanced disease stages, clinical assessment is challenging and requires continuous prolonged periods of evaluation to reach an accurate picture of symptoms and their fluctuations. [20,2520–22]

The majority of PD studies that have measured FM used rating scales like the MDS-UPDRS, infrequent events (e.g., falls) or subjective reports (e.g., diaries or questionnaires). Objective assessments, including the five-time sit-to-stand (FTSTS) test and the timed up-and-go (TUG) test, are two of the most commonly used tools. [23–2520,26–28] In 2015, Parashos and colleagues validated the "Ambulatory Capacity Measure". This is a measure of functional capacity, previous used in clinical trials, derived from UPDRS items related to falls, freezing, walking, gait and postural instability. It showed to be a good instrument, highly correlated with some of the most used outcome tool to assess functional capacity. [2919,30] However, there is still no consensus about which screening tools are preferred or which outcomes are most suitable for monitoring FM. [12,22,31,3222]

With technological advances, numerous devices have been created not only with the capacity of reliably evaluating fluctuating or rare events (e.g., freezing of gait or falls) that usually occur outside clinical visits, but also for obtaining more global, objective, and sensible outcomes for

assessing patients' performance in ADL. [22,3334] Yet, is still lacking to establish a specific protocol or metrics to measure PD-sensitive and specific FM behaviours. [22,3519,21,25,28,36–38]

6) Improving functional mobility in PD

Due to PD heterogeneity, patients' experience of mobility impairment and respective coping strategies are very personal. In order to find an effective option is crucial to understand the patients' needs and offer suggestions according to local offerings, personal preferences, and cultural background. [3122,25,39,40]

Exercise programs

Evidence shows that critical aspects of PD patients' FM impairments (e.g., postural instability) are unresponsive to pharmacological and surgical therapies, making physical therapy an attractive option. [40]

Previous animal studies have demonstrated that intense exercise programs can increase dopamine synthesis and release and improve brain function. Aerobic exercise (e.g., treadmill training) has shown to improve gait parameters, quality of life, and levodopa efficacy in PD patients. However, once FM also depends on other components such as dynamic balance, dual tasking, and other sensorimotor skills, aerobic training is not sufficient to improve FM in PD. [25,39] Task-specific exercises targeting a single, specific balance or gait impairment, in PD patients have also been tested with positive results. [25,41]

Rehabilitation programs have been reported to be effective in preventing and improving PD patients' FM when focusing on aerobic exercises and self-initiated movements, big and quick movements, large and flexible centers of mass control, reciprocal and coordinated movements of arms and legs, and rotational movements of torso over pelvis and pelvis over legs. [42]

Strategy training

Strategy training is one of the key elements of physiotherapy PD management. It is defined as teaching the person how to move more easily and to maintain postural stability by using cognitive strategies. This includes two different methods: acquiring new motor skills (learning strategies) and compensating for movement disorders by bypassing the defective basal ganglia (compensating strategies). [41]

There is growing evidence that, at least in early PD, the capacity to learn new motor skills is not affected. [25,41,43] One study showed that PD patients with mean disease duration of 7 years have the capacity to learn new upper-limb movement sequences, improve performance and retain it for 48 hours. [25,44] Another study evaluated a multiple-task gait-training program in mild PD patients (H&Y stages II–III), reporting that study participants could maintain their learned increased multiple-task walking speed over 3 weeks. [19,45]

Compensatory strategies have been shown to be effective in moderate to severe PD patients, however requiring high mental effort and with relatively short-term effects. They include: the use of visual (e.g., white lines on the floor) and auditory (e.g., rhythmical beat provided by a metronome) external cues, the visualization of walking with long steps, mental rehearsal of the desired movement pattern before performing the action and breaking down long or complex motor sequences into parts and focusing on the performance of each individual segment (segmentation).

Through the mechanism of consciously thinking about the desired movement, using the frontal cortex to regulate movement size or timing instead of the defective basal ganglia, PD patients arguably compensate for the neurotransmitter imbalance in the basal ganglia obtaining a more normal gait pattern. [19,25,27] The type of strategy, the frequency and duration of training should be considered according to disease severity, the capacity to learn, and whether there are coexisting conditions that limit the ability to practice (Table 1). [19,25,27]

Mild to moderate disease	**Training strategy:** learning strategies to improve performance through practice **Program:** - 3 times/week - Periods of 6 to 8 weeks (motor skill acquisition) - Burst of therapy 2 to 3 times/year (to promote retention of training)
Severe disease **Cognitive impairments** **Compromised skill acquisition**	**Training strategy:** compensatory strategies to by-pass the defective basal ganglia **Use:** External cues, reminders and segmentation of action into simple components **Multi-tasking activities:** use as training strategy, educate the patients on its risks

Table 1 - Strategies training guide adapted from Morris et al. (2010)

Assistive mobility devices

PD patients with FM impairments need to be able to move effortlessly, in a reasonable amount of time throughout their day, accessing the same environments as others. [37]

The use of assistive mobility devices (e.g. wheelchairs, walker) increases the ability of individuals to work, perform self-care, and engage in leisure and social activities independently, enhancing their functional performance, autonomy and participation. [2,24,31,37,46,47]

Despite the potential advantages of assistive mobility devices, they are often underused or abandoned. The reason relates to a mismatch between a patient's functional needs, preferences and environmental constrains, and health professionals' perspectives. In 2017, Bettecken et al. [38] reported a relationship between PD patients' gait velocity using an assistive mobile device and their HrQoL. Surprisingly, the study did not show a relevant contribution of gait velocity to HrQoL. Also, a relevant portion of PD patients with high HrQoL preferred a low self-preferred gait velocity to the use of an assistive mobile device.

In a study to identify clinicians', patients' and caregivers' perspectives about relevant parameters and assessment tools for PD symptoms [15], Ferreira and colleagues reported that patients and

caregivers have different perspectives when selecting the most relevant parameters for evaluating gait and sway domains. Patients and caregivers both highlighted the capability of performing ADL as the most important parameter. For clinicians, time consumed doing specific tasks was the most useful parameter.

7) Implications for clinical practice and research

If PD patients are unable to move at an intensity and frequency that life requires, they may become excluded from social and occupational environments, which may negative impacts theirs global health status. [48–50]

Although the assessment of specific outcomes, like level of rigidity or intensity of tremor, is important, previous studies have shown that functional limitations, rather than physical impairments, were the most problematic aspect of a PD patient's disability profile. [51] The standard scale for evaluating impairments in PD is the MDS-UPDRS. However, besides being highly time-consuming, the objective evaluation of functional activities is limited. The TUG test is the most used tool to classify FM and has been shown to be a valid predictor of performance in ADL. Yet, an exhaustive measurement system that adequately assesses FM is still needed. [52]

More studies are needed to understand the relationship between the use of assistive mobility devices, PD patients' FM and HrQoL. Perceived control may be the key aspect in explaining the intriguing conclusion that Bettecken and colleagues found in their study. [14] As mentioned above, perceived control is a powerful predictor of functioning and it seems that some patients place more value on the capability of performing ADL rather than the time it takes to perform specific tasks. [39] We hypothesize that assistive mobility devices are acknowledge by patients as an effective solution only when perceived as a control gain. Otherwise, the use of assistive mobility devices is seen as a loss of autonomy with negative impact in HrQoL (even objectively improving gait characteristics such as velocity). It would also be interesting and useful to study if, for those PD patients who remain in employment, or who maintain an active social life, this hypothesis is valid.

8) Conclusion

Back to our initial question: is there a difference in the FM of two Parkinson's disease (PD) patients with similar gait disturbance, one using an assistive mobility device, the other not? How do health professionals account for these differences?

This question can be seen from two different perspectives.

As a physiological ability, the two patients have the same degree of FM, since what differentiated them was the use of an external device.

As an outcome measure eligible to be improved by a therapeutic intervention, the answer is not so clear. On one hand, assistive mobility devices enable a more active and safer lifestyle, allowing patients to continue to be engaged with their social and occupational environment. For this reason the patient with an assistive mobility device has better functional mobility. On the other hand, this would only be true if the use of these devices increases patients' perceived control of their situation.

Understanding the determinants of FM in individuals with PD, such as the precedence of perceived control over an improved gait velocity, will help clinicians to more easily select the most appropriate therapeutic interventions based on an accurate, global, and personalized evaluation of patients' problems. [30,38].

From this review on PD patients FM, we highlight: 1) its benefits as a more global and functional outcome of patient assessment; 2) the important role of exercise programs, training strategies and assistive devices in improving patients' functionality and participation in social environments; and lastly, 3) the importance of taking into account patients' personal needs and wishes and environmental factors in order to optimize treatment strategies.

CHAPTER 3

Measurement instruments to assess functional mobility in Parkinson's disease: a systematic review

Measurement instruments to assess Functional Mobility in Parkinson's disease: a systematic review

Raquel Bouça-Machado, MSc[a,b], Gonçalo S. Duarte, MD[a,c], Maria Patriarca[b], Ana Castro Caldas, MD[b], Joana Alarcão, MSc[d], Ricardo M. Fernandes, MD, PhD[a,c,e], Tiago A. Mestre, MD, PhD[f], Ricardo Matias, PhD[g,h], Joaquim J. Ferreira, MD, PhD[a,b,c]

a - Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

b - CNS-Campus Neurológico Sénior, Torres Vedras, Portugal

c - Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

d - Center for Evidence-Based Medicine, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

e - Department of Pediatrics, Santa Maria Hospital, Lisbon, Portugal

f - Parkinson's disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa Brain and Research Institute, Ottawa, Canada

g - Champalimaud Research and Clinical Centre, Champalimaud Centre for the Unknown, Lisbon, Portugal

h- Human Movement Analysis Lab, Escola Superior Saúde – Instituto Politécnico de Setúbal, Setúbal, Portugal

Contents of this chapter were extracted from the peer-reviewed publication with the following reference: **Bouça-Machado R**, Duarte GS, Patriarca M, et al. Measurement Instruments to Assess Functional Mobility in Parkinson's Disease: A Systematic Review. Mov Disord Clin Pract. 2019;7(2):129-139. Published 2019 Dec 11.

Raquel Bouça-Machado conceptualized the review, conducted data collection and analysis, and drafted the manuscript.

Abstract

Background: Functional mobility (FM) is a person's ability to move to accomplish activities of daily living, it bridges the concepts of mobility and functional ability. There is frequently a loss of FM in Parkinson's disease (PD). Several instruments have been used to assess this concept in PD, however, there is no consensus on which are the most appropriate.

Objective: We aimed to identify and critically appraise which measurement instruments have been used to assess FM.

Methods: A systematic review was conducted using the databases CENTRAL, MEDLINE, Embase, and PEDro from their inception to January 2019 to identify all observational and experimental studies conducted in PD or atypical parkinsonism that included a FM assessment. Two reviewers independently screened citations, extracted data, and assessed clinimetric properties.

Results: We included 95 studies that assessed FM in PD. Fifty-five (57.9%) studies mentioned FM in the manuscript, and 39 (41.1%) specified the measurement tools used to evaluate FM. FM was the primary outcome in 12 (12.6%) studies. The timed up and go test was the most frequently used measurement tool. Only one study presented a definition of FM. Several overlapping terms were used, the most common being mobility.

Conclusion: Several studies reported the use of FM measurement tools in PD, though with frequent misconceptions, an inadequate context of use, or suboptimal assessment. We propose the establishment of the concept of FM applied to PD, followed by the adequate clinimetric validation of existing measurement tools to provide a comprehensive and reliable evaluation of FM in PD.

Key words: Parkinson's disease, functional mobility, measurement instruments, systematic review, outcome measures

Functional mobility (FM) has been described as a person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living at home, at work, and in the community (Fig. 1). [19,64] Although poorly defined, the concept of FM has been used in several recent research studies as a more global and illustrative outcome of patients' health status in their environment. [64,65]

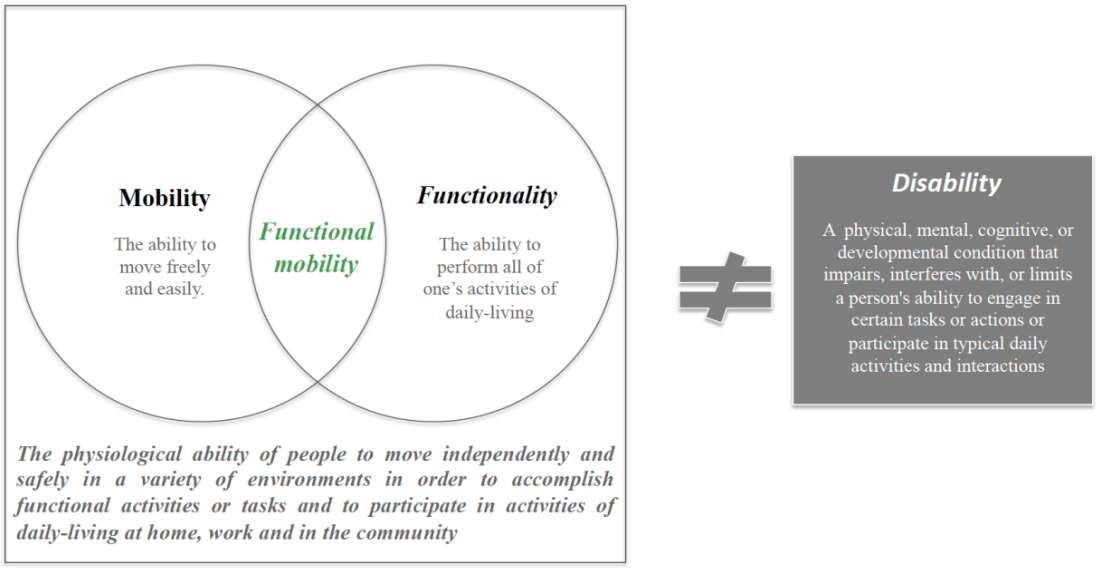


Figure 1 – Definition of functional mobility [64]

Reduction in FM is common and has a multifactorial nature in Parkinson's disease (PD). [64] Motor symptoms may contribute directly, through gait impairments, and indirectly due to bradykinesia, rigidity and the presence of postural deformities (e.g., camptocormia or antecollis), which affect PD patients' gait, balance, and transitions. (2) Also, the inability to simultaneously perform a cognitive and a motor task, and the presence of orthostatic hypotension symptoms and fatigue complaints, seems also to play an important role. [64] FM is associated with significant associated disability and loss of independence leading to immobility and institutionalization. Recognizing limitations in FM is important to better understand and address patients' daily real-life needs and to monitoring them over time. [10,66]

In spite of being loosely defined, several tests and rating scales have been used to assess FM in PD patients, [65,66] but there is no consensus on the most adequate tools for screening or for using as outcome measures to monitor change over time. This lack of consensus limits the interpretation results from studies and hampers the evaluation of therapeutics and the discussion among peers.
The present review aims to investigate which measurement tools have been used to evaluate FM in PD studies. Recommendations on which tools can be used and the need for modifications or replacements are made based on the results.

Methods

Defining the concept

FM is not a concept defined in the International Classification of Functioning, Disability, and Health (ICF) and lacks a formal definition. To overcome this limitation, we adopted a definition previously used by Forhan&Gill, 2013 [19] in a study on obesity. To check the adequacy of our choice, we matched the adopted definition with those founded in a Medline/PubMed electronic open search, conducted to look for a formal definition of FM (regardless of the research topics). We found six additional papers that defined FM (6–11). Although few, and none presenting a formal definition of FM, all shared with the Forhan&Gill description, the idea that FM is a subject's ability to move in his/her environment, focused on gait, balance, and transfers, in order to accomplish functional tasks of everyday living (e.g. walking in a corridor at work, climbing stairs at home, getting up from bed, rising from a chair to answer the phone, standing, bending to reach an object). Therefore, we assume this as the most suitable definition to be used in the context of this systematic review.

Literature search

We searched CENTRAL, MEDLINE, Embase, and PEDro from their inception to January 2019 using a pre-defined search strategy (Appendix 1) designed by the authors in conjunction with the Cochrane's highly sensitive search strategy [67] and previous reviews in PD [68]. Being aware of the laxity of the definition, we also ran some open electronic searches, in order to minimize the number of studies not found in the formal electronic search. Reference lists from the identified articles were cross-checked to identify any further potentially eligible studies.

Study selection

We included any observational and experimental study conducted in PD patients or atypical parkinsonisms. For intervention or controlled studies, there were no restrictions regarding the type of intervention or control arms. Studies had to include a FM assessment and to describe what measurement tools were used (mentioned in the abstract and/or in the manuscript). In order to get a full picture of the measurement tools that have been and could potentially be used to measure FM we also included studies for which the description of the outcome measures matched the pre-defined concept of FM, as per consensus of the current authors (i.e., to present one or a set of instruments that measured gait, transfer, and/or balance). Studies did not need to present a definition of FM to be included in this review.

We excluded reviews and studies written in languages other than English, French, Spanish, and Portuguese. Two authors (RBM, MP) independently screened abstracts obtained from the database search. The full texts of potentially relevant articles were retrieved for further assessment. Disagreements were resolved by consensus or by consultation with a third reviewer (GSD).

Data extraction

Four pre-defined domains of items were extracted: general information (title, year, and journal of publication, aim of the study, study design, population, sample size, and intervention and comparator if applicable), concept of FM (presence of the concept of FM in the title and/or in the manuscript, if a definition of FM was presented and if other terms were used as synonyms), FM outcome tools (if FM was the primary outcome measure, which instruments were used, and the time point measures), and feasibility of the instrument (completion time, number of required instruments, easy administration, interpretability, patients' comprehensibility, length of the outcome measurement instrument, ease of standardization, and clinician's comprehensibility).

We divided studies into those that specifically used the concept of FM and those that, while not mentioning the concept of FM used outcome measures that could fit the concept according to our best judgment. Within the studies using the concept of FM, we divided those that specified which measurement tools were used to measure FM from those that only mentioned evaluation of FM in the aims or conclusions of the study.

Two authors (RBM, MP) independently extracted data. Discrepancies were resolved through discussion or by consultation with a third reviewer (GSD).

Assessment of measurement properties

Based on previous reviews we divided the measurement tools into clinically-based tests, patient-reported outcomes, and gait quantification methods. [52]

The recommendations were based on the criteria previously used in other reviews. [69,70] These included: 1) use in the assessment of FM, 2) use in published studies by individuals other than the developers, and 3) a "successful" clinimetric test (i.e. to have demonstrated the reliability, validity, and sensitivity to change of the instrument).

Measurement tools were classified as recommended, suggested, or listed, respectively, based on the number of criteria met and the feasibility evaluation. [71]

The search for studies assessing the clinimetric properties of the included measurement tools was made based on previous research [52] and on the references of each measurement tool presented in the included studies.

Statistical analysis

The primary outcome was to identify the measurement instruments currently used to evaluate FM in people with PD. We summarized the publication characteristics using frequencies and percentages.

Results

The electronic and hand searches identified 2463 citations. After screening titles and abstracts 103 articles were deemed potentially eligible. Full-text assessment for eligibility resulted in 8 studies being excluded. Overall, the main reasons for exclusion were: inadequately defined outcome (n = 1395) and inappropriate study population (n = 222) (Appendix 2).

1) General data

Of the 95 included articles, 63 (66.3%) were interventional studies, 94 (98.4%) were conducted in PD patients, with a sample median [range] size of 32 [1, 3408]. According to the year of publication, the earliest study was published in 2003, being 2014 and 2015 the years with the

highest number of included studies (n=15 in each). All interventional studies evaluated non-pharmacological interventions.

Fifty-five (57.9%) of the included studies specifically mentioned the concept of FM in the manuscript, 39 (41.1%) specified the measurement tools used to evaluate FM, and in 12 (12.6%) FM was the primary outcome. Forty studies were deemed to have used the concept of FM according to the reviewers. (Fig. 2)

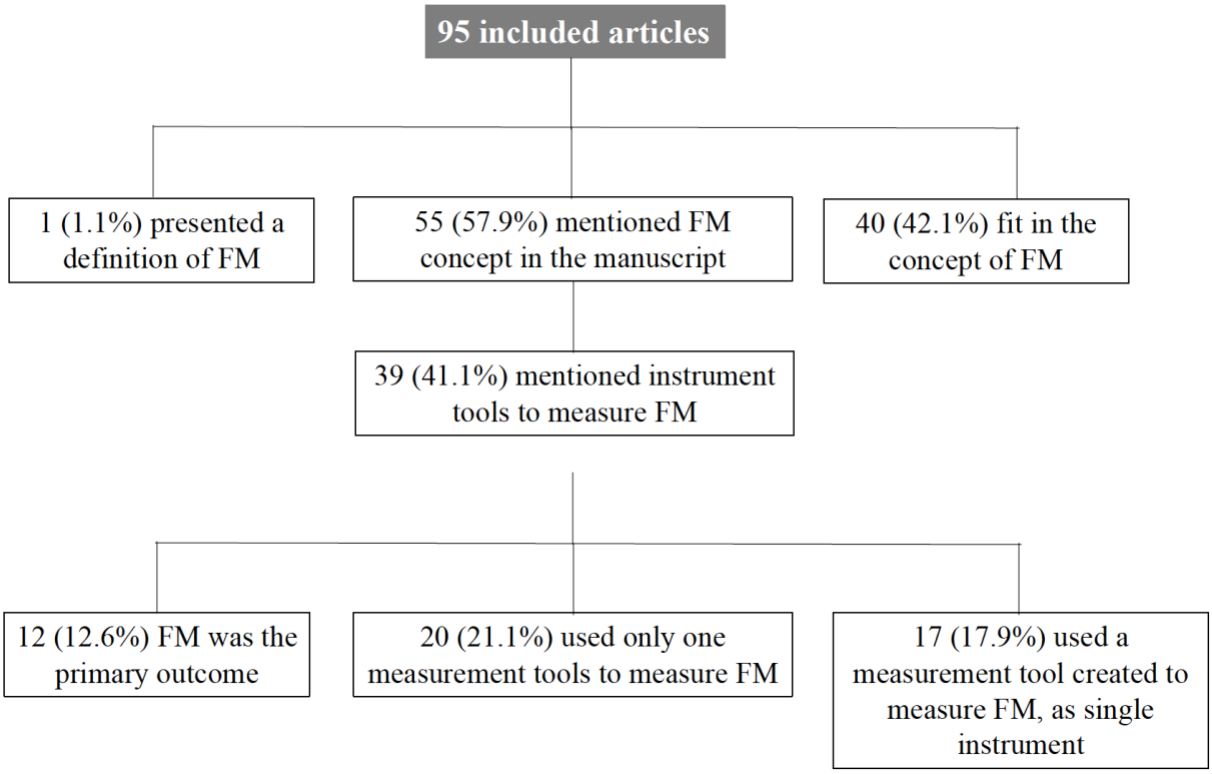


Figure 2 - Number of included studies specifically mentioning the concept of FM and respective measurement tools in the manuscript

2) Studies explicitly using the concept of FM

Of the 39 studies (41.1%) in which a measurement tool(s) was specified to evaluate FM, 34 (87.2%) were clinically-based tests, six (15.4%) combined clinically-based tests with gait quantification methods, one (2.6%) combined clinically-based tests with patient-reported outcomes and one (2.6%) used only gait-quantification methods.

The Timed Up and Go (TUG) test was the most frequently reported tool used as a single instrument (75% of studies, n=15). The Short Physical Performance Battery, the Five Times Sit-to-stand test, the Modified Parkinson Activity Scale and the Dual-task TUG (cognitive) were also applied. (Fig. 3) In those articles that used a combination of measurement tools to assess FM (n=19, 48.7%), the most frequent associations were TUG with a: dual-task test, balance test, gait assessment, and/or a transfer evaluation. (Fig. 3) The association of the TUG test with a second gait, balance, or transfers test was the most used way (75%, n=9) used to measure the primary outcome (n=12, 30.8%), followed by the single TUG test (n=2, 16.7%) and the single Five times sit-to-stand test (8.3%, n=1).

3) Studies that match the concept of FM

Forty studies (42.1%) evaluated a set of outcomes including functional assessment of gait, balance, and transfers that we considered to match the concept of FM.

Of these 40 studies, 29 (72.5%) used clinically-based tests as measurement tools, 6 (15%) used a combination of a clinically-based and gait quantification method, and 3 (7.5%) a combination of a clinically-based test and patient-reported outcomes. One study (2.5%) only used gait quantification methods and another study (2.5%) associated clinically-based tests with gait quantification method analysis and patient-reported outcomes.

Regarding clinically-based tests, in four studies (10%), the TUG was used as the only instrument. All other studies used a combination of measurement tools, the most used were the TUG (57.5%, n=23), the 6-minute walk test (30%, n=12), and the Berg balance scale (30%, n=12). (Fig. 3)

4) Quality assessment of outcome measurement instruments

All measurement tools were administered to a PD population, with data on their use in clinical studies beyond the group that developed the instrument. [52] Tables 1 and 2 summarize some of the characteristics of the most cited measurement instruments in the included studies. A more detailed description of the clinimetric properties (the previously published results of reliability, validity, and sensitivity to change of each instrument) and feasibility issues is presented below. The instruments have been divided according to whether they were used as a single instrument to measure FM or as part of a combination of instruments.

Measurement tools specifically used to assess FM						Measurement tools not specific used to assess FM	
One only instrument tool	**% (n)**	**As a set of outcomes tools**				**As a set of outcomes tools**	**% (n)**
Timed Up and Go test	75% (15)		**TUG with...**			Timed up-and-go	57.5% (23)
The Short Physical Performance Battery	10% (2)	**Dual-task**	**Balance**	**Gait**	**Transfers**	6- Minute Walk Test	30% (12)
Five Times Sit-to-Stand Test	5% (1)	Cognitive	Berg	10-m walk test	5x Sit to Stand test	Berg Balance Scale	30% (12)
Modified Parkinson activity scale	5% (1)	Manual	Mini-best	6-minute walk test	360º turn	10-m walk test	22.5% (9)
Dual task Timed Up and Go (cognitive)	5% (1)		Functional reach	Dynamic gait index	Bed mobility test	Mini-BESTest	22.5% (9)
						UPDRS Part III	22.5% (9)
						Functional Reach Test	17.5% (7)

Figure 3 – Measurement tools specifically used to measure FM and those used in studies that fit the FM concept

4.1) A single instrument to measure FM

The Timed Up and Go Test [25,52,72,73]

Construct assessed: Functional mobility.

Test description: The participant is required to get up from a standard chair, to walk three meters at a comfortable and safe pace, turn and walk back to sit down on the chair. The use of assistive devices is allowed.

Clinimetric properties: Planned comparisons using independent-sample t tests were used to investigate changes in patients' TUG scores in the "off" and "on" phases. Results showed differences across the stages of the medication, with a moderately strong correlation (r= 0.74, n=12, p=0.003) between "off" and "on" phase scores. Results demonstrate that TUG scores could be used to differentiate the performance of subjects with PD from controls and also to detect differences between the "on" and "off" phases of the medication cycle. No ceiling effects were found. Floor effects exist at scores of 10 to 15 seconds. The TUG demonstrated adequate test-retest and inter-rater reliability in PD. Intraclass correlation coefficients (ICC) were used to investigate the agreement between experienced and inexperienced raters in different phases of the levodopa cycle. Results showed a high degree of agreement across different conditions (ICCs between 0.87-0.99). Absolute minimal detectable change values in PD varied from 3.5 to 11 seconds, whereas relative changes greater than 29.8% may reflect "true" change. Longer times to complete the test proved to be associated with an increased risk of falls.

Feasibility: An easy and quick test to administer. Limited to patients capable of walking (with or without assistive devices) and who are able to follow instructions. The safety training may interfere

Instruments	Single instrument to measure FM	Created to measure FM	Applied in PD to measure FM	Applied beyond original developers	Construct assessed	Reliability	Validity	Sensitive to change	Feasibility issues	Classification
Timed Up and Go test	Yes	Yes	Yes	Yes	Functional mobility	Yes	Yes	Yes	No	Recommended
Dual-task Timed Up and Go	Yes	Yes	Yes	Yes	Functional mobility	No	No	No	No	Suggested
Modified Parkinson Activity Scale	Yes	Yes	Yes	Yes	Functional mobility	Yes	Yes	Yes	Yes	Suggested
Five Times Sit-to-Stand Test	Yes	No	Yes	Yes	Lower extremity strength	Yes	Yes	Yes	No	Listed
The Short Physical Performance Battery	Yes	No	Yes	Yes	Lower extremity physical performance status	Yes	No	No	No	Listed
10-Meters Walk Test	No	No	Yes	Yes	Walking speed	Yes	Yes	Yes	No	Listed
6- Minute Walk Test	No	No	Yes	Yes	Physical capacity	Yes	Yes	Yes	Yes	Listed
360° Turn Test	No	No	No	Yes	Turning ability, Freezing of gait	Yes	No	No	No	Listed
Berg Balance Scale	No	No	Yes	Yes	Functional standing Balance	Yes	Yes	Yes	No	Listed
Mini-best Test	No	No	Yes	Yes	Balance	Yes	Yes	Yes	No	Listed
Functional Reach Test	No	No	No	Yes	Static balance	Yes	Yes	Yes	Yes	Listed
UPDRS Part III	No	No	No	Yes	Motor performance	Yes	Yes	Yes	Yes	Listed

Table 1 – Characteristics and classification of the most cited measurement tools

Instruments	Completion time (sec)	Required equipment (n)	Easy administration	Interpretability	Patient's comprehension	Length of the outcome measurement instrument	Ease of standardization	Ease of comprehensibility by clinician
Timed Up and Go test	5	3	Yes	Yes	Adequate	Adequate	Yes	Yes
Dual-task Timed Up and Go	< 5	4	Yes	Yes	Adequate	Adequate	Yes	Yes
Modified Parkinson Activity Scale	10-15	8	No	Yes	Adequate	Too long	Yes	Yes
Five Times Sit-to-Stand Test	< 5	2	Yes	Yes	Adequate	Adequate	Yes	Yes
The Short Physical Performance Battery	10-15	5	Yes	Yes	Adequate	Adequate	Yes	Yes
10-Meters Walk Test	5	3	Yes	Yes	Adequate	Adequate	Yes	Yes
6- Minute Walk Test	< 10	4	No	Yes	Adequate	Too long	Yes	Yes
360° Turn Test	< 5	1	Yes	Yes	Adequate	Adequate	Yes	Yes
Berg Balance Scale	10-20	6	Yes	Yes	Adequate	Adequate	Yes	Yes
Mini-best Test	10-15	7	Yes	Yes	Adequate	Adequate	Yes	Yes
Functional Reach Test	< 5	3	Yes	Yes	Difficult	Adequate	Yes	Yes
UPDRS Part III	< 10	0	Yes	Yes	Adequate	Too long	No	Yes

Table 2 – Feasibility characteristics of the most cited measurement tools

with TUG results since patients take more time if focused on the use of safety strategies when getting up, turning, and sitting down.

Dual-task Timed Up and Go Test (TUG DT) [74,75]

Construct assessed: Functional mobility in dual-task conditions.

Test description: The participant is required to stand up from a chair, walk three meters at a comfortable and safe speed, then turn and walk back to the chair and sit down. In the TUG cognitive, while performing the test, the participant is asked to count backward by threes to a random number between 20 and 100. In the TUG manual, the participant is required to hold a cup filled with water during the test. The use of assistive devices is allowed.

Clinimetric properties: Unknown for PD patients. In healthy older adults, the TUG dual-task manual and cognitive strongly correlate with the Berg Balance Test (r = -0.72 and r = -0.66, respectively). Retest reliability is very good (TUG manual: $r_{T1\text{-}T2} = 0.97$ and $r_{T1\text{-}T3} = 0.98$; and TUG cognitive: $r_{T1\text{-}T2} = 0.98$ and $r_{T1\text{-}T3} = 0.98$). The intra-rater reliability is very high with ICC values of 0.99 and 0.94 for the TUG manual and cognitive, respectively.

Feasibility: Quick and easy to apply tests to determine dual-task interference in FM and a predictive test to assess risk for falls. They may be more useful than TUG without dual-task for evaluating intervention effects, since the interference of safety strategies is minimized. Limited to patients who are capable of walking (with or without assistive devices), and who are able to follow instructions, and who are not cognitively impaired.

The Modified Parkinson Activity Scale (mPAS) [25,76,77]

Construct assessed: Functional mobility.

Test description: The mPAS includes 18 activities covering three FM aspects: chair transfers (2 items), gait akinesia (6 items), and bed mobility (8 items). Raters evaluate the quality of the movement while patients perform the tasks.

Clinimetric properties: Specifically designed for the PD population. Based on 195 of observations, mPAS has no ceiling effect, good concurrent validity (0.64 with UPDRS motor scores and 0.79 with VAS-Global Functioning), good inter-rater agreement with no differences between experts and non-experts (p=0.28).

Feasibility: It requires several accessories and space (e.g. a bed, a chair, sheets, and a blanket), which may hinder its use in daily practice.

The Five Times Sit-to-stand Test (FTSTS) [78,79]

Construct assessed: Lower extremity strength.

Test description: Participants began the test seated in an armless chair with their arms folded across their chest and with their back against the chair. The rater asks the participant to stand up and sit down five times as quickly as he/she can without the use of the upper limbs.

Clinimetric properties: The FTSTS significantly correlated ($p<0.01$) with the Mini-Best test and the 6-minute walk test. It is able to discriminate between fallers and non-fallers, with an area under the curve of 0.77. It has shown to have high inter-rater and test-retest reliability, with an ICC of 0.99 and 0.76, respectively.

Feasibility: The FTSTS requires a minimum of instrumentation, is a quick and objective measure to determine whether an individual with PD may be at risk for falling. The potential use of compensatory strategies in the sit-to-stand movement may impair the test's capacity for measuring disease progression. It does not provide detailed information on balance limitations during gait-related activities and stationary balance. In people with PD, balance and bradykinesia seem to be the most important constructs influencing the results of the test.

The Short Physical Performance Battery (SPPB) [80–84]

Construct assessed: Lower extremity physical performance status.

Test description: A small battery including three components of daily activities: balance (ability to stand for three seconds with the feet together side-by-side, semi-tandem, and tandem), walking ability (two timed trials of 3 meters walked at a fast pace), and transfers (time to rise from a chair five times). The SPPB utilizes an ordinal ranking system, from 0 to 12, where higher scores indicate better lower extremity function.

Clinimetric properties: Significantly correlates with disability measures (Older Americans Resource and Services Activities of Daily Living and Instrumental ADL subscale) and disease severity (Hoehn and Yahr, UPDRS II, III, and total score). Although this test has been applied to PD patients, neither its relative and absolute reliability nor its responsiveness have been calculated. In community-dwelling older populations and patients with chronic kidney disease, the SPPB has

an excellent test-retest reliability (ICC = 0.82 and 0.94, respectively). This battery also has good sensitivity to change in myocardial infarction, stroke, hip fracture, and congestive heart failure patients.

Feasibility: A practical measure rapid to administer and requiring minimal equipment. It has been found to be too easy for highly functioning patients.

4.2) Measurement tools used in combination to measure FM

10-Meters Walk Test (10-MWT) [52,85–87]

Construct assessed: Walking speed.

Test description: The participant is asked to walk a distance of 10 meters at their self-selected or maximal speed. The time and number of steps needed to perform the task are recorded. Assistive devices are allowed.

Clinical properties: The test positively correlates with the 6MWT (gait endurance), has low to moderate correlation with the Mini-best test (balance), and a low correlation the UPDRS subscales (disease severity). The test has moderate to high test-retest reliability in PD (ICCs: 0.75-0.98), with MDC values of 0.18 and 0.25 m/s. Responsiveness was determined by significant differences after rehabilitation programs and deep brain stimulation.

Feasibility: It is a frequently used test in PD clinical trials. It is easy to administer and useful for identifying changes in gait over time in mild to moderate PD. The presence of freezing of gait or postural instability may hinder the outcome.

6-Minute Walk Test (6-MWT) [52,85,88]

Construct assessed: Physical capacity.

Test description: Subjects are asked to cover as much ground as possible on a standardized walkway for six minutes. Assistive devices are allowed, patients are permitted to pause if necessary.

Clinimetric properties: Its correlation with the UPDRS motor section is weak (it does not seem to be related with disease severity), however, it moderately to strongly correlates with the Berg Balance Scale, 10-MWT, and TUG. The responsiveness of the 6-MWT has been demonstrated in PD. The test has adequate test-retest, inter-rater reliability with ICCs ranging from 0.88 to 0.95. It

seems to be a good predictor of a patients' ability to walk outside independently and safely, and useful for identifying improvements in gait endurance after treatment.

Feasibility: The major limitations of this test's use in clinical practice are the time and space needed. It can only be applied to patients with the capacity to walk (with or without assistive devices). Performance in PD may depend on the presence of freezing, balance, and bradykinesia. Learning effects may occur.

360º Turn Test [89–92]

Construct assessed: Turning ability, freezing of gait.

Test description: The participant is required to make quick 360º turns, in both directions, while standing. The time, number of steps, and presence of freezing episodes are recorded.

Clinimetric properties: The test has high test-retest reliability as a functional test, with an ICC of 0.95. No further published data on reliability, validity, and responsiveness were found on the 360º turn test as a measure of turning ability. However, a study aiming to evaluate reliability, validity, and responsiveness of the timed 360° turn test in PD patients was registered in clinicaltrials.gov in July 2018 (ClinicalTrials.gov Identifier: NCT03587168). As a measure of freezing of gait, it has high inter-rater reliability (agreement 97%, Cohen's kappa 0.93)

Feasibility: Although an easy and quick test to evaluate the presence of freezing of gait, turning ability and, indirectly functionality, it is not a movement very frequent in daily life and does not provide much information on patients' FM. It is also limited to patients without postural instability.

Berg Balance Scale (BBS) [52,85,93,94]

Construct assessed: Functional standing balance.

Test description: The scale consists of 14 items, each scored from 0 to 4, to measure a subject's ability to maintain positions or movements of increasing difficulty by diminishing the base of support. Tasks include sitting, standing, standing to a single-leg stance, and positional changes.

Clinimetric properties: BBS score significantly correlates with indicators of motor functioning (UPDRS motor score, $r = -0.58$, $p<0.005$), stage of disease (Hoehn and Yahr Scale staging, $r = -0.45$, $P<0.005$), and daily living capacity (S&E ADL Scale rating, $r = 0.55$, $P<0.005$). A ceiling effect has been reported. The ICCs for test-retest reliability are above 0.90. A value for minimal detectable change has been calculated (MDC=5).

Feasibility: The BBS is a relatively safe and simple to administer instrument. It may not be very useful in mild to moderate PD patients due to ceiling effects. It does not take into account the quality of movement, and therefore, may be less useful in PD where motor control is a bigger contributor to poor balance than muscle weakness.

Mini-best Test [52,95,96]

Construct assessed: Balance.

Test description: The Mini-Best test is a 14-item tool to measure dynamic balance, which is associated with movement during transfers and gait, as well as external perturbations and cognitive dual-task performance. It includes six domains: biomechanical constraints, verticality/stability limits, anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait.

Clinimetric properties: The Mini-Best test has a strong relationship with the BESTest total score (r=0.955) and a comparable ability to discriminate between fallers and non-fallers. It has a high inter-rater and test-retest reliability (ICC= 0.91 and =0.92, respectively). Information on minimal clinically important difference is available.

Feasibility: Although it requires equipment it is feasible for use in clinical practice.

Functional reach test (FRT) [52,85,97]

Construct assessed: Static balance.

Test description: A ruler is mounted on the wall at shoulder height. The participant is required to reach forward the maximal distance beyond the arm's length, while maintaining a fixed base of support in the standing position.

Psychometric properties: FR significantly correlates with the UPDRS (r = 0.69; $p < 0.001$) and Hoehn and Yahr (r = 0.71; $p < 0.001$). The test has a moderate (0.44-0.51) to strong (0.72- 0.76) correlation with balance master items and reaching tasks. ICC values in test-retest reliability were 0.84 for a 1-day testing interval, and 0.73-0.74 for 1 week. Responsiveness in PD has been demonstrated by significant differences in scores between exercise and control groups. MDC values range from 4 to 11.5 cm.

Feasibility: The FRT is a practical balance tool used to evaluate the effect of interventions. It is limited to patients who can stand for 1 minute without support and patients frequently need to be helped to correctly perform the required movement.

Unified Parkinson's Disease Rating Scale (UPDRS) - Part-III [10,98,99]
Construct assessed: Motor performance.
Test description: A subsection of the most widely used clinical rating scale in PD to assess disease severity and progression, and to determine treatment-related benefits. Part III comprises 11 items, including ratings for tremor, slowness (bradykinesia), stiffness (rigidity), and balance. Punctuated from zero to four, with a higher score showing a higher level of disability.
Clinimetric properties: The UPDRS has adequate face validity, satisfactory construct validity, and is sensitive to changes in clinical status. It has excellent internal consistency throughout disease progression measured with the Hoehn and Yahr scale, and adequate inter- and intra-rater reliability.
Feasibility: Used in almost all PD clinical trials. It provides a comprehensive assessment, approaching several crucial constructs in PD that can be used across all patients regardless of severity, treatment, or age. Even in the revised version, the MDS-UPDRS has no item, or set of items, that specifically measure FM and it still very time consuming to use in everyday clinical practice.

5) Defining functional mobility concept
Of the 95 included studies, one defined the concept of FM, 55 (57.9%) mentioned the concept in the manuscript. Among these, other concepts were used as synonyms for FM, the most used term was mobility (18.2%, n=10). In the studies that did not overtly use the term FM but for which we considered FM was assessed, the most used expressions were mobility (25%, n=10) or mobility in association with functional activities/performance, motor function, gait-related activity, or balance (25%, n=10). (Appendix 3)

Conclusion
The assessment of FM has been included in PD studies and has increased over the years. FM is an outcome that may best convey the patient's overall health status in his/her environment. FM

incorporates a series of ill-defined and loosely used concepts that are generally considered to assess motor function in the context of functional activities/performance. Several measurement tools have been used to measure FM, especially in association with TUG.

1) Functional mobility measurement instruments

1.1) Recommended and suggested measurement tools

Among the reviewed instruments, only the TUG and mPAS were designed and are validated to measure FM in PD. The TUG DT, although an update of TUG and frequently used in PD clinical studies, has not been assessed clinimetrically. The TUG is an easy and quick to apply test that is broadly used in PD. It is limited to subjects who have the ability to walk, follow instructions, and who do not suffer from severe freezing episodes. Although this test includes the three anchors of FM (gait, balance, and transfers), and is considered a good predictor of FM, it is still a little distant from the reality of daily-living activities, which hampers its ability to capture the patient's functional status in his/her environment. [52,66] This may explain the frequent association of TUG with one or more scales found in our results.

The mPAS is a scale specifically designed to evaluate PD that overcomes this limitation by assessing functional gait, balance, and transfers through different scenarios. Its major limitation is the number of accessories, space, and time needed to perform the test. The bed mobility items require a bed (large enough to turn to both sides), sheet, and a blanket, which may not be practical or feasible in all centers. [52,76]

1.2) Listed measurement tools

The FTSTS and the SPPB, although used as single instruments to measure FM, are not validated to measure FM in PD. The FTSTS test assesses lower extremity strength asking the patient to stand up and sit five times, which is not representative of the FM concept. Although the SPPB can be considered to assess the three anchors of FM (the FTSTS, 1 test of static balance (10 seconds with the feet together, in semi-tandem and full tandem) and a 3m-walk), uses very little functional and isolated tests, making its adequacy to measure FM, in our opinion questionable. Compared with the SPPB, the TUG seems more attractive since it includes the anchors, in a simpler test, and above all, in a sequential way, which makes it more functional and closer to the movements of daily life.

1.3) Potential measurement tools to assess FM

One psychometric study [100], has assessed, with positive results, a new scale to assess FM in PD: the Lindop Parkinson's Disease Mobility Assessment (LPA). This is a 10-item rating scale that covers the same constructs as the mPAS in a simplified form. This scale was validated in 2009 but we did not find any studies that have used it to assess FM in PD. Nevertheless, it seems that it could be an alternative to the mPAS.

Although not validated for measuring FM in PD, the Mini-BEST test seems worthy of being studied as an isolated tool to measure FM. Like the mPAS, the Mini-BEST assesses the three constructs of FM through different tasks, with the added value of including the TUG DT test, the assessment of gait in association with common tasks of daily living (e.g. changes in gait speed, walk with head turn, walk with pivotal turn and step over obstacles), and the assessment of reactive postural control in four directions. It does not include the assessment of bed mobility.

Nine of the included studies (9.5%) used kinematic gait parameters to assess FM. Since FM is a more global and illustrative outcome of patients' health status, the use of technology-based objective measures is very attractive. However, the most suitable parameters and instrument to this end need to be defined.

A 2016 study reviewed *Instruments to Assess Posture, Gait, and Balance in Parkinson's Disease* [52], a topic that overlaps largely with the aim of this review. However, there is an essential difference between these two reviews. Although posture, gait, and balance are crucial aspects of FM, the operationalization of this concept requires their simultaneous presence (along with transfers) during a task of daily living. The assessment of the three parameters, either separately or without carrying out a functional task, should not be considered an FM assessment.

2) The concept of functional mobility

Although frequently mentioned and increasingly used in clinical studies, the concept of FM is not included in the ICF. [63] Only one of the 95 studies (1.1%) defined FM in the manuscript.

In the absence of a universally accepted definition of FM, we adopted the Forhan&Gill, 2013 [19] definition, previously used in a study on obesity, after verifying its suitability through a match with other definitions found on an electronic search conducted in Medline/PubMed to appraise for other operational definitions of FM. All the definitions share the anchor that FM is the subject's ability to move within a natural environment and to perform everyday tasks and the operationalization by

the assessment of gait, balance, and transfers during the performance of a functional task. Frequently, the concept of mobility was used as a synonym of FM in the included studies. In order to verify what was understood by mobility, we reviewed its current ICF definition. According to this, mobility is defined as "moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation". (47) This is a broader concept than FM as it is not restricted to actions conducted with the purpose of completing an activity of daily living, which is mandatory for FM. Although we acknowledge the absence of a universal definition for FM, we believe that the Forhan&Gill, 2013 [19] description, adopted in this review, is the most consensual definition of FM. Therefore, in the context of this review, we have defined FM, as a domain of mobility, focused on a person's physiological ability to move independently and safely within a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living. (1)

Among the measurement tools assessed in this review on FM, the TUG seems the most suitable for use in clinical practice and research, having been designed to evaluate FM and displaying strong clinimetric properties.

A limitation for establishing the most appropriate outcome tools is the absence of an established concept of FM and the misuse of several overlapping terms. We recommend the use of the Forhan & Gill [19], as the most consensual and pragmatic operational definition of FM. Based on this, we suggest to validate the existing tools (e.g. the Mini-Best test) and potentially develop novel scales that measure FM in PD. We also highlight the need to study how FM behaves in the context of clinical trials, concretely its responsiveness to change in the assessment of pharmacological and non-pharmacological therapeutic interventions. The combination of various validated tools will possibly provide a more complete measurement of FM. The use of technology-based objective measures is increasingly being used to asses PD patients, with the added value of tracking FM from the users' daily routine, using a smartphone or a similar device, without the need of any explicit test. Although still very new and fragile, future studies should also explore these as potential outcome tools for measuring FM.

Appendix 1

Search strategy for functional mobility in Parkinson's disease research: a systematic review

CENTRAL search strategy for RCTs

1. MeSH descriptor: [Parkinson Disease] explode all trees
2. Parkinson*:TI,AB,KY
3. #1 OR #2
4. MeSH descriptor: [Mobility Limitation] explode all trees
5. MeSH descriptor: [Motor Activity] explode all trees
6. funtion* adj3 mobil*:TI,AB,KY
7. #4 OR #5 OR #6
8. #3 AND #7
9. Limit #8 to Trials

MEDLINE search strategy for RCTs

1. exp Parkinson Disease/
2. Parkinson*.ti,ab.
3. 1 or 2
4. "randomized controlled trial".pt.
5. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
6. (retraction of publication or retracted publication).pt.
7. or/4-6
8. (animals not humans).sh.
9. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
10. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
11. or/8-10
12. 7 not 11
13. exp Mobility Limitation/
14. exp Motor Activity/
15. (mobil* or mov* or motion) adj2 functio*.ti,ab.
16. funtion* adj3 mobil*.ti,ab.
17. mobil* adj3 dificult*.ti,ab.
18. or/13-17
19. 3 and 12 and 18

MEDLINE search strategy for observational studies

1. exp Parkinson Disease/
2. Parkinson*.ti,ab.
3. or/1-2
4. Epidemiologic studies/
5. exp Case control studies/
6. exp Cohort studies/
7. Case control.af.
8. (cohort adj (study or studies)).af.
9. Cohort analy$.af.
10. (follow up adj (study or studies)).af.
11. (observational adj (study or studies)).af.
12. Longitudinal.af.
13. Retrospective.af.
14. Regression.af.
15. or/4-14
16. exp Mobility Limitation/
17. exp Motor Activity/
18. funtion* adj3 mobil*.ti,ab.
19. mobil* adj3 dificult*.ti,ab.
20. (mobil* or mov* or motion) adj2 functio*.ti,ab.
21. or/16-20
22. 3 and 15 and 21

Embase search strategy for RCTs

1. exp Parkinson Disease/
2. Parkinson*.ti,ab.
3. or/1-2
4. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab.
5. RETRACTED ARTICLE/
6. or/4-5
7. (animal$ not human$).sh,hw.
8. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
9. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
10. or/7-9
11. 6 not 10
12. exp Mobility Limitation/

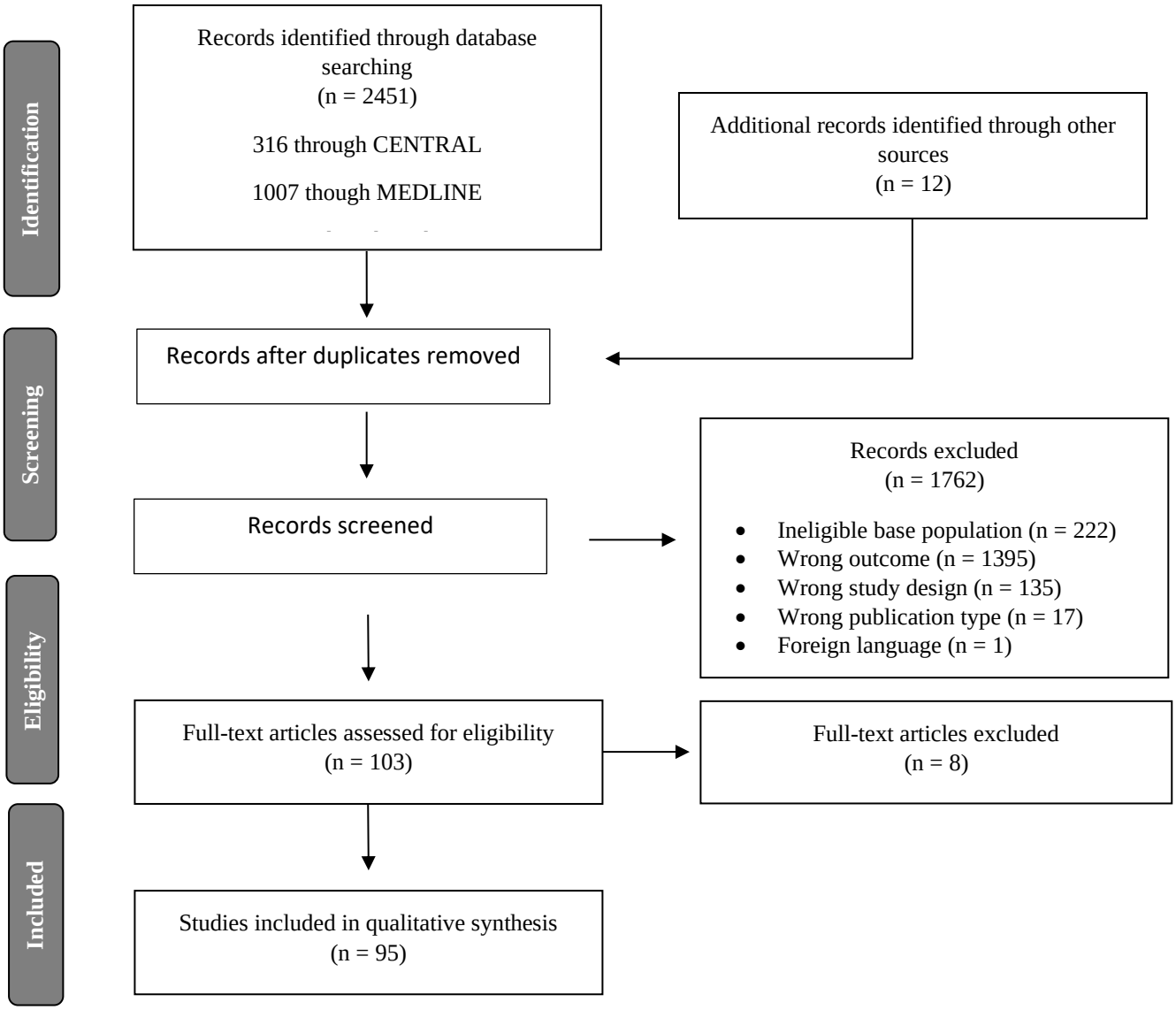
13. exp Motor Activity/
14. funtion* adj3 mobil*.ti,ab.
15. mobil* adj3 dificult*.ti,ab.
16. (mobil* or mov* or motion) adj2 functio*.ti,ab.
17. or/12-16
18. 3 and 11 and 17

Embase search strategy for observational studies

1. exp Parkinson Disease/
2. Parkinson*.ti,ab.
3. or/1-2
4. Cohort analysis/
5. Case control study/
6. (cohort adj (study or studies)).mp.
7. (case control adj (study or studies)).tw.
8. (follow up adj (study or studies)).tw.
9. (observational adj(study or studies)).tw.
10. (epidemiologic$ adj (study or studies)).tw.
11. (longitudinal adj (study or studies)).tw.
12. or/4-11
13. exp Mobility Limitation/
14. exp Motor Activity/
15. funtion* adj3 mobil*.ti,ab.
16. mobil* adj3 dificult*.ti,ab.
17. (mobil* or mov* or motion) adj2 functio*.ti,ab.
18. or/13-17
19. 3 and 12 and 18

Appendix 2

Flow diagram of study selection process



Appendix 3

Functional mobility related concepts used in the included studies

Other concept used by authors	Used FM concept (n=55)	Fit in the FM concept (n=40)
Mobility	18.2% (10)	25% (10)
Mobility and ... (functional activities/performance, motor function, gait-related activity, balance)	10.9% (6)	25% (10)
Motor- or Physical performance/function	10.9% (6)	22.5% (9)
Balance and gait/walking ability/functionality	10.9% (6)	12.5% (5)
Ambulatory activity	3.6% (2)	5% (2)
Functional capabilities, functional activities, functionality	10.9% (6)	5% (2)
Gait, balance, bed mobility	0% (0)	2.5% (1)
Walking capacity and transfers ability	0% (0)	2.5% (1)
Only FM concept	67.3% (37)	0% (0)

CHAPTER 4

Patients and health professionals' perspective of Functional Mobility in Parkinson's disease

Patients and health professionals' perspective of Functional Mobility in Parkinson's disease

Raquel Bouça-Machado, MSc[1,2], Nilza Gonçalves, MSc[1], Inês Lousada[2], Maria A. Patriarca[2], Patrícia Costa[2], Raquel Nunes[2], Susana Dias[2], Ana Castro Caldas, MD[2], Anabela Valadas, MD[2,3], Patrícia Pita Lobo, MD[2,3], Leonor Correia Guedes, MD, PhD[1,2,3], Mário Miguel Rosa, MD, PhD[1,3], Miguel Coelho, MD, PhD[1,2,3], Joaquim J. Ferreira, MD, PhD[1,2,4]

1 - Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal

2 - CNS-Campus Neurológico, Torres Vedras, Portugal

3 - Department of Neuroscience and Mental Health, Neurology, Hospital de Santa Maria, CHULN, Lisbon, Portugal

4 - Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

Contents of this chapter were extracted from the peer-reviewed publication with the following reference: **Bouça-Machado R,** Gonçalves N, Lousada I, Patriarca MA, Costa P, Nunes R, Dias S, Caldas AC, Valadas A, Lobo PP, Guedes LC, Rosa MM, Coelho M and Ferreira JJ (2020) Patients and Health Professional's Perspective of Functional Mobility in Parkinson's Disease. *Front. Neurol.*11:575811. doi: 10.3389/fneur.2020.575811

Raquel Bouça-Machado design the study, conducted data collection and analysis, and drafted the manuscript.

Abstract

Background: Functional mobility (FM) is the person's ability to move to accomplish daily living tasks and activities. FM limitations are common in Parkinson's disease, increase with disease progression and can be highly disabling. Although several studies in PD field use this concept, only recently, a formal definition has been proposed.

Objective: We aimed to explore patients' and health professionals' perspectives of FM in PD.

Methods: A focus group methodology has been used. Four focus groups, with a total of ten patients and ten health professionals, were performed. Six patients were early-stage and four advance stage. The health professionals' group was composed of five neurologists and five physiotherapists. The suitability of the new concept, the impact of FM limitations in PD patients' daily routine and the potential benefit of walking aids have been discussed.

Results: All participants were able to provide a spontaneous definition of FM, matching with the proposed concept. All agreed that PD affects patients' FM, increasing the limitations with disease progression, and with the existence of a serious prejudice with walking aids that hinders its use. Early-stage patients' perspective seems to be more in line with neurologists' perspective, while the views of advanced-stage patients were closer to physiotherapists' views.

Conclusion: FM concept was considered as intuitive and useful. FM limitations have an important physical and social impact in the advance stage of the disease. Although patients and health professionals acknowledge walking aids benefit improving patients' FM, the prejudice associated with this type of tools, limits its recommendation and use.

Keywords: Functional mobility, Parkinson's disease, Focus groups, Walking aids

Introduction

Parkinson's disease (PD) is a complex and fluctuating neurodegenerative disorder associated with the presence of motor and non-motor symptoms, which can be very disabling and highly affect patients quality of life.[101] Despite an optimal disease management, many of these symptoms improve only partially and aggravate with disease progression, resulting in recurrent falls, reduced mobility, and loss of independence.[20,28,101]

Functional mobility (FM) is the capacity of people to move from one place to another, in order to participate in the activities of daily living (ADL) at home, work and in the community. This concept includes movements like standing, bending, walking and climbing and contributes greatly to the subject's health-related quality of life. [19]

In PD, both motor and non-motor symptoms, contribute to the appearance of FM limitations. Although poorly defined, this concept has been frequently used in PD research. Recently, due to its frequent misuse, was felt the need to clarify and to establish a formal concept of FM to be applied to PD.[102]

The present study aims to explore, through a focus group methodology, PD patients and health professionals' perspective on the proposed concept of FM, exploring also the impact of FM limitations in patients' daily life and the strategies to deal with it. We hope like this to clarify the suitability of the new concept of FM in PD and to promote a more holistic and functional approach to the patients' needs.

Methods

Study design and patients' recruitment

A focus group methodology was used. Four focus groups were undertaken, two with patients (early and advance disease stage) and two with health professionals (physiotherapist and neurologist – movement disorders specialists). Patients were included if they had: 1) PD diagnosis, according to the Movement Disorders Society clinical diagnostic criteria; 2) a Hoehn Yahr (HY) stage between I and IV under dopaminergic medication (MED ON); 3) ability to communicate with the

investigator, and to understand and comply with the requirements of the study; and 4) ability to provide written informed consent to participate in the study. Patients were excluded if they have been diagnosed with an atypical parkinsonism.

Health professionals were included if they work regularly with the PD population for at least one year. Participants were recruited from CNS - Campus Neurológico, a specialized movement disorders center (Torres Vedras, Portugal) and from the Deep Brain Stimulation surgery waiting list of the Movement Disorders outpatient clinic of a tertiary university hospital (Hospital Santa Maria, Lisbon, Portugal). The CNS Local Ethical Committee approved the study (Ref. 04-2018) and all participants provided written informed consent.

Focus Groups

All participants that fulfilled inclusion criteria were invited to participate. Information about objectives, duration, procedures, and voluntariness was provided and the informed consent was obtained. Demographic and clinical data were collected for each PD patient. Patients were assessed in "ON" state medication.

The focus groups followed a semi-structured script, including questions concerning patients and health professionals' thoughts on the concept of FM, the impact and strategies to deal with FM limitations in daily life, and on the role of walking aids. (Appendix 1)

Each focus group took up to 90 minutes (75 minutes to focus group questions and 15 to close). At the beginning of each interview, participants were reminded of the purpose of the study and guaranteed confidentiality. Participants were encouraged to interact with each other, with the author intervening solely to keep the discussion on the topic, and to encourage the more reserved members of the group to speak.

The focus group was recorded, with the agreement of all participants.

Data analysis

The audio recordings were transcribed and read until it reaches an overall understanding.

Transcripts of the focus groups were divided into meaningful categories and themes. In a second step, was performed a thorough read of the data to ensure the identified themes were evident and a true reflection of the data. Researchers moved back and forth in a reflexive process until consensus was reached.

Descriptive statistics were used for demographic, clinical, and therapeutic data.

Results

Twenty participants were included in the study: six early-stage patients, four advanced-stage patients, five physiotherapist, and five neurologists. The mean age of patients was 68.0 ± 9.9 years (71.7 ± 9.0 in early-stage and 60.7 ± 8.3 in advanced-stage), with a mean disease duration of 8 ± 5.2 years (7.0 ± 6.1 in early-stage and 10.0 ± 3.0 in advanced-stage) and a mean Hoehn and Yard score of 2.2 ± 0.4 (2.0 ± 0.4 in early-stage and 2.5 ± 0.6 in advanced-stage). (Table 1)

	All patients (n=10)	Early-stage group (n=6)	Late-stage group (n=4)
Gender, M/F	7/3	3/1	4/2
Age at onset, mean years (SD)	68 ± 9.9	71.7 ± 9.0	60.7 ± 8.3
Disease Duration, mean years (SD)	8 ± 5.2	7.0 ± 6.1	10.0 ± 3.0
% Tremor as first symptom	60%	50%	66.7%
MDS-UPDRS Part II, mean (SD)	12.4 ± 8.1	8.0 ± 2.3	21.43 ± 8.5
MDS-UPDRS Total Score, mean (SD)	62.4 ± 23.6	61.0 ± 26.8	90.7 ± 18.3
HY, mean (SD)	2.2 ± 0.4	2.0 ± 0.0	2.5 ± 0.6

Table 1 – Demographic and clinical data

Patients in the early stage group were autonomous, with an active lifestyle, maintained through their professional job and/or exercise. Patients in the advanced-stage group were almost all retired,

had less autonomy and need more family support. For those who were employed, working conditions have been adapted to their specific needs.

Health professionals' experience with PD varied between 1 and 5 years in the physiotherapists' group and between 5 and 20 years in the neurologist group. All neurologist were movement disorders specialists and all the physiotherapist worked in a specialized movement disorders center.

1) The concept of functional mobility

All groups were able to present a spontaneous definition of FM that match with the one used by authors. All agree that FM reflects the difficulties of PD patients in daily life. (Table 2, Appendix 1)

What does the concept of functional mobility suggest?	
Early-stage patients	Late-stage patients
• Ability to move • What we do in daily life • Easy performing tasks • The functionality of my mobility is impaired • Something that never worried me	• Autonomy in daily life • Not needing others • It's getting out on the street without anyone noticing that I have Parkinson's • Wanting to do and look like you don't know how • Its dressing and move in bed
Physiotherapists	Neurologists
• Movement to perform a function • Daily life • Functionality • Functional movement • Different degrees of limitation	• Ease to displacement • Move to a goal • Movement to perform a task • Autonomy • Related with the WHO concept of Disability. The opposite of impairment.

Table 2 – Key aspects mentioned by the four groups about the concept of FM

Early-stage group

Early-stage PD patients associate the concept of FM with the ability to move and with easy performing of daily life tasks. For this group of patients, FM is something that won't worry them in their actual state.

Advance-stage group

Advance-stage PD patients associate FM with autonomy in daily life and with not being noticed by others in a public environment. Dressing and turning in bed were mentioned as activities related to FM.

Physiotherapists group

Physiotherapists described FM as movement for a function or the ability to accomplishing the daily tasks important for the subject, even with limitations.

Neurologist group

Neurologists described FM as the movement needed to perform a task regardless of how you do it. Also, as something that includes purposed displacements and transfers. For them, the concept of FM is close to the World Health Organization (WHO) concept of disability, as opposed to impairment, and should not be limited by the existence of displacement. In their opinion, the key aspect is the intention to accomplish a task or achieve a goal.

Neurologists highlighted the importance of having an operationalized concept of FM. In their opinion this outcome may express better patients' perception of their overall health status and may help to adopt a more patient-centered approach. They also suggested FM as a potential useful outcome for the rehabilitation field.

2) The impact of FM *limitations in patients' life*

Early-stage group

Early-stage PD patients mentioned to have more difficulty in some specific tasks (e.g. down the stairs), but mainly to need more time to complete their usual tasks. In their opinion, except for direct family members and close friends, their FM limitations were not noticed by others. This group was not able to identify the best therapeutic strategy to deal with FM limitations. They hypothesize that exercise may be one of them, based on their experience of its benefits. (Table 3, Appendix 1)

What is the impact of FM limitations on the patient's daily life?	
Early-stage patients	Late-stage patients
• A higher difficulty to perform some tasks but mainly a slower rhythm • Friends and distant family are unaware • Close family refers a slowdown, difficulties in tasks like buttoning • Exercise, cognitive training are efficacious strategies to deal with FM limitations	• Clear perception of FM limitations associated with the disease • The most limiting factor of activities of daily living • The "OFF" periods are the worst moments of the day • Look for strategies to minimize the symptoms of the disease • Feel ashamed for drawing others' attention
Physiotherapists	Neurologists
• First limitations: stand up from a chair, get out of the bed or from the car • Associated with the stage of the disease • Initial devaluation, followed by sadness and frustration • In physiotherapy sessions patients learn how to deal with the limitations. Some patients find their own strategies.	• Vary from patient to patient, according lifestyle and tolerance with himself • Patients develop their strategies to overcome limitations until the moment they stop working • Sometimes the perspective of the impact of limitations and treatment goals between a patient and a neurologist does not coincide. The perspective between patient and caregiver is also different.

Table 3 – Key aspects mentioned by the four groups about the impact of FM limitations on the patient's life

Advance-stage group

Advance-stage PD patients acknowledge to have limitations in FM and consider them the main limiting factor of daily activities, especially in "OFF" periods of medication. They refer that this type of limitations frequently draws others' attention to them, making them feel ashamed. Patients try to avoid these situations through social isolation or finding strategies to mask the signs of the disease. According to their perspective, family and closest friends are usually supportive, while friends and colleagues have more difficulties understanding the fluctuations of the disease. This usually contributes to social isolation and a higher burden to the family members. Medication adjustments, based on patients' priorities, and the use of walking aids were spontaneously referred as strategies to overcome daily life difficulties related to FM.

Physiotherapist

Physiotherapist associated the onset of FM limitations with disease progression. According to their experience, the first FM limitations, mentioned to or noticed by the physiotherapist, are getting up from a chair, getting out of bed or from the car. In physiotherapists' perception, patients start by devaluate these limitations, progressing for a feeling of sadness and frustration.

It was highlighted the importance of physiotherapy sessions to maintain PD patients' functionality in daily routine. It was emphasized the importance of patients' education and movement strategy training to overcome patients' FM limitations. It was referred that some patients have more difficulty learning due to the feeling of frustration or to a higher negative emotional burden. In the physiotherapists' perspective, the collaboration of the psychology team is important in these cases. It was also referred that pharmacological interventions enhance the results of physiotherapy interventions, whereby this group supports that the management of PD FM limitations should be a joint work of the multidisciplinary team.

Neurologists

In neurologists' opinion, the interference of FM limitations depends on the patients' characteristics, such as affected side, expectations and lifestyle (active, retired). Some patients, less demanding with themselves, seems to tolerate better disability.

To neurologist, patients usually self-manage FM limitations until they can no longer do it. They develop their own strategies, such as wearing buttons-free clothes, shoes without laces or getting up early to be able to perform all the necessary tasks. It was referred that these limitations and strategies are not always noticed by the neurologist who follows them in the consultation. Neurologists also underline that patient's and caregiver's perspective differs on this topic.

3) The use of walking aids

Early-stage group

For early-stage patients, the ability to complete a task and performing it successfully were the aspects they valued most in their daily lives, at the expense of the time needed.

The regular use of walking aids is not considered by this group of participants. They believe that a good monitorization by specialized professionals and easy access to information about the disease is enough. Some mentioned to have used Nordic walk sticks to perform exercise and found it useful. All were open and suggested the development of technological devices that help them with disease-related problems, such a device that reminds them to correct their posture. When asked about the key requirements of walking aids, it was mentioned the need for softeners to smooth the gait, the ability to adapt to different surfaces, to be light, and to have handles that allow the use of hands. (Table 4, Appendix 1)

Advanced-stage group

None of the patients used walking aids regularly. They see it as potentially helpful, but they try to postpone its use as much as possible, through medication adjustments. Advance-stage patients

have doubts about their usefulness due to the presence of motor fluctuation (in the "ON" medication state they do not think to need this kind of help), of postural instability and upper limb problems (which in their perspective hampers its use). Patients who have already used walking aids, did it on their initiative, without medical advice, training or adaptation. The occurrence of falls, the feeling of insecurity, and the resistance to use again on medical recommendation after a bad experience, were mentioned.

Due to the lack of experience with walking aids, patients didn't feel able to define their key characteristics.

The use of walking aids	
Early-stage patients	Late-stage patients
• The ability to complete a task successfully is the aspect more valuable. The time is no longer a priority when you know you have PD. • The use of walking aids depends on the needs of each patient. PD don't need this type of solutions. A good management of the disease, prevention and education by a specialist are more appropriated. • Patients were open to the use technological devices or Nordic sticks. • Due to the lack of experience, patients only mentioned suggestion for Nordic sticks. They mentioned the existence of shock absorbers to smooth the gait, tips adapted to different types of surfaces, light and with handles that allow to open the hands.	• Patients try to delay the use of walking aidst through medication adjustments. • The patients used walking aids, by their own initiative, to get down, get up or when the gait was unstable. They did not have any period training. Falls occurred. • Due to the existence of "ON" periods in which they have acceptable functionality, they do not consider the use of permanent walking aids. • Patients express some reluctance to use walking aids due to the associated social stigma. • A bad experience with walking aids, without training or adaptation period, creates an insecurity that conditions future uses.
Physiotherapists	Neurologists

- The presence of imbalances and an increased risk of falling are the first warning signs for the need of walking aids.
- They are usually faced in a negative way, as a sign of disease progression and a greater level dependence.
- The fear of falling helps accepting the recommendation of a walking aid.
- The choice of a walking aids should be personalized.
- According to the patient's clinical characteristics.
- This recommendation sometimes does not coincide with the physiotherapist' opinion, who usually finds it too early.
- The stigma associated with walking aids influences the patient's receptivity and the neurologist's decision to suggest its use.
- Patients face the recommendation as a defeat and with frustration.

Table 4 – Key aspects mentioned by the four groups about use of walking aids

Physiotherapist

To physiotherapists, a threat patients' safety (e.g. increased postural instability or the occurrence of falls) determines the recommendation of walking aids. According to them, this type of help is not always well received. Sometimes is perceived as something negative, as a sign of disease progression and of greater dependence. The fear of falling was mentioned as a factor that facilitates its use. It was also referred that some patients start using walking aids too early, without clinical recommendation. Physiotherapists stressed the need to adapt walking aids to patient characteristics and needs, and the importance of a supervised period of training. General key characteristics were not mentioned.

Neurologists

In the neurologists' perspective, walking aids should be prescribed according to the patient's clinical characteristics. Neurologist referred to approach this topic during consultations, but to leave the decision to the physiatrist or physiotherapist, since they are more prepared to make a formal recommendation. It was also mentioned that their opinion about the need of this type of aids does not always coincide with the physiotherapists' opinion.

In neurologists' perspective, the use of walking aids is often seen by patients as a loss of autonomy and never as a gain in FM, due to the stigma associated with its use. They referred the need to approach the topic carefully and that patients' reaction is usually of defeated, frustration, or become offended. Neurologists emphasize the importance of a training period. They also recognized that the recommendation of a walking aids is sometimes hindered by their own prejudice in relation to this type of aids. This sometimes makes them postpone its recommendation, more than would be desirable.

Neurologists believe that the characteristics of a walking aid should be indicated by physiatrist or physiotherapist.

Discussion

Ten patients and 10 health professionals participated in the focus groups. All patients were assessed in "ON" state medication. Patients in the advanced-stage group, were all recruited from the DBS surgery waiting list, whereby although younger, had a more severe type of PD.

1) The concept of functional mobility

Although none of the groups has provided a definition that fits the proposed definition perfectly, the FM concept seems to be well understood by patients and professionals and to reflect patients' daily life difficulties and disease progression.

Early-stage patients and neurologists seem to be more focused in the component of mobility, where advanced-stage patients and physiotherapists highlight more functioning. In reality, FM is a specific type of mobility, that requires a displacement and the engagement in tasks and activities in the home, work and in the community. (Table 2)

In the neurologists' opinion, the FM concept should not be limited by the need for displacement but defined as the ability to do what one proposes. This idea seems to be present in other groups since references to functional tasks like dressing, shaving or drinking water, were frequent. However, the existence of a displacement is a key component of the concept. FM is the ability of a person to move and is operationalized by the assessment of gait, balance, and transfers during

the performance of a functional task.[19,102] This requires displacement and excludes all types of upper limb mobility. Also, this suggestion of a broader concept of FM falls into the definition of mobility (i.e., as "moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation." [63]), whereby its adoption would be to give a new name to an existing and already established concept. (Table 2 and 5)

Functional Mobility	A person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living, at home, work and in the community.
Mobility	The ability to move by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation.
Functioning	The individual's ability to execute a task or an action of daily life activities. Refers to all body functions, activities and participation.
Disability	A physical, mental, cognitive, or developmental condition that impairs, interferes with, or limits a person's ability to engage in certain tasks or actions or participate in typical daily activities and interactions
Independence	The ability to carry out activities that support one's own lifestyle and to control the care given by others.
Autonomy	Self-rule that is free from both controlling interference by others and from limitations, such as inadequate understanding, that prevent meaningful choice

Table 5 – Definition of FM and related concepts.[63,64,103]

The way the different groups described the concept seems to reflect their personal knowledge and experience of FM limitations. While early-stage patients and neurologists seem to see it as a minor or distant problem, advanced-stage patients and physiotherapists face it as a current and major problem.

Neurologists also suggest the use of FM as an outcome that better reflects the patient's perception and needs regarding their overall health status. This seems to go in line with the idea previously published that although the assessment of specific disease-related outcomes (e.g. tremor, rigidity) is important, to evaluate functional limitations is crucial to get a better idea of PD patient's disability profile.[28]

2) The impact of FM *limitations in patients' life*

Once more the perspective of early-stage patients seems closer to neurologists and advanced-stage patients to physiotherapists. To advanced patients and physiotherapists, with a closer experience of FM limitations, was easier to describe its interference in daily activities, its social impact, and to mention strategies to overcome them.

The awareness of having a disease and the experience of limitations, even minor, in daily life, leads patients to value more the ability to complete successfully a task, rather than the time needed to perform it.[37,60] This is noteworthy since one of the main reasons for being excluded from work and community environments is to be unable to move at an intensity and frequency that life requires.[64] This goes in line with the idea of a previous paper on FM in PD, in which the author refers the superiority of perceived control above velocity.[59,64] As mentioned in the paper, the understanding of these determinants will help health professionals to have a more patient-centered intervention. In a time where personalized interventions are gaining relevancy, being aware of these aspects is crucial and may help to blur the differences between patients and neurologists and/or caregivers' perspectives.

It's also relevant the social impact of the disease. Patients feel ashamed in public environments because of tremor and functional limitations, and little understood by friends because of the fluctuating aspect of the disease. Neurologist mentioned that the impact and degree of discomfort with FM limitations vary with the level of tolerance of patients. According to a 2017 cross-sectional study[104] the stigma of the disease and patients' emotional well-being affects not only the patients but also caregivers. In line with this, we hypothesize that a joint work from the psychology team with physiotherapy for teaching compensatory strategies may be useful to help patients dealing with FM limitations and to lessen the disease burden for patients and caregivers.

3) The use of walking aids

The stigma associated with the use of walking aids hinders its use by patients, in early- and advance-stage of the disease and interferes with neurologists' recommendations. Although walking aids could allow for a more active lifestyle, the fact of being associated with disability, prevent them of being faced as something that may enhance perceived control of their situation.[64]

It's interesting the openness and acceptance of walking aids based on technological devices or in instruments that do not have the classic appearance of walking aids (e.g. Nordic sticks). It's is also curious that, even when patients suggest the development of technological walking aids, they don't seem to want them to be faster or to have a more active lifestyle, but to correct aspects that draws others attention (posture, dyskinesias, freezing).

Due to the size of our sample and the fact that all patients have the same nationality, we recognize that these results were influenced by cultural factors. We recommend a multinational study to clarify this topic.

Conclusion

FM limitations were acknowledged by early stage PD patients, representing an important limiting factor of daily activities and social participation for advance stage patients. The proposed concept of FM to be applied to PD seems to be well understood by patients and health professionals and to reflect the impact of disease progression in patients' life. Although walking aids have the potential to increase patients' FM, they are seen as a sign of dependency, therefore they are not well accepted. Future bioengineering studies should focus on a technological solution and avoid the look of classical walking aids. We recommend the adoption of FM as an outcome, in clinical routine and research, as a strategy to get a better perception of patients' overall health status and to adopt a more patient-centered approach.

Appendix 1

Focus groups script

1) Focus Groups with PD patients

The researchers will meet the PD focus group subjects and pose the questions present on the first column of **Error! Reference source not found.** while making sure they address the topics of column 2. This shall take up to 60 minutes (55 minutes to focus groups questions and 5 to close). At the beginning of each interview, participants will be reminded of the purpose of the study and guaranteed confidentiality. Further, it will be told to show respect for others' views and take turns in speaking. The participants will be encouraged to interact with each other, with the author intervening solely to keep the discussion on topic, and to encourage the more reserved members of the group to speak. In the beginning of the interview, after the opening question, the concept of functional mobility will be explained.

Functional mobility is the physiological ability of people to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living (ADL), at home, work and in the community.

Category	Questions	Make sure the participants address
Opening questions	How long have you been diagnosed with Parkinson's disease? Do you maintain an active lifestyle? What does the concept of functional mobility mean to you?	To introduce the topic of discussion and get people to start thinking and talking about their connection with the topic.
Impact of functional mobility limitations in patients' life	Since disease onset did you feel more difficulties moving around to perform ADL, in home, work or during other social interactions?	• Onset of difficulties • Which ADLs
	You think that this is a problem properly understood by health professionals, family and coworkers?	• Difficulties reporting these limitations and its impact • Impact in home, work or leisure activities • Social embarrassment or potential misunderstanding of difficulties
	In your opinion which were the most efficacious strategies to help you copying with the functional mobility impairments?	The role of pharmacological and non-pharmacological interventions

The use of walking aids	When do you have an activity to perform, which aspect do you values most? (ability to perform correctly, the time needed, autonomy/perceived control, etc.)	
	Would you like to use walking aids to help you in your daily life tasks?	• Previous experiences with walking aids • Shortcomings of safety devices • Perceived control • Autonomy
	In what situations would you consider using walking aids?	• Personal factors (e.g. to be more independent) • Activities that justify its use (e.g. possibility to work, to go for shopping, feeling of safety)
	Which are the most important characteristics to adhere to walking aids?	Examples: dimensions, weight, adjustment, safety, durability, easy of use, comfort, effectiveness.
Ending questions	Thank you for your time today. Is there anything that you would like to say that I have not covered?	---

2) Focus groups with health professionals

The researchers will meet the health professionals group and pose the questions present on the first column of table while making sure they address the topics of column two. This shall take up to 60 minutes (55 minutes to focus groups questions and 5 to close).

At the beginning of each interview, participants will be reminded of the purpose of the study and guaranteed confidentiality. Further, it will be told to show respect for others' views and take turns in speaking. The participants will be encouraged to interact with each other, with the author intervening solely to keep the discussion on topic, and to encourage the more reserved members of the group to speak. In the beginning of the interview, after the opening question, the concept of functional mobility will be explained.

Functional mobility is the physiological ability of people to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living (ADL), at home, work and in the community.

Category	Question	Make sure the participants address
Opening questions	How long do you work with Parkinson disease patients? What does the concept of functional mobility mean to you?	To introduce the topic of discussion and get people to start thinking and talking about their connection with the topic.
Impact of functional mobility limitations in patients' life	When do you think that PD patients' functional mobility limitations start? Which are the main problem related with functional mobility in daily life?	• Onset of difficulties • Which ADLs
	How do you think that PD patients cope with functional mobility limitations? Patients express easily this type of difficulties?	• Difficulties reporting these limitations and its impact • Impact in home, work or leisure activities • Social embarrassment or potential misunderstanding of difficulties
	In your opinion which were the most efficacious strategies to help PD patients copying with the functional mobility impairments?	The role of pharmacological and non-pharmacological interventions
The use of walking aids	Which are the most important aspects when a PD patient has to perform an ADL? (ability to perform correctly, the time needed, autonomy/perceived control, safety, etc.)	
	When do you consider recommending the use of walking aids to a patient?	• Functional state of patients • Rehabilitation potential • Personal or professional demands
	How do patients respond to the possibility of using a walking aid?	• Perceived control • Autonomy • Activities that justify its use (e.g. possibility to work, to go for shopping, feeling of safety)
	Which are the most important characteristics to adhere to walking aids?	Examples: dimensions, weight, adjustment, safety, durability, easy of use, comfort, effectiveness.
Ending questions	Thank you for your time today. Is there anything that you would like to say that I have not covered?	---

Appendix 2

Illustrative quotes of the topics approached during the focus groups

The concept of FM	
Early-stage patients	“Is what we do on a daily basis” “Is whether or not we continue to have the same facility in carrying out activities we did before, at least we have the perception of having this type disease” “Is the ability to move”
Advance-stage patients	“Autonomy for day-to-day” “Don't need others” "Is to be able to go out on the street without anyone noticing that I have Parkinson's" “Is wanting to do things and it seems like I don't know how to do it” “Is to get dressed and move in bed”
Physiotherapists	“It's a person's functionality… I can move my arm, but what is it for if I can't grab things, I can't eat” "It is a movement that we have, which can be more or less limited, but which can be useful in our daily lives, and for the things that are important to us" “Being able to move in a functional way” "I move to a role" “Work on mobility in order to guarantee some coordination afterwards for the function performed, because this is often what they are looking for”
Neurologist	“The ease of movement of patients” "The ease, or the movement that is needed to perform a task or function"

	"Transfers" "In a broader sense, it is doing what they want regardless of how you do it" "Functional mobility would be close to the WHO concept of disability as opposed to impairment, which is physical disability only"
The impact of FM limitations in patients' life	
Early-stage patients	"Functional mobility is something that I never worried about until I had this thing (the disease)" "My functional mobility is impaired" "The rhythm in the bathroom (…) is slower" "Our rhythm is different from what we had 10 years ago" "Friends don't see the difficulty of buttoning; (…) My wife sees it." "The problem of the tremor, and not living together (...) people ask (...) I tell people that it is anxiety, and everything is under control, people remain in their ignorance." "I think physical exercise is essential… don't stop!" "If you do nothing with your brain you also lose it"
Advance-stage patients	"I have difficulty getting on and off a public transport… more to get off than to go up, if it is on a public transport standing up, everything is looking at me" "When I call attention, I feel very ashamed (…) sometimes to prevent people from looking at me, I do something (…) I start running (…) my left toes start to close and I can't walk, so the only way to unlock it is to try to run or walk faster so your fingers don't close " "Some friends are aware of the disease, others are not… they start asking me questions about the disease that it is difficult for me to answer (…) it seems that they do not look very well at what I was and what I am." "I removed the shower doors so that he had better mobility in and out of the bathtub"

Physiotherapists	“There is the phase of devaluing, in the beginning, and then the phase of frustration” “They end up adjusting the situation… for example, I have a patient who, as he couldn’t turn around in bed, already lies in the position where he will stay all night. If he has several chairs at home, he sits on the tallest.”
Neurologist	“It depends on the patient, it depends on the patient's level of demand, if he is a designer or an architect right at the beginning of the illness, this interferes with his profession… if he is a person who is less demanding with himself, he tolerates much more the incapacity that goes by having" "It depends on things as simple as whether he is right-handed or left-handed (...) for example the hand that is slow on the right and he is left-handed often comes to the doctor much later than vice versa" “The patient has a tremor in his hand and does not say that it bothers him” “The patient has many dyskinesias and that doesn't bother him” “It is the patient himself who is managing to a point where he can no longer manage” “Sometimes at the consultation we think he can't walk and he just wants to button his shirt, and for us it's a bit disconcerting, we will adjust the medication and get him going, this is an extreme, get him to do something else and he just wants to do this (…) you have to be methodical in the consultation to get this. ”
The use of walking aids	
Early-stage patients	“To perform a task” “To complete successfully” “Time is no longer a priority. When we realize that we have the disease, time is no longer a priority.” “Having a sensor that would tell us “look, you're in the wrong position” or “straighten your back”, that is what my daughter says.” "Parkinson's does not ask for these solutions" “I don't need it for now”

	"It depends a lot on the degree and the needs of each one (...) all this must be faced in a progressive way and according to the need of each one ... but at this moment I say no, give me idea that I don't need anything"
Advance-stage patients	"I was also told to walk with a cane, I don't use it because I'm ashamed." "I consider using it, but I don't know, so far I haven't decided yet" "When I'm OFF (...) I think it will help not to fall, not to hit the walls of buildings" "There were times when I staggered a lot and when I got up from a chair, sofa or something, I had to lean against the wardrobe, touch the furniture, and so it went right to the bathroom, for my initiative I took a crutch to see if it worked." "We have to learn to walk with a cane, to know if the feet go first, if you go right, left ..." "There are times when I need it but there are other times when I don't" "I don't think this will help me much in my balance, because my lack of balance is such that there is a cane that works (…) I also have problems with my hand and arms" "Walking aids don't give me the safety I need"
Physiotherapists	"Imbalances and the risks of falling are the first warning signs to think of a walking aid." "Only those who are afraid of falling will accept it well" "There are people who use the walking aid early!"
Neurologist	"I think that physiotherapists are more competent than me to say if that patient benefits from having a walker or a wheelchair" "Many times, the patients face the use of a walker or a wheelchair not as a gain in functional mobility, that is, but as a loss of autonomy associated with the stigma that a wheelchair has."

	"We are arriving a little late (…) Leads that many patients to have very serious complications. The risk for an 80-year-old patient of having a fractured femoral neck is never to be able to walk or sit again. It is going from being able to walk to being bedridden." "Patients are offended" "It's a stigma, they think whoever gets to the chair doesn't get out of the chair" "It is necessary to convince that the chair is a help and not a definitive thing." "I try to convince, (...) it takes a lot time of the consultation." "We have to assume that it is a stigma between us and people, so that we can change our attitude and build change"

CHAPTER 5

Gait kinematic parameters in Parkinson's disease: a systematic review

Gait kinematic parameters in Parkinson's disease: a systematic review

Raquel Bouça-Machado MSc,[1,2] Constança Jalles MD,[1*] Daniela Guerreiro PT,[2*] Filipa Pona-Ferreira PT,[2*] Diogo Branco PE,[4] Tiago Guerreiro PhD[4], Ricardo Matias PhD,[5,6] Joaquim J. Ferreira MD, PhD[1,2,7]

1 - Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Avenida Professor Egas Moniz, 1649-028, Lisboa, Portugal

2 - CNS - Campus Neurológico Sénior, Torres Vedras, Portugal

4 – LASIGE, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal

5 – Champalimaud Research and Clinical Centre, Champalimaud Centre for the Unknown, Lisbon, Portugal

6 - Human Movement Analysis Lab, Escola Superior Saúde – Instituto Politécnico de Setúbal, Setúbal, Portugal

7 - Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

*These authors contributed equally to the present systematic review

Contents of this chapter were extracted from the peer-reviewed publication with the following reference: **Bouça-Machado R**, Jalles C, Guerreiro D, et al. Gait Kinematic Parameters in Parkinson's Disease: A Systematic Review [published online ahead of print, 2020 May 12]. J Parkinsons Dis. 2020;10.3233/JPD-201969.

Raquel Bouça-Machado conceptualized the review, conducted data collection and analysis, and drafted the manuscript.

Abstract

Background: Gait impairments are common and highly disabling for Parkinson's disease (PD) patients. With the development of technology-based tools, it is now possible to measure the spatiotemporal parameters of gait with a reduced margin of error, thereby enabling a more accurate characterization of impairment.

Objective: To summarize and critically appraise the characteristics of technology-based gait analysis in PD and to provide mean and standard deviation values for spatiotemporal gait parameters.

Methods: A systematic review was conducted using the databases CENTRAL, MEDLINE, Embase, and PEDro from their inception to September 2019 to identify all observational and experimental studies conducted in PD or atypical parkinsonism that included a technology-based gait assessment. Two reviewers independently screened citations and extracted data.

Results: We included 95 studies, 82.1% (n=78) reporting a laboratory gait assessment and 61.1% (n=58 studies) using a wearable sensor. The most frequently reported parameters were gait velocity, stride and step length, and cadence. A statistically significant difference was found when comparing the mean values of each of these parameters in PD patients versus healthy controls. No statistically significant differences were found in the mean value of the parameters when comparing wearable versus non-wearable sensors, different types of wearable sensors, and different sensor locations.

Conclusion: Our results provide useful information for performing objective technology-based gait assessment in PD, as well as mean values to better interpret the results. Further studies should explore the clinical meaningfulness of each parameter and how they behave in a free-living context and throughout disease progression.

Key words: Parkinson's disease, gait, objective assessment, technology, wearable sensor.

Background

Parkinson's disease (PD) gait impairments increase with disease progression and are a marker of global health, cognition status, falls risk, and institutionalization. [105,106]

The use of accurate and reliable quantitative information about the mechanics of PD gait is perhaps one of the most promising outcomes that enables early diagnosis, assessment of disease progression and evaluation of therapeutic interventions. [14,107] In the last decades, with the appearance of technology-based objective measures (TOMs), the evaluation of different spatial and temporal parameters of gait paved the way for a more ecological (i.e. closer to patients' real-life environment performance) and efficient assessment, with a reduced margin of error. Two types of devices have been commonly used: non-wearable sensors (NWS) and wearable sensors (WS). [107] The NWS are considered the gold standard. They require a controlled and calibrated environment, where individuals walk with skin-mounted markers whose instantaneous positions are obtained using stereophotogrammetry (motion capture) most often based on optoelectronic sensors. WS are small, lightweight sensors (e.g. inertial measurement units) that are attached to one or several body segments, enabling human motion reconstruction in both the context of a laboratory or during activities of daily living. [107]

The International Society of Biomechanics has attempted to standardize reports of joint motion in the field of biomechanics for human movement [108]. However, in the PD field, there is a lack of consensus on the best type of sensors and which gait spatiotemporal parameters are clinically relevant. This limits the use of objective measurements of gait in clinical practice and research. [109–111] Therefore, we aimed to summarize and critically appraise the characteristics of technology-based gait analysis in PD and to provide mean and standard deviation values for spatiotemporal gait parameters.

Methods

Literature search

We searched CENTRAL, MEDLINE, and PEDro from their inception to September 2019 using "Parkinson*", "Gait", "Walking", "Accelerometer", "Algorithm" and "Body-fix sensor" as key words. Reference lists from the identified articles were cross-checked to identify any further potentially eligible studies.

Study selection

We included all observational and experimental studies, or study protocols, conducted in PD patients or atypical parkinsonisms, that included a technology-based gait analysis focused on continuous gait disturbances and that specified which parameters had been studied. There were no restrictions regarding the type of intervention in the active and control arms.

We excluded reviews and studies written in languages other than English, French, Spanish, and Portuguese. All retrieved abstracts were independently screened by two authors. The full texts of potentially relevant articles were retrieved for further assessment. Disagreements were resolved by consensus.

Data extraction

Five pre-defined domains of items were extracted: general information (year and journal of publication, aim of the study, study design, population, intervention, time point assessments, technology development phase), gait assessment supplies (equipment, type of sensor, type of assessment), gait assessment procedures (protocol, medication status, and other outcome tools) and gait parameters values.

According to Maetzler's classification [109], we classified studies according to their technology development phase, which covered three phases: i) preclinical development and testing (those studies focused on how to measure, i.e., testing algorithms or validating a new gait assessment system), ii) clinical development and testing phase (studies focused on the parameters that can be measured and on their clinical relevance) and iii) clinical validation (experimental and observational studies that use gait analysis as an outcome).

We also used an adaptation of the conceptual model of gait presented by Del Din, 2016 [112] to present and analyze the gait parameters reported in the included studies. Parameters that were only reported in one study, and not fitting the model, were included in the "other parameters" section. Data were extracted by two independent authors. Discrepancies were resolved through discussion.

Data analysis

We summarized the publication characteristics using frequencies and percentages. Review Manager software (v 5.3; Cochrane Collaboration) was used for calculating pooled mean difference (MD) and the 95% confidence interval (CI). Heterogeneity was assessed using the Q

test and I^2 statistic. An I^2 value of < 25% was chosen to represent low heterogeneity and an I^2 value of > 75% to indicate high heterogeneity. A random-effects model was used to pool all outcomes. A p-value of < 0.05 was considered to be statistically significant.

Results

The electronic and hand searches identified 3727 citations. Full-text assessment for eligibility resulted in 95 studies being included (Fig 1). Overall, the main reasons for exclusion were inappropriate study population (n = 2607) and inadequately defined outcome (n = 378) (Appendix 1).

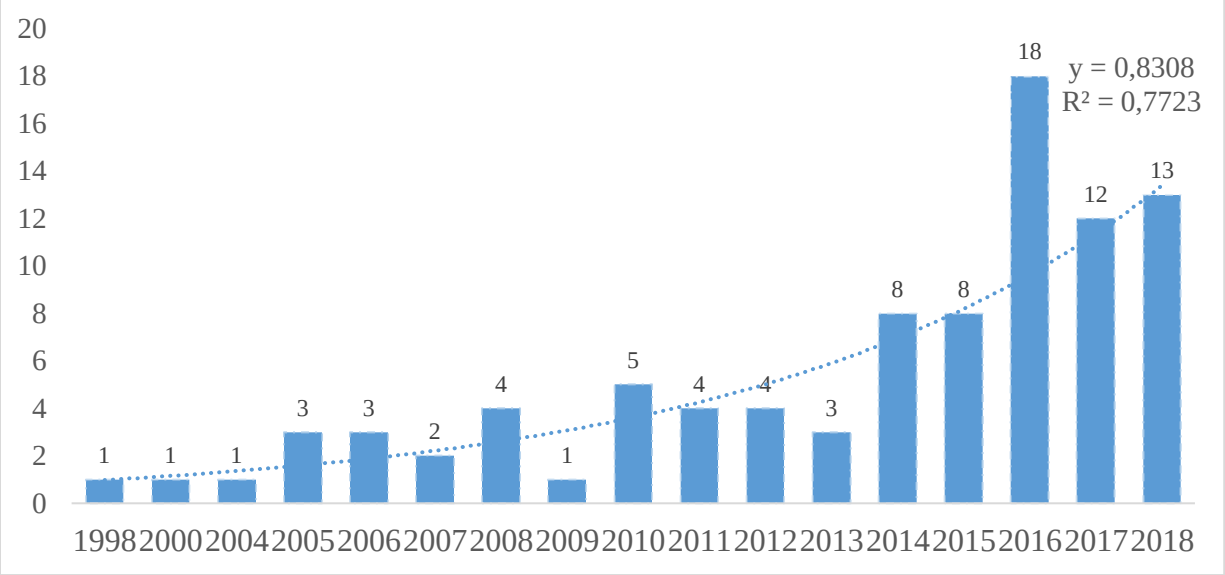


Figure 1 – Number of studies including a technology-based assessment per year in PD

The most common study designs used were case-control studies (34.7%, n=33), cross-sectional studies (28.4%, n=27), and randomized controlled trials (27.4%, n=26). Of the 95 included studies, 61.1% (n=58 studies) used WS, 32.6% (n=31 studies) NWS, and 6.3% (n=6 studies) both types of devices. Seventy-eight studies (82.1%) reported a laboratory gait assessment, 6.3% (n=6) a free-living assessment, and 11.6% (n=11) made the assessment in both contexts. (Table 1)

Since only two studies [112,113] presented values for spatiotemporal gait parameters in free-living assessments, and patients are known to perform differently in the laboratory and free-living contexts, these values were excluded from data analysis. [114]

Gait parameters measured with non-wearable sensors

Table 3 lists the gait parameters using NWS reported in the included studies; the most frequently used unit of measurement and the mean and standard deviations of the reported values are also listed.

The most frequently reported parameters (≥ 20% of the studies) were gait velocity (81.1%, n=30, PD mean value = 0.99 ± 0.24 m/sec), stride length (56.8%, n=21, PD mean value = 1.06 ± 0.18 m), cadence (48.7%, n=18, PD mean value = 102.71 ± 10.50 steps/min), step length (46.0%, n=17, PD mean value = 0.58 ± 0.13 m), double support phase (27.0%, n=10, PD mean value = 25.89 ± 7.23 %) and step width (24.3%, n=9, PD mean value = 0.13 ± 0.02 m).

Gait parameters measured with wearable sensors

Table 2 lists the gait parameters assessed with a WS reported in the included studies; the most frequently used unit of measurement and the mean and standard deviations of the reported values are also listed.

The more frequently reported parameters (≥ 20% of the studies) were gait velocity (60.9%, n=39, PD mean value = 1.01 ± 0.26 m/sec), stride length (37.5%, n=24, PD mean value = 1.14 ± 0.25 m), stride time (28.1%, n=18, PD mean value = 1.18 ± 0.18 sec), cadence (28.1%, n=18, PD mean value = 106.42 ± 19.60 steps/min), step length (23.4%, n=15, PD mean value = 0.60 ± 0.06 m), step time (21.9%, n=14, PD mean value = 0.55 ± 0.03 sec), stride time variability (21.9%, n=14, PD mean value = 4.33 ± 2.81% of the coefficient of variation (%CV)) and step time variability (20.3%, n=13, PD mean value = 0.02 ± 0.00 sec).

Three studies evaluated gait in a controlled environment and nine in a free-living context. Due to both the low number of studies presenting a value for this parameter and the heterogeneity of the measurement units, we did not summarize the data nor present a reference value.

Demographic and clinical characteristics | Non-wearable devices (n=37)		
	PD	**HC**
Age (Mean, SD (n))	67.64 ± 4.76 (33)	66.72 ± 5.96 (9)
Average % Male (Mean, SD (n))	65.25 ± 15.83 (26)	48.14 ± 13.02 (9)
Height (Mean, SD (n))	1.68 ± 0.07 (13)	1.68 ± 0.05 (7)
BMI (Mean, SD (n))	26.34 ± 1,92 (17)	27.23 ± 1,68 (7)
Disease duration (Mean, SD (n))	7.71 ± 2.51 (28)	NA
UPDRS III (Mean, SD (n))	29.31 ± 8.24 (26)	NA
Hoenh & Yahr (Mean, SD (n))	2.46 ± 0.40 (27)	NA

Gait Parameters Mean Values						
Domain	**Variable**	**Studies (n)**	**Units**	**Most frequent unit (n,%)**	**PD mean value (mean, SD (n))**	**HC mean value (mean, SD (n))**
Ambulatory activity	Step count	3	number or mean number of steps	NA	NA	NA
	Gait Velocity	30	km/h, m/s, cm/s	m/s (22, 73.33%)	1.00 ± 0.25 (19)	1.15 ± 0.32 (5)
	Cadence	18	strides/min, steps/min	steps/min (15, 83.33%)	104.04 ± 9.57 (15)	NA
Pace	Stride length	21	cm, m	m (11, 52.38%)	0,99 ± 0.22 (19)	1,20 ± 0.28 (4)
	Stride velocity	1	m/s	NA	NA	NA
	Step length	17	cm, m	m (13, 76.47%)	0.54 ± 0.13 (17)	0.64 ± 0.06 (6)
	Step velocity	2	m/s	m/s (2, 100.00%)	0.98 ± 0.21 (2)	1.10 ± 0.26 (2)
	Stance phase	8	% of gait cycle	% of gait cycle (8, 100.00%)	65.47 ± 3.76 (8)	NA
	Swing phase	5	% of gait cycle	% of gait cycle (4, 80.00%)	34.98 ± 1.92 (4)	NA
	Swing velocity	2	m/s	m/s (2, 100%)	1.73 ± 0.08 (2)	NA
	Double support phase	10	% of gait cycle	% of gait cycle (8, 80.00%)	22.71 ± 8.94 (8)	NA
Rhythm	Stride time	6	msec, seconds, strides/second	seconds (3, 50.00%)	1.22 ± 0.12 (3)	NA
	Step time	6	msec, seconds	seconds (3, 50.00%)	0.60 ± 0.05 (3)	NA
	Stance time	4	seconds	seconds (3, 75%)	0.74 ± 0.11 (3)	NA
	Swing time	4	msec, seconds	seconds (3, 75.00%)	0.43 ± 0.07 (3)	NA
	Double support time	4	msec, seconds	seconds (2, 50.00%)	0.34 ± 0.19 (2)	NA
Variability	Stride time variability	2	SD, % CV	NA	NA	NA

	Stride length variability	2	SD, % CV	NA	NA	NA
	Step length variability	2	m	m (2, 100%)	0.020 ± 0.000 (2)	0.019 ± 0.001 (2)
	Step time variability	3	msec, %CV	NA	NA	NA
	Step velocity variability	1	m/s	NA	NA	NA
	Stance time variability	1	Unk	NA	NA	NA
	Swing time variability	0	NA	NA	NA	NA
	Double support variability	1	%	NA	NA	NA
Asymmetry	Step time asymmetry	1	Unk	NA	NA	NA
	Stance time asymmetry	1	Unk	NA	NA	NA
	Swing time asymmetry	1	Unk	NA	NA	NA
Postural control	Step length asymmetry	2	cm, m	NA	0.030 ± 0.014 (2)	NA
	Step width	9	m	m (8, 88.89%)	0.129 ± 0.027 (9)	0.100 ± 0.014 (2)
Other parameters						
Range of motion of shoulder, trunk, hip, pelvis, knee, ankle						
Support base (cm), Latency of postural response to backward translation of center of mass						
Maximal voluntary contraction, rate and peak rate of force development						
Peak heel clearance (mm), Landing (heel) gradient, Take-off toe (gradient), Max and Min toe clearance (mm)						
Magnitude, Smoothness, Attenuation, Regularity, Symmetry, Harmonic ratio						
Fractal index						
Phase Coordination Index (PCI, %), Asymmetry Index						

Table 1 – Demographic data, clinical data and mean values of gait parameters assessed with non-wearable devices. Unk – Unkown, NA – Not applicable, SD – Standard Deviation; CV - Coefficient of Variation.

PD patients versus healthy controls

We were able to perform a forest plot analysis comparing the mean values of PD patients versus healthy controls (HC) for the following gait parameters: gait velocity, cadence, stride length, stride time, stride time variability, step length, step time, swing time, and double support time. All, except step time using WS, presented a statistically significant difference between groups. For gait velocity and stride length, a statistically significant difference between groups was found in WS assessment, but not in the assessment using NWS. (Appendix 2)

Wearable versus non-wearable sensors assessment

Comparison between the two types of devices was possible for gait velocity, stride, and step length. While gait velocity presented a statistically significant difference ($p=0.04$, $I^2= 76.7\%$), there was no difference between WS and NWS in stride ($p=0.35$, $I^2= 0\%$) or step length ($p=0.14$, $I^2= 55\%$). (Appendix 2)

Type of wearable sensor

The use of an accelerometer was compared with the use of other types of sensors for gait velocity. The subgroup analysis was not statistically significant ($p=0.18$ and $I^2= 44.7\%$). Both groups showed a statistically significant difference between PD and HC ($p \leq 0.05$). The available data did not allow other comparisons for this topic. (Appendix 2)

Sensor location

The impact of sensor location (lower back versus feet versus other locations) was studied for gait velocity, stride time, and stride time variability. No differences between groups were registered. Heterogeneity (I^2) ranged between 0 – 52.9%. All the parameters, except for stride time variability, using the sensor in the lower back, showed a statistically significant difference between PD and HC ($p \leq 0.05$). (Appendix 2)

Demographic and clinical characteristics | Wearable devices (n=64)		
	PD	**HC**
Age (Mean, SD (n))	66.98 ± 6.89 (56)	63.40 ± 13.04 (27)
Average % Male (Mean, SD (n))	60.69 ± 15.60 (53)	50.42 ± 18.02 (25)
Height (Mean, SD (n))	1.69 ± 0,04 (27)	1.69 ± 0,06 (14)
BMI (Mean, SD (n))	25,76 ± 1,42 (35)	25,49 ± 1,77 (17)
Disease duration (Mean, SD (n))	6.78 ± 5.38 (33)	NA
UPDRS III (Mean, SD (n))	29.46 ± 12.88 (35)	NA
Hoenh & Yard (Mean, SD (n))	2,28 ± 0,44 (39)	NA

Gait Parameters						
Domain	**Variable**	**Studies (n)**	**Units**	**Most frequent unit (n,%)**	**PD mean value (mean, SD (n))**	**HC mean value (mean, SD (n))**
Ambulatory activity	Step count	12	number of steps, steps/day	number of steps (7, 53.85%)	NA	NA
	Gait Velocity	39	cm/sec, m/sec	m/sec (34, 87.18%)	1.01 ± 0.26 (32); 1.04 ± 0.19 (DT, 8)	1.19 ± 0.31 (17); 1.22 ± 0.1 (DT,3)
	Cadence	18	Hz, steps/min, steps/sec	steps/min (12, 66.67%)	106.68 ± 20.57 (11)	113.34 ± 7.55 (6)
Pace	Stride length	24	m, cm, % of the stature	meters (17, 70.83%)	1.14 ± 0.28 (18)	1.37 ± 0,08 (8)
	Stride velocity	2	seconds	NA	NA	NA
	Step length	15	cm, m	m (12, 80.00%)	0.55 ± 0.13 (13)	0.61 ± 0.21 (8)
	Step velocity	8	m/sec	m/sec (6, 75,00%)	1.18 ± 0.06 (6)	1.31 ± 0.07 (3)
	Stance phase	2	%	% (2, 100,00%)	60.25 ± 1.76 (2)	57.45 ± 2.75 (2)
	Swing phase	7	% gait cycle	% gait cycle (7, 100%)	36.95 ± 5.11 (7)	39.21 ± 3.62 (4)
	Double support phase	8	% gait cycle	% gait cycle (8, 100%)	29.03 ± 5.00 (8)	23.40 ± 5.83 (6)
Rhythm	Stride time	18	%, msec, seconds	seconds (14, 77.78%)	1.18 ± 0.18 (12)	1.09 ± 0.07 (9)
	Step time	14	msec, seconds	seconds (7, 50.00%)	0.55 ± 0.03 (7)	0.54 ± 0.02 (4)
	Stance time	9	seconds	seconds (5, 55.56%)	0.74 ± 0.07 (5)	0.71 ± 0.03 (3)
	Swing time	12	msec, seconds	seconds (6, 50.00%)	0.39 ± 0.03 (6)	0.39 ± 0.02 (4)
	Double support time	1	msec	NA	NA	NA
Variability	Stride time variability	14	%CV	% CV (12, 85.71%)	3.84 ± 2.94 (12)	2.18 ± 0.59 (9)
	Step length variability	6	m	m (4, 66,67%)	0.032 ± 0.012 (4)	NA
	Step time variability	13	%CV, msec, seconds	seconds (5, 38.46%)	0.030 ± 0.005 (5)	0.022 ± 0.004 (2)

	Step velocity variability	7	m/sec	m/sec (5, 71.43%)	0.057 ± 0.021 (5)	0.055 ± 0.015 (3)
	Stance time variability	8	%CV, seconds	seconds (4, 50.00%)	0.036 ± 0.015 (4)	0.024 ± 0.003 (2)
	Swing time variability	13	%CV, seconds	% CV (7, 53.85%)	4.714 ± 3.388 (7)	2.481 ± 0.624 (5)
	Double support variability	3	%, CV	% CV (3, 100.00%)	9.803 ± 4.617 (3)	6.552 ± 2.224 (3)
Asymetry	Stride time asymetry	1	% of stature	NA	NA	NA
	Step time asymetry	10	msec, sec	seconds (4, 40,00%)	0.021 ± 0.010 (4)	0.011 ± 0.010 (2)
	Stance time asymetry	7	seconds	seconds (4, 57.1%)	0.021 ± 0.010 (4)	0.011 ± 0.005 (2)
	Swing time asymetry	9	msec, seconds	seconds (4, 44.44%)	0.020 ± 0.009 (4)	0.012 ± 0.002 (2)
Postural control	Step length asymetry	8	m	m (6, 75,00%)	0.024 ± 0.011 (6)	0.010 ± 0.004 (3)
	Step width	2	m	m (2, 100.00%)	0.080 ± 0.014 (2)	NA
Other parameters						
Ambulatory activity (walking bouts, total time, activity counts/day)						
Arm swing amplitude, variability, asymmetry, jerk						
Angular velocity of shanks, thighs, trunk and head						
Range of head, trunk, shank, thigh and knee rotation						
Entropy (measure of variability)						
Energy, Power						
Magnitude, Smoothness, Attenuation, Regularity, Symmetry, Harmonic ratio, Jerk						
SPARC (measure of smoothness)						

Table 2 – Demographic data, clinical data and mean values of gait parameters assessed with wearable devices. Unk – Unkown, NA – Not applicable, SD – Standard Deviation; CV - Coefficient of Variation.

Sample characteristics

Studies using non-wearable sensors

Eleven studies used a healthy control group. The mean age of PD patients was 67.1 ± 4.8 years (n= 29 studies) and of 66.3 ± 5.7 years (n= 7 studies) in HC. The mean percentage of male patients was 63.5 ± 16.0 % for PD (n= 22 studies) and of 49.0 ± 11.2 for HC (n= 7 studies). The mean disease duration of PD patients was 7.9 ± 2.3 years (n= 25 studies). The mean Hoehn and Yahr (HY) score was 2.5 ± 0.4 (77.1%, n= 27 studies), and the mean motor score for the Unified Parkinson's Disease Rating Scale (UPDRS III) was 28.9 ± 7.9 points (71.4%, n= 25 studies) (Table 1).

Studies using wearable sensors

Twenty-nine studies used a healthy control group. The mean age of PD patients was 66.8 ± 6.8 years (82.3%, n= 51 studies) and of 65.1 ± 11.3 in HC (35.5%, n= 22 studies). The mean percentage of male patients was 60.4 ± 15.9 % for PD (77.4%, n= 48 studies) and of 47.4 ± 16.2 for HC (30.6%, n= 19 studies). The mean disease duration of PD patients was 6.7 ± 5.4 years (51.6%, n= 32 studies). The mean HY score was 2.3 ± 0.4 (61.3%, n= 38 studies), and the mean motor score for the UPDRS III was 30.0 ± 13.9 points (53.2%, n= 33 studies) (Table 2).

General characteristics of technology-based gait analysis in PD

From the 95 included studies, according to the technology development phase classification: 24.2% of the studies (n=23) were in the preclinical development and testing phase, 31.6% (n=30) were in the clinical development and testing phase and 44.2% (n=42) belong to the clinical validation phase.

Preclinical development and testing phase

In 56.5% (n=13) of the 23 studies, gait assessment was performed in the laboratory, in 17.4% (n=4) it was performed in a free-living context, and in 26.1% (n=6) it was performed in both contexts.
In 87.0% (n=20) WS was used, while 13.0% (n=3) used both type of devices. The most common types of sensors were accelerometers (56.5%, n=13), accelerometers and gyroscopes (17.4%, n=4), only gyroscopes (8.7%, n=2) and smartphones (using an accelerometer and gyroscope, 8.7%, n=2).

The most common position for the sensor was on the lower back, between the second and fifth lumbar vertebras (43.5%, n=10 of the studies). (Table 3)

Clinical development and testing phase

In 83.3% (n=25) of the 30 studies, gait assessment was performed in the laboratory, while in 6.7% (n=2) it was performed in a free-living context, and in 10.0% (n=3) it was performed in both contexts.

In 76.7% of the studies (n=23) a WS was used, 16.7% (n=5) used NWS and 6.7% (n=2) used both type of devices. Accelerometer (68.0%, n=17) and force-sensitive insoles (16.0%, n=4) were the most frequently used type of sensor. The most common position for the sensor was in the lower back, between the second and fifth lumbar vertebras (72.0%, n=18) (Table 3).

Clinical validation phase

The majority of the assessments were performed in the laboratory (95.2%, n=40). NWS was used in 61.9% (n=26) of the studies, a WS in 35.7% (n=15) and both devices in one study. Accelerometers (60.0%, n=9) were the most frequently used type of sensor. The most common position for the sensor was on the lower back and the feet/ankles (33.3%, n=5). (Table 3)

	Preclinical development and testing	Clinical development and testing	Clinical validation	Total
N	23	30	42	95
Type of assessment				
Lab	13	25	40	78
FL	4	2	0	6
Both	6	3	2	11
Type of device				
Wearable	20	23	15	58
Non wearable	0	5	26	31
Both	3	2	1	6
Type of sensor				
Accelerometer	13	17	9	39
Accelerometer and gyroscope	4	2	3	9
Force-sensitive insoles	0	4	3	7
Accelerometer, gyroscope and magnetometer	1	2	0	3
Gyroscopes	2	0	0	2
Smartphone - Accelerometer and gyroscope	2	0	0	2
Pressure sensor	1	0	0	1
Magnetometers	0	0	1	1
Location of the sensor				
Lower back (L2-L5)	10	18	2	30
Ankles/Feet	3	4	3	10
Lower back and ankles/feet	2	2	5	9
4-6 sensors	3	0	1	4
Other	3	1	0	4
Lower back and wrists	0	0	1	1
Unknown	2	0	4	6
Medication state				
ON-phase medication	5	15	28	48
OFF-phase medication	1	1	5	7
ON- and OFF-phase medication	1	2	1	4
Not described	12	10	8	30
Not applicable (Free-living)	4	2	0	6

Table 3 – General characteristics of technology-based gait analysis in PD

Protocol details

Table 4 shows the characteristics of the gait assessment protocol. The most frequently used distance in laboratory assessments was 10 meters (n=23), the shortest distance reported was 3 meters and the longest 500 meters. Table 5 compares PD patients' gait velocity using a gait assessment protocol with less than 10 meters, 10 meters and more than 10 meters. Due to the heterogeneity of the data, this comparison was only performed for gait velocity and a forest plot analysis was not possible.

Protocol details		
Laboratory assessment		
Distance		
	Median [Min, Max in meters]	10 [3,500]
	Mode (n, %)	10 (23, 24.2%)
Trials		
	Mean, SD	4,52 ± 2,98
Protocol		
	Self-selected comfortable speed	44
	Self-selected comfortable and dual task	8
	Self-selected comfortable, fast speed and dual task	6
	Self-selected comfortable and fast speed	5
	Self-selected comfortable and cueing	4
	Fast speed	2
	Fast, normal, and slow speed	2
	Other	7
	Unknown	11
Free-living assessment		
Duration		
	7 days	10
	3 days	3
	10 days	2

Table 4 – Protocol details of laboratory and free-living gait assessments

	Wearable	Non-Wearable
Less than 10 meters (mean, SD (n))	0.9 ± 0.2 (5)	0.9 ± 0.3 (7)
10 meters (mean, SD (n))	1.0 ± 0.1 (7)	0.9 ± 0.4 (8)
More than 10 meters (mean, SD (n))	1.1 ± 0.3 (18)	NA

Table 5 – Analysis of gait speed according to the distance covered in the gait protocol.

The mean number of trials was 4.3 ± 2.9. In 46.1% of the studies (n=41), gait assessment was performed at a self-selected comfortable speed. In free-living assessments, the most common duration of data collection was 7 days (58.8%, n=10).

In 58.5% of studies (n=48), patients were in an "ON-state" during the assessment, in 7.4% (n=7) in an "OFF-state" and in 4.2% of the studies (n=4) the assessment was performed in both conditions. (Table 4) Table 6 compares the PD mean values with and without having into account the "ON/OFF" medication state.

	Wearable devices		
	All	**"ON" State Medication**	**Healthy controls**
Gait velocity	1.01 ± 0.26 (32)	1.06 ± 0.20 (29)	1.19 ± 0.31 (17)
Cadence	106.68 ± 20.57 (11)	112.33 ± 8.89 (10)	113.34 ± 7.55 (6)
Stride Length	1.14 ± 0.28 (18)	1.15 ± 0.26 (15)	1.37 ± 0,08 (8)
Stride Time	1.18 ± 0.17 (13)	1.18 ± 0.18 (12)	1.09 ± 0.07 (9)
Stride Time Var	3.84 ± 2.94 (12)	4.01 ± 3.02 (11)	2.18 ± 0.59 (9)
Double support phase	29.03 ± 5.00 (8)	29.22 ± 5.37 (7)	23.40 ± 5.83 (6)
	Non-wearable devices		
	All	**"ON" State Medication**	**Healthy controls**
Gait velocity	1.00 ± 0.25 (19)	1.01 ± 0.25 (18)	1.15 ± 0.32 (5)
Cadence	104.04 ± 9.57 (15)	105.75 ± 7.15 (14)	NA
Stride Length	0.77 ± 0.40 (19)	0.77 ± 0.43 (17)	1,20 ± 0.28 (4)
Step Length	0.54 ± 0.13 (17)	0.55 ± 0.13 (16)	0.64 ± 0.06 (6)

Table 6 – Analysis of PD gait parameters according to the "ON/OFF" medication state during the gait assessment.

Due to the low number of studies assessing gait in "OFF" state medication (n=11, 11.6%) and the heterogeneity of the data, this analysis was only possible to perform for some gait parameters and did not allow for a forest plot analysis. Except for stride time variability, all the mean values of the studies only including an "On" state medication assessment, were closer to those from the HC group.

Discussion

The number of studies including a technology-based gait assessment is increasing (Fig. 1). Of the 95 studies included, the majority performed a laboratory assessment (82.1%, n=78) and used WS (61.1%, n=58). Accelerometers were the most frequently used type of sensor (67.2%, n=39), usually on the lower back (51.7%, n=30). The sample characteristics of the included studies were very similar, not allowing for subgroup analysis.

1) What should be measured?

The most frequently reported parameters in the included studies were gait velocity, stride and step length, and cadence. Compared to HC, PD patients had decreased velocity, reduced stride and step length, decreased swing time, increased stride time, stride time variability and dual support time ($p < 0.05$). These differences are in line with the usual description of PD gait impairments, i.e., a slow, short-stepped, shuffling, with a forward-stooped posture and asymmetrical arm swing. [110,115,116]

Beyond this, a large number of different, or differently measured gait parameters, were found in the included studies. From a clinical point of view, not every parameter that can be measured should be measured. [109,111] The collection and interpretation of the data must lead to justified outcomes, i.e., those with an impact on activities of daily living, displayed in a visually intuitive format that covers the clinical information needs of the stakeholders (health professionals, patients, and caregivers). [109,111] For this, gait parameters should be correlated with robust measures of clinical meaningfulness, such as the MDS-UPDRS motor score or the Timed Up and Go Test (TUG). Once the most suitable parameters to measure PD gait impairments in different contexts are established, then the minimal clinically important differences should be addressed for each. [109,111] Other measures emerging from the nonlinear analysis of human variability (e.g. entropy, fractals, and others) can give us a more accurate angle of patients' gait dynamics in a real-life

environment. However, work is needed to make them more intuitive and clinically informative. [109,111]

Although currently, sensor-based gait analysis has demonstrated feasibility and applicability for objectively assess PD gait impairments, differences still exist measuring the same parameter, with different devices or devices from different manufacturers. [14,117,118] This highlights the difficulty of accurately measuring the spatiotemporal gait parameters and the need to continue developing valid and reliable mathematical algorithms. Despite the major technological advances and the current possibility of capturing and store extremely high amounts of data with TOMs, the ability to algorithmically analyze (eliminating the noise) and summarize the clinically relevant data to stakeholders remains limited. [14]

2) Which devices should be used?

The comparison between assessments using WS and NWS was investigated for gait velocity, stride and step length parameters. A statistically significant difference between groups was found in gait velocity ($p = 0.04$). Although it was the analysis with the highest number of studies (n=18), due to the level of heterogeneity (I2 = 76.7%), the results should be interpreted with caution. We believe that the differences in the type of devices and in the assessment protocols of the included studies might have contributed to this result.

No statistically significant difference was found in the two other parameters (stride length – $p = 0.35$, step length – $p = 0.14$). Taking into account the low value for heterogeneity ($I^2 = 0\%$, $p < 0{,}001$), we believe that wearable sensors can be used in place of NWS (the gold standard of gait analysis).

WS have the added value of enabling the assessment of gait during activities of daily living in the patients' actual environment. However, more studies exploring how gait parameters behave in a real-world context are needed. [107]

It was only possible to explore the impact of the type of WS for gait velocity. This was undertaken by comparing the use of accelerometer (used in 67.2% of the WS) with all other types of sensors. Accelerometers allow the measurement of dynamic accelerations of a body, when submitted to an external force, and provide information about the device orientation related to gravity. [14,117,118] They are frequently combined with a gyroscope, which allow for the measurement of angular velocities. [14,117,118] In some devices, a 3D-magnetometer is also added for orientation purposes.

Since no difference was found in this subgroup analysis (accelerometer versus all other types of sensors) and both groups were able to detect a statistically significant difference between PD and HC, we believe that for an accurate assessment and monitorization of PD patients' gait impairments, the use of a single accelerometer is feasible. However, for the assessment of turns or of a more complex movement that requires the information captured by angular velocity, wearable devices including at least a gyroscope, seem more suitable.

In the included studies, only one study used an isolated magnetometer for gait analysis. Since magnetometers are very sensitive to magnetic changes (e.g. those produced by proximity with ferromagnetic objects) and therefore to many external interferences, they are more frequently used as a complement to accelerometers and gyroscopes, than as a single sensor. [14,117,118]

3) Where to place the sensor?

Our results showed that in 46.9% (n=30) of the studies using WS, the sensor was used on the lower back, between the second and the fifth lumbar vertebra. Although it was only possible to investigate the impact of sensor location for three parameters, it was limited to the comparison between lower back, feet and all other locations, the results consistently show no statistically significant difference between groups. Stride time variability measured with the sensor in the lower back was the only parameter that did not show a statistically significant difference between PD and HC. However, a heterogeneity (I2) of 82% was found, whereby these results should be interpreted carefully.

Several gait analyses protocols have been used. However, an optimal and standardized method remains for establishing. [118] The number and location of the sensors are key aspects for the success of assessments with TOMs, especially in a free-living context. [111,119] To increase wearing compliance without hindering the precision of data collection the number of sensors should be kept to a minimum, and the least obtrusive devices preferred. [111,119] Today, although the lower back is not considered the most comfortable and unobtrusive location, it has been shown that a single sensor (accelerometer) in this location is able to capture with precision, physical activity and gait parameters in a laboratory and free-living context. [119,120] Recently, there has been a move toward using sensors on the wrist or embedded in smartphones. However, problems still exist when collecting data. Kim et al., 2019 [119] report that sensors used on the wrist tend to overestimate the number of steps and the time spent at different intensities of activity. Höchsmann et al., 2018 [121]

compared the accuracy of step detection of a smartphone (placed in a trouser pocket, shoulder bag, and backpack) with a WS used on the wrist and waist. At a gait velocity of 4.8 km/h (shoulder bag and backpack) and 6.0 km/h (all positions), smartphones did not exceed a 1% error deviation from the gold standard (threshold to be considered an accurate measurement). However, for a gait velocity of 1.6 km/h, a 3% error was found. In a free-living context, smartphones underestimate the number of steps. [121] Another limitation of free-living assessment with smartphones is the place where it is used. While for men a trouser pocket is a commonly preferred position, for women it is more likely to be the purse or backpack. [121] In the search for a solution for a smartphone-based body location the magnetometer sensor will most certainly be a crucial sensor to consider when dealing with the device's orientation.

4) Which gait assessment protocol

The comparison between all the included studies and those that only used an assessment in "ON" state medication, revealed that PD gait parameters under the effect of the medication are closer to the HC. Only stride time variability did not follow this pattern. According to the literature [115] , stride time variability is increased in PD patients and diminishes in response to dopaminergic medication. In our analysis, we found that the difference between PD and HC increased when only studies assessing gait in "ON" state medication, were taking into account. However, this result should be interpreted with caution, since this was only a basic comparison of means and gait protocols differentiated substantially in the included studies.

The distance covered during gait analysis varied in the included studies. According to the analysis performed, the distance doesn't seem to have a high impact on gait velocity tested in a controlled environment. However, the data from the included studies doesn't allow us to conclude on this topic. More studies are needed to understand the implications of gait protocol length in PD gait parameters.

Almost half of the included studies (43.2%, n=41) used only a self-selected comfortable speed, during gait assessment. Since some of the gait parameters, like stride length and cadence, are sensitive to velocity and to the presence of concurrent attention demands, gait assessment protocols should include different velocities and both single- and dual-task activities. [122]

The most common duration of free-living assessment data collection was seven days, varying between three and ten days. Based on our results, we cannot conclude if this is the best option.

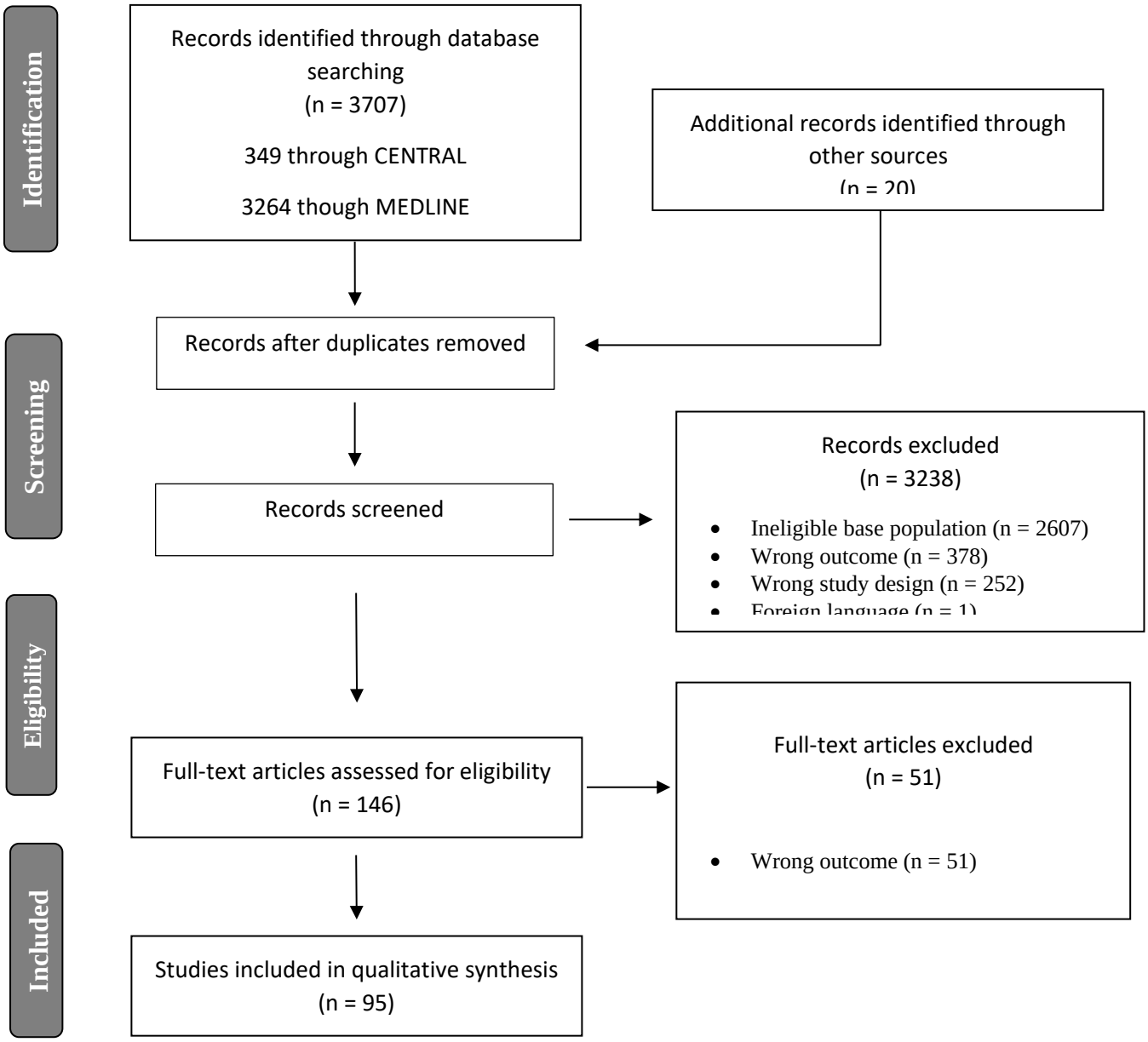
These are challenging assessments due to the heterogeneity of ambulatory activity within habitual environments. We believe that the duration of data collection during free-living assessments should be a balance between not performing a burdensome assessment and the ability to collect enough and precise data to obtain a pattern of patients' performance during the day. [111] As a fluctuating disease, the duration applied in other research fields, may not be appropriate. This topic should be addressed in future studies.

Conclusion

Our results support previous descriptions of PD gait impairments when compared with HC. No statistically significant differences were found for the impact of different types of devices (WS vs NWS), or different types or locations of wearable sensors during assessments. Future studies should test the reported gait parameters against validated clinical meaningful outcome measures in PD to select those most suitable for evaluating and monitoring the progression of gait impairments in PD. More studies are also needed to explore gait parameter behavior in a free-living context, with more complex movements (e.g. including turns, sequences of movements and others).

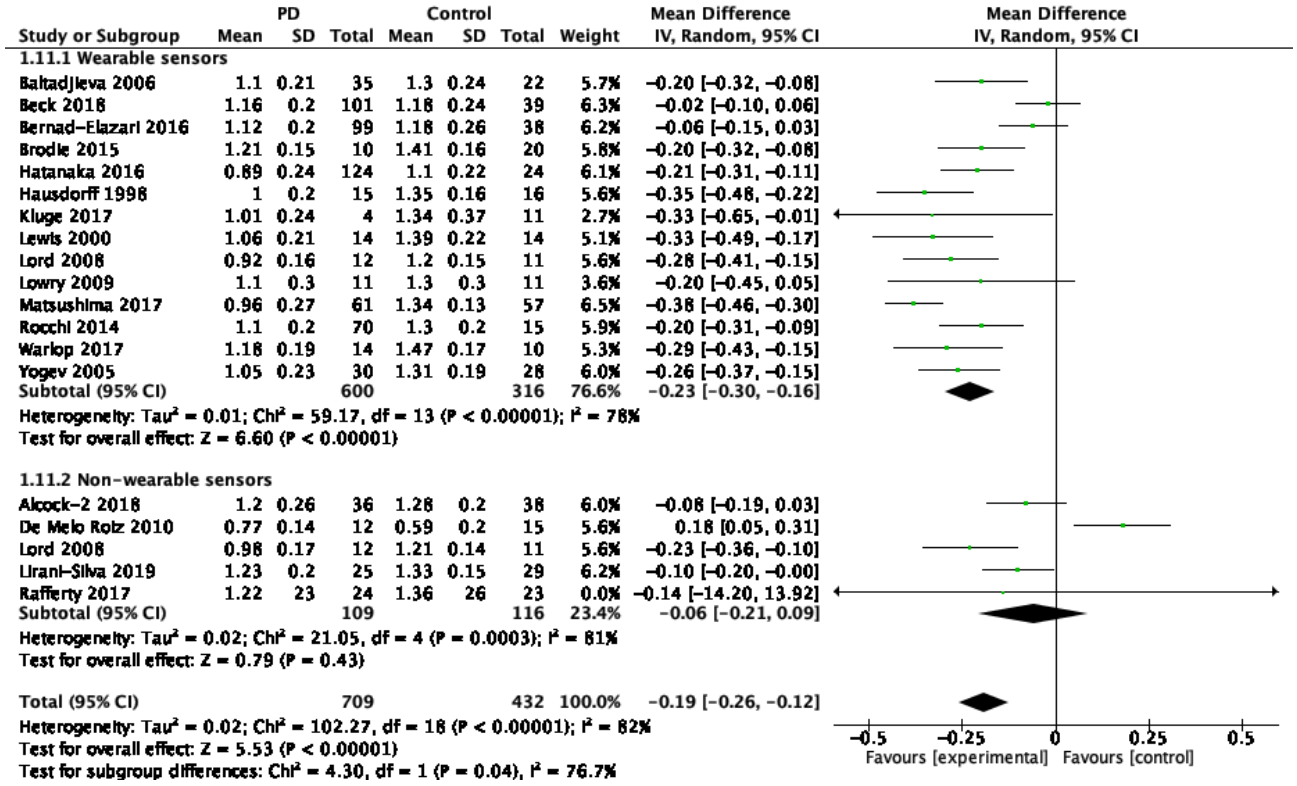
Appendix 1

Flow diagram of study selection process

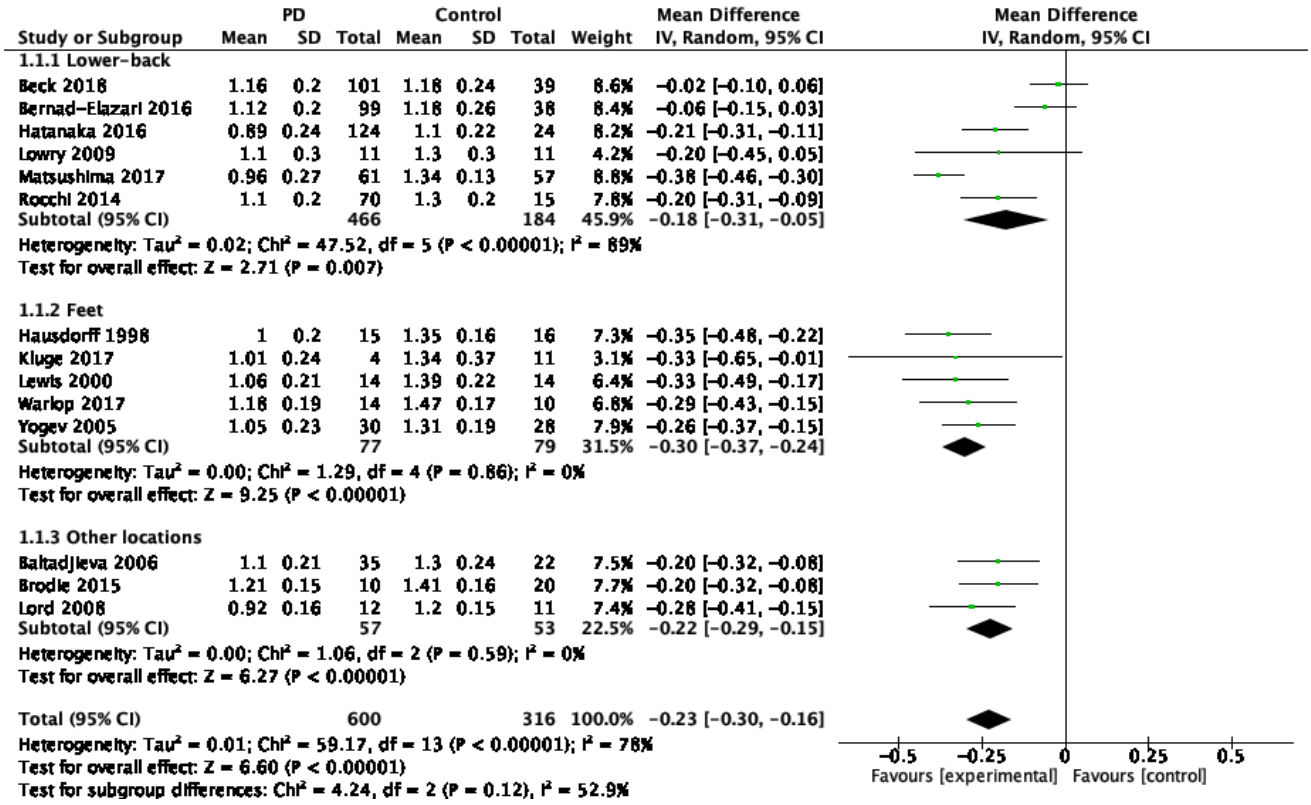


Appendix 2

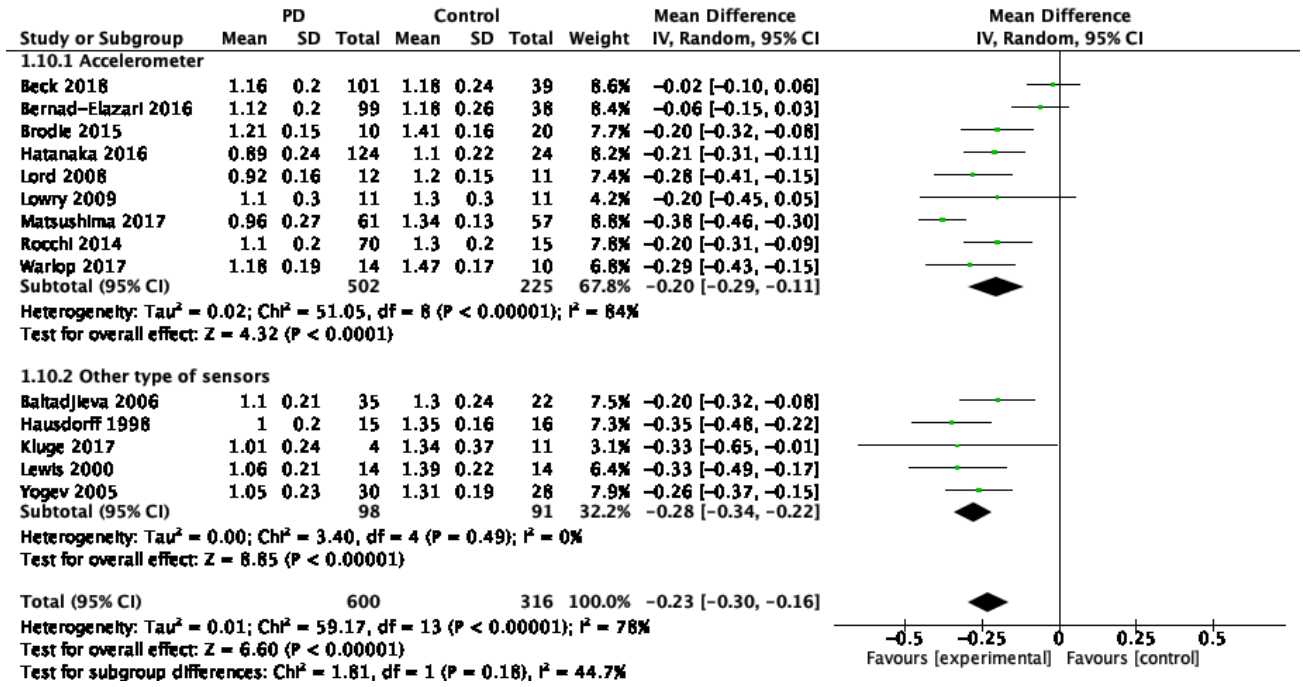
Forest plot analysis for the different gait parameters



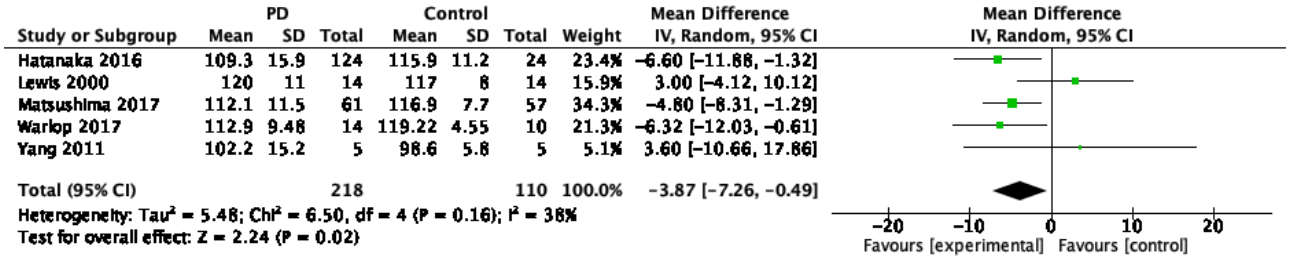
Forest Plot 1 – Gait velocity parameter: comparison between different type of devices (WS and NWS)



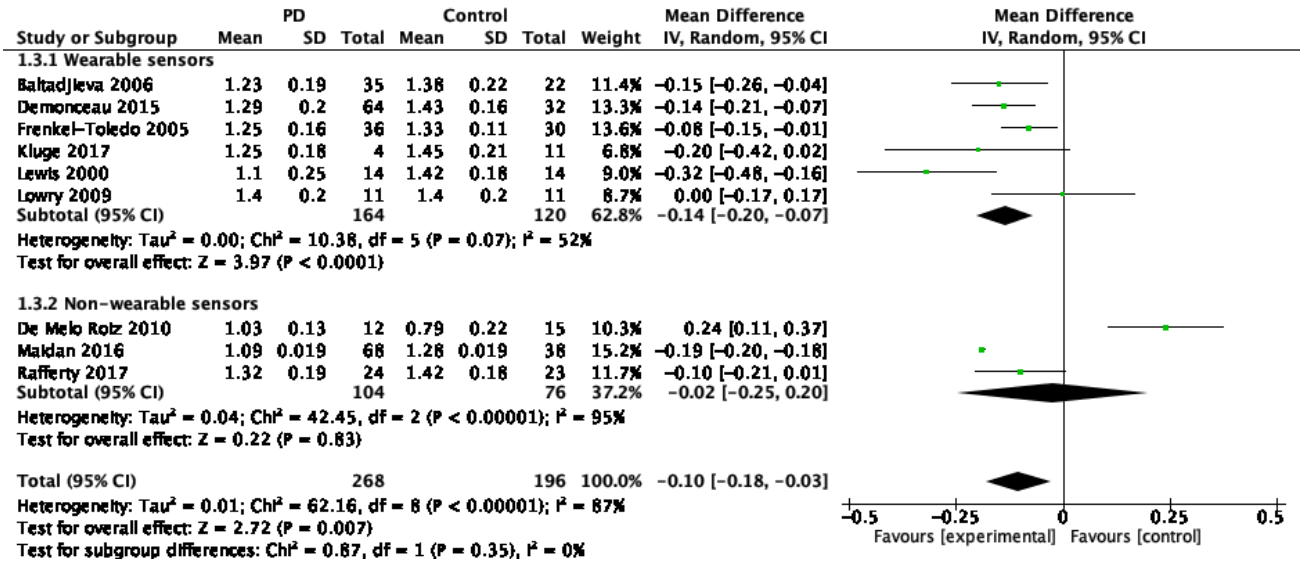
Forest Plot 2 – Gait velocity: comparison between different sensor locations



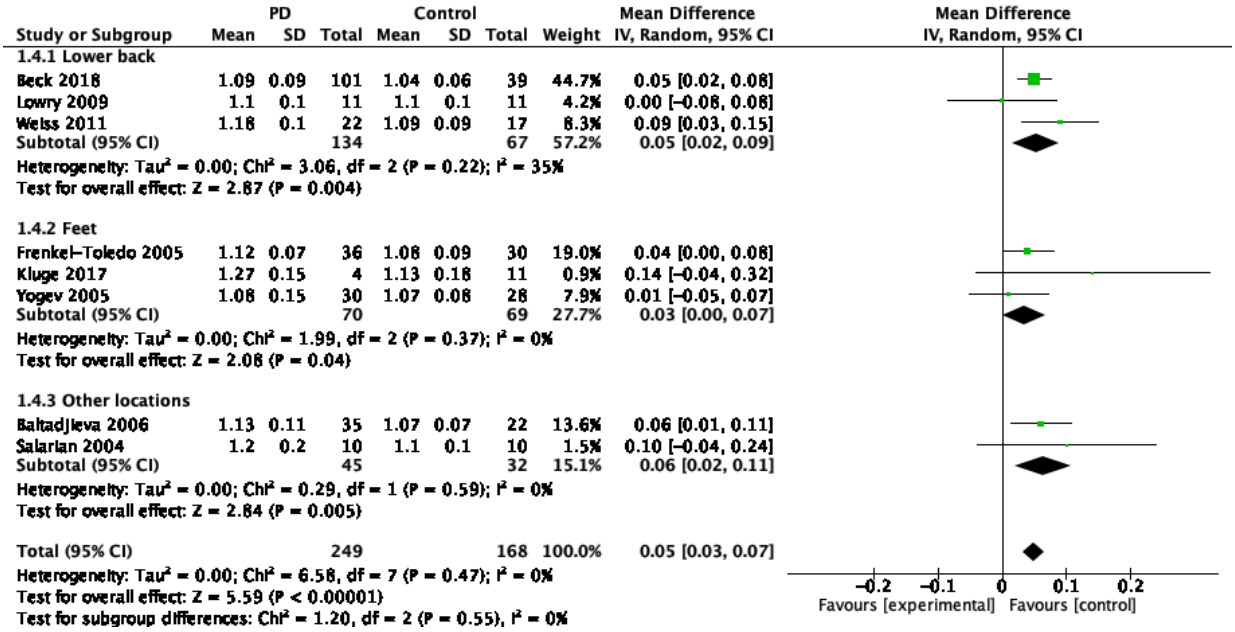
Forest Plot 3 – Gait velocity: comparison between different type of sensors



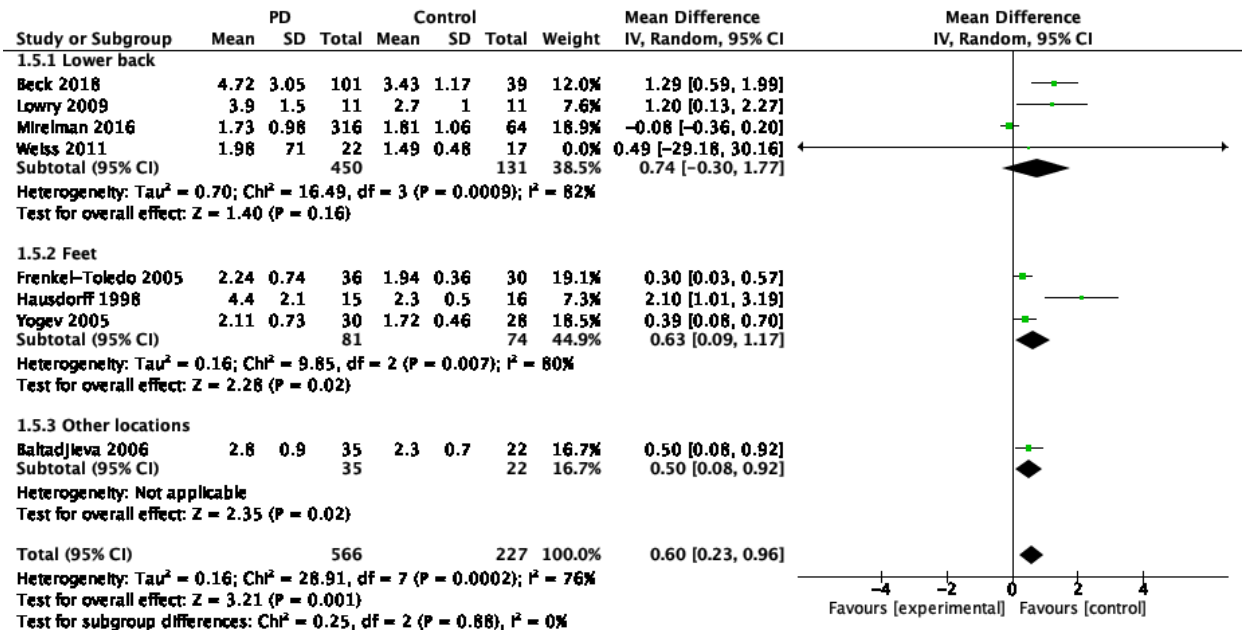
Forest Plot 4 – Cadence: comparison between of the mean values between PD and HC subjects using WS



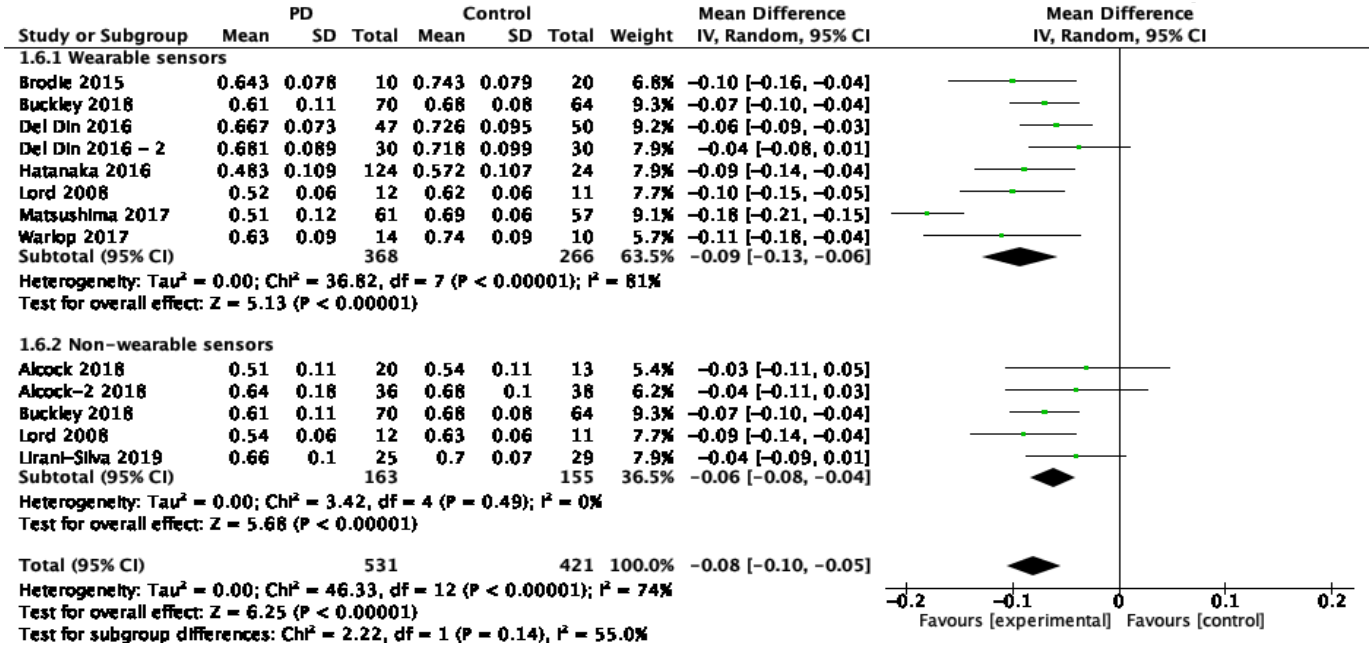
Forest Plot 5 – Stride length: comparison between different type of devices (WS and NWS)



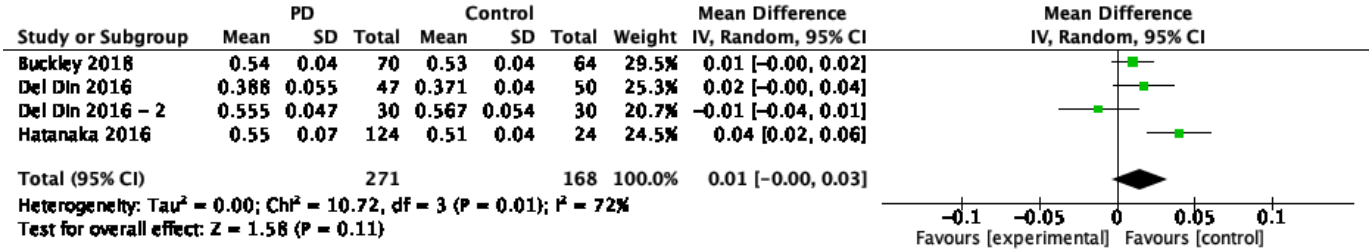
Forest Plot 6 – Stride time: comparison between different sensor locations



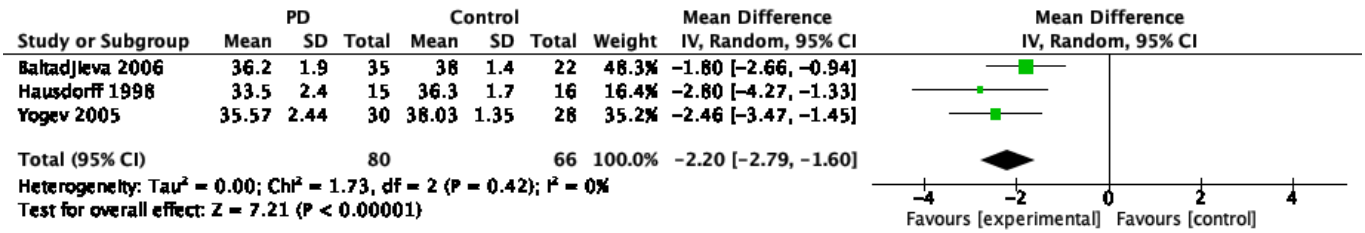
Forest Plot 7 – Stride time variability: comparison between different sensor locations



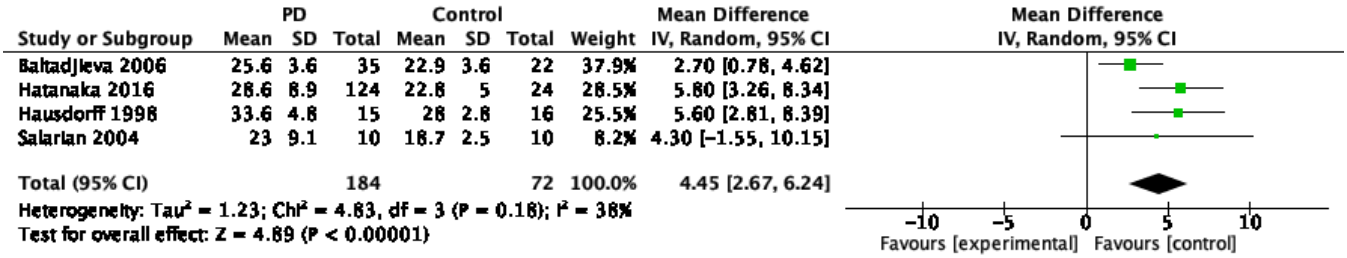
Forest Plot 8 – Step length: comparison between different type of devices (WS and NWS)



Forest Plot 9 – Step time: comparison between of the mean values between PD and HC subjects using WS



Forest Plot 10 – Swing time: comparison between of the mean values between PD and HC subjects using WS



Forest Plot 11 – Double support time: comparison between of the mean values between PD and HC subjects using WS

CHAPTER 6

Kinematic and clinical outcomes to evaluate the effect of a multidisciplinary intervention on Parkinson's disease functional mobility

Kinematic and clinical outcomes to evaluate the effect of a multidisciplinary intervention on Parkinson's disease functional mobility

Raquel Bouça-Machado, MSc[1,2], Diogo Branco, MSc[3], Gustavo Fonseca, BSc[3], Raquel Fernandes[2], Daisy Abreu[2], Tiago Guerreiro PhD[3], Joaquim J Ferreira, MD, PhD*[1,2, 4] on behalf of the CNS physiotherapy study group

1 - Instituto de Medicina Molecular, Lisbon, Portugal

2 - CNS - Campus Neurológico Sénior, Torres Vedras, Portugal

3 – LASIGE, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal

4 - Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

Collaborators (CNS physiotherapy study group): Daniela Guerreiro, Verónica Caniça, Francisco Queimado, Pedro Nunes, Alexandra Saúde, Laura Antunes, Joana Alves, Beatriz Santos, Inês Lousada, Maria A. Patriarca, Patrícia Costa, Raquel Nunes e Susana Dias.

Contents of this chapter were extracted from the peer-reviewed publication with the following reference:
Bouça-Machado R, Branco D, Fonseca G, Fernandes R, Abreu D, Guerreiro T, Ferreira JJ and The CNS Physiotherapy Study Group. Kinematic and Clinical Outcomes to Evaluate the Efficacy of a Multidisciplinary Intervention on Functional Mobility in Parkinson's Disease. Front. Neurol. 2021; 12:637620. doi: 10.3389/fneur.2021.637620.

Raquel Bouça-Machado design and conducted the study, performed data analysis and drafted the manuscript.

Abstract

Introduction: Functional mobility (FM) is a concept that incorporates the capacity of a person to move independently and safely to accomplish tasks. It has been proposed as a Parkinson's disease (PD) functional and global health outcome. In this study, we aimed to identify which kinematic and clinical outcomes changes better predict FM changes when PD patients are submitted to a specialized multidisciplinary program.

Methods: PD patients engaged in a pre-defined specialized multidisciplinary program were assessed at admission and discharge. Change from baseline was calculated for all kinematic and clinical outcomes and Timed Up and Go (TUG) was defined as the primary outcome for FM. A stepwise multivariate linear regression was performed to identify which outcome measures better predict TUG changes.

Results: Twenty-four patients were included in the study. The change in TUG Cognitive test, supervised step length, and free-living (FL) step time asymmetry were identified as the best predictors of TUG changes. The supervised step length and FL step time asymmetry were able to detect a small to moderate effect of the intervention (d values ranging from -0.26 to 0.42).

Conclusions: Our results support the use of kinematic outcome measures to evaluate the efficacy of multidisciplinary interventions on PD FM. The TUG Cognitive, step length, and FL step time asymmetry were identified as having the ability to predict TUG changes. More studies are needed to identify the minimal clinically important difference for step length and FL step time asymmetry in response to a multidisciplinary intervention for PD FM.

Keywords: Parkinson's disease, Functional Mobility, Outcome measures, Gait, Sensors, Digital health, Wearable, Technology.

Introduction

Functional mobility (FM) in Parkinson's disease (PD) has been recently described as a person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living at home, at work, and in the community.[64,102] From the early disease stage, PD patients experience limitations in their FM. With disease progression, these limitations are usually a major cause of disability and loss of independence.[64]

FM has been reported as a useful outcome measure to understand patients' overall health status, to address their daily needs related to mobility and social participation, and for monitoring, in a closer and more realistic fashion, the impact of disease progression and the effect of therapeutic interventions.[10,66,102] The Timed Up and Go (TUG) test is a quick and easy to use test, specifically designed to measure FM that includes the three anchors of the concept, i.e., gait, balance, and postural transitions.[52,66,102] Although it is the recommended tool for assessing FM in PD, other clinical tests are also used.[52,66,102]

The development of technology-based objective measures (TOMs) and the possibility of using accurate and reliable quantitative information to evaluate PD patients' gait, enable a more objective and ecological (i.e. closer to patients' real-life environment performance) perspective of patients' FM.[14,107] A recent systematic review on outcome measures for assessing FM in PD included nine studies using kinematic gait parameters.[102] The authors emphasize the important role of TOMs in monitoring FM throughout disease progression. They also highlight that despite the capacity of current devices to capture large amounts of data and a great diversity of parameters, the best kinematic parameters for assessing FM in PD remain to be defined.[102]

In this study, we aimed to identify which kinematic and clinical outcome measures better predict FM changes when PD patients are submitted to a specialized multidisciplinary intervention.

Methods

Study design

A pragmatic prospective clinical study was conducted.

Objective

To identify the kinematic and clinical outcomes measures that better predict FM changes when PD patients are submitted to a specialized multidisciplinary intervention.

Participants

Study participants were recruited from CNS - Campus Neurológico, a tertiary specialized movement disorders center in Portugal. Patients were eligible if they had a diagnosis of probable or clinically established PD (according to the International Parkinson and Movement Disorder Society criteria), had engaged in the specialized multidisciplinary program for parkinsonian patients at the CNS between January and September 2019, and if they agreed to participate. Exclusion criteria were the inability to adopt a standing position and/or to walk three meters, postural instability compromising patient safety during the assessment, and the presence of cognitive deficits preventing understanding the test instructions (according to physiotherapist best judgment). The study was undertaken with the understanding and written consent of each participant, with the approval from the CNS Ethics Committee (Ref. 10/19), and in compliance with national legislation and the Declaration of Helsinki. Participants were required to agree to all aspects of the study and were able to leave the study at any time.

Therapeutic intervention

The specialized multidisciplinary program combined pharmacological and non-pharmacological therapies, including up to 20 hours per week of individually tailored neurorehabilitation sessions of physiotherapy, occupational therapy, speech therapy, and cognitive training, according to the patient's needs and rehabilitation goals. All rehabilitation sessions had a duration of 50 minutes.

The physiotherapy sessions aim to optimize independence, safety, and well-being, through movement rehabilitation, the maximization of functionality, and minimization of secondary complications. The sessions focused on physical capacity training, gait, mobility, balance, sensorimotor coordination, and development, as well as teaching the patient and the usual caregivers adaptive strategies to enhance functionality.

Clinical assessment protocol

Patients were assessed in ON-state medication, by a trained health professional from each area, 48 hours following admission and before discharge. The following parameters were collected:

- Demographic and clinical data;
- Disease severity: Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score and score from each sub-section,[98] Hoehn and Yard scale,[98,123] Clinical and Patient Global Impression (CGI and PGI, respectively) of Severity and Change;[124]
- Motor function: The Timed Up and Go (TUG) test with and without a cognitive and manual dual-task,[72,73,125] Mini-Best test,[52,95,96] Five times Sit-to-Stand test (5 STS),[78,79] Schwab and England scale.[126]

Analysis of kinematic data

Kinematic gait parameters were collected during the supervised motor assessments and for three days at the end of each assessment, in a free-living (FL) context. Each participant wore a single tri-axial accelerometer-based body-worn monitor (*Axivity* AX3) on their lower back (L5), programmed to capture raw data at 100Hz with a dynamic range of +-8g. Each subject performed two trials of each assessment, on each visit, and wore the AX3 for three days after each assessment. In the supervised motor assessment, the physiotherapist used a mobile application to mark the start and end of each trial, which was synced with the AX3 internal clock. Departing from the segmentation of test trials provided by the application, we manually adjusted the start and end of each test to match with the exact start and end of the movement and removed reported periods of pause. To extract meaningful data from the raw accelerometer signal, we started by resampling data to 100 Hz using linear interpolation, to mitigate known fluctuations of the sample rate.[127] Afterward, offset was removed as well as machine noise using a 2nd order Butterworth low pass filter of 17 Hz.[128] We focused the kinematic gait analysis in the study of spatiotemporal gait parameters. To extract gait parameters, the process was divided into two steps. First, we identified the walking bouts as the 2-second moving windows where summed standard deviations of tri-axial accelerations were above 0.1.[129] Then, an algorithm to detect Initial Contact (IC) / Final Contact (FC) points was applied, from which we calculated the gait parameters.[112] A concurrent validity analysis of the reported number of steps (by the physiotherapist observing the trial) and the automatic detection revealed an intra-class correlation above 0.85.

In the FL context, where walking bouts are not previously annotated, a conservative approach was followed, meaning that high precision was sought (seeking that all detected bouts are indeed bouts), even if at the cost of lower recall (i.e. not all bouts are detected). Pre-processing of FL raw data followed a similar approach as the controlled assessment (resample and filtering). To improve walking bout detection in FL, we estimated an optimized scale of the Gaussian continuous wavelet transform[130] ('gaus2') and considered only the segments with a duration above 5 seconds and at least 5 detected ICs. Additionally, the first and last detected steps of each bout were trimmed off, given their specific transition characteristics. All remaining bouts (and steps) were subject to extraction of parameters. An average per subject of 285.3 (sd=175.2, min=17, max=622) walking bouts were extracted at the period of admission and an average of 270.4 (sd=129.0, min=32, max=647) were detected at the period of discharge, in the three day-period. Gait parameters were calculated from the detected bouts as in the supervised motor assessment.[112] Following previously published evidence in FL assessment, gait parameters were categorized in bouts from 5 to 15 seconds, 15 to 30 seconds, 30 to 60 seconds, and longer than 60 seconds.[112] Our implementation of the extraction of gait parameters from walking bouts is available and open-sourced (https://github.com/Gustavo-SF/gait_extractor).

Statistical analysis

Descriptive statistics were used for demographic, clinical, and therapeutic data. Continuous outcomes were defined as change from baseline for all the previously mentioned outcome measures and presented as a mean ± standard deviation (SD).

Our main goal was to explore the best predictors of changes in TUG (the gold standard for evaluating FM in PD). To do this, stepwise multiple linear regressions analyses were performed using different independent variables (clinical measures, gait parameter assessment during the 10-meter walk test, and FL gait parameters analyzed in bouts longer than 60 seconds). To validate the analysis, the normal distribution of residuals and the absence of multicollinearity were ascertained. Only the outcome measures able to detect an effect of the intervention were used in the main analysis. This required an assessment, before our main analysis, of the existence of an intervention effect and the ability of the included outcome measures to detect it. We started by studying normality, using the Kolmogorov-Smirnov and the Shapiro-Wilk tests, and applying the paired-samples T-test and the Wilcoxon S-R test to each parameter to analyze the effects of the program

(statistical significance was set at $p < 0.05$). Cohen's d was employed as a measure of effect size to assess small (0.20-0.49), medium (0.50-0.80), and large (> 0.80) effects.[131]

We also performed some exploratory analysis to better understand how the outcome measures, selected as best predictors of FM changes, behave if used as the primary outcome in a future study. Power analysis and sample size calculations were performed using G*Power software, to understand how many participants would be needed to enable statistically significant results (80% power) if the TUG test or one of the outcome measures able to detect at least a small effect size, were used as the primary outcome in a clinical study. A significance level of $\alpha = 0.05$ and a power $= 1 - \beta = 0.80$ were assumed. To explore the variability of the different gait parameters, a power analysis assuming 10%, 20%, and 30% of change from baseline and using the mean SD of change from baseline, was calculated for each parameter. The choice of the 30% magnitude of effect was based on the minimal clinically important difference (MCID) reported for the TUG test, the recommended measurement tool for assessing FM in PD. It also used a 20% magnitude of effect, based on MCID reported for spatial asymmetry in a previous study evaluating the effect of rehabilitation training on PD patients' gait parameters (25.76%).[132]

Additionally, and also as an exploratory analysis, we applied paired-sample t-test and the Wilcoxon S-R test to the different bout lengths of FL assessment to investigate how the length of the bout contributes to the existence of a statistically significant difference between admission and the end of the program (significance was achieved with a p-value<0.05).

Results

Cohort demographic and clinical data

Of the 54 PD patients who engaged in a CNS specialized multidisciplinary program between January and September 2019, a total of 24 participants were included in this study. The reasons for exclusion were lack of collaboration/missing data (27.8%, n= 15), motor inability to perform the assessments (18.5%, n= 10) and the presence of cognitive impairment and behavioral disturbances (9.3%, n= 5). Eight patients did not perform the FL assessment due to behavioral disturbances and refusal of the belt that supports the trunk sensor. Some of the included patients did not fulfill all the clinical assessment battery due to fatigue and lack of collaboration. The mean age of the participants was 73.0 ± 8.0 years, 66.7% (n=16) were men. At admission, the average disease duration was 8.0 ± 5.1 years, with a mean Hoehn and Yahr stage of 2.3 ± 0.9 and a mean

MDS-UPDRS motor score of 39.4±12.8. All patients were under antiparkinsonian treatment, 50% (n=12) had motor fluctuations.

Patients' demographic and clinical characteristics of admission and discharge are summarized in Table 1. Table 2 summarizes the changes in gait parameters values in both assessment conditions.

Demographic features (n=24)				
Age (Mean, SD)			73.04±8.00	
Male sex (% (n))			66.67% (16)	
Body Mass Index (BMI) (Mean, SD)			25.79±3.90	
Time since diagnosis (Mean, SD)			8.04±5.10	
Presence of motor fluctuations (% (n))			50% (12)	
Clinical data (Mean (SD), [Range])				
	Admission	**Discharge**	**Change**	**p-value**
MDS-UPDRS I (range 0-52; n = 19; ↓)	13.95±7.09	8.25±4.90	-5.53±6.81 (39.6%)	**0.002**
MDS-UPDRS II (range 0-52; n = 19; ↓)	17.18±9.24	12.65±7.04	-4.95±10.02 (28.8%)	**0.045**
MDS-UPDRS III (range, 0-132; n = 19; ↓)	39.36±12.77	32.20±12.22	-8.52±9.92 (21.7%)	**0.001**
MDS-UPDRS IV (range 0-24; n = 19; ↓)	1.95±2.82	1.35±2.16	-0.21±2.53 (10.8%)	0.721
MDS-UPDRS Total (range 0-260; n = 19; ↓)	72.45±25.75	54.45±20.50	-19.26±22.18 (26.6%)	**0.001**
Hoehn and Yahr stage (range 1-5; n = 24; ↓)	2.30±0.93	2.35±0.71	0.09±0.68 (3.9%)	0.540
Schwab and England (range 0-100; n = 24; ↑)	73.75±16.37	75.83±15.86	2.08±8.33 (2.8%)	0.225
TUG Normal (n = 24; ↓)	13.36±7.27	11.68±4.75	-1.69±6.90 (12.7%)	0.243
TUG DT Cognitive (n = 23; ↓)	17.22±10.42	14.10±7.29	-2.80±8.91 (16.3%)	0.146
TUG DT Manual (n = 19; ↓)	12.80±5.21	11.37±4.35	-0.92±8.69 (7.2%)	0.417
Mini-best (range 0-28; n = 19; ↑)	20.19±3.97	20.70±4.59	0.63±3.25 (3.1%)	0.408
5 Sit-to-Stand Normal (n = 22; ↓)	19.36±6.99	14.29±5.24	-4.31±2.94 (22.3%)	**0.000**
5 Sit-to-Stand Fast (n = 22; ↓)	17.56±4.91	13.25±5.19	-5.07±3.48 (28.9%)	**0.000**
	Severity (Baseline)		**Change** (Discharge)	
Clinical Global Impression (n = 24; ↓)	4.0 ± 0.83		2.83 ± 0.82	
Patient Global Impression (n = 24; ↓)	3.91 ± 1.02		2.50 ± 0.86	

Table 1 – Demographical and clinical characteristics of the sample. ↑ - a higher score means an improvement, ↓ - a lower score means an improvement. The paired-samples T-Ttest and the Wilcoxon S-

R tests were applied to investigate the existence of a statistically significant difference between admission and the end of the program. Significance was achieved with a p-value <0.05.

All the clinical and gait parameters from the supervised assessment showed an improvement, having reached statistical significance ($p \leq 0.05$) in the MDS-UPDRS parts I, II, III, and total score, in the 5STS test and the following gait parameters: gait velocity, stride and step velocity, step length and swing time asymmetry (Tables 1 and 2). The improvement in the TUG test did not reach statistical significance, contrary to gait velocity, stride and step velocity, step length, and swing time asymmetry measured during the test. In FL conditions an improvement was detected when the analysis was made using bouts of at least 30 seconds. Specifically, the following gait parameters have reached statistical significance ($p \leq 0.05$): cadence, step time, stance time, swing time and double support time when data was analysed in bouts of 30 to 60 seconds and stance, swing and double support phases when bouts of more than 60 seconds were used in the analysis. (Table 2 and Appendix 1).

Gait parameters Supervised assessment	Supervised assessment						Free-living assessment		
	TUG normal			10-meter walk test			Bouts longer than 60 seconds		
	Admission	Change from baseline	p-value	Admission	Change from baseline	p-value	Admission	Change from baseline	p-value
Gait Velocity (m/s)	0.71±0.19	0.06±0.13 (8.5%)	**0.037**	0.82±0.21	0.05±0.18 (6.1%)	0.188	0.59±0.14	0.04±0.13 (6.8%)	0.209
Cadence (steps/min)	118.77±12.00	1.94±13.02 (1.6%)	0.472	119.92±13.72	3.66±12.95 (3.1%)	0.180	104.93±10.33	-0.92±9.17 (0.9%)	0.695
Stride length (m)	0.78±0.18	0.06±0.14 (7.7%)	0.057	0.89±0.20	0.04±0.17 (4.5%)	0.204	0.69±0.16	0.05±0.13 (7.2%)	0.160
Stride velocity (m/s)	0.71±0.19	0.06±0.13 (8.5%)	**0.033**	0.82±0.21	0.05±0.18 (6.1%)	0.225	0.59±0.14	0.04±0.13 (6.8%)	0.202
Step length (m)	0.39±0.09	0.03±0.07 (7.7%)	**0.049**	0.45±0.10	0.02±0.08 (4.4%)	0.230	0.34±0.08	0.02±0.06 (5.9%)	0.171
Step velocity (m/s)	0.72±0.19	0.06±0.13 (8.3%)	**0.037**	0.82±0.21	0.05±0.18 (6.1%)	0.182	0.60±0.14	0.04±0.13 (6.7%)	0.220
Stance phase (% of gait cycle)	75.26±1.36	-0.11±1.35 (0.2%)	0.708	75.35±0.49	-0.18±1.32 (0.2%)	0.514	75.11±0.55	0.20±0.36 (0.3%)	**0.047**
Swing phase (% of gait cycle)	24.74±1.36	0.11±1.35 (0.5%)	0.708	24.65±0.49	0.18±1.32 (0.7%)	0.514	24.89±0.55	-0.20±0.36 (0.8%)	**0.047**
Double support phase (% of gait cycle)	25.33±1.33	-0.13±1.36 (0.5%)	0.643	25.34±0.51	-0.19±1.27 (0.8%)	0.476	25.11±0.54	0.19±0.36 (0.8%)	**0.050**
Step time (seconds)	0.56±0.06	-0.02±0.06 (3.6%)	0.893	0.55±0.07	-0.01±0.06 (1.8%)	0.525	0.60±0.06	0.002±0.06 (0.3%)	0.896
Stance time (seconds)	0.84±0.09	-0.01±0.09 (1.2%)	0.800	0.83±0.10	-0.01±0.09 (1.2%)	0.589	0.90±0.09	0.004±0.09 (0.4%)	0.845
Swing time (seconds)	0.28±0.04	0.002±0.04 (0.7%)	0.828	0.27±0.03	-0.001±0.03 (3.7%)	0.902	0.30±0.03	-0.001±0.03 (0.3%)	0.930
Double support time (seconds)	0.28±0.03	-0.004±0.03 (1.4%)	0.561	0.28±0.03	-0.004±0.03 (1.4%)	0.916	0.30±0.03	0.004±0.03 (1.3%)	0.583
Stride time variability (% CV)	0.07±0.04	-0.004±0.04 (5.7%)	0.636	0.04±0.02	-0.001±0.03 (2.5%)	0.880	0.12±0.03	-0.01±0.04 (8.3%)	0.393
Step length variability (% CV)	0.05±0.02	-0.003±0.03 (6%)	0.516	0.03±0.01	0.004±0.02 (13.3%)	0.260	0.06±0.01	0.003±0.02 (5%)	0.446
Step time variability (% CV)	0.05±0.03	-0.002±0.03 (4%)	0.730	0.03±0.02	-0.0004±0.02 (1.3%)	0.930	0.09±0.02	-0.01±0.03 (11.1%)	0.210
Step velocity variability (% CV)	0.11±0.04	-0.008±0.04 (7.3%)	0.352	0.06±0.02	0.01±0.04 (16.7%)	0.163	0.13±0.03	0.004±0.03 (3.1%)	0.657

Stance time variability (% CV)	0.06±0.03	-0.005±0.03 (8.3%)	0.384	0.03±0.02	-0.002±0.02 (6.7%)	0.665	0.10±0.03	-0.01±0.03 (10%)	0.340
Swing time variability (% CV)	0.03±0.02	-0.006±0.02 (20%)	0.884	0.02±0.01	0.001±0.02 (20%)	0.862	0.05±0.02	-0.01±0.02 (20%)	0.216
Double support variability (% CV)	0.03±0.02	-0.003±0.02 (10%)	0.455	0.02±0.01	0.00002±0.01 (0.1%)	0.994	0.05±0.02	-0.01±0.02 (20%)	0.163
Stride time asymmetry (% CV)	0.01±0.01	0.002±0.02 (20%)	0.959	0.01±0.01	-0.001±0.01 (10%)	0.584	0.01±0.004	-0.001±0.01 (1%)	0.300
Step time asymmetry (% CV)	0.02±0.02	0.005±0.02 (25%)	0.262	0.03±0.02	0.003±0.02 (10%)	0.496	0.03±0.02	-0.01±0.02 (33.3%)	0.318
Stance time asymmetry (% CV)	0.02±0.02	-0.003±0.02 (15%)	0.622	0.02±0.02	-0.003±0.02 (15%)	0.420	0.02±0.01	-0.01±0.02 (50%)	0.153
Swing time asymmetry (% CV)	0.02±0.01	0.008±0.02 (40%)	**0.036**	0.02±0.01	-0.003±0.02 (15%)	0.423	0.02±0.01	-0.01±0.02 (50%)	0.195
Step length asymmetry (% CV)	0.03±0.02	-0.002±0.02 (6.7%)	0.605	0.02±0.02	0.0002±0.02 (1%)	0.959	0.02±0.01	-0.002±0.01 (10%)	0.504

Table 2 – Admission (i.e., baseline) and change from baseline values (i.e., mean Post-Pre assessment difference and respective percentage value) of gait parameters in the supervised and free-living assessments. The paired-samples T-test and the Wilcoxon S-R tests were applied for each parameter to investigate the existence of a statistically significant difference between admission and the end of the program (statistical significance was achieved with p-value <0.05).

Dependent variable: TUG change from baseline	**Predictors**	**R^2**	**Adjusted R^2**	**R^2 Change**	***F***	**p-value**	**Unstandardized B**	**Standardized Coefficients ß**	**Collinearity VIF**
Independent variables: Clinical outcome measures	**TUG Cognitive**	0.75	0.72	0.75	23.59	0.001	0.42	0.86	1.000
Independent variables: Kinematic outcome measures – Supervised assessment	**Step length**	0.55	0.53	0.55	27.11	0.000	-61.96	-0.74	1.000
Independent variables: Kinematic outcome measures – Free-living assessment	**Step time asymmetry**	0.55	0.51	0.55	16.79	0.001	104.88	0.74	1.000

Table 3 – Stepwise multiple linear regression analysis with TUG as a dependent variable and 1) the clinical outcome measures, 2) gait parameters assessed during the 10-meter walk test, in supervised conditions, 3) gait parameters assessed in free-living conditions and analyzed in bouts longer than 60 seconds, as independent variables.

Prediction of FM changes

The stepwise multivariate linear regression analysis, between TUG (dependent variable) and the clinical outcome measures able to detect an effect, indicated the TUG Cognitive as the best variable to predict TUG changes (Adjusted R^2 = 0.72). The same analysis using supervised and FL kinematic gait parameters as independent variables identified step length (Adjusted R^2 = 0.53) and step time asymmetry (Adjusted R^2 = 0.51), as the best predictors of TUG changes for each assessment condition (Table 3).

Responsiveness to intervention

The TUG test was able to detect a small effect size (d = -0.24) of the intervention (Appendix 2). From the supervised assessment, the outcome measures able to detect a large effect size were the STS Normal (d = -1.46) and Fast (d = -1.47) and the MDS-UPDRS total score (d = -0.87).
From the FL assessment, the outcome parameters with higher sensitivity to the intervention were stance time asymmetry (d = -0.38), stride length (d = 0.37), double support time variability (d = -0.37), and step length (d = 0.36).

Sample size calculation

A power analysis was performed to understand how many participants would be needed to enable statistically significant results (80% power), if the TUG test or one of the outcome measures able to detect at least a small effect size, were used as a primary outcome in a clinical study. Appendix 2 summarizes the sample size calculations assuming 10%, 20%, and 30% change from baseline.

Discussion

Although this study was not designed to conclude on efficacy, the results obtained suggest an overall improvement (Table 1 and 2). This enables us to identify the best predictors of FM changes when PD patients are submitted to a specialized multidisciplinary program. It also enables performing other exploratory analyses to better understand how the outcome measures behave if used as primary outcomes in future studies.

From the pool of outcome measures able to detect at least a small effect size of the intervention, those identified as the best predictors of TUG changes were the TUG Cognitive, step length, and step time asymmetry.

Clinical assessment

The TUG Cognitive test was the clinical parameter with the best ability to predict TUG changes. This can be explained because the TUG Cognitive is a modified version of the TUG (i.e., it adds a cognitive task to the motor task).[74,75] Since daily activities frequently require motor and cognitive tasks to be carried out simultaneously, this version of the test may give a more realistic perspective of the patients' FM. However, as it is only a modified version of the same test, some major limitations remain (e.g., it is limited to patients without significant postural instability and is subject to learning effects).

The Mini-BESTest test was not sensitive to the intervention and the observed differences were not statistically significant. However, this is a very complete clinical test that includes the assessment of static and dynamic balance (i.e., biomechanical constraints, verticality/stability limits, anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait) and the TUG Cognitive test itself. [52,95,96] Although not formally validated to measure FM, this instrument provides a more complete approach to the three anchors of the concept, i.e., gait, balance, and postural transitions.[52,95,96] We believe that future studies should clarify the Mini-BESTest's suitability to assess FM changes.

Clinical versus Kinematic assessment

Our results identified step length and step time asymmetry as the gait parameters with the best ability to predict TUG (and FM) changes, in supervised and FL conditions, respectively. Compared with the TUG, both showed higher responsiveness to change.

FM is a major source of disability for PD patients and requires an individualized and complex management approach that strongly depends on the information about the actual state of the patients in their daily lives.[64] Although the TUG remains the gold standard for assessing PD FM, as is the case for all traditional clinical scales, it presents some limitations that can be overcome by the use of TOMs.[15]

To optimize the accuracy of clinical evaluation, evidence suggests that patients should focus on the goal of the task asked and not on the movement required to achieve it. This is hampered when a reassessment using the TUG test takes place after a multidisciplinary program. During the physiotherapy sessions of the program, patients usually learn safety strategies to apply during walking and postural transitions that require being focused on the movement while doing it. Many of these strategies are applied during the TUG test, thereby hindering its ability to detect an improvement in patients' FM.[15]

There is increasing evidence that TOMs may improve the sensitivity, accuracy, reproducibility, and feasibility of data capture, detecting improvements that the clinical tests are not able to find.[14] Previous studies reported a greater sensitivity of TOMs, over the traditional clinical scales, in differentiating the gait and turning of PD patients from healthy controls.[15]

The use of outcome measures of higher sensitivity and accuracy, which can predict TUG changes (step length and step time asymmetry), may help obtain a more complete and objective evaluation of patients' FM limitations and thereby favoring more personalized clinical decision-making.[14,133]

In the research field, the use of standardized outcome measures, with high responsiveness to change and low variability, not only enables better interpretation and discussion of research findings but also avoids unnecessary increases in complexity, duration, and financial expenses of studies.[14]

Despite the benefits associated with the use of TOMs for assessing FM, from our experience they also have some limitations. The currently available sensors, although smaller and lighter, remain too intrusive, leading patients to reject their use. Also, in PD patients with behavioral changes, the use of sensors may not be possible. One of the patients was excluded from the FL analysis, after having thrown away the sensors during an episode of delirium.

Supervised versus free-living assessment

According to our results, the responsiveness of the outcomes and their ability to predict TUG changes differ depending on the type of assessment.

There is a growing awareness that, depending on the assessment conditions, the results related to gait and postural transitions can differ substantially, with a weak association between the results

in both scenarios having been reported.[133,134] Many factors can contribute to these differences: 1) the clear and standardized environment in supervised assessment, in the absence of distractions, emphasizes a measure of someone's best, rather than their usual performance; 2) FL conditions, with narrow corridors, variable lighting, obstacles, etc., forces continuous gait adaptations, inducing large variability and asymmetry in walking patterns; 3) movements in a supervised assessment are triggered by instruction, while FL movements are usually self-initiated, goal-directed, and embedded in a rich behavioral environment; and 4) patients frequently improve their performance when they know that they are being evaluated.[112,133,134]

In the FL context, gait parameters, and therefore FM, may not only be influenced by physical characteristics, but also by ongoing environmental and cognitive challenges.[134] Variability and asymmetry related parameters are especially sensitive to behavioral and environmental factors, better reflecting patients' interaction with the context and their ability to adapt gait patterns.[133,134] We hypothesize that this may be one of the causes of step time asymmetry identified as the FL kinematic gait parameter, that better predicts TUG changes. Although it has only captured a small effect size of the intervention, having a high ecological validity, FL step time asymmetry seems to provide a more realistic picture of the impact of the disease in PD FM, whereby even small changes should be valued.[15]

Length of walking bouts

We performed an exploratory analysis to understand how FL gait parameters behave when different bout lengths were used in the analysis. According to our results, there appears to be a link between the ability to capture an improvement and the length of the bout. The longer the walking bouts, the higher the velocity and length of stride/step and the lower the cadence, variability, and asymmetry.

A previous study exploring the impact of environment and bout length in PD patients' gait, reached similar conclusions, i.e., the longer the bouts, the higher the increase in step velocity, step length, swing time variability, and the lower the variability and asymmetry of gait. The authors also reported the parameters analyzed in longer bouts were more similar to those measured in a supervised environment.[112]

Walking bout length is influenced by the type of environment and activity patients are engaged in.[112] Currently, the most suitable length of walking bouts used in FL analysis is not established.[112]

The majority of studies investigating gait characteristics in FL conditions use bouts longer than 60 seconds. However, it has been reported that PD patients in FL conditions more often perform a large number of very short bouts (≤ 10 seconds), than prolonged bouts.[112] According to the literature, bouts of 30 to 60 seconds usually represent indoor activities, while bouts greater than 120 seconds correspond to walking outdoors. Only bouts with at least 30 to 60 seconds were able to discriminate PD patients from healthy controls.[112]

Limitations

This study presents two major limitations: a small sample size (n=24) and high heterogeneity in the included population. We believe that these aspects may overestimate the variability of the measurement tools, influencing the power calculations. We expect that future studies, with a large and less heterogeneous population, will need a smaller sample size. As an open non-controlled study, we hypothesize that in future larger, controlled trials, the detected effect size will be smaller. However, since this was not an efficacy study (due to the absence of a control group) and an improvement was observed, despite these limitations, we believe that our results are informative and important for the PD field. Also, we believe that the use of broad inclusion criteria in this study, not only did not interfere with its aims but better mimic the real scenario of the intervention and assessments, increasing its external validity. To minimize the impact, the study was conducted in a single tertiary care center.

According to our results, the TUG test did not achieve a statistically significant improvement. However, some of the gait parameters (including step length), not only reached a statistically significant result but showed a higher sensitivity to change. Since all other results point to an improvement at the end of the program, we believe that this difference may be explained by the greater accuracy and sensitivity to change of TOMs when compared to the traditional clinical scales. A previous study has already highlighted this potential problem, highlighting that the validation of TOMs is often based on their correlation with validated clinical measures and that results may be undesirable, due to the superior capacity of TOMs for capturing the phenomena of interest.[135]

Conclusion

Although we cannot attribute the observed improvements to the specialized multidisciplinary program, our results suggest a methodological approach for identifying outcome measures to assess FM changes, in response to a therapeutic intervention.

From all the outcome measures included in the study, only the TUG Cognitive, step length, and FL step time asymmetry were identified as having the ability to predict TUG changes. The kinematic parameters seem to present higher responsiveness to change when compared with the traditional clinical tests. According to our results, supported by published evidence, the longer the bouts, the higher the sensitivity of detecting an improvement.

Our results support the use of kinematic assessments in evaluating the effect of multidisciplinary interventions in PD FM. The FL step time asymmetry seems a very promising outcome measure to assess FM in PD. Nevertheless, there are some aspects of FL assessments that need to be improved, such as establishing the best data collection protocol and developing less intrusive sensors.

To improve the interpretation of results of responsiveness to change in a complex and fluctuating disease such as PD, it is necessary to clarify the variation of gait parameters in the absence of pharmacological and non-pharmacological therapeutic interventions. This requires repeating the assessment protocol in ON- and OFF-state medication and several times during a short period, thereby clarifying the effect of pharmacological interventions, permitting an understanding of the impact of motor fluctuations and minimizing the interference of disease progression. More studies are also needed to explore the cut-off points from which FM is considered to be affected and the smallest amount of change, in the identified parameters, considered important by the patient or clinician (i.e., the minimal clinically important difference).

Appendix 1 - Analysis of change from baseline values of gait parameters in free-living according to different bout lengths. The Paired-Samples T-Test and the Wilcoxon S-R tests were applied for each parameter to investigate the existence of a statistically significant difference between admission and the end of the program. Significance was achieved with p-value<0.05.

Gait Parameters Free-living assessment	Average		Bouts 15 seconds		Bouts 15-30 seconds		Bouts 30-60 seconds		Bouts 60 seconds	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value	Change	p-value
Gait Velocity (m/s)	-0.01±0.04	0.569	-0.01±0.04	0.288	-0.02±0.08	0.424	0.01±0.11	0.792	0.04±0.13	0.209
Cadence (steps/min)	3.55±7.57	0.080	-3.47±8.82	0.137	-3.06±6.60	0.084	-3.22±4.48	**0.011**	-0.92±9.17	0.695
Stride length (m)	0.002±0.06	0.859	-0.004±0.06	0.809	-0.005±0.08	0.809	0.02±0.15	0.517	0.05±0.13	0.160
Stride velocity (m/s)	-0.01±0.05	0.591	-0.01±0.04	0.364	-0.02±0.08	0.451	0.01±0.11	0.754	0.04±0.13	0.202
Step length (m)	0.002±0.03	0.725	-0.004±0.03	0.642	-0.004±0.04	0.728	0.01±0.07	0.488	0.02±0.06	0.171
Step velocity (m/s)	-0.01±0.04	0.478	-0.01±0.04	0.281	-0.02±0.08	0.398	0.01±0.11	0.721	0.04±0.13	0.220
Stance phase (% of gait cycle)	-0.001±0.40	0.995	-0.09±0.45	0.422	0.10±0.72	0.581	0.09±0.39	0.395	0.20±0.36	**0.047**
Swing phase (% of gait cycle)	0.001±0.40	0.995	0.09±0.45	0.422	-0.10±0.72	0.581	-0.09±0.39	0.395	-0.20±0.36	**0.047**
Double support phase (% of gait cycle)	-0.01±0.42	0.929	-0.10±0.47	0.387	0.09±0.71	0.618	0.10±0.41	0.340	0.19±0.36	**0.050**
Step time (seconds)	0.02±0.04	0.096	0.01±0.05	0.242	0.02±0.04	0.087	0.02±0.03	**0.011**	0.002±0.06	0.896
Stance time (seconds)	0.02±0.06	0.126	0.02±0.07	0.293	0.03±0.06	0.100	0.04±0.05	**0.006**	0.004±0.09	0.845
Swing time (seconds)	0.01±0.02	0.119	0.01±0.02	0.307	0.01±0.02	0.264	0.01±0.01	**0.006**	-0.001±0.03	0.930
Double support time (seconds)	0.01±0.02	0.159	0.01±0.03	0.406	0.01±0.02	0.200	0.01±0.02	**0.010**	0.004±0.03	0.583
Stride time variability (% CV)	-0.004±0.03	0.513	-0.004±0.03	0.585	-0.01±0.04	0.389	-0.01±0.04	0.248	-0.01±0.04	0.393
Step length variability (% CV)	0.0001±0.01	0.980	0.0004±0.03	0.904	-0.003±0.02	0.493	-0.005±0.02	0.227	0.003±0.02	0.446
Step time variability (% CV)	-0.003±0.02	0.473	-0.004±0.02	0.469	-0.004±0.02	0.553	-0.01±0.03	0.294	-0.01±0.03	0.210
Step velocity variability (% CV)	-0.003±0.03	0.699	-0.002±0.03	0.840	-0.01±0.03	0.268	-0.01±0.03	0.119	0.004±0.03	0.657
Stance time variability (% CV)	-0.004±0.02	0.480	-0.004±0.02	0.501	-0.01±0.03	0.494	-0.01±0.04	0.186	-0.01±0.03	0.340
Swing time variability (% CV)	-0.005±0.02	**0.007**	-0.005±0.02	**0.001**	-0.004±0.02	0.413	-0.01±0.02	0.202	-0.01±0.02	0.216
Double support time variability (% CV)	-0.002±0.01	0.070	-0.002±0.02	0.244	-0.004±0.02	0.418	-0.01±0.02	0.242	-0.01±0.02	0.163
Stride time asymmetry (% CV)	-0.001±0.004	0.284	-0.002±0.01	0.660	0.0001±0.004	0.881	-0.001±0.004	0.571	-0.001±0.01	0.300

Step time asymmetry (% CV)	-0.001±0.01	0.200	-0.001±0.01	0.138	-0.001±0.02	0.903	-0.003±0.02	0.531	-0.01±0.02	0.318
Stance time asymmetry (% CV)	-0.002±0.01	0.321	-0.004±0.01	0.573	0.002±0.01	0.619	-0.0001±0.01	0.977	-0.01±0.02	0.153
Swing time asymmetry (% CV)	-0.003±0.01	0.219	-0.003±0.01	0.123	0.0001±0.01	0.982	-0.001±0.01	0.741	-0.01±0.02	0.195
Step length asymmetry (% CV)	-0.002±0.005	0.146	-0.001±0.01	0.174	-0.005±0.01	**0.029**	-0.001±0.01	0.648	-0.002±0.01	0.504

Appendix 2 - Clinical and gait parameters able to detect an effect of the intervention (Cohen's d ≥ 0.20)

	Cohen's d	**Sample size** (80% power, 30% from baseline)	**Sample size** (80% power, 20% from baseline)	**Sample size** (80% power, 10% from baseline)
Supervised assessments				
TUG	-0.24	26	55	211
5 Sit-to-Stand Fast	-1.47	5	8	22
5 Sit-to-Stand Normal	-1.46	5	8	23
MDS-UPDRS Total score	-0.87	11	21	76
Stride velocity	0.46	6	9	30
Gait Velocity	0.45	6	9	30
Step velocity	0.45	8	14	47
Swing time asymmetry	0.45	107	237	941
Step length	0.42	5	9	27
Stride length	0.41	6	9	27
TUG Cognitive	-0.31	26	55	213
Schwab and England	0.25	4	5	13
Step time asymmetry	0.23	131	254	1575
Free-living assessment				
Stance time asymmetry	-0.38	54	210	1302
Stride length	0.37	6	9	30
Double support time variability	-0.37	16	45	210
Step length	0.36	6	8	34
Swing time asymmetry	-0.34	54	210	1302
Stride velocity	0.33	7	12	39
Gait Velocity	0.33	9	18	63
Step time variability	-0.33	16	32	119
Step velocity	0.32	7	12	39
Swing time variability	-0.32	17	34	154

Stride time asymmetry	-0.27	327	1302	1302
Step time asymmetry	-0.26	67	147	580
Stance time variability	-0.25	16	32	119
Stride time variability	-0.22	16	54	210
Step length variability	0.20	9	16	65

CHAPTER 7

General discussion

Due to the world's rapidly aging population, the incidence of Parkinson's disease (PD) is expected to increase during the next few decades, demanding the development of strategies to optimize the quality of PD care and the reduction of healthcare costs.[3,136] To this end, the establishment of disease-specific outcomes that are reliable and meaningful to both patients and health professionals, is crucial.[136,137]

Although major advances have been made in recent years to establish the most appropriate outcomes and measurement tools for use in the PD field, many inconsistencies still exist.[60,137] This hinders the possibility of summarizing and comparing results from different studies and of clarifying the real benefit of the interventions tested.[60,137]

The present thesis seeks to propose a new outcome for the PD field that aggregates these two characteristics: being meaningful and easy to report by patients and providing a more global perspective of a patient's health status in their daily life activities. In concrete, we focused on the concept of FM, studying its relevance for the PD field. Sequential steps have been followed.

We started with an evidence-based understanding of how FM concepts fit in the PD field. Then we proposed a definition of FM to be applied to the PD field and clarified its significance and relevance for patients and health professionals. Once the usefulness of the concept was clear, we studied the most appropriate outcome tools for evaluating it. We identified the Timed Up and Go (TUG) test as the gold standard measurement tool for assessing FM in PD. Due to the increasing relevancy of kinematic gait analysis in the PD field, we found it necessary to study kinematic gait parameters to better understand this new type of analysis. Finally, through a pragmatic clinical study, we explored the outcome measures used during admission and prior to discharge that better predict FM changes in response to a specialized multidisciplinary program for PD. Besides TUG Cognitive, two kinematic gait parameters are highlighted: step velocity and step time asymmetry. We believe that the information generated here allows us to discuss more deeply on the two main goals of this thesis: 1) to investigate the clinical and research applicability of the concept of FM in PD and 2) to identify the most suitable clinical and technological outcome measures for assessing the response of FM to a therapeutic intervention.

Does the Concept of Functional Mobility Apply to the Parkinson's Disease Field?

PD is a complex and progressive disease, with a direct impact on patients' general mobility and with a variable response to medication.[136,137] According to our narrative review, supported by the patients' and health professionals' perspectives during the focus group study, PD symptoms, even when mild and with a good response to medication, may interfere with patients' daily life. Patients in the early disease stages reported the need for more time to perform tasks. Family members describe changes in patients' mobility. As the disease progresses, the limitations in gait, balance, and transfers (the three key features of FM) become more marked, with a poorer response to medication. This usually interferes with a patient's movements, hampering their autonomy and negatively impacting social relationships, either due to the difficulty of family and friends to understand the disease fluctuations or because patients feel ashamed for drawing the attention of others.

Due to this significant impact, not only at a physical but also at psychological and social levels, FM deserves to be considered as a potential outcome to be studied. This goes in line with the results of previous studies according to which, although the assessment of specific outcomes (e.g. the level of rigidity or intensity of tremor) is important, a more global evaluation, focusing on functional limitations (rather than physical impairments), is more meaningful, since it represents the most problematic aspects of a PD patient's disability profile.[10,60]

According to the results of our focus groups, patients valued the use of the FM concept for being easy to describe and for expressing something that truly affects their daily lives. From the health professional's perspective, the concept is useful to help patients' communicating their perception of their overall health status and to help clinicians adopt a more patient-centered approach. At a time when personalized therapeutic interventions are becoming increasingly relevant, these results should not be overlooked. Also, the inclusion of the concept of FM in PD clinical practice and research should be considered.

As far as we could ascertain, when we approached the concept of FM, there was no formal definition available. In this thesis, we adopted the definition used by Forhan&Gill in 2013[19], which seems the most complete and easy to understand. To ensure that we were not attributing a different name to a concept that already existed and if this was in fact the best description, we matched the Forhan&Gill,2013 definition with others founded in the literature (in a search not limited to the

PD field). We also explored the perception of patients and health professionals about the adopted definition. In the Medline/PubMed electronic open search, all the definitions found shared with the Forhan&Gill description, the idea that FM is a patient's ability to move in his/her environment, focused on gait, balance, and transfers, in order to accomplish functional tasks of everyday living. When the patients and health professionals participating in the focus group were asked to define FM, they were all able to provide a correct, albeit approximate, definition. They also agreed with the one proposed when it was presented. Based on this, we advocate applying the Forhan&Gill, 2013 definition of FM to the PD field.

Which are the Most Suitable Outcome Measures to Assess Functional Mobility in Parkinson's Disease?

Over time, PD symptoms not only increase in severity but also in number, leading to increasing disability and severe complications. Close monitoring of the different disease manifestations over time is vital for improving disease knowledge, monitoring its course, and optimizing patient care.[10]

Choosing the most suitable outcome measures is a complex task. Qualitative information from patient-reported outcomes is important for pragmatic management and planning, but quantitative data is essential for the decision-making process and the interpretation of results across studies.[10,11,137] An ideal outcome measure is meaningful to patients, easy to measure, reliable, and responsive to therapeutic interventions.[10,11,137]

Clinical outcomes

According to our results, several instruments have been used to assess FM in PD. The Timed Up and Go (TUG) test was created for this purpose and is the gold standard for evaluating FM. This is an easy and quick to apply test, which has been validated and is broadly used in the PD field. It includes the three key features of the FM definition proposed in this thesis (gait, balance, and transfers).

In the studies included in this thesis, other clinical tests have been highlighted as potential outcome measures to assess FM in PD. From these, we highlighted the TUG Cognitive test and the Mini-

Best test. Although neither of these was submitted to a proper validation process in a PD population, they might provide more comprehensive information of patients' FM, and are therefore mentioned in this discussion. The TUG Cognitive is an adaptation of the TUG test, whereby a cognitive task is added to the classical motor task of the TUG test. We argue that this might be more representative of the real-life challenges since the majority of activities of daily living require more than one task to be performed simultaneously (e.g., to talk while walking). The Mini-Best test, besides including the TUG Cognitive test, includes the simulation of different types of gait present in everyday life (gait with obstacles, with pivot turn, and with head turns) and the evaluation of dynamic balance (specifically of reactive postural control). According to the results of our clinical study, the TUG Cognitive test (i.e., the changes in the TUG Cognitive test) was identified as one of the best outcome measures to predict TUG changes and presents a better responsiveness to change to a specialized multidisciplinary program for PD. The Mini-Best test did not show such favorable results. However, because it is such a complete test and offers a more comprehensive approach, we believe it deserves to be studied in more detail.

Technology-based objective measures

Typically, PD assessment is based on the information collected, through the clinical interview and answers to rating scales or questionnaires, during the in-person visits to the doctor's office or at the beginning of a rehabilitation program.[10] According to our focus group, FM is not a parameter assessed by neurologists but it is usually evaluated by physiotherapists, as the TUG test is the instrument most frequently used.

Although these traditional assessment methods have been used for a long time in clinical practice and large clinical trials, the information gathered is limited to a brief snapshot of patients' health status, hindered by the presence of recall bias, rater level of expertise, subjective reporting, and lack of sensitivity to subtle changes.[10]

Recently, as a result of the advances and availability of high-speed internet connections, the development of smaller, more compact, and affordable devices, and the increase in technological literacy of the general population, there has been a growing interest in developing technology-based objective measures (TOMs) to quantitatively capture movement patterns of PD patients,

during in-person visits and in activities of daily living.[10,135] TOMs share similar goals to clinical measures, in terms of eliciting useful information about symptom monitoring and disease management. They have the added value of reduce assessments bias, increasing the accuracy of endpoints, minimizing intra- and inter-rater variability, presenting greater sensitivity to subtle changes, and enabling the evaluation of patients at a distance.[10,135] In the research field, these benefits are expected to contribute to a decrease in the sample size of clinical trials, shortening their duration, and lowering their cost.[10,135]

According to our results, the majority of PD assessments using TOMs are performed in a supervised (in-clinic) environment, using wearable sensors. Currently, the capacity of capturing data is very high. However, the ability to analyze and transform data into relevant clinical information is still limited. In particular, a large number of gait parameters can now be obtained from kinematic gait analysis but there is still a great heterogeneity in the way they are captured (i.e., in the assessment protocols: where, how, for how long and using which devices) and clear guidelines on how to interpret clinical meaningfulness are lacking. The results of our systematic review on the gait parameters support the use of a single accelerometer on the lower back (between the second and fifth lumbar vertebrae) for accurate assessment and monitoring of PD patients' gait impairments. However, for more complex movements (e.g., including turns, sequences of movements, and others) the results suggest that, at the very least, the device should also incorporate a gyroscope.

The most frequently reported parameters in the published evidence are gait velocity, stride and step length, and cadence. In our clinical study, in order to explore the best kinematic parameters to predict TUG changes we first analyzed the responsiveness of the included outcomes and, using those that were able to detect at least a small effect of the intervention, we performed a stepwise multiple linear regression analysis with TUG as a dependent variable. The results showed that, depending on the type of assessment, the sensitivity of the kinematic parameters and their ability to predict TUG changes are different. While in the supervised assessment, the gait parameter (changes from baseline) that best predicted TUG changes was step length, in the free-living assessment it was step time asymmetry.

Although supervised, in-person assessments using TOMs can overcome some of the limitations associated with the traditional clinical outcome measures, they still only provide a brief snapshot

of the PD patient's condition, having a limited ability to reflect the patient's performance at home. They are usually complemented by the use ON/OFF diaries for prolonged monitoring. However, these are usually associated with low adherence and recall bias.[138] Toosizadeh et al., 2015,[138] in a study comparing supervised and free-living (in-home) assessments, report significant differences in PD patients' motor performance between both, with a tendency to perform better during in-clinic assessments.

The analysis of responsiveness to change showed that both supervised step length and free-living step time asymmetry have a higher sensitivity to the intervention than the TUG or the TUG Cognitive tests. Considering PD is a fluctuating disease, with episodic events (e.g., freezing of gait) and FM as a global outcome, intrinsically linked to a patient's activities of daily living and environment, it is reasonable that kinematic parameters, particularly sensitive to behavioral and environmental factors, would be the best outcome measures to predict FM changes. This information provides a more reliably and ecological perception of FM changes on daily performance, which could be very useful for monitoring disease progression and the effect of therapeutic interventions. [10,60,135,138]

In our opinion, the identification of a good free-living parameter to assess FM in PD does not exclude the use of supervised clinical and technological assessments. Clinical assessments can add, for example, the patient's perspective through patient-reported outcomes, and supervised objective assessments provide information on a patient's best performance. Therefore, according to the aim of the assessment, clinicians and researchers should choose the most appropriate type of assessment and corresponding outcome measure.

Implications for Parkinson's Disease Clinical Practice

If PD patients are unable to move at an intensity and frequency required by their daily living activities, they will not be able to keep up with the demands associated with social or work life.

FM should be monitored in PD, not only for the impact that FM-associated problems can have on physical, psychological, and social levels but also for the information it provides about disease progression and the effect of therapeutic interventions. FM is also a feature that can be improved through a PD-specialized multidisciplinary intervention, or through walking aids that enable

patients to move effortlessly in a reasonable amount of time and thereby maintain access to the same environments as others.

The use of walking aids to optimize PD patients' FM is not a straightforward question. Objectively these types of aids, if adapted and after training with a physiotherapist, allow patients to move more quickly, safely, and over greater distances. Patients can, therefore, continue to be engaged with their social and occupational activities. However, the ability to perform a task autonomously (i.e., without the help of third parties or instruments) is more important for patients that the time spent performing or the associated effort. Also, walking aids are, in the patients' perspective, profoundly linked to the perception of disability and dependence. This usually hinders the acceptance and long-time adherence of patients to this type of solution.

According to our results, two conditions can change patients' perception of walking aids: (1) if the patient perceives the walking aid as something that will enhance the feeling of control during daily activities, increasing their autonomy; and (2) if the design and perception of walking aids changes, i.e., if they are considered in a positive light as enhancing capacity, instead of compensating for a disability (e.g. patients easily accept Nordic walking sticks and some motorized wheelchairs because they are associated with exercise and activity or technological advances).

As neurologists mention in the focus group study, the assessment of FM may help to adopt a more patient-centered approach. In the clinical setting, the TUG test seems the most feasible way to assess FM. However, this is not the best option when reevaluating FM at the end of multidisciplinary or physiotherapy programs for PD. We suggest adding kinematic gait analyses to the assessment battery as they seem more able to detect subtle changes in patients' FM and the results are not affected by the safety strategies learned during the program. Although there are still several aspects to be refined, we advise that, when possible, these evaluations are accompanied by a free-living assessment and that changes in step time asymmetry be considered to obtain a more realistic perspective of a patient's FM.

Currently, there are no cut-offs to classify the severity of FM changes. In the future, it would be important to study this values for the TUG, TUG Cognitive, step length and step time asymmetry. It would also be important to determine the smallest amount of change considered important by the patient and clinician (MCID) for both the kinematic parameters, in order to better interpret the effect of therapeutic interventions.

Implications for the Parkinson's Disease Research Field

Despite the developments in the methods for measuring motor symptoms (e.g. tremor), these do not always provide an accurate perspective of patients' performances in real-life.[139]

FM is an outcome that provides a more realistic and global portrayal of patients' functional state in daily life, and is, at the same time, easy to understand and meaningful for patients.

According to our results, FM can be measured through an easy and quick clinical test or kinematic gait analysis in supervised or free-living conditions. It is now important to clarify how FM changes with disease progression and also how it varies in the absence of an intervention.

The use of TOMs in PD clinical trials remains very low, they are only used as secondary or exploratory outcomes.[135,140] We believe that their use as primary outcomes could, in the near future, be a very helpful solution for conducting clinical trials. The use of FM measures through TOMs in a research context will help obtain more meaningful and accurate information, detect more subtle changes, and reduce the sample sizes needed to enable statistically significant results. We expect that this reduces clinical trial durations, burden, and costs.

The integration of TOMs in PD research depends on solving the concerns limiting their use. These include the lack of clear guidelines to interpret results of this type of assessment, the absence of clear diagnostic and severity cut-offs and MCID, the lack of a standardized assessment protocol, the lack of validation across proprietary platforms, the problems with patient's adherence, and the regulatory barriers in approving the wider use of these technologies, and finally, the scarce information on how they behave in large clinical trials.[135,140]

Supported by our clinical study, we believe that TOMs were more able to capture a change than the TUG test. We call attention to this aspect in the validation of TOMs. Their validation is often based on their correlation with previously validated clinical scales, which may be undesirable if TOMs have a superior capacity to capture the phenomena of interest.[135] Researchers should approach this topic and provide clear recommendations.

Conclusion and Future Steps

The present work clarifies the appropriateness of the concept of FM in the PD field and the most suitable outcome measures to be used in its assessment.

FM is a global outcome, impaired since the early stages of PD, that has the key characteristics of a strong outcome measure: it is intelligible and meaningful to patients and health professionals, it provides more global and ecological information, and it is easy to measure. We support the use of FM for PD assessment and free-living monitoring, as a way to promote a more patient-centered approach.

According to our results, the TUG test is the gold standard for FM evaluation. However, both step length and free-living step time asymmetry seem to have a higher ability to capture FM changes in response to a therapeutic intervention.

We believe that the use of FM in PD clinical practice and research can be a great asset. To make this possible, the changes in FM due to disease progression should be studied in a large and long-term clinical study, the cut-off of severity and the MCID for each of the outcome measures recommended for PD FM assessment should be defined, and the issues related to the integration of TOMs in PD clinical practice and research, resolved.

ACKNOWLEDGMENTS

Throughout the writing of this dissertation, I have received a great deal of support and assistance and I wish to express my sincere gratitude to

Professor Joaquim Ferreira, for his continuous support and immense knowledge. Above all, I would like to thank his exigence, generosity, and opportunities given.

Professor Ricardo Matias, for sharing his knowledge and for his support and enthusiasm.

All the CNS team, for their patience, energy, and unconditional collaboration.

Professor Leonor Correia-Guedes, Professor Miguel Coelho, Professor Mário Miguel Rosa, for receiving me so well when I started working in the JJ Ferreira Lab and for all the support and examples of scientific exigence.

All members of the JJ Ferreira Lab for sharing their knowledge and for all our work and time together.

Finally, but most importantly, I would like to thank my family for the example, guidance, and support given over the years.

REFERENCES

1. Erro, R. & Stamelou, M. The Motor Syndrome of Parkinson's Disease. in *International Review of Neurobiology* vol. 132 25–32 (Academic Press Inc., 2017).

2. Poewe, W. The natural history of Parkinson's disease. *J. Neurol.* **253**, 2–6 (2006).

3. Dorsey, E. R. & Bloem, B. R. The Parkinson pandemic - A call to action. *JAMA Neurology* 1–2 (2018) doi:10.1001/jamaneurol.2017.3299.

4. Coelho, M. & Ferreira, J. J. *The Natural History of Parkinson's Disease*. *Movement Disorders Curricula* (Springer Vienna, 2017). doi:10.1007/978-3-7091-1628-9.

5. Coelho, M. *et al.* Late-stage Parkinson's disease: The Barcelona and Lisbon cohort. *J. Neurol.* **257**, 1524–1532 (2010).

6. Salat, D., Noyce, A. J., Schrag, A. & Tolosa, E. Challenges of modifying disease progression in prediagnostic Parkinson's disease. *Lancet Neurol.* **15**, 637–648 (2016).

7. Todorova, A., Jenner, P. & Ray Chaudhuri, K. Non-motor Parkinson's: integral to motor Parkinson's, yet often neglected. *Pract. Neurol.* **14**, 310–22 (2014).

8. Carne, W. *et al.* Efficacy of multidisciplinary treatment program on long-term outcomes of individuals with Parkinson's disease. *J. Rehabil. Res. Dev.* **42**, 779–786 (2005).

9. van der Marck, M. A. A. *et al.* Multidisciplinary care for patients with Parkinson's disease. *Park. Relat. Disord.* **15**, S219–S223 (2009).

10. Bhidayasiri, R. & Martinez-Martin, P. Clinical Assessments in Parkinson's

Disease. *Int. Rev. Neurobiol.* **132**, 129–182 (2017).

11. Marras, C. & Lang, A. E. Outcome measures for clinical trials in Parkinson's disease: achievements and shortcomings. *Expert Rev. Neurother.* **4**, 985–993 (2004).

12. Postuma, R. B. *et al.* MDS clinical diagnostic criteria for Parkinson's disease. *Mov. Disord.* **30**, 1591–1601 (2015).

13. Goetz, C. G. *et al.* Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Mov. Disord.* **22**, 41–47 (2007).

14. Espay, A. *et al.* Technology in Parkinson disease: Challenges and Opportunities. *Mov. Disord.* **00**, 1–11 (2016).

15. Del Din, S., Godfrey, A., Mazzà, C., Lord, S. & Rochester, L. Free-living monitoring of Parkinson's disease: Lessons from the field. *Mov. Disord.* **31**, 1293–1313 (2016).

16. Brognara, L., Palumbo, P., Grimm, B. & Palmerini, L. Assessing Gait in Parkinson's Disease Using Wearable Motion Sensors: A Systematic Review. *Diseases* **7**, 18 (2019).

17. Harvey, A., Graham, H. K., Morris, M. E., Baker, R. & Wolfe, R. The functional mobility scale: Ability to detect change following single event multilevel surgery. *Dev. Med. Child Neurol.* **49**, 603–607 (2007).

18. Angelin, A. C., Sposito, A. M. P. & Pfeifer, L. I. Influence of functional mobility and manual function on play in preschool children with cerebral palsy. *Hong Kong J. Occup. Ther.* **31**, 46–53 (2018).

19. Forhan, M. & Gill, S. V. Obesity, functional mobility and quality of life. *Best*

Pract. Res. Clin. Endocrinol. Metab. **27**, 129–137 (2013).

20. Raggi, A. *et al.* Disability and profiles of functioning of patients with Parkinson's disease described with ICF classification. *Int. J. Rehabil. Res.* **34**, 141–150 (2011).

21. Duncan, R. P. & Earhart, G. M. Are the Effects of Community-Based Dance on Parkinson Disease Severity, Balance, and functional mobility reduced with time? A 2-year prospective pilot study. *J. Altern. Complement. Med.* **20**, 757–63 (2014).

22. Magrinelli, F. *et al.* Pathophysiology of Motor Dysfunction in Parkinson's Disease as the Rationale for Drug Treatment and Rehabilitation. *Parkinson's Disease* vol. 2016 1–18 (2016).

23. Kalia, L. V & Lang, A. E. Parkinson's disease. *Lancet* **6736**, 1–17 (2015).

24. Sveinbjornsdottir, S. The clinical symptoms of Parkinson's disease. *J. Neurochem.* **139**, 318–324 (2016).

25. Keus, S. *et al. European Physiotherapy Guideline for Parkinson's Disease*. *KNGF/ParkinsonNet* vol. 1 (2014).

26. Raggi, A. *et al.* The ICF as a framework to collect and interpret data on the extent and variety of disability in neurological conditions. *NeuroRehabilitation* **36**, 17–22 (2015).

27. Raggi, A. *et al.* Determinants of disability using count-based approaches to ICF-based definition of neurological disability. *NeuroRehabilitation* **36**, 23–29 (2015).

28. Leonardi, M., Raggi, A., Ajovalasit, D., Bussone, G. & D'Amico, D. Functioning and disability in Parkinson's disease. *Disabil. Rehabil.* **32 Suppl**

1, S23–S32 (2010).

29. Leonardi, M. *et al.* ICF in neurology: Functioning and disability in patients with migraine, myasthenia gravis and Parkinson's disease. *Disabil. Rehabil.* **31**, S88–S99 (2009).

30. King, L. A. & Horak, F. B. Delaying Mobility Disability in People With Parkinson Disease Using a Sensorimotor Agility Exercise Program. *Phys. Ther.* **89**, 384–393 (2009).

31. Williams, D. R. & Litvan, I. Parkinsonian syndromes. *Contin. Lifelong Learn. Neurol.* **19**, 1189–1212 (2013).

32. Robichaud, J. A. & Corcos, D. M. Motor Deficits, Exercise, and Parkinson's Disease. *Quest* **57**, 79–101 (2005).

33. Yoshii, F., Moriya, Y., Ohnuki, T., Ryo, M. & Takahashi, W. Postural deformities in Parkinson's disease -Mutual relationships among neck flexion, fore-bent, knee-bent and lateral-bent angles and correlations with clinical predictors. *J. Clin. Mov. Disord.* **3**, 1 (2016).

34. Merola, A. *et al.* Orthostatic hypotension in Parkinson's disease: Does it matter if asymptomatic? *Parkinsonism Relat. Disord.* **33**, 65–71 (2016).

35. Boersma, I., Jones, J., Carter, J., Bekelman, D. & Miyasaki, J. M. Parkinson disease patient's perspectives on palliative care needs What are they telling us? *Neurol. Clin. Pract.* **6**, 209–219 (2016).

36. Schilling, B. K. *et al.* Impaired leg extensor strength in individuals with Parkinson disease and relatedness to functional mobility. *Park. Relat. Disord.* **95**, 776–780 (2009).

37. McQuillen, A. D., Licht, M. H. & Licht, B. G. Contributions of disease

severity and perceptions of primary and secondary control to the prediction of psychosocial adjustment to Parkinson's disease. *Heal. Psychol.* **22**, 504–512 (2003).

38. Burgess, S. & Rassmusson, X. Parkinson ' s Narratives : Onset Experiences and Perceived Benefits of Preferred Physical Activity. *Adv. Soc. Sci. Res. J.* **3**, 150–160 (2016).

39. Horak, F. B. Objective Biomarkers of Balance and Gait for Parkinson's Disease using Body Worn Sensors. **28**, 1544–1551 (2013).

40. Morris, M. E., Huxham, F., McGinley, J., Dodd, K. & Iansek, R. The biomechanics and motor control of gait in Parkinson disease. *Clin. Biomech.* **16**, 459–470 (2001).

41. Mak, M. K. Y. & Hui-Chan, C. W. Y. Switching of movement direction is central to Parkinsonian bradykinesia in sit-to-stand. *Mov. Disord.* **17**, 1188–1195 (2002).

42. Van Uem, J. M. T. *et al.* Quantitative timed-up-and-go parameters in relation to cognitive parameters and health- related quality of life in mild-to-moderate Parkinson's disease. *PLoS One* **11**, 1–15 (2016).

43. Zijlstra, A., Mancini, M., Lindemann, U., Chiari, L. & Zijlstra, W. 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**, 75 (2012).

44. Louter, M. *et al.* Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency. *Sleep Med.* **14**, 668–674 (2013).

45. Koerts, J., König, M., Tucha, L. & Tucha, O. Working capacity of patients

with Parkinson's disease – A systematic review. *Parkinsonism Relat. Disord.* **27**, 9–24 (2016).

46. Wilcox, S. K. Extending palliative care to patients with Parkinson's disease. *Br. J. Hosp. Med. (London, Engl. 2005)* **71**, 26–30 (2010).

47. Lomax, C. L., Brown, R. G. & Howard, R. J. Measuring disability in patients with neurodegenerative disease using the 'Yesterday Interview'. *Int. J. Geriatr. Psychiatry* **19**, 1058–1064 (2004).

48. Karakaya, M. G., Bilgin, S. C., Ekici, G., Köse, N. & Otman, A. S. Functional mobility, depressive symptoms, level of independence, and quality of life of the elderly living at home and in the nursing home. *J. Am. Med. Dir. Assoc.* **10**, 662–666 (2009).

49. Lin, S. I., Lee, H. C., Chang, K. C., Yang, Y. C. & Tsauo, J. Y. Functional mobility and its contributing factors for older adults in different cities in Taiwan. *J. Formos. Med. Assoc.* 1–8 (2013) doi:10.1016/j.jfma.2016.01.011.

50. Podsiadlo, D., Richardson, S., Podsiadlo, J. D., Bscpt, S. & Richardson, M. D. J. The Timed "Up & Go": A Test of Basic Functional Mobility for Frail Elderly Persons. *J. Am. Geriatr. Soc.* **39**, 142–148 (1991).

51. Parashos, S. A. *et al.* Validation of an ambulatory capacity measure in Parkinson disease: A construct derived from the unified Parkinson's disease rating scale. *J. Parkinsons. Dis.* **5**, 67–73 (2015).

52. Bloem, B. R. *et al.* Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. *Mov. Disord.* **31**, 1342–55 (2016).

53. Morris, M. E., Martin, C. L. & Schenkman, M. L. Striding out with

Parkinson disease: evidence-based physical therapy for gait disorders. *Phys. Ther.* **90**, 280–288 (2010).

54. Behrman, A. L., Cauraugh, J. H. & Light, K. E. Practice as an intervention to improve speeded motor performance and motor learning in Parkinson's disease. *J. Neurol. Sci.* **174**, 127–136 (2000).

55. Canning, C. G., Ada, L. & Woodhouse, E. Multiple-task walking training in people with mild to moderate Parkinson's disease: a pilot study. *Clin. Rehabil.* **22**, 226–233 (2008).

56. Meyer, A. Focus on Pediatrics : Functional Mobility vs . Exercise. *Directions* **3**, 46–48 (2009).

57. Auger, C. *et al.* Powered Mobility for Middle-Aged and Older Adults. *Am. J. Phys. Med. Rehabil.* **87**, 666–680 (2008).

58. Kumar, A. *et al.* Test-retest reliability of the functional mobility assessment (FMA): A pilot study. *Disabil. Rehabil. Assist. Technol.* **8**, 213–219 (2013).

59. Bettecken, K. *et al.* Association of kinematic gait parameters with health-related quality of life in Parkinson's disease. *PLoS ONE, eingereicht* 1–11 (2017).

60. Ferreira, J. J. *et al.* Clinical parameters and tools for home-based assessment of Parkinson's disease: Results from a delphi study. *J. Parkinsons. Dis.* **5**, 281–290 (2015).

61. Swarowsky, A., Santos, M. P., Silva, B. A., Ovando, A. C. & Ilha, J. Comparison between two functional mobility scales for Parkinson's disease directly applied to physical therapy practice : cross-cultural adaptation and measurement properties. *Eur. J. Phys. Rehabil. Med.* (2016).

62. van Uem, J. M. T. *et al.* Health-Related Quality of Life in patients with Parkinson's disease-A systematic review based on the ICF model. *Neurosci. Biobehav. Rev.* **61**, 26–34 (2016).

63. World Health Organization. *Towards a Common Language for Functioning, Disability and Health: The International Classification of Functioning, Disability and Health*. *International Classification* vol. 1149 (2002).

64. Bouça-Machado, R., Maetzler, W. & Ferreira, J. J. What is Functional Mobility Applied to Parkinson's Disease? *J. Parkinsons. Dis.* **8**, 121–130 (2018).

65. Santos, M. P., Da Silva, B. A., Ovando, A. C., Ilha, J. & Swarowsky, A. Comparison between two functional mobility scales for Parkinson's disease directly applied to physical therapy practice: cross-cultural adaptation and measurement properties. *Eur J Phys Rehabil Med* **53**, 664–675 (2017).

66. Verheyden, G. *et al.* Psychometric properties of 3 functional mobility tests for people with Parkinson disease. *Phys. Ther.* **94**, 230–9 (2014).

67. Higgins JPT. Cochrane Handbook for Systematic Reviews of Interventions. *The Cochrane Collaboration* 1–265 (2006) doi:10.3233/PRM-2010-0129.

68. Leal Rato, M. *et al.* Nocebo response in Parkinson's disease: A systematic review and meta-analysis. *Park. Relat. Disord.* **65**, 13–19 (2019).

69. Elble, R. *et al.* Task force report: Scales for screening and evaluating tremor: Critique and recommendations. *Mov. Disord.* **28**, 1793–1800 (2013).

70. Antonini, A. *et al.* Wearing-off scales in Parkinson's disease: Critique and recommendations. *Mov. Disord.* **26**, 2169–2175 (2011).

71. Prinsen, C. A. C. *et al.* How to select outcome measurement instruments for

outcomes included in a ‘Core Outcome Set’ - a practical guideline. *Trials* **17**, 1–10 (2016).

72. Morris, S., Morris, M. E. & Iansek, R. Reliability of measurements obtained with the Timed ‘Up, & Go’ Test in people with Parkinson disease. *Phys. Ther.* **81**, 810–818 (2001).

73. Podsiadlo, D; Richardson, S. The Timed ”Up & Go”: A test of basic functional mobility for frail elderly persons. *J. Am. Geriatr. Soc.* **39**, 142–148 (1991).

74. Campbell, C. M., Rowse, J. L., Ciol, M. A. & Shumway-cook, A. The effect of cognitive demand on timed up and go performance in older adults with and without Parkinson Disease. *Neurol. Rep.* **27**, 2–7 (2003).

75. Hofheinz, M. & Schusterschitz, C. Dual task interference in estimating the risk of falls and measuring change: A comparative, psychometric study of four measurements. *Clin. Rehabil.* **24**, 831–842 (2010).

76. Keus, S. H. J., Nieuwboer, A., Bloem, B. R., Borm, G. F. & Munneke, M. Clinimetric analyses of the Modified Parkinson Activity Scale. *Park. Relat. Disord.* **15**, 263–269 (2009).

77. Nieuwboer, A., De Weerdt, W., Dom, R., Bogaerts, K. & Nuyens, G. Development of an activity scale for individuals with advanced Parkinson disease: reliability and ‘on-off’ variability. *Phys. Ther.* **80**, 1087–1096 (2000).

78. Mayhew, T. & Rothstein, J. Measurement of muscle performance with instruments. *Percept. Mot. Skills* **80**, 163–166 (1995).

79. Duncan, R. P., Leddy, A. L. & Earhart, G. M. Five times sit-to-stand test

performance in Parkinson's disease. *Arch. Phys. Med. Rehabil.* **92**, 1431–1436 (2011).

80. Alfieri, F. M. *et al.* Functional mobility and balance in community-dwelling elderly submitted to multisensory versus strength exercises. *Clin. Interv. Aging* **5**, 181–185 (2010).

81. Pavasini, R. *et al.* Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. *BMC Med.* **14**, 1–9 (2016).

82. Rikli, R. E. & Jones, C. J. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. *Gerontologist* **53**, 255–267 (2013).

83. de Villar, L. O. P. *et al.* Test-retest reliability and minimal detectable change scores for the short physical performance battery, one-legged standing test and timed up and go test in patients undergoing hemodialysis. *PLoS One* **13**, 1–16 (2018).

84. Freire, A. N., Guerra, R. O., Alvarado, B., Guralnik, J. M. & Zunzunegui, M. V. Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. *J. Aging Health* **24**, 863–878 (2012).

85. Steffen, T. & Seney, M. Test-Retest Reliability and Minimal Detectable Change on Balance and Ambulation Tests, the 36-Item Short-Form Health Survey, and the Unified Parkinson Disease Rating Scale in People With Parkinsonism. *Phys. Ther.* **88**, 733–746 (2008).

86. Combs, S. A., Diehl, M. D., Filip, J. & Long, E. Short-distance walking speed tests in people with Parkinson disease: Reliability, responsiveness, and

validity. *Gait Posture* **39**, 784–788 (2014).

87. Hassett, L., de Bie, R. A., Moseley, A. M., Bosman, J. M. & van Loo, M. A. Test–re-test reliability of walking speed, step length and step width measurement after traumatic brain injury: a pilot study. *Brain Inj.* **18**, 1041–1048 (2004).

88. Guyatt, G. H. *et al.* The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* **132**, 919–923 (1985).

89. Schenkman, M., Cutson, T. M., Kuchibhatla, M., Chandler, J. & Pieper, C. Reliability of Impairment and Physical Performance Measures for Persons With Parkinson's Disease. *Phys. Ther.* **77**, 19–27 (2017).

90. Suteerawattananon, M. & Protas, E. J. Reliability of outcome measures in individuals with Parkinson's disease. *Physiother. Theory Pract.* **16**, 211–218 (2000).

91. Ziegler, K., Schroeteler, F., Ceballos-Baumann, A. O. & Fietzek, U. M. A new rating instrument to assess festination and freezing gait in Parkinsonian patients. *Mov. Disord.* **25**, 1012–1018 (2010).

92. Snijders, A. H., Haaxma, C. A., Hagen, Y. J., Munneke, M. & Bloem, B. R. Freezer or non-freezer: Clinical assessment of freezing of gait. *Park. Relat. Disord.* **18**, 149–154 (2012).

93. Qutubuddin, A. A. *et al.* Validating the Berg Balance Scale for patients with Parkinson's disease: A key to rehabilitation evaluation. *Arch. Phys. Med. Rehabil.* **86**, 789–792 (2005).

94. Berg, K., Wood-dauphinee, S. L., Williams, J. I. & Maki, B. Measuring Balance in the Elderly : Validation of an Instrument. *Can. J. Public Heal.* **83**,

S7–S11 (2014).

95. Franchignoni, F., Horak, F., Godi, M., Nardone, A. & Giordano, A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J. Rehabil. Med.* **42**, 323–331 (2013).

96. Leddy, A. L., Crowner, B. E. & Earhart, G. M. Utility of the mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J. Neurol. Phys. Ther.* **35**, 90–97 (2011).

97. Duncan, P. W., Weiner, D. K., Chandler, J. & Studenski, S. Functional reach: A new clinical measure of balance. *Journals Gerontol.* **45**, 192–197 (1990).

98. Goetz, C. G. *et al.* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Mov. Disord.* **23**, 2129–2170 (2008).

99. Movement Disorder Society. The Unified Parkinson's Disease Rating Scale (UPDRS): Status and Recommendations. *Mov. Disord.* **18**, 738–750 (2003).

100. Santos, M. P., da Silva, B. A., Ovando, A. C., Ilha, J. & Swarowsky, A. Comparison between two functional mobility scales for Parkinson's disease directly applied to physical therapy practice: cross-cultural adaptation and measurement properties. *Eur. J. Phys. Rehabil. Med.* **53**, 664–675 (2017).

101. Tosserams, A., de Vries, N. M., Bloem, B. R. & Nonnekes, J. Multidisciplinary Care to Optimize Functional Mobility in Parkinson Disease. *Clinics in Geriatric Medicine* vol. 36 159–172 (2020).

102. Bouça-Machado, R. *et al.* Measurement Instruments to Assess Functional Mobility in Parkinson's Disease: A Systematic Review. *Movement Disorders*

Clinical Practice vol. 7 129–139 (2020).

103. Varelius, J. The value of autonomy in medical ethics. *Med. Heal. Care Philos.* **9**, 377–388 (2006).

104. Rajiah, K., Maharajan, M. K., Yeen, S. J. & Lew, S. Quality of Life and Caregivers' Burden of Parkinson's Disease. *Neuroepidemiology* vol. 48 131–137 (2017).

105. Morris, R. *et al.* A model of free-living gait: A factor analysis in Parkinson's disease. *Gait Posture* **52**, 68–71 (2017).

106. Geroin, C. *et al.* Does dual-task training improve spatiotemporal gait parameters in Parkinson's disease? *Park. Relat. Disord.* **55**, 86–91 (2018).

107. Muro-de-la-Herran, A., García-Zapirain, B. & Méndez-Zorrilla, A. Gait analysis methods: An overview of wearable and non-wearable systems, highlighting clinical applications. *Sensors (Switzerland)* **14**, 3362–3394 (2014).

108. Wu, G. *et al.* ISB recommendation on definitions of joint coordinate system of various joints for the reporting of human joint motion - Part I: Ankle, hip, and spine. *Journal of Biomechanics* vol. 35 543–548 (2002).

109. Maetzler, W., Klucken, J. & Horne, M. A clinical view on the development of technology-based tools in managing Parkinson's disease. *Mov. Disord.* **31**, 1263–1271 (2016).

110. Hass, C. J. *et al.* Quantitative normative Gait data in a large cohort of ambulatory persons with parkinson's disease. *PLoS One* **7**, 1–5 (2012).

111. Espay, A. J. *et al.* A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health

technologies. *Movement Disorders* vol. 34 657–663 (2019).

112. Del Din, S., Godfrey, A., Galna, B., Lord, S. & Rochester, L. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. *J. Neuroeng. Rehabil.* **13**, 46 (2016).

113. Del Din, S., Godfrey, A. & Rochester, L. Validation of an Accelerometer to Quantify a Comprehensive Battery of Gait Characteristics in Healthy Older Adults and Parkinson's Disease: Toward Clinical and at Home Use. *IEEE J. Biomed. Heal. Informatics* **20**, 838–847 (2016).

114. Heijmans, M. *et al.* Monitoring Parkinson's disease symptoms during daily life: a feasibility study. *npj Park. Dis.* **5**, (2019).

115. Hausdorff, J. M. Gait dynamics in Parkinson's disease: Common and distinct behavior among stride length, gait variability, and fractal-like scaling. *Chaos* **19**, (2009).

116. König, N., Singh, N. B., Baumann, C. R. & Taylo, W. R. Can gait signatures provide quantitative measures for aiding clinical decision-making? A systematic meta-analysis of gait variability behavior in patients with Parkinson's disease. *Frontiers in Human Neuroscience* vol. 10 (2016).

117. Schlachetzki, J. C. M. *et al.* Wearable sensors objectively measure gait parameters in Parkinson's disease. *PLoS One* **12**, (2017).

118. Rovini, E., Maremmani, C. & Cavallo, F. How wearable sensors can support parkinson's disease diagnosis and treatment: A systematic review. *Frontiers in Neuroscience* vol. 11 (2017).

119. Kim, D. W., Hassett, L. M., Nguy, V. & Allen, N. E. A Comparison of Activity Monitor Data from Devices Worn on the Wrist and the Waist in

People with Parkinson's Disease. *Mov. Disord. Clin. Pract.* 1–7 (2019) doi:10.1002/mdc3.12850.

120. Godfrey, A. *et al.* Towards holistic free-living assessment in Parkinson's disease: Unification of gait and fall algorithms with a single accelerometer. *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS* **2016-Octob**, 651–654 (2016).

121. Höchsmann, C. *et al.* Validity of activity trackers, smartphones, and phone applications to measure steps in various walking conditions. *Scand. J. Med. Sci. Sport.* **28**, 1818–1827 (2018).

122. Van Wegen, E. *et al.* The effects of visual rhythms and optic flow on stride patterns of patients with Parkinson's disease. *Park. Relat. Disord.* **12**, 21–27 (2006).

123. Hoehn, M. M. & Yahr, M. D. Parkinsonism: onset, progression, and mortality. *Neurology* **17**, 427–442 (1967).

124. Martínez-Martín, P. *et al.* Analysis of four scales for global severity evaluation in Parkinson's disease. *NPJ Park. Dis.* **2**, 16007 (2016).

125. Bloem, B. R. *et al.* Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. *Movement Disorders* vol. 31 1342–1355 (2016).

126. Bjornestad, A., Tysnes, O. B., Larsen, J. P. & Alves, G. Reliability of Three Disability Scales for Detection of Independence Loss in Parkinson's Disease. *Parkinsons. Dis.* **2016**, (2016).

127. Doherty, A. *et al.* Large scale population assessment of physical activity using wrist worn accelerometers: The UK biobank study. *PLoS One* **12**,

(2017).

128. Hickey, A., Del Din, S., Rochester, L. & Godfrey, A. Detecting free-living steps and walking bouts: validating an algorithm for macro gait analysis. *Physiol. Meas.* **38**, N1–N15 (2017).

129. Lyons, G. M., Culhane, K. M., Hilton, D., Grace, P. A. & Lyons, D. A description of an accelerometer-based mobility monitoring technique. *Med. Eng. Phys.* **27**, 497–504 (2005).

130. Pham, M. H. *et al.* Validation of a step detection algorithm during straight walking and turning in Patients with Parkinson's disease and older adults using an inertial measurement unit at the lower back. *Front. Neurol.* **8**, 1–9 (2017).

131. Aron, A. *Statistics for Psychology*. (2003).

132. Serrao, M. *et al.* Prediction of responsiveness of gait variables to rehabilitation training in Parkinson's disease. *Front. Neurol.* **10**, (2019).

133. Warmerdam, E. *et al.* Long-term unsupervised mobility assessment in movement disorders. *The Lancet Neurology* vol. 19 462–470 (2020).

134. Rispens, S. M. *et al.* Fall-related gait characteristics on the treadmill and in daily life. *J. Neuroeng. Rehabil.* **13**, (2016).

135. Artusi, C. A. *et al.* Integration of technology-based outcome measures in clinical trials of Parkinson and other neurodegenerative diseases. *Park. Relat. Disord.* **46**, S53–S56 (2018).

136. Pasluosta, C. F., Gassner, H., Winkler, J., Klucken, J. & Eskofier, B. M. An emerging era in the management of Parkinson's disease: Wearable technologies and the internet of things. *IEEE J. Biomed. Heal. Informatics*

19, 1873–1881 (2015).

137. De Roos, P. *et al.* A Consensus Set of Outcomes for Parkinson's Disease from the International Consortium for Health Outcomes Measurement. *J. Parkinsons. Dis.* **7**, 533–543 (2017).

138. Toosizadeh, N. *et al.* Motor performance assessment in Parkinson's disease: Association between objective in-clinic, objective in-home, and subjective/semi-objective measures. *PLoS One* **10**, 1–15 (2015).

139. Ferreira, J. J. *et al.* Quantitative home-based assessment of Parkinson's symptoms: The SENSE-PARK feasibility and usability study. *BMC Neurol.* **15**, 89 (2015).

140. Maetzler, W. & Rochester, L. Body-worn sensors--the brave new world of clinical measurement? *Mov. Disord.* **30**, 1203–1205 (2015).

LIST OF PUBLICATIONS

Bouça-Machado R, Maetzler W, Ferreira JJ. What is Functional Mobility Applied to Parkinson's Disease? J Parkinsons Dis. 2018;8(1):121-130. **IF: 5.178.**

Bouça-Machado R, Duarte GS, Patriarca M, et al. Measurement Instruments to Assess Functional Mobility in Parkinson's Disease: A Systematic Review. Mov Disord Clin Pract. 2019;7(2):129-139. Published 2019 Dec 11. **IF: 0.76.**

Bouça-Machado R, Gonçalves N, Lousada I, Patriarca MA, Costa P, Nunes R, Dias S, Caldas AC, Valadas A, Lobo PP, Guedes LC, Rosa MM, Coelho M and Ferreira JJ (2020) Patients and Health Professional's Perspective of Functional Mobility in Parkinson's Disease. Front. Neurol. 11:575811. doi: 10.3389/fneur.2020.575811. **IF: 2.889.**

Bouça-Machado R, Jalles C, Guerreiro D, et al. Gait Kinematic Parameters in Parkinson's Disease: A Systematic Review. J Parkinsons Dis. 2020;10.3233/JPD-201969. **IF: 5.178.**

Bouça-Machado R, Branco D, Fonseca G, Fernandes R, Abreu D, Guerreiro T, Ferreira JJ and The CNS Physiotherapy Study Group. Kinematic and Clinical Outcomes to Evaluate the Efficacy of a Multidisciplinary Intervention on Functional Mobility in Parkinson’s Disease. Front. Neurol. 2021; 12:637620. doi: 10.3389/fneur.2021.637620. **IF: 2.889.**

FACSIMILE

Journal of Parkinson's Disease 8 (2018) 121–130
DOI 10.3233/JPD-171233
IOS Press

Review

What is Functional Mobility Applied to Parkinson's Disease?

Raquel Bouça-Machado[a,b], Walter Maetzler[c] and Joaquim J. Ferreira[a,b,d,*]
[a]*Instituto de Medicina Molecular, Lisbon, Portugal*
[b]*CNS-Campus Neurológico Sénior, Torres Vedras, Portugal*
[c]*Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany*
[d]*Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Portugal*

Accepted 1 November 2017

Abstract. Although yet poorly defined and often misused, the concept of functional mobility has been used in research studies as a more global and ecological outcome of patients' health status. Functional mobility is a person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living, at home, work and in the community. Parkinson's disease (PD) has a direct impact on patients' motor control and on mobility in general. Even with optimal medical management, the progression of PD is associated with mounting impairments at different levels of body function, causing marked limitations in a wide variety of activities, as well as a severe disability and loss of autonomy. Despite this, for everyday functioning PD patients need to have a good functional mobility that allow them to get around effortlessly in a reasonable amount of time to access to the same environments as others. This paper reviewed the concept of functional mobility applied to PD. This was done through an International Classification of Functioning and Disability (ICF) perspective. Recommendations to address the known factors that contribute to a poor functional mobility were outlined while suggestions for clinical practice and research were made.

Keywords: Functional mobility, international classification of functioning, disability and health, Parkinson's disease

INTRODUCTION

What is functional mobility? Is there a difference in the functional mobility of two Parkinson's disease (PD) patients with similar gait disturbance, one using an assistive mobility device, the other not? How do health professionals account for these differences? This paper reviewed the functional mobility concept and its implications for PD patients' everyday functioning. It followed the International Classification of Functioning, Disability and Health (ICF) model. The ICF model goes beyond the usual focus on a diagnosis, incorporating detailed information on how functional, societal aspects, and contextual factors contribute to a patient's health condition. Therefore, it allows to better understand and describe health and health-related problems and to improve communication between patients, health professionals, researchers, and policy makers [1, 2]. This model have been previously used for studying PD patients' disability [3–5] and quality-of-life [6].

A PubMed search, from inception to June 2017, was made using the following search terms were: "Functional mobility", "Mobility", "Disability", "Participation restrictions" and "Parkinson's disease". Language and publication restrictions were not applied. Being a narrative review a systematic selection of the included studies was also not

*Correspondence to: Joaquim J. Ferreira, Laboratorio de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal. Tel.: +351 21 7802120; E-mail: joaquimjferreira@gmail.com.

ISSN 1877-7171/18/$35.00 © 2018 – IOS Press and the authors. All rights reserved
This article is published online with Open Access and distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC 4.0).

performed. In order to fully address the opening question, the concept of functional mobility was introduced and, through the ICF model, the factors related with PD body functions impairments and activity limitations that could affect functional mobility were presented. It was also discussed how functional mobility limitation may restrict patients' everyday functioning and the potential impact of contextual factors. Additionally, in the end of the review, the most suitable outcome tools and interventions to address PD functional mobility limitations were appraised.

FUNCTIONAL MOBILITY

Functional mobility is increasingly used as an outcome in clinical studies as it may provide a more global and functional perspective of patients' health conditions. However, it is still a poorly defined concept, being commonly equated with mobility or functionality (Fig. 1). According to Forhan & Gill in a review on obesity [7], functional mobility is the physiological ability of people to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living (ADL), at home, work and in the community. It includes movements like standing, bending, walking and climbing, which are the building blocks of ADL, and hence crucial to an individual's independent living and global health status [7–11]. Impaired functional mobility has been found to be associated with a greater risk of falls, loss of independence, and institutionalization [4, 10].

INTERNATIONAL CLASSIFICATION OF FUNCTIONING AND DISABILITY (ICF)

As formulated by the World Health Organization (WHO) in 2001, the ICF is conceptualized as a universal framework focused on the description of how people live with a health condition (Fig. 2) [4, 7, 12]. Three levels of human functioning are classified: 1) body functions and structures as physiological and psychological functions, as well as body impairments, and anatomical deficiencies; 2) limitations in performing tasks or actions; and 3) participation restrictions in daily-life. Contextual factors can be either personal, such as age, gender, experiences, and interests; or environmental like physical, social, and attitudinal environment. This model assumes that all levels of human functioning and contextual factors are interconnected, i.e., impairments in body functions and structures may induce problems in activities that leads to participation restrictions, which can be facilitated or hindered by environmental or personal factors [1, 3].

PARKINSON'S DISEASE

PD is the second most common neurodegenerative disease [3, 13, 14]. It is characterized by its motor (bradykinesia, associated with rest tremor and rigidity) and non-motor problems [1, 15, 16].

Despite the variety of therapeutic options, disease progression usually leads to impairments at different levels of body function, limitations in a wide variety of ADL, and in severe disability, social

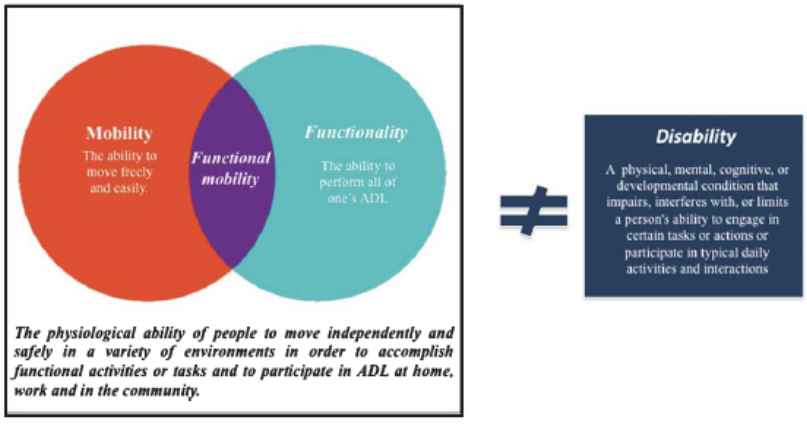


Fig. 1. Functional mobility concept.

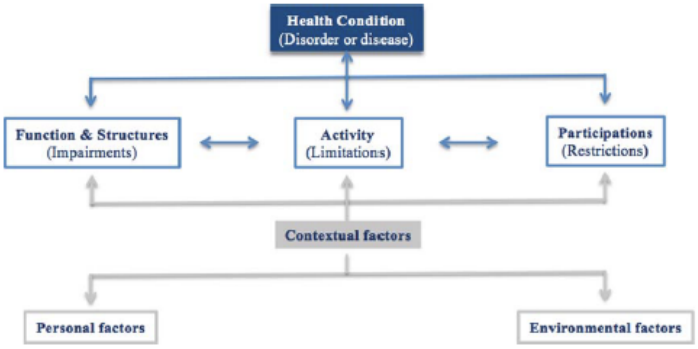


Fig. 2. ICF framework. Adapted from World Health Organization (2002) [12].

embarrassment and increasing dependence. Gradually, it reduces health-related quality of life (HrQoL) and increases the burden of patients and caregivers [3, 5, 17, 18].

FUNCTIONAL MOBILITY IN PD: ICF-BASED METHODOLOGY

In order to improve patients' global health status and reduce disease burden associated with functional immobility, it is important to understand a patient's personal needs, activity and environment [4]. In this section, we present the three levels of human functioning included in the ICF framework: 1) the impairments to body structures and functions relevant to PD patients' functional mobility; 2) how the activities that compose functional mobility are compromised by these impairments, in a functional perspective; 3) participation restrictions that PD patients may encountered, induced by functional mobility limitations; 4) lastly, some examples of frequent personal and environmental factors that influence the first three domains are presented (Figs. 3 and 4).

Body functions and structures domain

Functional mobility requires dynamic neural control to quickly and effectively adapt locomotion, balance, and postural transitions to changing environmental and task conditions. This in turn requires sensorimotor agility that involves: 1) coordination of complex sequences of movements, 2) on-going evaluation of environmental cues and contexts, 3) the ability to quickly switch motor programs with environmental changes, and 4) the ability to maintain safe mobility during multiple motor and cognitive tasks [7, 11].

Motor symptoms

Motor symptoms may contribute to functional mobility impairments directly, through gait impairments cause by non-dopaminergic pathways degeneration and indirectly due to bradykinesia and rigidity, which affect PD patients gait, balance and transitions [14, 19–21]. Gait impairments are complex to characterize because of the difficulty in distinguishing between the specific contribution of sensory, motor, and cognitive deficits and other factors like fear, muscle weakness or misjudgement of hazard risk. Evidence suggests that in later stage cholinergic dysfunction in the pedunculopontine nucleus has a key role in gait disturbance [14].

With disease progression, severe and disabling postural deformities are usually present (e.g., camptocormia, antecollis, pisa syndrome or scoliosis). These interfere with daily living activities, often leading to falls. Although still not well understood, a series of central and peripheral causes have been proposed to explain the complex and multifaceted underlying pathophysiology of these deformities [14, 22].

Non-motor symptoms

Functional mobility is also affected by PD non-motor symptoms.

The inability to simultaneously carry out a cognitive and a motor task is a predictor of falls and a critical element to functional mobility. This has been found to be more difficult for PD patients than

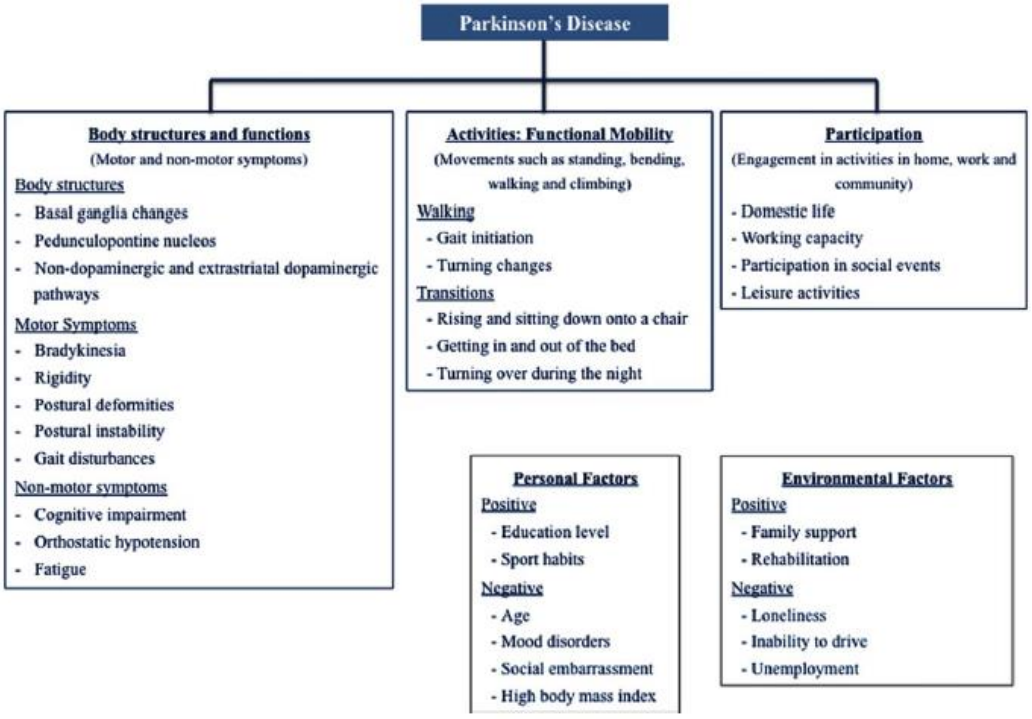


Fig. 3. The concept of functional mobility applied to PD in an ICF perspective.

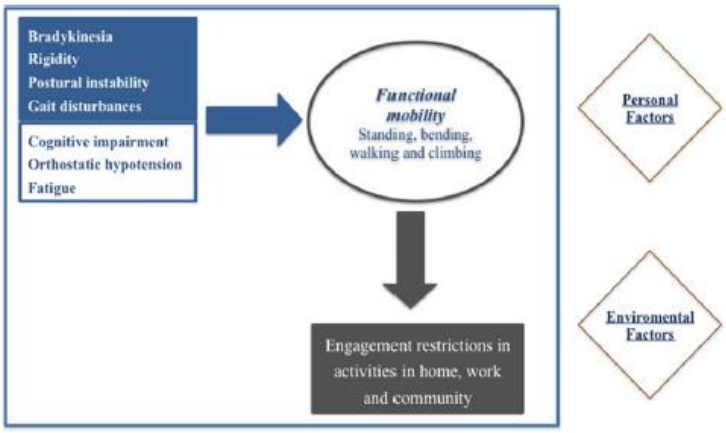


Fig. 4. Human domains and contextual factors contribution to PD functional mobility.

healthy controls, especially when walking is one of the tasks [11].

Dysautonomia seems also to play an important role in PD functional mobility. In concrete, orthostatic hypotension symptoms are a frequent complaint, associated to a higher prevalence of falls and a more rapid PD progression. It also affects mobility in general, patients' confidence in their own abilities and may undermine an active style of life [23].

Additionally, patients have frequently fatigue complaints, which has physical and psychological repercussions in PD functional mobility. The feeling of being tired all day and of not knowing how to get through the day makes fatigue, in patients perspective one of the symptoms most difficult to cope with [14, 24].

Activity domain

In PD, activity limitations range from minor difficulties (e.g., fine motor coordination tasks) to more serious problems (e.g., skilled ADL motor tasks). Patients generally experience a loss of functional mobility resulting from the neurodegenerative effects of the disease in posture, balance, postural stability, and gait. Loss of independence in performing activities arises in the transition between Hoehn and Yahr (H&Y) stages III and IV, and activities such as walking, housework, dressing and transfers are the most affected [1, 5, 7, 9, 13, 25, 26].

Walking

Patients describe gait disorders as a loss of confidence in walking, a feeling of imbalance or reduced ability to negotiate uneven terrain or stairs. A slower walking speed is often the first noticeable sign of parkinsonism [19].

Gait is defined as the forward propulsion of the body with rhythmical coordination of all four limbs combined with control of dynamic equilibrium of the body's center of mass. It is also a complex sensorimotor activity that involves spatial-temporal coordination of the legs, trunk and arms, as well as dynamic equilibrium.

Gait of PD patients have been shown to be: 1) significantly slower (typically 40–60 m/min rather than 75–90/min in age-matched controls), 2) with less foot clearance (foot's height during the swing phase) and an increased double phase support in the gait cycle (from the usual 20–30% of the gait cycle to over 35%), 3) with smaller step lengths (0.4–0.9 m for PD patients after withdrawal of medication or 0.8–1.0 m for those at the end-of-dose compared with 1.2–1.5 m for healthy older people), 4) narrow based, 5) asymmetrically reduced or absent arm swing 6) and stooped posture. Small shuffling steps (resulting from the reduced ground clearance and increased double phase support in gait cycle), a bilaterally reduced arm swing and slow, en bloc turns are also common [1, 14, 27, 28].

Walking problems are usually more pronounced during gait initiation, turning, walking through doorways and when performing simultaneous motor or cognitive tasks. These relates with the triggering of festination and freezing episodes, characterize by the sudden inability to generate effective stepping movements [28]. During festination episodes, the feet are behind the center of gravity, which causes rapid small steps. Freezing episodes are described by patients as having the feet "glued to the floor", which usually does not present as complete akinesia, but rather as shuffling with small steps or trembling of the legs.

Transitions

Throughout the course of disease, transitions become truly affected and predict risk of falls. Are particularly problematic: rising from, and sitting down on a chair, getting in or out and turning over in bed [1, 27]. Sitting-to-standing is a complex component of some everyday functional tasks that requires the body to accelerate forward and then upward, and to transfer from a large to a small base of support to achieve an uprightb stance [1, 29]. PD patients exhibit a general slowness when compared to control subjects in performing this tasks with a spatiotemporal pattern preserved [30]. This indicates that PD patients' problems are not related with the selection, but in initiating and sequencing the appropriate motor program. Additionally, task analysis has shown that PD patients take a significantly longer time to complete each individual phase and a have a significantly smaller peak hip extension and ankle dorsiflexion torque when compared with control subjects [29]. The likely responsible factors are weak limb support against gravity (particularly reduced muscle power of the hip extensors), the difficulty in muscle activation and the inability to counteract unexpected external forces, vestibular impairment, and orthostatic hypotension [1, 29, 31]. PD patients seem also to have less body position changes during the night compared to the general population, which may affect sleep quality. Impaired bed mobility is often attributed to nocturnal hypokinesia, yet pain and overall muscle weakness and external factors such as bedcovers or reduced levels of levodopa at night, may also contribute to difficulty turning over in bed. The precise causal mechanism is still not clear [1, 32].

Participation domain

Participation problems are aspects of life as a member of society hindered by activity limitations [11]. Impairments in PD patients' functional mobility, may

compromise involvement in leisure, work or social aspects of life in both household and community settings.

Working capacity, often affected in PD patients, is a concrete example of an important participation restriction related with functional mobility, not only because of work role in active fighting against exclusion from social and occupational environments, but also as livelihood [7, 33].

Contextual factors

Contextual factor could be personal or environmental, and have a positive or negative effect.

Age, a high body mass index, feeling disabled and social embarrassed represent some examples of personal factors with potential negative influence on PD patients' functional mobility. In contrast, high education levels and sport habits are examples of factors with a positive influence [1, 7, 18].

Similarly, unemployment, loneliness and the inability to drive, are examples of possible environmental negative factors. The existence of family caregivers is the most valued environmental positive factor, once PD patients rely on them for most of their ADL needs [1, 7, 18].

Within personal factors, perceived control (i.e., the person's belief of controlling the situations and act in accordance to that) is a prime candidate and a powerful predictor of active life and functional mobility [26]. PD clearly affects patients' perceived control, not only because of the impact of motor and non-motor symptoms on daily functional mobility, but also because of the unpredictability and social embarrassment frequently associated. This has multiple manifestations in patients' life, such as: to avoid walking on the street or in less familiar places due to fear of falling, concerns scheduling appointments because of not being sure of being able to get through it or to stay away from public places or social events to prevent feeling embarrassed with disease limitations [2, 16, 19, 26, 34, 35].

FUNCTIONAL MOBILITY: SCALES AND TOOLS AVAILABLE

Functional mobility is a global disease-related feature that may provide adequate information about treatment responses and disease course, as it may encompasses one of the outcomes most relevant to patients' daily lives [9].

Due to the heterogeneity and complexity of PD, its fluctuating nature and unpredictable medication response in advanced disease stages, clinical assessment is challenging and requires continuous prolonged periods of evaluation to reach an accurate picture of symptoms and their fluctuations [36].

The majority of PD studies that have measured functional mobility used rating scales like the MDS-UPDRS, infrequent events (e.g., falls) or subjective reports (e.g., diaries or questionnaires). Objective assessments, including the five-time sit-to-stand (FTSTS) test and the timed up-and-go (TUG) test, are two of the most commonly used tools [10, 37, 38]. In 2015, Parashos and colleagues validated the "Ambulatory Capacity Measure". This is a measure of functional capacity, previous used in clinical trials, derived from UPDRS items related to falls, freezing, walking, gait and postural instability. It showed to be a good instrument, highly correlated with some of the most used outcome tool to assess functional capacity [39]. However, there is still no consensus about which screening tools are preferred or which outcomes are most suitable for monitoring functional mobility [40].

With technological advances, numerous devices have been created not only with the capacity of reliably evaluating fluctuating or rare events (e.g., freezing of gait or falls) that usually occur outside clinical visits, but also for obtaining more global, objective, and sensible outcomes for assessing patients' performance in ADL [41]. Yet, is still lacking to establish a specific protocol or metrics to measure PD-sensitive and specific functional mobility behaviours [27].

IMPROVING FUNCTIONAL MOBILITY IN PD

Due to PD heterogeneity, patients' experience of mobility impairment and respective coping strategies are very personal. In order to find an effective option is crucial to understand the patients' needs and offer suggestions according to local offerings, personal preferences, and cultural background [9, 11].

Exercise programs

Evidence shows that critical aspects of PD patients' functional mobility impairments (e.g., postural instability) are unresponsive to pharmacological and surgical therapies, making physical therapy an attractive option [9, 11].

Previous animal studies have demonstrated that intense exercise programs can increase dopamine synthesis and release and improve brain function. Aerobic exercise (e.g., treadmill training) has shown to improve gait parameters, quality of life, and levodopa efficacy in PD patients. However, once functional mobility also depends on other components such as dynamic balance, dual tasking, and other sensorimotor skills, aerobic training is not sufficient to improve functional mobility in PD [11]. Task-specific exercises targeting a single, specific balance or gait impairment, in PD patients have also been tested with positive results [9].

Rehabilitation programs have been reported to be effective in preventing and improving PD patients' functional mobility when focusing on aerobic exercises and self-initiated movements, big and quick movements, large and flexible centers of mass control, reciprocal and coordinated movements of arms and legs, and rotational movements of torso over pelvis and pelvis over legs [11].

Strategy training

Strategy training is one of the key elements of physiotherapy PD management. It is defined as teaching the person how to move more easily and to maintain postural stability by using cognitive strategies. This includes two different methods: acquiring new motor skills (learning strategies) and compensating for movement disorders by bypassing the defective basal ganglia (compensating strategies) [42].

There is growing evidence that, at least in early PD, the capacity to learn new motor skills is not affected [42]. One study showed that PD patients with mean disease duration of 7 years have the capacity to learn new upper-limb movement sequences, improve performance and retain it for 48 hours [42, 43]. Another study evaluated a multiple-task gait-training program in mild PD patients (H&Y stages II–III), reporting that study participants could maintain their learned increased multiple-task walking speed over 3 weeks [42, 44].

Compensatory strategies have been shown to be effective in moderate to severe PD patients, however requiring high mental effort and with relatively short-term effects. They include: the use of visual (e.g., white lines on the floor) and auditory (e.g., rhythmical beat provided by a metronome) external cues, the visualization of walking with long steps, mental rehearsal of the desired movement pattern before performing the action and breaking down long or complex motor sequences into parts and focusing on the performance of each individual segment (segmentation).

Through the mechanism of consciously thinking about the desired movement, using the frontal cortex to regulate movement size or timing instead of the defective basal ganglia, PD patients arguably compensate for the neurotransmitter imbalance in the basal ganglia obtaining a more normal gait pattern [42]. The type of strategy, the frequency and duration of training should be considered according to disease severity, the capacity to learn, and whether there are coexisting conditions that limit the ability to practice (Table 1) [42].

Assistive mobility devices

PD patients with functional mobility impairments need to be able to move effortlessly, in a reasonable

Table 1
Strategies training guide adapted from Morris et al. (2010) [42]

	Training strategy: learning strategies to improve performance through practice
Mild to moderate disease	**Program:** – 3 times/week – Peroids of 6 to 8 weeks (motor skill acquisition) – Burst of therapy 2 to 3 times/year (to promote retention of training)
Severe disease **Cognitive impairments** **Compromised skill acquisition**	**Training strategy:** compensatory strategies to by-padd the defective basal ganglia **Use:** External cues, reminders and segmentation of action into simple components **Multi-tasking activities:** use as training strategy, educate the patients on its risks

amount of time throughout their day, accessing the same environments as others [45].

The use of assistive mobility devices (e.g., wheelchairs, walker) increases the ability of individuals to work, perform self-care, and engage in leisure and social activities independently, enhancing their functional performance, autonomy and participation [45–47].

Despite the potential advantages of assistive mobility devices, they are often underused or abandoned. The reason relates to a mismatch between a patient's functional needs, preferences and environmental constrains, and health professionals' perspectives. In 2017, Bettecken et al. [48] reported a relationship between PD patients' gait velocity using an assistive mobile device and their HrQoL. Surprisingly, the study did not show a relevant contribution of gait velocity to HrQoL. Also, a relevant portion of PD patients with high HrQoL preferred a low self-preferred gait velocity to the use of an assistive mobile device. In a study to identify clinicians', patients' and caregivers' perspectives about relevant parameters and assessment tools for PD symptoms [49], Ferreira and colleagues reported that patients and caregivers have different perspectives when selecting the most relevant parameters for evaluating gait and sway domains. Patients and caregivers both highlighted the capability of performing ADL as the most important parameter. For clinicians, time consumed doing specific tasks was the most useful parameter.

IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

If PD patients are unable to move at an intensity and frequency that life requires, they may become excluded from social and occupational environments, which may negative impacts theirs global health status [7, 29].

Although the assessment of specific outcomes, like level of rigidity or intensity of tremor, is important, previous studies have shown that functional limitations, rather than physical impairments, were the most problematic aspect of a PD patient's disability profile [5, 7]. The standard scale for evaluating impairments in PD is the MDS-UPDRS. However, besides being highly time-consuming, the objective evaluation of functional activities is limited. The TUG test is the most used tool to classify functional mobility and has been shown to be a valid predictor of performance in ADL. Yet, an exhaustive measurement system that adequately assesses functional mobility is still needed [3, 7, 8].

More studies are needed to understand the relationship between the use of assistive mobility devices, PD patients' functional mobility and HrQoL. Perceived control may be the key aspect in explaining the intriguing conclusion that Bettecken and colleagues found in their study [48]. As mentioned above, perceived control is a powerful predictor of functioning and it seems that some patients place more value on the capability of performing ADL rather than the time it takes to perform specific tasks [26, 49]. We hypothesize that assistive mobility devices are acknowledge by patients as an effective solution only when perceived as a control gain. Otherwise, the use of assistive mobility devices is seen as a loss of autonomy with negative impact in HrQoL (even objectively improving gait characteristics such as velocity). It would also be interesting and useful to study if, for those PD patients who remain in employment, or who maintain an active social life, this hypothesis is valid.

CONCLUSION

Back to our initial question: is there a difference in the functional mobility of two PD patients with similar gait disturbance, one using an assistive mobility device, the other not? How do health professionals account for these differences?

This question can be seen from two different perspectives.

As a physiological ability, the two patients have the same degree of functional mobility, since what differentiated them was the use of an external device.

As an outcome measure eligible to be improved by a therapeutic intervention, the answer is not so clear. On one hand, assistive mobility devices enable a more active and safer lifestyle, allowing patients to continue to be engaged with their social and occupational environment. For this reason, the patient with an assistive mobility device has better functional mobility. On the other hand, this would only be true if the use of these devices increases patients' perceived control of their situation.

Understanding the determinants of functional mobility in individuals with PD, such as the precedence of perceived control over an improved gait velocity, will help clinicians to more easily select the most appropriate therapeutic interventions based on

an accurate, global, and personalized evaluation of patients' problems [7, 27, 31].

From this review on PD patients functional mobility, we highlight: 1) its benefits as a more global and functional outcome of patient assessment; 2) the important role of exercise programs, training strategies and assistive devices in improving patients' functionality and participation in social environments; and lastly, 3) the importance of taking into account patients' personal needs and wishes and environmental factors in order to optimize treatment strategies.

ACKNOWLEDGMENTS

No specific funding was received for this work.

CONFLICTS OF INTEREST

The authors have no conflict of interest to report.

REFERENCES

[1] Keus S, Munneke M, Graziano M, Paltamaa J, Pelosin E, Domingos J, Bruhlmann S, Ramaswamy B, Prins J, Struiksma C, Rochester L, Nieuwboer A, & Bloem B, on behalf of the Guideline Development Group (2014) European Physiotherapy Guideline for Parkinson's Disease, 1st ed. The Netherlands.

[2] Lomax CL, Brown RG, & Howard RJ (2004) Measuring disability in patients with neurodegenerative disease using the "Yesterday Interview." *Int J Geriatr Psychiatry*, **19**, 1058-1064.

[3] Raggi A, Leonardi M, Ajovalasit D, Carella F, Soliveri P, Albanese A, & Romito L (2011) Disability and profiles of functioning of patients with Parkinson's disease described with ICF classification. *Int J Rehabil Res*, **34**, 141-150.

[4] Leonardi M, Meucci P, Ajovalasit D, Albanesi F, Cerniauskaite M, Invernizzi V, Lembo R, Quintas R, Sattin D, Carella F, Romito L, Soliveri P, Bussone G, D'amico D, Maggi L, Mantegazza R, & Raggi A (2009) ICF in neurology: Functioning and disability in patients with migraine, myasthenia gravis and Parkinson's disease. *Disabil Rehabil*, **31**, S88-S99.

[5] Leonardi M, Raggi A, Ajovalasit D, Bussone G, & D'Amico D (2010) Functioning and disability in Parkinson's disease. *Disabil Rehabil*, **32**(Suppl 1), S23-S32.

[6] van Uem JMT, Marinus J, Canning C, van Lummel R, Dodel R, Liepelt-Scarfone I, Berg D, Morris ME, & Maetzler W (2016) Health-Related Quality of Life in patients with Parkinson's disease-A systematic review based on the ICF model. *Neurosci Biobehav Rev*, **61**, 26-34.

[7] Forhan M, & Gill SV (2013) Obesity, functional mobility and quality of life. *Best Pract Res Clin Endocrinol Metab*, **27**, 129-137.

[8] Swarowsky A, Santos MP, Silva BA, Ovando AC, & Ilha J (2016) Comparison between two functional mobility scales for Parkinson's disease directly applied to physical therapy practice: Cross-cultural adaptation and measurement properties. *Eur J Phys Rehabil Med*, in press.

[9] Burgess S, & Rassmusson X (2016) Parkinson's narratives: Onset experiences and perceived benefits of preferred physical activity. *Adv Soc Sci Res J*, **3**, 150-160.

[10] Lin SI, Lee HC, Chang KC, Yang YC, & Tsauo JY (2017) Functional mobility and its contributing factors for older adults in different cities in Taiwan. *J Formos Med Assoc*, **116**, 72-79.

[11] King LA, & Horak FB (2009) Delaying mobility disability in people with Parkinson disease using a sensorimotor agility exercise program. *Phys Ther*, **89**, 384-393.

[12] World Health Organization (2002) Towards a common language for functioning, disability and health: The International Classification of Functioning, Disability and Health. *Int Classif*, **1149**, 1-22.

[13] Duncan RP, & Earhart GM (2014) Are the effects of community-based dance on Parkinson disease severity, balance, and functional mobility reduced with time? A 2-year prospective pilot study. *J Altern Complement Med*, **20**, 757-763.

[14] Magrinelli F, Picelli A, Tocco P, Federico A, Roncari L, Smania N, Zanette G, & Tamburin S (2016) Pathophysiology of motor dysfunction in Parkinson's disease as the rationale for drug treatment and rehabilitation. *Parkinsons Dis*, **2016**, 1-18.

[15] Kalia LV, & Lang AE (2015) Parkinson's disease. *Lancet*, **6736**, 1-17.

[16] Sveinbjornsdottir S (2016) The clinical symptoms of Parkinson's disease. *J Neurochem*, **139**, 318-324.

[17] Raggi A, Leonardi M, Covelli V, Sattin D, Scaratti C, Schiavolin S, Willems M, & Meucci P (2015) The ICF as a framework to collect and interpret data on the extent and variety of disability in neurological conditions. *NeuroRehabilitation*, **36**, 17-22.

[18] Raggi A, Covelli V, Leonardi M, Meucci P, Scaratti C, Schiavolin S, Willems M, & Sattin D (2015) Determinants of disability using count-based approaches to ICF-based definition of neurological disability. *NeuroRehabilitation*, **36**, 23-29.

[19] Williams DR, & Litvan I (2013) Parkinsonian syndromes. *Contin Lifelong Learn Neurol*, **19**, 1189-1212.

[20] Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, & Deuschl G (2015) MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord*, **30**, 1591-1601.

[21] Robichaud JA, & Corcos DM (2005) Motor deficits, exercise, and Parkinson's disease, *Quest*, **57**, 79-101.

[22] Yoshii F, Moriya Y, Ohnuki T, Ryo M, & Takahashi W (2016) Postural deformities in Parkinson's disease -Mutual relationships among neck flexion, fore-bent, knee-bent and lateral-bent angles and correlations with clinical predictors. *J Clin Mov Disord*, **3**, 1.

[23] Merola A, Romagnolo A, Rosso M, Lopez-Castellanos JR, Wissel BD, Larkin S, Bernardini A, Zibetti M, Maule S, Lopiano L, & Espay AJ (2016) Orthostatic hypotension in Parkinson's disease: Does it matter if asymptomatic? *Parkinsonism Relat Disord*, **33**, 65-71.

[24] Boersma I, Jones J, Carter J, Bekelman D, & Miyasaki JM (2016) Parkinson disease patient's perspectives on palliative care needs What are they telling us? *Neurol Clin Pract*, **6**, 209-219.

[25] Schilling BK, Karlage RE, LeDoux MS, Pfeiffer RF, Weiss LW, & Falvo MJ (2009) Impaired leg extensor strength in

individuals with Parkinson disease and relatedness to functional mobility. *Park Relat Disord*, **15**, 776-780.

[26] McQuillen AD, Licht MH, & Licht BG (2003) Contributions of disease severity and perceptions of primary and secondary control to the prediction of psychosocial adjustment to Parkinson's disease, *Heal Psychol*, **22**, 504-512.

[27] Horak FB (2013) Objective biomarkers of balance and gait for Parkinson's disease using body worn sensors. *Mov Disord*, **28**,1544-1551.

[28] Morris ME, Huxham F, McGinley J, Dodd K, & Iansek R (2001) The biomechanics and motor control of gait in Parkinson disease. *Clin Biomech*, **16**, 459-470.

[29] Mak MKY, & Hui-Chan CWY (2002) Switching of movement direction is central to Parkinsonian bradykinesia in sit-to-stand. *Mov Disord*, **17**, 1188-1195.

[30] Van Uem JMT, Walgaard S, Ainsworth E, Hasmann SE, Heger T, Nussbaum S, Hobert MA, Micó-Amigo EM, Van Lummel RC, Berg D, & Maetzler W (2016) Quantitative timed-up-and-go parameters in relation to cognitive parameters and health- related quality of life in mild-to-moderate Parkinson's disease. *PLoS One*, **11**, 1-15.

[31] Zijlstra A, Mancini M, Lindemann U, Chiari L, & Zijlstra W (2012) 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**, 75.

[32] Louter M, van Sloun RJG, Pevernagie DAA, Arends JBAM, Cluitmans PJ, Bloem BR, & Overeem S (2013) Subjectively impaired bed mobility in Parkinson disease affects sleep efficiency. *Sleep Med*, **14**, 668-674.

[33] Koerts J, König M, Tucha L, & Tucha O (2016) Working capacity of patients with Parkinson's disease – A systematic review. *Parkinsonism Relat Disord*, **27**, 9-24.

[34] Wilcox SK (2010) Extending palliative care to patients with Parkinson's disease. *Br J Hosp Med (London, Engl 2005)*, **71**, 26-30.

[35] Poewe W (2006) The natural history of Parkinson's disease. *J Neurol*, **253**, 2-6.

[36] Del Din S, Godfrey A, Mazzá C, Lord S, & Rochester L (2016) Free-living monitoring of Parkinson's disease: Lessons from the field. *Mov Disord*, *31*, 1293-1313.

[37] Karakaya MG, Bilgin SC, Ekici G, Köse N, & Otman AS (2009) Functional mobility, depressive symptoms, level of independence, and quality of life of the elderly living at home and in the nursing home. *J Am Med Dir Assoc*, **10**, 662-666.

[38] Podsiadlo D, & Richardson S (1991) The Timed "Up & Go": A test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*, **39**, 142-148.

[39] Parashos SA, Elm J, Boyd JT, Chou KL, Dai L, Mari Z, Morgan JC, Sudarsky L, & Wielinski CL (2015) Validation of an ambulatory capacity measure in Parkinson disease: A construct derived from the unified Parkinson's disease rating scale. *J Parkinsons Dis*, **5**, 67-73.

[40] Bloem BR, Marinus J, Almeida Q, Dibble L, Nieuwboer A, Post B, Ruzicka E, Goetz C, Stebbins G, Martinez-Martin P, Schrag A, & Movement Disorders Society Rating Scales Committee (2016) Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. *Mov Disord*, **31**, 1342-1355.

[41] Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, Eskofier BM, Merola A, Horak F, Lang AE, Reilmann R, Giuffrida J, Nieuwboer A, Horne M, Little MA, Litvan I, Simuni T, Dorsey ER, Burack MA, Kubota K, Kamondi A, Godinho C, Daneault JF, Mitsi G, Krinke L, Hausdorff JM, Bloem BR, Papapetropoulos S, & Movement Disorders Society Task Force on Technology (2016) Technology in Parkinson disease: Challenges and opportunities. *Mov Disord*, **31**, 1272-1282.

[42] Morris ME, Martin CL, & Schenkman ML (2010) Striding out with Parkinson disease: Evidence-based physical therapy for gait disorders. *Phys Ther*, **90**, 280-288.

[43] Behrman AL, Cauraugh JH, & Light KE (2000) Practice as an intervention to improve speeded motor performance and motor learning in Parkinson's disease. *J Neurol Sci*, **174**, 127-136.

[44] Canning CG, Ada L, & Woodhouse E (2008) Multiple-task walking training in people with mild to moderate Parkinson's disease: A pilot study. *Clin Rehabil*, **22**, 226-233.

[45] Meyer A (2009) Focus on pediatrics: Functional mobility vs. exercise. *Directions*, **3**, 46-48.

[46] Auger C, Demers L, Gélinas I, Jutai J, Fuhrer MJ, & DeRuyter F (2008) Powered mobility for middle-aged and older adults. *Am J Phys Med Rehabil*, **87**, 666-680.

[47] Kumar A, Schmeler MR, Karmarkar AM, Collins DM, Cooper R, Cooper RA, Shin H, & Holm MB (2013) Test-retest reliability of the functional mobility. assessment (FMA): A pilot study. *Disabil Rehabil Assist Technol*, **8**, 213-219.

[48] Bettecken K, Bernhard F, Sartor J, Hobert M, Hofmann M, Gladow T, van Uem J, Liepelt-Scarfone I, & Maetzler W (2017) Association of kinematic gait parameters with health-related quality of life in Parkinson's disease. *PLoS One* **12**, e0176816.

[49] Ferreira JJ, Santos AT, Domingos J, Matthews H, Isaacs T, Duffen J, Al-Jawad A, Larsen F, Artur Serrano J, Weber P, Thoms A, Sollinger S, Graessner H, & Maetzler W (2015) Clinical parameters and tools for home-based assessment of Parkinson's disease: Results from a delphi study. *J Parkinsons Dis*, **5**, 281-290.

Movement Disorders
CLINICAL PRACTICE

REVIEW

Measurement Instruments to Assess Functional Mobility in Parkinson's Disease: A Systematic Review

Raquel Bouça-Machado, MSc,[1,2] Gonçalo S. Duarte, MD,[1,3] Maria Patriarca, BPT,[2] Ana Castro Caldas, MD,[2] Joana Alarcão, MSc,[4] Ricardo M. Fernandes, MD, PhD,[1,3,5] Tiago A. Mestre, MD, PhD,[6] Ricardo Matias, PhD,[7,8] and Joaquim J. Ferreira, MD, PhD[1,2,*]

ABSTRACT: **Background:** Functional mobility (FM) is a person's ability to move to accomplish activities of daily living; it bridges the concepts of mobility and functional ability. There is frequently a loss of FM in Parkinson's disease (PD). Several instruments have been used to assess this concept in PD; however, there is no consensus on which are the most appropriate.

Objective: We aimed to identify and critically appraise which measurement instruments have been used to assess FM.

Methods: A systematic review was conducted using the databases CENTRAL, MEDLINE, Embase, and PEDro from their inception to January 2019 to identify all observational and experimental studies conducted in PD or atypical parkinsonism that included an FM assessment. Two reviewers independently screened citations, extracted data, and assessed clinimetric properties.

Results: We included 95 studies that assessed FM in PD. Fifty-five (57.9%) studies mentioned FM in the article, and 39 (41.1%) specified the measurement tools used to evaluate FM. FM was the primary outcome in 12 (12.6%) studies. The Timed Up and Go test was the most frequently used measurement tool. Only one study presented a definition of FM. Several overlapping terms were used, the most common being mobility.

Conclusion: Several studies reported the use of FM measurement tools in PD, though with frequent misconceptions, an inadequate context of use, or suboptimal assessment. We propose the establishment of the concept of FM applied to PD, followed by the adequate clinimetric validation of existing measurement tools to provide a comprehensive and reliable evaluation of FM in PD.

Functional mobility (FM) has been described as a person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living at home, at work, and in the community (Fig. 1).[1,2] Although poorly defined, the concept of FM has been used in several recent research studies as a more global and illustrative outcome of patients' health status in their environment.[2,3]

Reduction in FM is common and has a multifactorial nature in Parkinson's disease (PD).[2] Motor symptoms may contribute directly, through gait impairments, and indirectly because of bradykinesia, rigidity, and the presence of postural deformities (e.g., camptocormia or antecollis), which affect PD patients' gait, balance, and transitions.[2] Also, the inability to simultaneously perform a cognitive and a motor task, and the presence of orthostatic hypotension symptoms and fatigue complaints, seems also to play an important role.[2] FM is associated with significant associated disability and loss of independence leading to immobility and institutionalization. Recognizing limitations in FM is important to better understand and address patients' daily real-life needs and monitoring them over time.[4,5]

[1]*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal;* [2]*CNS–Campus Neurológico Sénior, Torres Vedras, Portugal;* [3]*Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal;* [4]*Center for Evidence-Based Medicine, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal;* [5]*Department of Pediatrics, Santa Maria Hospital, Lisbon, Portugal;* [6]*Parkinson's disease and Movement Disorders Center, Division of Neurology, Department of Medicine, The Ottawa Hospital Research Institute, University of Ottawa Brain and Research Institute, Ottawa, Ontario, Canada;* [7]*Champalimaud Research and Clinical Centre, Champalimaud Centre for the Unknown, Lisbon, Portugal;* [8]*Human Movement Analysis Lab, Escola Superior Saúde–Instituto Politécnico de Setúbal, Setúbal, Portugal*

***Correspondence to:** Professor Joaquim J. Ferreira, Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Avenida Professor Egas Moniz, 1649-028 Lisbon, Portugal; E-mail: joaquimjferreira@gmail.com

Keywords: Parkinson's disease, functional mobility, measurement instruments, systematic review, outcome measures.

Relevant disclosures and conflicts of interest are listed at the end of this article.

Received 29 August 2019; revised 28 October 2019; accepted 20 November 2019.

Published online 11 December 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12874

© 2019 International Parkinson and Movement Disorder Society

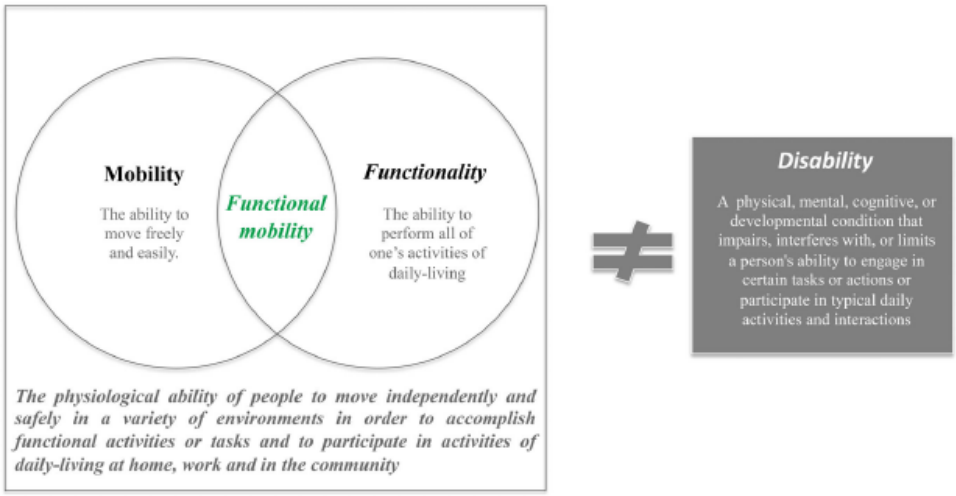


FIG. 1. Definition of FM.[2]

In spite of being loosely defined, several tests and rating scales have been used to assess FM in PD patients,[3,5] but there is no consensus on the most adequate tools for screening or for using as outcome measures to monitor change over time. This lack of consensus limits the interpretation of results from studies and hampers the evaluation of therapeutics and discussion among peers.

The present review aims to investigate which measurement tools have been used to evaluate FM in PD studies. Recommendations on which tools can be used and the need for modifications or replacements are made based on the results.

Methods

Defining the Concept

FM is not a concept defined in the International Classification of Functioning, Disability, and Health (ICF) and lacks a formal definition. To overcome this limitation, we adopted a definition previously used by Forhan and Gill[1] in a study on obesity. To check the adequacy of our choice, we matched the adopted definition with those founded in a Medline/PubMed electronic open search, conducted to look for a formal definition of FM (regardless of the research topics). We found six additional articles that defined FM.[6–11] Although few, and none presenting a formal definition of FM, all shared with the Forhan and Gill description, the idea that FM is a subject's ability to move in his or her environment, focused on gait, balance, and transfers, in order to accomplish functional tasks of everyday living (e.g., walking in a corridor at work, climbing stairs at home, getting up from bed, rising from a chair to answer the phone, standing, and bending to reach an object). Therefore, we assume this as the most suitable definition to be in the context of this systematic review.

Literature Search

We searched CENTRAL, MEDLINE, Embase, and PEDro from their inception to January 2019 using a predefined search strategy (Supporting Information Appendix 1) designed by the authors in conjunction with Cochrane's highly sensitive search strategy[12] and previous reviews in PD.[13] Being aware of the laxity of the definition, we also ran some open electronic searches, in order to minimize the number of studies not found in the formal electronic search. Reference lists from the identified articles were cross-checked to identify any further potentially eligible studies.

Study Selection

We included any observational and experimental study conducted in PD patients or atypical parkinsonisms. For intervention or controlled studies, there were no restrictions regarding the type of intervention or control arms. Studies had to include an FM assessment and describe what measurement tools were used (mentioned in the abstract and/or in the article). In order to get a full picture of the measurement tools that have been and could potentially be used to measure FM, we also included studies for which the description of the outcome measures matched the predefined concept of FM, as per consensus of the current

authors (i.e., to present one or a set of instruments that measured gait, transfer, and/or balance). Studies did not need to present a definition of FM to be included in this review.

We excluded reviews and studies written in languages other than English, French, Spanish, and Portuguese. Two authors (R.B.M., M.P.) independently screened abstracts obtained from the database search. The full texts of potentially relevant articles were retrieved for further assessment. Disagreements were resolved by consensus or by consultation with a third reviewer (G.S.D.).

Data Extraction

Four predefined domains of items were extracted: general information (title, year, and journal of publication, aim of the study, study design, population, sample size, and intervention and comparator, if applicable); concept of FM (presence of the concept of FM in the title and/or in the article, if a definition of FM was presented and if other terms were used as synonyms); FM outcome tools (if FM was the primary outcome measure, which instruments were used, and the time-point measures); and feasibility of the instrument (completion time, number of required instruments, easy administration, interpretability, patients' comprehensibility, length of the outcome measurement instrument, ease of standardization, and clinician's comprehensibility).

We divided studies into those that specifically used the concept of FM and those that, while not mentioning the concept of FM, used outcome measures that could fit the concept according to our best judgment. Within the studies using the concept of FM, we divided those that specified which measurement tools were used to measure FM from those that only mentioned evaluation of FM in the aims or conclusions of the study.

Two authors (R.B.M., M.P.) independently extracted data. Discrepancies were resolved through discussion or by consultation with a third reviewer (G.S.D.).

Assessment of Measurement Properties

Based on previous reviews, we divided the measurement tools into clinically based tests, patient-reported outcomes, and gait quantification methods.[14]

Recommendations were based on the criteria previously used in other reviews.[15,16] These included: (1) use in the assessment of FM; (2) use in published studies by individuals other than the developers; and (3) a "successful" clinimetric test (i.e., to have demonstrated the reliability, validity, and sensitivity to change of the instrument).

Measurement tools were classified as recommended, suggested, or listed, respectively, based on the number of criteria met and the feasibility evaluation.[17]

The search for studies assessing the clinimetric properties of the included measurement tools was made based on previous research[14] and on the references of each measurement tool presented in the included studies.

Statistical Analysis

The primary outcome was to identify the measurement instruments currently used to evaluate FM in people with PD. We summarized the publication characteristics using frequencies and percentages.

Results

The electronic and hand searches identified 2,463 citations. After screening titles and abstracts, 103 articles were deemed potentially eligible. Full-text assessment for eligibility resulted in eight studies being excluded. Overall, the main reasons for exclusion were: inadequately defined outcome (n = 1,395) and inappropriate study population (n = 222; Supporting Information Appendix 2).

General Data

Of the 95 included articles, 63 (66.3%) were interventional studies and 94 (98.4%) were conducted in PD patients, with a sample median [range] size of 32 [1, 3,408]. According to the year of publication, the earliest study was published in 2003, being 2014 and 2015 the years with the highest number of included studies (n = 15 in each). All interventional studies evaluated non-pharmacological interventions.

Fifty-five (57.9%) of the included studies specifically mentioned the concept of FM in the article, 39 (41.1%) specified the measurement tools used to evaluate FM, and in 12 (12.6%) FM was the primary outcome. Forty studies were deemed to have used the concept of FM according to the reviewers (Fig. 2).

Studies Explicitly Using the Concept of FM

Of the 39 studies (41.1%) in which a measurement tool(s) was specified to evaluate FM, 34 (87.2%) were clinically based tests, six (15.4%) combined clinically based tests with gait quantification methods, one (2.6%) combined clinically based tests with patient-reported outcomes, and one (2.6%) used only gait quantification methods.

The Timed Up and Go (TUG) test was the most frequently reported tool used as a single instrument (75% of studies; n = 15). The Short Physical Performance Battery (SPPB), the Five Times Sit-to-Stand test (FTSTS), the Modified Parkinson Activity Scale (mPAS), and the Dual-Task TUG (TUG-DT; cognitive) were also applied (Table 1). In those articles that used a combination of measurement tools to assess FM (n = 19; 48.7%), the most frequent associations were TUG with a: dual-task test, balance test, gait assessment, and/or a transfer evaluation (Table 3). The association of the TUG test with a second gait, balance, or transfers test was the most used way (75%; n = 9) used to measure the primary outcome (n = 12; 30.8%), followed by the single TUG test (n = 2; 16.7%) and the single FTSTS test (8.3%; n = 1).

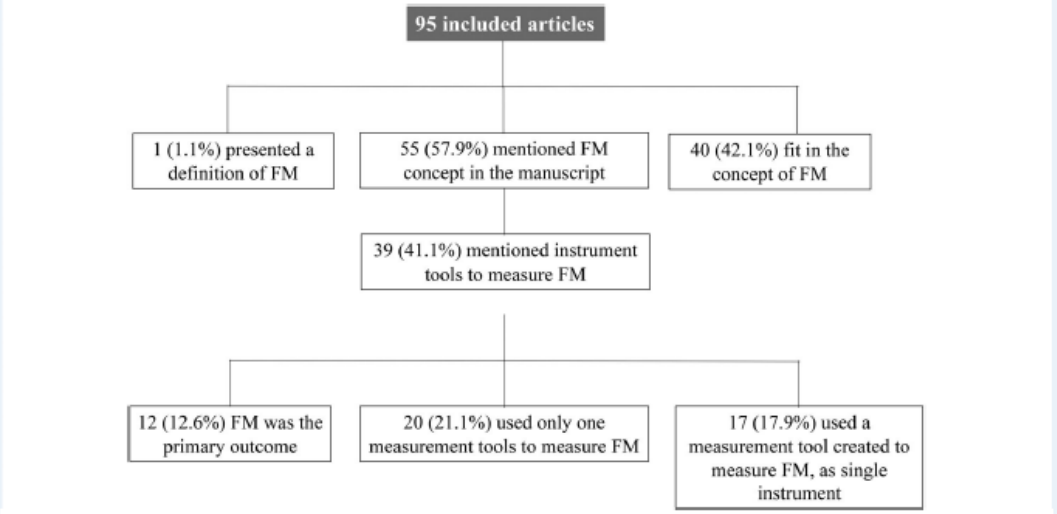


FIG. 2. Number of included studies specifically mentioning the concept of FM and respective measurement tools in the article.

Studies That Match the Concept of FM

Forty studies (42.1%) evaluated a set of outcomes including functional assessment of gait, balance, and transfers that we considered to match the concept of FM.

Of these 40 studies, 29 (72.5%) used clinically based tests as measurement tools, six (15%) used a combination of a clinically based and gait quantification method, and three (7.5%) a combination of a clinically based test and patient-reported outcomes. One study (2.5%) only used gait quantification methods, and another study (2.5%) associated clinically based tests with gait quantification method analysis and patient-reported outcomes.

Regarding clinically based tests, in four studies (10%), the TUG test was used as the only instrument. All other studies used a combination of measurement tools; the most used were the TUG test (57.5%; n = 23), the 6-minute walk test (6MWT; 30%; n = 12), and the Berg Balance Scale (BBS; 30%; n = 12; Table 3).

Quality Assessment of Outcome Measurement Instruments

All measurement tools were administered to a PD population, with data on their use in clinical studies beyond the group that developed the instrument.[14] Tables 2 and 3 summarize some of the characteristics of the most cited measurement instruments in the included studies. A more detailed description of the clinimetric properties (the previously published results of reliability, validity, and sensitivity to change of each instrument) and feasibility issues is presented below. The instruments have been divided according to whether they were used as a single instrument to measure FM or as part of a combination of instruments.

A single instrument to measure FM

The TUG Test

Construct assessed: Functional mobility.

Test description: The participant is required to get up from a standard chair, to walk 3 m at a comfortable and safe pace, turn, and walk back to sit down on the chair.[11,14,18,19] The use of assistive devices is allowed.

Clinimetric properties: Planned comparisons using independent-sample *t* tests were used to investigate changes in patients' TUG scores in the *off* and *on* phases. Results showed differences across the stages of the medication, with a moderately strong correlation (r = 0.74; n = 12; *P* = 0.003) between *off* and *on* phase scores. Results demonstrate that TUG scores could be used to differentiate the performance of subjects with PD from controls and also to detect differences between the *on* and *off* phases of the medication cycle. No ceiling effects were found. Floor effects exist at scores of 10 to 15 seconds. The TUG test demonstrated adequate test-retest and inter-rater reliability in PD. Intraclass correlation coefficients (ICCs) were used to investigate the agreement between experienced and inexperienced raters in different phases of the levodopa cycle. Results showed a high degree of agreement across different conditions (ICCs between 0.87 and 0.99). Absolute minimal detectable change values in

TABLE 1 *Measurement tools specifically used to measure FM and those used in studies that fit the FM concept*

	Measurement Tools Specifically Used to Assess FM					Measurement Tools Not Specifically Used to Assess FM	
One Only Instrument Tool	% (n)	As a Set of Outcomes Tools				As a Set of Outcomes Tools	% (n)
Timed Up and Go Test	75% (15)			TUG with…		Timed Up and Go	57.5% (23)
The Short Physical Performance Battery	10% (2)	Dual-task	Balance	Gait	Transfers	6-minute walk test	30% (12)
Five Times Sit-to-Stand Test	5% (1)	Cognitive	Berg	10-m walk test	5× Sit to Stand test	Berg Balance Scale	30% (12)
Modified Parkinson Activity Scale	5% (1)	Manual	Mini-BESTest	6-minute walk test	360-degree turn	10-m walk test	22.5% (9)
Dual-Task Timed Up and Go (cognitive)	5% (1)		Functional reach	Dynamic gait index	Bed mobility test	Mini-BESTest	22.5% (9)
						UPDRS Part III	22.5% (9)
						Functional Reach Test	17.5% (7)

TABLE 2 *Characteristics and classification of the most cited measurement tools*

Instruments	Single Instrument to Measure FM	Created to Measure FM	Applied in PD to Measure FM	Applied Beyond Original Developers	Construct Assessed	Reliability	Validity	Sensitive to Change	Feasibility Issues	Classification
Timed Up and Go Test	Yes	Yes	Yes	Yes	Functional mobility	Yes	Yes	Yes	No	Recommended
Dual-Task Timed Up and Go	Yes	Yes	Yes	Yes	Functional mobility	No	No	No	No	Suggested
Modified Parkinson Activity Scale	Yes	Yes	Yes	Yes	Functional mobility	Yes	Yes	Yes	Yes	Suggested
Five Times Sit-to-Stand Test	Yes	No	Yes	Yes	Lower extremity strength	Yes	Yes	Yes	No	Listed
The Short Physical Performance Battery	Yes	No	Yes	Yes	Lower extremity physical performance status	Yes	No	No	No	Listed
10-m walk test	No	No	Yes	Yes	Walking speed	Yes	Yes	Yes	No	Listed
6-minute walk test	No	No	Yes	Yes	Physical capacity	Yes	Yes	Yes	Yes	Listed
360 Degree Turn Test	No	No	No	Yes	Turning ability, freezing of gait	Yes	No	No	No	Listed
Berg Balance Scale	No	No	Yes	Yes	Functional standing Balance	Yes	Yes	Yes	No	Listed
Mini-BESTest	No	No	Yes	Yes	Balance	Yes	Yes	Yes	No	Listed
Functional Reach Test	No	No	No	Yes	Static balance	Yes	Yes	Yes	Yes	Listed
UPDRS Part III	No	No	No	Yes	Motor performance	Yes	Yes	Yes	Yes	Listed

TABLE 3 *Feasibility characteristics of the most cited measurement tools*

Instruments	Completion Time (sec)	Required Equipment (n)	Easy Administration	Interpretability	Patient's Comprehension	Length of the Outcome Measurement Instrument	Ease of Standardization	Ease of Comprehensibility by Clinician
Timed Up and Go Test	5	3	Yes	Yes	Adequate	Adequate	Yes	Yes
Dual-Task Timed Up and Go	<5	4	Yes	Yes	Adequate	Adequate	Yes	Yes
Modified Parkinson Activity Scale	10 to 15	8	No	Yes	Adequate	Too long	Yes	Yes
Five Times Sit-to-Stand Test	<5	2	Yes	Yes	Adequate	Adequate	Yes	Yes
The Short Physical Performance Battery	10 to 15	5	Yes	Yes	Adequate	Adequate	Yes	Yes
10-m walk test	5	3	Yes	Yes	Adequate	Adequate	Yes	Yes
6-minute walk test	<10	4	No	Yes	Adequate	Too long	Yes	Yes
360 Degree Turn Test	<5	1	Yes	Yes	Adequate	Adequate	Yes	Yes
Berg Balance Scale	10 to 20	6	Yes	Yes	Adequate	Adequate	Yes	Yes
Mini-BESTest	10 to 15	7	Yes	Yes	Adequate	Adequate	Yes	Yes
Functional Reach Test	<5	3	Yes	Yes	Difficult	Adequate	Yes	Yes
UPDRS Part III	<10	0	Yes	Yes	Adequate	Too long	No	Yes

PD varied from 3.5 to 11 seconds, whereas relative changes >29.8% may reflect "true" change. Longer times to complete the test proved to be associated with an increased risk of falls.

Feasibility: An easy and quick test to administer. Limited to patients capable of walking (with or without assistive devices) and who are able to follow instructions. The safety training may interfere with TUG results given that patients take more time if focused on the use of safety strategies when getting up, turning, and sitting down.

The Dual-Task TUG test

Construct assessed: Functional mobility in dual-task conditions.

Test description: The participant is required to stand up from a chair, walk 3 m at a comfortable and safe speed, then turn and walk back to the chair and sit down.[20,21] In the TUG cognitive, while performing the test, the participant is asked to count backward by threes to a random number between 20 and 100. In the TUG manual, the participant is required to hold a cup filled with water during the test. The use of assistive devices is allowed.

Clinimetric properties: Unknown for PD patients. In healthy older adults, the TUG-DT manual and cognitive strongly correlate with the Berg Balance Test ($r = -0.72$ and $r = -0.66$, respectively). Retest reliability is very good (TUG manual: $r_{T1\text{-}T2} = 0.97$ and $r_{T1\text{-}T3} = 0.98$; and TUG cognitive: $r_{T1\text{-}T2} = 0.98$ and $r_{T1\text{-}T3} = 0.98$). Intra-rater reliability is very high with ICC values of 0.99 and 0.94 for the TUG manual and cognitive, respectively.

Feasibility: Quick and easy-to-apply tests to determine dual-task interference in functional mobility and a predictive test to assess risk for falls. They may be more useful than TUG without dual-task for evaluating intervention effects, given that the interference of safety strategies is minimized. Limited to patients who are capable of walking (with or without assistive devices), able to follow instructions, and not cognitively impaired.

The mPAS

Construct assessed: Functional mobility.

Test description: The mPAS includes 18 activities covering three functional mobility aspects: chair transfers (two items), gait akinesia (six items), and bed mobility (eight items).[11,22,23] Raters evaluate the quality of the movement while patients perform the tasks.

Clinimetric properties: Specifically designed for the PD population. Based on 195 observations, the mPAS has no ceiling effect, good concurrent validity (0.64 with UPDRS motor scores and 0.79 with Visual Analogue Scale/Global Functioning), and good inter-rater agreement with no differences between experts and nonexperts ($P = 0.28$).

Feasibility: It requires several accessories and space (e.g., a bed, a chair, sheets, and a blanket), which may hinder its use in daily practice.

The FTSTS

Construct assessed: Lower extremity strength.

Test description: Participants began the test seated in an armless chair with their arms folded across their chest and with their back

against the chair.[24,25] The rater asks the participant to stand up and sit down five times as quickly as he/she can without the use of the upper limbs.

Clinimetric properties: The FTSTS significantly correlated ($P < 0.01$) with the Mini-BESTest and the 6MWT. It is able to discriminate between fallers and nonfallers, with an area under the curve of 0.77. It has shown to have high inter-rater and test-retest reliability, with an ICC of 0.99 and 0.76, respectively.

Feasibility: The FTSTS requires a minimum of instrumentation and is a quick and objective measure to determine whether an individual with PD may be at risk for falling. The potential use of compensatory strategies in the sit-to-stand movement may impair the test's capacity for measuring disease progression. It does not provide detailed information on balance limitations during gait-related activities and stationary balance. In people with PD, balance and bradykinesia seem to be the most important constructs influencing the results of the test.

The SPPB

Construct assessed: Lower extremity physical performance status.

Test description: A small battery including three components of daily activities: balance (ability to stand for 3 seconds with the feet together side by side, semitandem, and tandem), walking ability (two timed trials of 3 m walked at a fast pace), and transfers (time to rise from a chair five times).[26–30] The SPPB utilizes an ordinal ranking system, from 0 to 12, where higher scores indicate better lower extremity function.

Clinimetric properties: Significantly correlates with disability measures (Older Americans Resource and Services Activities of Daily Living and Instrumental ADL subscale) and disease severity (H & Y, UPDRS-II and -III, and total score). Although this test has been applied to PD patients, neither its relative and absolute reliability nor its responsiveness have been calculated. In community-dwelling older populations and patients with chronic kidney disease, the SPPB has an excellent test-retest reliability (ICC = 0.82 and 0.94, respectively). This battery also has good sensitivity to change in myocardial infarction, stroke, hip fracture, and congestive heart failure patients.

Feasibility: A practical measure rapid to administer and requiring minimal equipment. It has been found to be too easy for highly functioning patients.

Measurement Tools Used in Combination to Measure FM

10 Meter Walk Test

Construct assessed: Walking speed.

Test description: The participant is asked to walk a distance of 10 m at their self-selected or maximal speed.[14,31–33] The time and number of steps needed to perform the task are recorded. Assistive devices are allowed.

Clinical properties: The test positively correlates with the 6MWT (gait endurance), has low-to-moderate correlation with the Mini-BESTest (balance), and a low correlation with the UPDRS subscales (disease severity). The test has moderate-to-high test-retest reliability in PD (ICCs, 0.75–0.98), with minimal detectable change (MDC) values of 0.18 and 0.25 m/s. Responsiveness was determined by significant differences after rehabilitation programs and DBS.

Feasibility: It is a frequently used test in PD clinical trials. It is easy to administer and useful for identifying changes in gait over time in mild to moderate PD. The presence of freezing of gait or postural instability may hinder the outcome.

6MWT

Construct assessed: Physical capacity.

Test description: Subjects are asked to cover as much ground as possible on a standardized walkway for 6 minutes.[14,31,34] Assistive devices are allowed; patients are permitted to pause, if necessary.

Clinimetric properties: Its correlation with the UPDRS motor section is weak (it does not seem to be related with disease severity); however, it moderately to strongly correlates with the BBS, 10 Meter Walk Test, and TUG. The responsiveness of the 6MWT has been demonstrated in PD. The test has adequate test-retest, inter-rater reliability with ICCs ranging from 0.88 to 0.95. It seems to be a good predictor of a patient's ability to walk outside independently and safely, and useful for identifying improvements in gait endurance after treatment.

Feasibility: The major limitations of this test's use in clinical practice are the time and space needed. It can only be applied to patients with the capacity to walk (with or without assistive devices). Performance in PD may depend on the presence of freezing, balance, and bradykinesia. Learning effects may occur.

360 Degree Turn Test

Construct assessed: Turning ability, freezing of gait.

Test description: The participant is required to make quick 360-degree turns, in both directions, while standing.[35–38] Time, number of steps, and presence of freezing episodes are recorded.

Clinimetric properties: The test has high test-retest reliability as a functional test, with an ICC of 0.95. No further published data on reliability, validity, and responsiveness were found on the 360 Degree Turn Test as a measure of turning ability. However, a study aiming to evaluate reliability, validity, and responsiveness of the timed 360 Degree Turn Test in PD patients was registered in clinicaltrials.gov in July 2018 (ClinicalTrials.gov Identifier: NCT03587168). As a measure of freezing of gait, it has high inter-rater reliability (agreement, 97%; Cohen's kappa: 0.93).

Feasibility: Although an easy and quick test to evaluate the presence of freezing of gait, turning ability, and, indirectly, functionality, it is not a movement very frequent in daily life and does not provide much information on patients' functional mobility. It is also limited to patients without postural instability.

BBS

Construct assessed: Functional standing balance.

Test description: The scale consists of 14 items, each scored from 0 to 4, to measure a subject's ability to maintain positions or movements of increasing difficulty by diminishing the base of support.[14,31,39,40] Tasks include sitting, standing, standing to a single-leg stance, and positional changes.

Clinimetric properties: BBS score significantly correlates with indicators of motor functioning (UPDRS motor score: r = –0.58; $P < 0.005$), stage of disease (H & Y scale staging: r = –0.45; $P < 0.005$), and daily living capacity (Schwab and England ADL Scale rating: r = 0.55; $P < 0.005$). A ceiling effect has been reported. The ICCs for test-retest reliability are above 0.90. A value for MDC has been calculated (MDC = 5).
Feasibility: The BBS is a relatively safe and simple to administer instrument. It may not be very useful in mild-to-moderate PD patients because of ceiling effects. It does not take into account the quality of movement and therefore may be less useful in PD, where motor control is a bigger contributor to poor balance than muscle weakness.

Mini-BESTest
Construct assessed: Balance.
Test description: The Mini-BESTest is a 14-item tool to measure dynamic balance, which is associated with movement during transfers and gait, as well as external perturbations and cognitive dual-task performance.[14,41,42] It includes six domains: biomechanical constraints, verticality/stability limits, anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait.
Clinimetric properties: The Mini-BESTest has a strong relationship with the BESTest total score (r = 0.955) and a comparable ability to discriminate between fallers and nonfallers. It has a high inter-rater and test-retest reliability (ICC = 0.91 and 0.92, respectively). Information on minimal clinically important difference is available.
Feasibility: Although it requires equipment, it is feasible for use in clinical practice.

Functional Reach Test
Construct assessed: Static balance.
Test description: A ruler is mounted on the wall at shoulder height.[14,31,43] The participant is required to reach forward the maximal distance beyond the arm's length, while maintaining a fixed base of support in the standing position.
Psychometric properties: Functional reach significantly correlates with the UPDRS (r = 0.69; $P < 0.001$) and H & Y (r = 0.71; $P < 0.001$). The test has a moderate (0.44–0.51) to strong (0.72–0.76) correlation with balance master items and reaching tasks. ICC values in test-retest reliability were 0.84 for a 1-day testing interval and 0.73 to 0.74 for 1 week. Responsiveness in PD has been demonstrated by significant differences in scores between exercise and control groups. MDC values range from 4 to 11.5 cm.
Feasibility: The Functional Reach Test is a practical balance tool used to evaluate the effect of interventions. It is limited to patients who can stand for 1 minute without support, and patients frequently need to be helped to correctly perform the required movement.

UPDRS Part III
Construct assessed: Motor performance.
Test description: A subsection of the most widely used clinical rating scale in PD to assess disease severity and progression and to determine treatment-related benefits.[4,44,45] Part III comprises 11 items, including ratings for tremor, slowness (bradykinesia), stiffness (rigidity), and balance. Punctuated from 0 to 4, with a higher score showing a higher level of disability.
Clinimetric properties: The UPDRS has adequate face validity, satisfactory construct validity, and is sensitive to changes in clinical status. It has excellent internal consistency throughout disease progression measured with the H & Y scale and adequate inter- and intrarater reliability.
Feasibility: Used in almost all PD clinical trials. It provides a comprehensive assessment, approaching several crucial constructs in PD that can be used across all patients regardless of severity, treatment, or age. Even in the revised version, the MDS-UPDRS has no item, or set of items, that specifically measure functional mobility, and it is still very time-consuming to use in everyday clinical practice.

Defining FM Concept

Of the 95 included studies, one defined the concept of FM and 55 (57.9%) mentioned the concept in the article. Among these, other concepts were used as synonyms for FM; the most used term was mobility (18.2%; n = 10). In the studies that did not overtly use the term FM, but for which we considered FM was assessed, the most used expressions were mobility (25%; n = 10) or mobility in association with functional activities/performance, motor function, gait-related activity, or balance (25%; n = 10; Supporting Information Appendix 3).

Conclusion

The assessment of FM has been included in PD studies and has increased over the years. FM is an outcome that may best convey the patient's overall health status in his or her environment. FM incorporates a series of ill-defined and loosely used concepts that are generally considered to assess motor function in the context of functional activities/performance. Several measurement tools have been used to measure FM, especially in association with TUG.

FM Measurement Instruments

Recommended and Suggested Measurement Tools

Among the reviewed instruments, only the TUG and mPAS were designed and are validated to measure FM in PD. The TUG-DT, although an update of TUG and frequently used in PD clinical studies, has not been assessed clinimetrically. The TUG test is an easy and quick-to-apply test that is broadly used in PD. It is limited to subjects who have the ability to walk, follow instructions, and who do not suffer from severe freezing episodes. Although this test includes the three anchors of functional

mobility (gait, balance, and transfers), and is considered a good predictor of FM, it is still a little distant from the reality of daily-living activities, which hampers its ability to capture the patient's functional status in his or her environment.[5,14] This may explain the frequent association of TUG with one or more scales found in our results.

The mPAS is a scale specifically designed to evaluate PD that overcomes this limitation by assessing functional gait, balance, and transfers through different scenarios. Its major limitation is the number of accessories, space, and time needed to perform the test. The bed mobility items require a bed (large enough to turn to both sides), sheet, and a blanket, which may not be practical or feasible in all centers.[14,22]

Listed Measurement Tools

The FTSTS and the SPPB, although used as single instruments to measure FM, are not validated to measure FM in PD. The FTSTS test assesses lower extremity strength asking the patient to stand up and sit five times, which is not representative of the FM concept. Although the SPPB can be considered to assess the three anchors of functional mobility (the FTSTS, one test of static balance [10 seconds with the feet together, in semitandem and full tandem], and a 3-m walk), it uses very little functional and isolated tests, making its adequacy to measure FM, in our opinion, questionable. Compared with the SPPB, the TUG test seems more attractive given that it includes the anchors, in a simpler test, and, above all, in a sequential way, which makes it more functional and closer to the movements of daily life.

Potential Measurement Tools to Assess FM

One psychometric study[46] has assessed, with positive results, a new scale to assess FM in PD: the Lindop Parkinson's Disease Mobility Assessment. This is a 10-item rating scale that covers the same constructs as the mPAS in a simplified form. This scale was validated in 2009, but we did not find any studies that have used it to assess FM in PD. Nevertheless, it seems that it could be an alternative to the mPAS.

Although not validated for measuring FM in PD, the Mini-BESTest seems worthy of being studied as an isolated tool to measure FM. Like the mPAS, the Mini-BESTest assesses the three constructs of FM through different tasks, with the added value of including the TUG-DT test, the assessment of gait in association with common tasks of daily living (e.g., changes in gait speed, walk with head turn, walk with pivotal turn, and step over obstacles), and the assessment of reactive postural control in four directions. It does not include the assessment of bed mobility.

Nine of the included studies (9.5%) used kinematic gait parameters to assess FM. Given that FM is a more global and illustrative outcome of patients' health status, the use of technology-based objective measures is very attractive. However, the most suitable parameters and instrument to this end need to be defined.

A 2016 study reviewed *Instruments to Assess Posture, Gait, and Balance in Parkinson's Disease*,[14] a topic that overlaps largely with the aim of this review. However, there is an essential difference between these two reviews. Although posture, gait, and balance are crucial aspects of FM, the operationalization of this concept requires their simultaneous presence (along with transfers) during a task of daily living. The assessment of the three parameters, either separately or without carrying out a functional task, should not be considered an FM assessment.

The Concept of FM

Although frequently mentioned and increasingly used in clinical studies, the concept of FM is not included in the ICF.[47] Only 1 of the 95 studies (1.1%) defined FM in the article.

In the absence of a universally accepted definition of FM, we adopted the Forhan and Gill[1] definition, previously used in a study on obesity, after verifying its suitability through a match with other definitions found on an electronic search conducted in MEDLINE/PubMed to appraise for other operational definitions of FM. All the definitions share the anchor that FM is the subject's ability to move within a natural environment and to perform everyday tasks and the operationalization by the assessment of gait, balance, and transfers during the performance of a functional task. Frequently, the concept of mobility was used as a synonym of FM in the included studies. In order to verify what was understood by mobility, we reviewed its current ICF definition. According to this, mobility is defined as "moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation."[47] This is a broader concept than FM given that it is not restricted to actions conducted with the purpose of completing an activity of daily living, which is mandatory for FM. Although we acknowledge the absence of a universal definition for FM, we believe that the Forhan and Gill[1] description, adopted in this review, is the most consensual definition of FM. Therefore, in the context of this review, we have defined FM as a domain of mobility, focused on a person's physiological ability to move independently and safely within a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living.[1]

Among the measurement tools assessed in this review on FM, the TUG test seems the most suitable for use in clinical practice and research, having been designed to evaluate FM and displaying strong clinimetric properties.

A limitation for establishing the most appropriate outcome tools is the absence of an established concept of FM and the misuse of several overlapping terms. We recommend the use of the Forhan and Gill[1] as the most consensual and pragmatic operational definition of FM. Based on this, we suggest to validate the existing tools (e.g., the Mini-BESTest) and potentially develop novel scales that measure FM in PD. We also highlight the need to study how FM behaves in the context of clinical trials,

concretely its responsiveness to change in the assessment of pharmacological and nonpharmacological therapeutic interventions. The combination of various validated tools will possibly provide a more complete measurement of FM. The use of technology-based objective measures is increasingly being used to asses PD patients, with the added value of tracking FM from the users' daily routine, using a smartphone or a similar device, without the need of any explicit test. Although still very new and fragile, future studies should also explore these as potential outcome tools for measuring FM.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

R.B.M.: 1A, 1B, 1C, 2A, 2B, 3A
G.S.D.: 1B, 1C, 2A, 2C, 3B
M.P.: 1C, 3B
A.C.C.: 2C, 3B
J.A.: 1C, 3B
R.M.F.: 2C, 3B
T.M.: 2C, 3B
R.M.: 2C, 3B
J.J.F.: 1A, 1B, 2A, 2C, 3B

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that neither the approval of an institutional review board nor patient consent was required for this work.

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial Disclosures for previous 12 months: R.B.M. received a PhD grant from Fundação para a Ciência e a Tecnologia (FCT) (SFRH/BD/120773/2016 to RBM). R.M.F. is a member of the IDMC for clinical trials conducted by ablynx/novartis and reviral in pediatric bronchiolitis and a member of CEC for a clinical trial conducted by janssen in RSV prevention. T.M. has consulted for CHDI Foundation/Management, Sunovion, and Valeo Pharma; is a member of the advisory boards of AbbVie; and has received grants from JPND, Ontario Research Funding, CIHR, The Michael J. Fox Foundation, Parkinson Canada, PDF/PSG, and LesLois Foundation. J.J.F. has consulted for Ipsen, GlaxoSmithKline, Novartis, Teva, Lundbeck, Solvay, Abbott, BIAL, Merck-Serono, and Merz; has received research grants from GlaxoSmithKline, Grunenthal, Teva, and Fundaço MSD; and has been employed by Laboratory of Clinical Pharmacology and Therapeutics of Lisbon.

References

1. Forhan M, Gill S V. Obesity, functional mobility and quality of life. *Best Pract Res Clin Endocrinol Metab* 2013;27:129–137.
2. Bouça-Machado R, Maetzler W, Ferreira JJ. What is functional mobility applied to Parkinson's disease? *J Parkinsons Dis* 2018;8:121–130.
3. Santos MP, Da Silva BA, Ovando AC, Ilha J, Swarowsky A. Comparison between two functional mobility scales for Parkinson's disease directly applied to physical therapy practice: cross-cultural adaptation and measurement properties. *Eur J Phys Rehabil Med* 2017;53:664–675.
4. Bhidayasiri R, Martinez-Martin P. Clinical assessments in Parkinson's disease. *Int Rev Neurobiol* 2017;132:129–182.
5. Verheyden G, Kampshoff CS, Burnett ME, et al. Psychometric properties of 3 functional mobility tests for people with Parkinson disease. *Phys Ther* 2014;94:230–239.
6. Scott-Roberts S, Purcell C. Understanding the functional mobility of adults with developmental coordination disorder (DCD) through the International Classification of Functioning (ICF). *Curr Dev Disord Rep* 2018;5:26–33.
7. Adair B, Said CM, Rodda J, Morris ME. Psychometric properties of functional mobility tools in hereditary spastic paraplegia and other childhood neurological conditions. *Dev Med Child Neurol* 2012;54:596–605.
8. Harvey A, Graham HK, Morris ME, Baker R, Wolfe R. The functional mobility scale: ability to detect change following single event multilevel surgery. *Dev Med Child Neurol* 2007;49:603–607.
9. Lawrence H, Hills S, Kline N, Weems K, Doty A. Effectiveness of exercise on functional mobility in adults with cerebral palsy: a systematic review. *Physiother Can* 2016;68:398–407.
10. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. *Phys Ther* 2000;80:896–903.
11. Keus S, Munneke M, Graziano M, et al. European Physiotherapy Guideline for Parkinson's Disease [Internet]. 1st ed, Vol. 1, KNGF/ParkinsonNet. The Netherlands; 2014. 1–191 pp. Available from: http://www.fizioterapeitiem.lv/attachments/article/307/4_eu_guideline_parkinson_201412-development.pdf. Accessed on April 19; 2016.
12. Higgins JPT. *Cochrane Handbook for Systematic Reviews of Interventions*. Higgins JP, Green S, eds. The Cochrane Collaboration. Oxford, UK: The Cochrane Collaboration; 2006:1–265.
13. Leal Rato M, Duarte GS, Ferreira AN, et al. Nocebo response in Parkinson's disease: a systematic review and meta-analysis. *Park Relat Disord* 2019;65:13–19.
14. Bloem BR, Marinus J, Almeida Q, et al. Measurement instruments to assess posture, gait, and balance in Parkinson's disease: critique and recommendations. *Mov Disord* 2016;31:1342–1355.
15. Elble R, Bain P, João Forjaz M, et al. Task force report: scales for screening and evaluating tremor: critique and recommendations. *Mov Disord* 2013;28:1793–1800.
16. Antonini A, Martinez-Martin P, Chaudhuri RK, et al. Wearing-off scales in Parkinson's disease: critique and recommendations. *Mov Disord* 2011;26:2169–75.
17. Prinsen CAC, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set"—a practical guideline. *Trials* 2016;17:1–10.
18. Morris S, Morris ME, Iansek R. Reliability of measurements obtained with the Timed "Up, & Go" Test in people with Parkinson disease. *Phys Ther* 2001;81:810–818.
19. Podsiadlo, D; Richardson S. The Timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991;39:142–148.
20. Campbell CM, Rowse JL, Ciol MA, Shumway-Cook A. The effect of cognitive demand on timed up and go performance in older adults with and without Parkinson disease. *Neurol Rep* 2003;27:2–7.
21. Hofheinz M, Schusterschitz C. Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. *Clin Rehabil* 2010;24:831–842.
22. Keus SHJ, Nieuwboer A, Bloem BR, Borm GF, Munneke M. Clinimetric analyses of the Modified Parkinson Activity Scale. *Parkinsonism Relat Disord* 2009;15:263–269.
23. Nieuwboer A, De Weerdt W, Dom R, Bogaerts K, Nuyens G. Development of an activity scale for individuals with advanced Parkinson disease: reliability and "on-off" variability. *Phys Ther* 2000;80:1087–1096.

24. Mayhew T, Rothstein J. Measurement of muscle performance with instruments. *Percept Mot Skills* 1995;80:163–166.
25. Duncan RP, Leddy AL, Earhart GM. Five times sit-to-stand test performance in Parkinson's disease. *Arch Phys Med Rehabil* 2011;92:1431–1436.
26. Alfieri FM, Riberto M, Gatz LS, et al. Functional mobility and balance in community-dwelling elderly submitted to multisensory versus strength exercises. *Clin Interv Aging* 2010;5:181–185.
27. Pavasini R, Guralnik J, Brown JC, et al. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. *BMC Med* 2016;14:1–9.
28. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. *Gerontologist* 2013;53:255–267.
29. de Villar LOP, Martínez-Olmos FJ, Junqué-Jiménez A, et al. Test-retest reliability and minimal detectable change scores for the short physical performance battery, one-legged standing test and timed up and go test in patients undergoing hemodialysis. *PLoS One* 2018;13:e0201035.
30. Freire AN, Guerra RO, Alvarado B, Guralnik JM, Zunzunegui MV. Validity and reliability of the short physical performance battery in two diverse older adult populations in Quebec and Brazil. *J Aging Health* 2012;24:863–878.
31. Steffen T, Seney M. Test-retest reliability and minimal detectable change on balance and ambulation tests, the 36-Item Short-Form Health Survey, and the Unified Parkinson Disease Rating Scale in people with parkinsonism. *Phys Ther* 2008;88:733–746.
32. Combs SA, Diehl MD, Filip J, Long E. Short-distance walking speed tests in people with Parkinson disease: reliability, responsiveness, and validity. *Gait Posture* 2014;39:784–788.
33. Hassett L, de Bie RA, Moseley AM, Bosman JM, van Loo MA. Test–retest reliability of walking speed, step length and step width measurement after traumatic brain injury: a pilot study. *Brain Inj* 2004;18:1041–1048.
34. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919–923.
35. Schenkman M, Cutson TM, Kuchibhatla M, Chandler J, Pieper C. Reliability of impairment and physical performance measures for persons with Parkinson's disease. *Phys Ther* 2017;77:19–27.
36. Suteerawattananon M, Protas EJ. Reliability of outcome measures in individuals with Parkinson's disease. *Physiother Theory Pract* 2000;16:211–218.
37. Ziegler K, Schroeteler F, Ceballos-Baumann AO, Fietzek UM. A new rating instrument to assess festination and freezing gait in Parkinsonian patients. *Mov Disord* 2010;25:1012–1018.
38. Snijders AH, Haaxma CA, Hagen YJ, Munneke M, Bloem BR. Freezer or non-freezer: clinical assessment of freezing of gait. *Parkonsonism Relat Disord* 2012;18:149–154.
39. Qutubuddin AA, Pegg PO, Cifu DX, Brown R, McNamee S, Carne W. Validating the Berg Balance Scale for patients with Parkinson's disease: a key to rehabilitation evaluation. *Arch Phys Med Rehabil* 2005;86:789–792.
40. Berg K, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. *Can J Public Heal* 2014;83(Suppl 2):S7–S11.
41. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med* 2013;42:323–331.
42. Leddy AL, Crowner BE, Earhart GM. Utility of the mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J Neurol Phys Ther* 2011;35:90–97.
43. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. *J Gerontol* 1990;45:192–197.
44. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008;23:2129–2170.
45. Movement Disorder Society. The Unified Parkinson's Disease Rating Scale (UPDRS): status and recommendations. *Mov Disord* 2003;18:738–750.
46. Santos MP, da Silva BA, Ovando AC, Ilha J, Swarowsky A. Comparison between two functional mobility scales for Parkinson's disease directly applied to physical therapy practice: cross-cultural adaptation and measurement properties. *Eur J Phys Rehabil Med* 2017;53:664–675.
47. World Health Organization. Towards a Common Language for Functioning, Disability and Health: The International Classification of Functioning, Disability and Health. *International Classification [Internet]*. 2002;1149:1–22. Available from: http://www.who.int/classifications/icf/training/icfbeginnersguide.pdf. Accessed on March 08; 2017.

Supporting Information

Supporting information may be found in the online version of this article.

Appendix 1. Search strategy for functional mobility in PD research: a systematic review.

Appendix 2. Flow diagram of study selection process.

Appendix 3. FM-related concepts used in the included studies.

frontiers in Neurology

ORIGINAL RESEARCH
published: 27 October 2020
doi: 10.3389/fneur.2020.575811

Patients and Health Professional's Perspective of Functional Mobility in Parkinson's Disease

Raquel Bouça-Machado[1,2], *Nilza Gonçalves*[1], *Inês Lousada*[2], *Maria A. Patriarca*[2], *Patrícia Costa*[2], *Raquel Nunes*[2], *Susana Dias*[2], *Ana Castro Caldas*[2], *Anabela Valadas*[1,2,3], *Patrícia Pita Lobo*[2,3], *Leonor Correia Guedes*[1,2,3], *Mário M. Rosa*[1,3,4], *Miguel Coelho*[1,2,3] *and Joaquim J. Ferreira*[1,2,3,4]*

[1] Faculdade de Medicina, Instituto de Medicina Molecular, Universidade de Lisboa, Lisbon, Portugal, [2] CNS-Campus Neurológico, Torres Vedras, Portugal, [3] Department of Neuroscience and Mental Health, Neurology, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte (CHULN), Lisbon, Portugal, [4] Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

OPEN ACCESS

Edited by:
Sanjay Pandey,
University of Delhi, India

Reviewed by:
Prachaya Srivanitchapoom,
Mahidol University, Thailand
Chien Tai Hong,
Taipei Medical University, Taiwan

****Correspondence:***
Joaquim J. Ferreira
joaquimjferreira@gmail.com

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: *24 June 2020*
Accepted: *31 August 2020*
Published: *27 October 2020*

Citation:
Bouça-Machado R, Gonçalves N, Lousada I, Patriarca MA, Costa P, Nunes R, Dias S, Caldas AC, Valadas A, Lobo PP, Guedes LC, Rosa MM, Coelho M and Ferreira JJ (2020) Patients and Health Professional's Perspective of Functional Mobility in Parkinson's Disease. Front. Neurol. 11:575811. doi: 10.3389/fneur.2020.575811

Background: Functional mobility (FM) is the person's ability to move to accomplish daily living tasks and activities. FM limitations are common in Parkinson's disease, increase with disease progression, and can be highly disabling. Although several studies in Parkinson's disease (PD) field use this concept, only recently, a formal definition has been proposed.

Objective: We aimed to explore patient's and health professional's perspectives of FM in PD.

Methods: A focus group methodology has been used. Four focus groups, with a total of 10 patients and 10 health professionals, were performed. Six patients were early stage and four advanced stage. The health professional's group was composed of five neurologists and five physiotherapists. The suitability of the new concept, the impact of FM limitations in PD patient's daily routine, and the potential benefit of walking aids have been discussed.

Results: All participants were able to provide a spontaneous definition of FM, matching with the proposed concept. All agreed that PD affects patient's FM, increasing the limitations with disease progression, and with the existence of a serious prejudice with walking aids that hinders its use. Early-stage patient's perspective seems to be more in line with neurologist's perspective, while the views of advanced-stage patients were closer to physiotherapist's views.

Conclusion: FM concept was considered as intuitive and useful. FM limitations have an important physical and social impact in the advanced stage of the disease. Although patients and health professionals acknowledge walking aid's benefit improving patient's FM, the prejudice associated with this type of tools limits its recommendation and use.

Keywords: functional mobility, Parkinson's disease, focus groups, concept, walking aids

INTRODUCTION

Parkinson's disease (PD) is a complex and fluctuating neurodegenerative disorder associated with the presence of motor and non-motor symptoms, which can be very disabling and highly affect patients' quality of life (1). Despite an optimal disease management, many of these symptoms improve only partially and aggravate with disease progression, resulting in recurrent falls, reduced mobility, and loss of independence (1–3).

Functional mobility (FM) is the capacity of people to move from one place to another, in order to participate in the activities of daily living (ADL) at home, work, and in the community. This concept includes movements like standing, bending, walking, and climbing and contributes greatly to the subject's health-related quality of life (4).

In PD, both motor and non-motor symptoms contribute to the appearance of FM limitations. Although poorly defined, this concept has been frequently used in PD research. Recently, due to its frequent misuse, there is a need to clarify and to establish a formal concept of FM to be applied to PD (5).

The present study aims to explore, through a focus group methodology, PD patients and health professional's perspective on the proposed concept of FM, exploring also the impact of FM limitations in patient's daily life and the strategies to deal with it. We hope to clarify the suitability of the new concept of FM in PD and to promote a more holistic and functional approach to the patient's needs.

METHODS

Study Design and Patient's Recruitment

A focus group methodology was used. Four focus groups were undertaken, two with patients (early and advanced disease stage) and two with health professionals (physiotherapist and neurologist—movement disorders specialists). Patients were included if they had the following: (1) PD diagnosis, according to the Movement Disorders Society clinical diagnostic criteria; (2) a Hoehn Yahr (HY) stage between I and IV under dopaminergic medication (MED ON); (3) the ability to communicate with the investigator and to understand and comply with the requirements of the study; and (4) the ability to provide written informed consent to participate in the study. Patients were excluded if they have been diagnosed with an atypical parkinsonism.

Health professionals were included if they work regularly with the PD population for at least 1 year. Participants were recruited from CNS—Campus Neurológico, a specialized movement disorders center (Torres Vedras, Portugal), and from the Deep Brain Stimulation surgery waiting list of the Movement Disorders outpatient clinic of a tertiary university hospital (Hospital Santa Maria, Lisbon, Portugal). The CNS Local Ethical Committee approved the study (Ref. 04-2018) and all participants provided written informed consent.

Focus Groups

All participants that fulfilled the inclusion criteria were invited to participate. Information about the objectives, duration, procedures, and voluntariness was provided and the informed consent was obtained. Demographic and clinical data were collected for each PD patient. Patients were assessed in "ON" state medication. To define early and advanced PD, the presence of motor complications with impact in patient's daily life, assessed through MDS-UPDRS part IV, was used.

The focus groups followed a semi-structured script, including questions concerning patients and health professional's thoughts on the concept of FM, the impact and strategies to deal with FM limitations in daily life, and on the role of walking aids (**Appendix 1**).

Each focus group took up to 90 min (75 min to focus group questions and 15 min to close). At the beginning of each interview, participants were reminded of the purpose of the study and guaranteed confidentiality. Participants were encouraged to interact with each other, with the author intervening solely to keep the discussion on the topic and to encourage the more reserved members of the group to speak.

The focus group was recorded, with the agreement of all participants.

Data Analysis

The audio recordings were transcribed and read until it reached an overall understanding.

Transcripts of the focus groups were divided into meaningful categories and themes. In a second step, a thorough read of the data was performed to ensure the identified themes were evident and a true reflection of the data was captured. Researchers moved back and forth in a reflexive process until consensus was reached.

Descriptive statistics were used for demographic, clinical, and therapeutic data.

RESULTS

Twenty participants were included in the study: six early-stage patients, four advanced-stage patients, five physiotherapists, and five neurologists. The mean age of patients was 68.0 $\pm$ 9.9 years (71.7 $\pm$ 9.0 in early stage and 60.7 $\pm$ 8.3 in advanced stage), with a mean disease duration of 8 $\pm$ 5.2 years (7.0 $\pm$ 6.1 in early stage and 10.0 $\pm$ 3.0 in advanced stage) and a mean Hoehn and Yahr score of 2.2 $\pm$ 0.4 (2.0 $\pm$ 0.4 in early stage and 2.5 $\pm$ 0.6 in advanced stage) (**Table 1**).

Patients in the early-stage group were autonomous, with an active lifestyle and/or exercise maintained through their professional job. Patients in the advanced-stage group were almost all retired, had less autonomy, and need more family support. For those who were employed, working conditions have been adapted to their specific needs.

Health professionals' experience with PD varied between 1 and 5 years in the physiotherapist group and between 5 and 20 years in the neurologist group. All neurologists were movement disorders specialists and all the physiotherapists worked in a specialized movement disorders center.

The Concept of Functional Mobility

All groups were able to present a spontaneous definition of FM that matches with the one used by the authors. All

TABLE 1 | Demographic and clinical data.

	All patients ($n = 10$)	Early-stage group ($n = 6$)	Late-stage group ($n = 4$)
Gender, M/F	7/3	3/1	4/2
Age at onset, mean years (SD)	68 ± 9.9	71.7 ± 9.0	60.7 ± 8.3
Disease duration, mean years (SD)	8 ± 5.2	7.0 ± 6.1	10.0 ± 3.0
% Tremor as first symptom	60%	50%	66.7%
MDS-UPDRS Part II, mean (SD)	12.4 ± 8.1	8.0 ± 2.3	21.43 ± 8.5
MDS-UPDRS Total score, mean (SD)	62.4 ± 23.6	61.0 ± 26.8	90.7 ± 18.3
HY, mean (SD)	2.2 ± 0.4	2.0 ± 0.0	2.5 ± 0.6

TABLE 2 | Key aspects mentioned by the four groups about the concept of FM.

What does the concept of functional mobility suggest?	
Early-stage patients	**Late-stage patients**
• Ability to move • What we do in daily life • Easy performing tasks • The functionality of my mobility is impaired • Something that never worried me	• Autonomy in daily life • Not needing others • It's getting out on the street without anyone noticing that I have Parkinson's • Wanting to do and look like you don't know how • Its dressing and move in bed
Physiotherapist	**Neurologists**
• Movement to perform a function • Daily life • Functionality • Functional movement • Different degrees of limitation	• Ease to displacement • Move to a goal • Movement to perform a task • Autonomy • Related with the WHO concept of Disability. The opposite of impairment.

agree that FM reflects the difficulties of PD patients in daily life (**Table 2**, **Appendix 1**).

Early-Stage Group

Early-stage PD patients associate the concept of FM with the ability to move and with easy performance of daily life tasks. For this group of patients, FM is something that will not worry them in their actual state.

Advanced-Stage Group

Advanced-stage PD patients associate FM with autonomy in daily life and with not being noticed by others in a public environment. Dressing and turning in bed were mentioned as activities related to FM.

Physiotherapist Group

Physiotherapists described FM as the movement for a function or the ability to accomplish the daily tasks important for the subject, even with limitations.

Neurologist Group

Neurologists described FM as the movement needed to perform a task regardless of how you do it and also as something that includes purposed displacements and transfers. For them, the concept of FM is close to the World Health Organization (WHO) concept of disability, as opposed to impairment, and should not be limited by the existence of displacement. In their opinion, the key aspect is the intention to accomplish a task or achieve a goal.

Neurologists highlighted the importance of having an operationalized concept of FM. In their opinion, this outcome may express better patient's perception of their overall health status and may help to adopt a more patient-centered approach. They also suggested FM as a potential useful outcome for the rehabilitation field.

The Impact of FM Limitations in Patient's Lives

Early-Stage Group

Early-stage PD patients mentioned having more difficulty in some specific tasks (e.g., going down the stairs), mainly the need more for time to complete their usual tasks. In their opinion, except for direct family members and close friends, their FM limitations were not noticed by others. This group was not able to identify the best therapeutic strategy to deal with FM limitations. They hypothesize that exercise may be one of them, based on their experience of its benefits (**Table 3**, **Appendix 1**).

Advanced-Stage Group

Advanced-stage PD patients acknowledge to have limitations in FM and consider them the main limiting factor of daily activities, especially in "OFF" periods of medication. They refer that this type of limitation frequently draws other's attention to them, making them feel ashamed. Patients try to avoid these situations through social isolation or finding strategies to mask the signs of the disease. According to their perspective, family and closest friends are usually supportive, while friends and colleagues have more difficulties understanding the fluctuations of the disease. This usually contributes to social isolation and a higher burden to the family members. Medication adjustments, based on patient's priorities, and the use of walking aids were spontaneously referred as strategies to overcome daily life difficulties related to FM.

Physiotherapists

Physiotherapists associated the onset of FM limitations with disease progression. According to their experience, the first FM limitations, mentioned to or noticed by the physiotherapist, are getting up from a chair and getting out of bed or from the car. In

TABLE 3 | Key aspects mentioned by the four groups about the impact of FM limitations on the patient's life.

What is the impact of FM limitations on the patient's daily life?	
Early-stage patients	**Late-stage patients**
• A higher difficulty to perform some tasks but mainly a slower rhythm • Friends and distant family are unaware • Close family refers a slowdown, difficulties in tasks like buttoning • Exercise, cognitive training are efficacious strategies to deal with FM limitations	• Clear perception of FM limitations associated with the disease • The most limiting factor of activities of daily living • The "OFF" periods are the worst moments of the day • Look for strategies to minimize the symptoms of the disease • Feel ashamed for drawing others' attention
Physiotherapists	**Neurologists**
• First limitations: stand up from a chair, get out of the bed or from the car • Associated with the stage of the disease • Initial devaluation, followed by sadness and frustration • In physiotherapy sessions patients learn how to deal with the limitations. Some patients find their own strategies.	• Vary from patient to patient, according lifestyle and tolerance with himself • Patients develop their strategies to overcome limitations until the moment they stop working • Sometimes the perspective of the impact of limitations and treatment goals between a patient and a neurologist does not coincide. The perspective between patient and caregiver is also different.

physiotherapist's perception, patients start by devaluating these limitations, progressing to a feeling of sadness and frustration.

The importance of physiotherapy sessions to maintain PD patient's functionality in daily routine was highlighted, and the importance of patient's education and movement strategy training to overcome FM limitations was emphasized. It was referred that some patients have more difficulty learning due to the feeling of frustration or due to a higher negative emotional burden. In the physiotherapist's perspective, the collaboration of the psychology team is important in these cases. It was also referred that pharmacological interventions enhance the results of physiotherapy interventions, whereby this group supports that the management of PD FM limitations should be a joint work of the multidisciplinary team.

Neurologists

In neurologists' opinion, the interference of FM limitations depends on the patient's characteristics, such as affected side, expectations, and lifestyle (active, retired). Some patients, less demanding with themselves, seem to tolerate disability better.

According to neurologists, patients usually self-manage FM limitations until they can no longer do it. They develop their own strategies, such as wearing button-free clothes and shoes without laces or getting up early to be able to perform all the necessary tasks. It was referred that these limitations and strategies are not always noticed by the neurologist who follows them in the consultation. Neurologists also underline that patient's and caregiver's perspectives differ on this topic.

The Use of Walking Aids

Early-Stage Group

For early-stage patients, the ability to complete a task and performing it successfully were the aspects they valued most in their daily lives, at the expense of the time needed.

The regular use of walking aids is not considered by this group of participants. They believe that good monitoring by specialized professionals and easy access to information about the disease are enough. Some mentioned to have used Nordic walk sticks to perform exercise and found it useful. All were open and suggested the development of technological devices that help them with disease-related problems, such as a device that reminds them to correct their posture. When asked about the key requirements of walking aids, it was mentioned the need for softeners to smooth the gait and the ability to adapt to different surfaces, to be light, and to have handles that allow the use of hands (**Table 4**, **Appendix 1**).

Advanced-Stage Group

None of the patients used walking aids regularly. They see it as potentially helpful, but they try to postpone its use as much as possible, through medication adjustments. Advanced-stage patients have doubts about their usefulness due to the presence of motor fluctuation (in the "ON" medication state, they do not think the need for this kind of help), postural instability, and upper limb problems (which in their perspective hampers its use). Patients who have already used walking aids did it on their initiative, without medical advice, training, or adaptation. The occurrence of falls, the feeling of insecurity, and the resistance to use again on medical recommendation after a bad experience were mentioned.

Due to the lack of experience with walking aids, patients did not feel being able to define their key characteristics.

Physiotherapists

To physiotherapists, a threat to patient's safety (e.g., increased postural instability or the occurrence of falls) determines the recommendation of walking aids. According to them, this type of help is not always well-received. Sometimes, it is perceived as something negative, as a sign of disease progression and of greater dependence. The fear of falling was mentioned as a factor that facilitates its use. It was also referred that some patients start using walking aids too early, without clinical recommendation. Physiotherapists stressed the need to adapt walking aids to patient characteristics and needs and the importance of a supervised period of training. General key characteristics were not mentioned.

Neurologists

In the neurologist's perspective, walking aids should be prescribed according to the patient's clinical characteristics.

TABLE 4 | Key aspects mentioned by the four groups about the use of walking aids.

The use of walking aids	
Early-stage patients	**Late-stage patients**
• The ability to complete a task successfully is the aspect more valuable. The time is no longer a priority when you know you have PD. • The use of walking aids depends on the needs of each patient. PD don't need this type of solutions. A good management of the disease, prevention and education by a specialist are more appropriated. • Patients were open to the use technological devices or Nordic sticks. • Due to the lack of experience, patients only mentioned suggestion for Nordic sticks. They mentioned the existence of shock absorbers to smooth the gait, tips adapted to different types of surfaces, light and with handles that allow to open the hands.	• Patients try to delay the use of walking aids through medication adjustments. • The patients used walking aids, by their own initiative, to get down, get up or when the gait was unstable. They did not have any period training. Falls occurred. • Due to the existence of "ON" periods in which they have acceptable functionality, they do not consider the use of permanent walking aids. • Patients express some reluctance to use walking aids due to the associated social stigma. • A bad experience with walking aids, without training or adaptation period, creates an insecurity that conditions future uses.
Physiotherapists	**Neurologists**
• The presence of imbalances and an increased risk of falling are the first warning signs for the need of walking aids. • They are usually faced in a negative way, as a sign of disease progression and a greater level dependence. • The fear of falling helps accepting the recommendation of a walking aid. • The choice of a walking aids should be personalized.	• According to the patient's clinical characteristics. • This recommendation sometimes does not coincide with the physiotherapist' opinion, who usually finds it too early. • The stigma associated with walking aids influences the patient's receptivity and the neurologist's decision to suggest its use. • Patients face the recommendation as a defeat and with frustration.

Neurologists referred to approach this topic during consultations but to leave the decision to the physiatrist or physiotherapist, since they are more prepared to make a formal recommendation. It was also mentioned that their opinion about the need for this type of aids does not always coincide with the physiotherapist's opinion.

In neurologist's perspective, the use of walking aids is often seen by patients as a loss of autonomy and never as a gain in FM, due to the stigma associated with its use. They referred the need to approach the topic carefully and that patient's reactions are usually defeat, frustration, or taking offense. Neurologists emphasize the importance of a training period. They also recognized that the recommendation of walking aids is sometimes hindered by their own prejudice in relation to this type of aids. This sometimes makes them postpone its recommendation, more than would be desirable.

Neurologists believe that the characteristics of a walking aid should be indicated by a physiatrist or physiotherapist.

DISCUSSION

Ten patients and 10 health professionals participated in the focus groups. All patients were assessed in "ON" state medication. Patients in the advanced-stage group were all recruited from the DBS surgery waiting list, whereby although younger and with a lower score in MDS-UPDRS part III (motor score), had a more disabled type of PD.

The Concept of Functional Mobility

Although none of the groups has provided a definition that fits the proposed definition perfectly, the FM concept seems to be well-understood by patients and professionals and reflects patient's daily life difficulties and disease progression.

Early-stage patients and neurologists seem to be more focused in the component of mobility, whereas advanced-stage patients and physiotherapists highlight more the component of function. In reality, FM is a specific type of mobility that requires displacement and the engagement in tasks and activities at home, work, and in the community (**Table 2**).

In the neurologist's opinion, the FM concept should not be limited by the need for displacement but is defined as the ability to do what one proposes. This idea seems to be present in other groups since references to functional tasks like dressing, shaving, or drinking water were frequent. However, the existence of a displacement is a key component of the concept. FM is the ability of a person to move and is operationalized by the assessment of gait, balance, and transfers during the performance of a functional task (4, 5). This requires displacement and excludes all types of upper limb mobility. Also, this suggestion of a broader concept of FM falls into the definition of mobility [i.e., as "moving by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation." (6)], whereby its adoption would be to give a new name to an existing and already established concept (**Tables 2, 5**).

The way the different groups described the concept seems to reflect their personal knowledge and experience on FM limitations. While early-stage patients and neurologists seem to see it as a minor or distant problem, advanced-stage patients and physiotherapists face it as a current and major problem.

Neurologists also suggest the use of FM as an outcome that better reflects the patient's perception and needs regarding their overall health status. This seems to go in line with the idea previously published that although the assessment of specific disease-related outcomes (e.g., tremor and rigidity) is important, evaluating functional limitations is crucial to get a better idea of a PD patient's disability profile (3). Future studies should explore if and how discrepancies about the concept between

TABLE 5 | The definition of FM and related concepts (6–8).

Functional mobility	A person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in the activities of daily living, at home, work and in the community.
Mobility	The ability to move by changing body position or location or by transferring from one place to another, by carrying, moving or manipulating objects, by walking, running or climbing, and by using various forms of transportation.
Functioning	The individual's ability to execute a task or an action of daily life activities. Refers to all body functions, activities and participation.
Disability	A physical, mental, cognitive, or developmental condition that impairs, interferes with, or limits a person's ability to engage in certain tasks or actions or participate in typical daily activities and interactions.
Independence	The ability to carry out activities that support one's own lifestyle and to control the care given by others.
Autonomy	Self-rule that is free from both controlling interference by others and from limitations, such as inadequate understanding, that prevent meaningful choice.

patients in different stages and health professionals affect the FM problem management.

The Impact of FM Limitations in Patient's Lives

Once more, the perspective of early-stage patients seems closer to neurologists and that of advanced-stage patients to physiotherapists. For advanced-stage patients and physiotherapists, with a closer experience of FM limitations, it was easier to describe its interference in daily activities and its social impact and to mention strategies to overcome them (**Table 6**).

The awareness of having a disease and the experience of limitations, even minor, in daily life lead patients to value more the ability to successfully complete a task, rather than the time needed to perform it (9, 10). This is noteworthy since one of the main reasons for being excluded from work and community environments is to be unable to move at an intensity and frequency that life requires (7). This goes in line with the idea of a previous paper on FM in PD, in which the author refers the superiority of perceived control above velocity (7, 11). As mentioned in the paper, the understanding of these determinants will help health professionals to have a more patient-centered intervention. In a time where personalized interventions are gaining relevancy, being aware of these aspects is crucial and may help to blur the differences between patients and neurologists and/or caregiver's perspectives.

It's also relevant the social impact of the disease. Patients feel ashamed in public environments because of tremor and functional limitations, and little understood by friends because of the fluctuating aspect of the disease. Neurologist mentioned that the impact and degree of discomfort with FM limitations vary with the level of tolerance of patients. According to a 2017 cross-sectional study (12), the stigma of the disease and patient's emotional well-being affect not only the patients but also caregivers. In line with this, we hypothesize that a joint work from the psychology team with physiotherapy for teaching compensatory strategies may be useful to help patients dealing with FM limitations and to lessen the disease burden for patients and caregivers. It would be interesting to know in future studies the weight of the different motor and non-motor symptoms for PD patient's FM problems. This may help to optimize the management of these problems.

TABLE 6 | The differences and similarities in the opinions of patients and health professionals.

Shared perspectives	
• FM is related to the ability to move and perform tasks in daily life	
• FM is impaired in PD	
• There are different degrees of limitation, associated with disease progression	
• Patients look for strategies to minimize FM limitations	
• Exercise, cognitive training are efficacious strategies to deal with FM limitations	
• There is a stigma associated with the use of walking aids	
Different perspectives	
Patients	**Health professionals**
What is the impact of FM limitations on the patient's daily life?	
• For early stage patients FM problems are mainly a problem of slower rhythm. • With the disease progression there is a clear perception of FM limitations, being the most limiting factor of activities of daily living • Advance stage patients feel ashamed for drawing others' attention	• First limitations: stand up from a chair, get out of the bed or from the car • Patients initially devalue the FM problems, then fell sadness and frustration. • Vary from patient to patient, according to lifestyle and tolerance with himself
The use of walking aids	
• From the perspective of early stage patients, walking aids are not necessary for PD. • For both early and advance patients FM problems can be solved with good management of the disease, prevention and education by a specialist • Patients try walking aids on their own initiative, without a previous training period. Falls occur. • For both early and advanced patients, the ability to complete a task successfully is more valuable than the time spent with it.	• The presence of imbalances and an increased risk of falling are the first warning signs for the need for walking aids. • Patients face the recommendation negatively. The fear of falling helps to accept the recommendation of a walking aid. • The choice of walking aid should be personalized, according to the patient's clinical characteristics. Physiotherapy sessions are important to a test and adapt to the walking aid that best suits the patient. • The time spent performing a task is also a concern.

The Use of Walking Aids

The stigma associated with the use of walking aids hinders its use by patients, in early and advances stage of the disease, and interferes with neurologist's recommendations. Although walking aids could allow for a more active lifestyle, the fact of being associated with disability prevent them from being considered as something that may enhance perceived control of their situation (7).

It is interesting to note the openness and acceptance of walking aids based on technological devices or in instruments that do not have the classic appearance of walking aids (e.g., Nordic sticks). It is also curious that even when patients suggest the development of technological walking aids, they do not seem to want to use them to be faster or to have a more active lifestyle, but to correct aspects that draws other's attention (posture, dyskinesias, and freezing).

Due to the size of our sample and the fact that all patients have the same nationality, we recognize that these results were influenced by cultural factors. We believe that the information generated here is important to highlight the relevance and usefulness of the concept of FM for PD management and research. However, we recommend conducting in the future a larger and multinational study.

CONCLUSION

Functional mobility limitations were acknowledged by early-stage PD patients, representing an important limiting factor of daily activities and social participation for advanced-stage patients. The proposed concept of FM to be applied to PD seems to be well-understood by patients and health professionals and reflects the impact of disease progression in patient's lives. Although walking aids have the potential to increase patient's FM, they are seen as a sign of dependency; therefore, they are not well-accepted. Future bioengineering studies should focus on a technological solution and avoid the look of classical walking aids. We recommend the adoption of FM as an outcome, in clinical routine and research, as a strategy to get a better perception of patient's overall health status and to adopt a more patient-centered approach.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CNS Local Ethical Committee (Ref. 04-2018). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RB-M conceptualized the study, executed the study and data analysis, and drafted and revised the manuscript. NG executed the study and data analysis and revised the manuscript. IL, MP, PC, RN, SD, AC, AV, PL, LG, MR, and MC executed the study and revised the manuscript. JF conceptualized the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors would like to thank to the Fundação para a Ciência e a Tecnologia (FCT) (SFRH/BD/120773/2016 to RB-M).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.575811/full#supplementary-material

REFERENCES

1. osserams A, Vries NMde, Bloem BR, Nonnekes J. Multidisciplinary care to optimize functional mobility in parkinson disease. *Clin Geriatr Med.* (2020) 36(Suppl. 1):159–72. doi: 10.1016/j.cger.2019.09.008
2. Raggi A, Leonardi M, Ajovalasit D, Carella F, Soliveri P, Albanese A, et al. Disability and profiles of functioning of patients with Parkinson's disease described with ICF classification. *Int J Rehabil Res.* (2011) 34(Suppl. 2):141–50. doi: 10.1097/MRR.0b013e328344ae09
3. Leonardi M, Raggi A, Ajovalasit D, Bussone G, D'Amico D. Functioning and disability in Parkinson's disease. *Disabil Rehabil.* (2010) 32(Suppl. 1):S23–32. doi: 10.3109/09638288.2010.511687
4. Forhan M, Gill SV. Obesity, functional mobility and quality of life. *Best Pract Res Clin Endocrinol Metab.* (2013) 27(Suppl. 2): 129–37. doi: 10.1016/j.beem.2013.01.003
5. Bouça-Machado R, Duarte GS, Patriarca M, Caldas AC, Alarcão J, Fernandes RM, et al. Measurement instruments to assess functional mobility in Parkinson's disease: a systematic review. *Mov Disord Clin Pract.* (2019) 7:129–39. doi: 10.1002/mdc3.12874
6. World Health Organization. Towards a common language for functioning, disability and health: the international classification of functioning, disability and health. *Int Classif.* (2002) 1149:1–22.
7. Bouça-Machado R, Maetzler W, Ferreira JJ. What is functional mobility applied to Parkinson's disease? *J Parkinsons Dis.* (2018) 8:121–30. doi: 10.3233/JPD-171233
8. Varelius J. The value of autonomy in medical ethics. *Med Heal Care Philos.* (2006) 9(Suppl. 3):377–88. doi: 10.1007/s11019-006-9000-z
9. McQuillen AD, Licht MH, Licht BG. Contributions of disease severity and perceptions of primary and secondary control to the prediction of psychosocial adjustment to Parkinson's disease. *Heal Psychol.* (2003) 22(Suppl. 5):504–12. doi: 10.1037/0278-6133.22.5.504
10. Ferreira JJ, Santos AT, Domingos J, Matthews H, Isaacs T, Duffen J, et al. Clinical parameters and tools for home-based assessment of Parkinson's disease: results from a delphi study. *J Parkinsons Dis.* (2015) 5(Suppl. 2):281–90. doi: 10.3233/JPD-140493
11. Bettecken K, Bernhard F, Sartor J, Hobert MA, Hofmann M, Gladow T, et al. Association of kinematic gait parameters with health-related quality of life in Parkinson's disease. *PLoS ONE.* (2017) 12:e0176816. doi: 10.1371/journal.pone.0176816
12. Rajiah K, Maharajan MK, Yeen SJ, Lew S. Quality of life and caregivers' burden of Parkinson's disease. *Neuroepidemiology.* (2017) 48(Suppl. 3–4):131–7. doi: 10.1159/000479031

Conflict of Interest: LG is a consultant for Novartis and Sanofi-Genzyme, a board of adviser for GMP-Orphan, and is employed at the Department of Neuroscience and Mental Health, Neurology, Hospital de Santa Maria, CHULN,

Lisbon, Portugal. JF is a consultant for Ipsen, GlaxoSmithKline, Novartis, Teva, Lundbeck, Solvay, Abbott, BIAL, Merck-Serono, and Merz; received grants from GlaxoSmithKline, Grunenthal, Teva, and Fundação MSD; and is employed at the Laboratory of Clinical Pharmacology and Therapeutics of Lisbon.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Bouça-Machado, Gonçalves, Lousada, Patriarca, Costa, Nunes, Dias, Caldas, Valadas, Lobo, Guedes, Rosa, Coelho and Ferreira. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Journal of Parkinson's Disease xx (20xx) x–xx
DOI 10.3233/JPD-201969
IOS Press

Review

Gait Kinematic Parameters in Parkinson's Disease: A Systematic Review

Raquel Bouça-Machado[a,b], Constança Jalles[a,1], Daniela Guerreiro[b,1], Filipa Pona-Ferreira[b,1], Diogo Branco[c], Tiago Guerreiro[c], Ricardo Matias[d,e] and Joaquim J. Ferreira[a,b,f,*]
[a]*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Avenida Professor Egas Moniz, Lisboa, Portugal*
[b]*CNS - Campus Neurológico Sénior, Torres Vedras, Portugal*
[c]*LASIGE, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal*
[d]*Champalimaud Research and Clinical Centre, Champalimaud Centre for the Unknown, Lisbon, Portugal*
[e]*Human Movement Analysis Lab, Escola Superior Saúde – Instituto Politécnico de Setúbal, Setúbal, Portugal*
[f]*Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal*

Accepted 15 April 2020

Abstract.
Background: Gait impairments are common and highly disabling for Parkinson's disease (PD) patients. With the development of technology-based tools, it is now possible to measure the spatiotemporal parameters of gait with a reduced margin of error, thereby enabling a more accurate characterization of impairment.
Objective: To summarize and critically appraise the characteristics of technology-based gait analysis in PD and to provide mean and standard deviation values for spatiotemporal gait parameters.
Methods: A systematic review was conducted using the databases CENTRAL, MEDLINE, Embase, and PEDro from their inception to September 2019 to identify all observational and experimental studies conducted in PD or atypical parkinsonism that included a technology-based gait assessment. Two reviewers independently screened citations and extracted data.
Results: We included 95 studies, 82.1% ($n = 78$) reporting a laboratory gait assessment and 61.1% ($n = 58$ studies) using a wearable sensor. The most frequently reported parameters were gait velocity, stride and step length, and cadence. A statistically significant difference was found when comparing the mean values of each of these parameters in PD patients versus healthy controls. No statistically significant differences were found in the mean value of the parameters when comparing wearable versus non-wearable sensors, different types of wearable sensors, and different sensor locations.
Conclusion: Our results provide useful information for performing objective technology-based gait assessment in PD, as well as mean values to better interpret the results. Further studies should explore the clinical meaningfulness of each parameter and how they behave in a free-living context and throughout disease progression.

Keywords: Parkinson's disease, gait, objective assessment, technology, wearable sensor

Uncorrected Author Proof

BACKGROUND

Parkinson's disease (PD) gait impairments increase with disease progression and are a marker of global health, cognition status, falls risk, and institutionalization [1, 2].

[1]These authors contributed equally to this work.

*Correspondence to: Joaquim J. Ferreira, MD, PhD, Laboratório de Farmacologia Clínica e Terapêutica, Faculdade de Medicina de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisbon, Portugal. Tel.: +351 21 7802120; E-mail: joaquimjferreira@gmail.com.

ISSN 1877-7171/20/$35.00 © 2020 – IOS Press and the authors. All rights reserved
This article is published online with Open Access and distributed under the terms of the Creative Commons Attribution Non-Commercial License (CC BY-NC 4.0).

The use of accurate and reliable quantitative information about the mechanics of PD gait is perhaps one of the most promising outcomes that enables early diagnosis, assessment of disease progression and evaluation of therapeutic interventions [3, 4]. In the last decades, with the appearance of technology-based objective measures (TOMs), the evaluation of different spatial and temporal parameters of gait paved the way for a more ecological (i.e., closer to patients' real-life environment performance) and efficient assessment, with a reduced margin of error. Two types of devices have been commonly used: non-wearable sensors (NWS) and wearable sensors (WS) [4]. The NWS are considered the gold standard. They require a controlled and calibrated environment, where individuals walk with skin-mounted markers whose instantaneous positions are obtained using stereophotogrammetry (motion capture) most often based on optoelectronic sensors. WS are small, lightweight sensors (e.g., inertial measurement units) that are attached to one or several body segments, enabling human motion reconstruction in both the context of a laboratory or during activities of daily living [4].

The International Society of Biomechanics has attempted to standardize reports of joint motion in the field of biomechanics for human movement [5]. However, in the PD field, there is a lack of consensus on the best type of sensors and which gait spatiotemporal parameters are clinically relevant. This limits the use of objective measurements of gait in clinical practice and research. [6–8]. Therefore, we aimed to summarize and critically appraise the characteristics of technology-based gait analysis in PD and to provide mean and standard deviation values for spatiotemporal gait parameters.

METHODS

Literature search

We searched CENTRAL, MEDLINE, and PEDro from their inception to September 2019 using "Parkinson*", "Gait", "Walking", "Accelerometer", "Algorithm" and "Body-fix sensor" as key words. Reference lists from the identified articles were cross-checked to identify any further potentially eligible studies.

Study selection

We included all observational and experimental studies, or study protocols, conducted in PD patients or atypical parkinsonisms, that included a technology-based gait analysis focused on continuous gait disturbances and that specified which parameters had been studied. There were no restrictions regarding the type of intervention in the active and control arms.

We excluded reviews and studies written in languages other than English, French, Spanish, and Portuguese. All retrieved abstracts were independently screened by two authors. The full texts of potentially relevant articles were retrieved for further assessment. Disagreements were resolved by consensus.

Data extraction

Five pre-defined domains of items were extracted: general information (year and journal of publication, aim of the study, study design, population, intervention, time point assessments, technology development phase), gait assessment supplies (equipment, type of sensor, type of assessment), gait assessment procedures (protocol, medication status, and other outcome tools) and gait parameters values.

According to Maetzler's classification [6], we classified studies according to their technology development phase, which covered three phases: i) preclinical development and testing (those studies focused on how to measure, i.e., testing algorithms or validating a new gait assessment system), ii) clinical development and testing phase (studies focused on the parameters that can be measured and on their clinical relevance) and iii) clinical validation (experimental and observational studies that use gait analysis as an outcome).

We also used an adaptation of the conceptual model of gait presented by Del Din, 2016 [9] to present and analyze the gait parameters reported in the included studies. Parameters that were only reported in one study, and not fitting the model, were included in the "other parameters" section. Data were extracted by two independent authors. Discrepancies were resolved through discussion.

Data analysis

We summarized the publication characteristics using frequencies and percentages. Review Manager software (v 5.3; Cochrane Collaboration) was used for calculating pooled mean difference (MD) and the 95% confidence interval (CI). Heterogeneity was assessed using the Q test and I^2 statistic. An I^2 value of

Uncorrected Author Proof

<25% was chosen to represent low heterogeneity and an I^2 value of >75% to indicate high heterogeneity. A random-effects model was used to pool all outcomes. A p-value of <0.05 was considered to be statistically significant.

RESULTS

The electronic and hand searches identified 3727 citations. Full-text assessment for eligibility resulted in 95 studies being included (Fig. 1). Overall, the main reasons for exclusion were inappropriate study population ($n=2607$) and inadequately defined outcome ($n=378$) (Supplementary Material 1).

The most common study designs used were case-control studies (34.7%, $n=33$), cross-sectional studies (28.4%, $n=27$), and randomized controlled trials (27.4%, $n=26$). Of the 95 included studies, 61.1% ($n=58$ studies) used WS, 32.6% ($n=31$ studies) NWS, and 6.3% ($n=6$ studies) both types of devices. Seventy-eight studies (82.1%) reported a laboratory gait assessment, 6.3% ($n=6$) a free-living assessment, and 11.6% ($n=11$) made the assessment in both contexts (Table 1).

Since only two studies [9, 10] presented values for spatiotemporal gait parameters in free-living assessments, and patients are known to perform differently in the laboratory and free-living contexts, these values were excluded from data analysis [11].

Gait parameters measured with non-wearable sensors

Table 3 lists the gait parameters using NWS reported in the included studies; the most frequently used unit of measurement and the mean and standard deviations of the reported values are also listed.

The most frequently reported parameters (≥20% of the studies) were gait velocity (81.1%, $n=30$, PD mean value = 0.99 ± 0.24 m/s), stride length (56.8%, $n=21$, PD mean value = 1.06 ± 0.18 m), cadence (48.7%, $n=18$, PD mean value = 102.71 ± 10.50 steps/min), step length (46.0%, $n=17$, PD mean value = 0.58 ± 0.13 m), double support phase (27.0%, $n=10$, PD mean value = 25.89 ± 7.23%) and step width (24.3%, $n=9$, PD mean value = 0.13 ± 0.02 m).

Gait parameters measured with wearable sensors

Table 2 lists the gait parameters assessed with a WS reported in the included studies; the most frequently used unit of measurement and the mean and standard deviations of the reported values are also listed.

The more frequently reported parameters (≥20% of the studies) were gait velocity (60.9%, $n=39$, PD mean value = 1.01 ± 0.26 m/s), stride length (37.5%, $n=24$, PD mean value = 1.14 ± 0.25 m), stride time (28.1%, $n=18$, PD mean value = 1.18 ± 0.18 s), cadence (28.1%, $n=18$, PD mean value = 106.42 ± 19.60 steps/min), step length (23.4%, $n=15$, PD mean value = 0.60 ± 0.06 m), step time (21.9%, $n=14$, PD mean value = 0.55 ± 0.03 s), stride time variability (21.9%, $n=14$, PD mean value = 4.33 ± 2.81% of the coefficient of variation (%CV)) and step time variability (20.3%, $n=13$, PD mean value = 0.02 ± 0.00 s).

Three studies evaluated gait in a controlled environment and nine in a free-living context. Due to both the low number of studies presenting a value for this parameter and the heterogeneity of the measurement units, we did not summarize the data nor present a reference value.

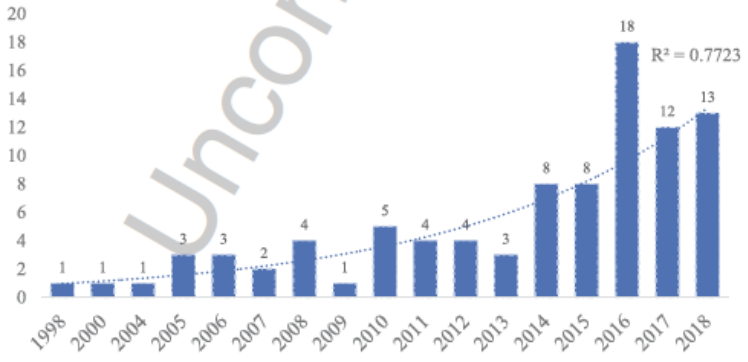


Fig. 1. Number of studies including a technology-based assessment per year in PD.

Uncorrected Author Proof

Table 2
Demographic data, clinical data and mean values of gait parameters assessed with wearable devices.
Unk, unkown; NA, not applicable; SD, standard deviation; CV, coefficient of variation

Demographic and clinical characteristics | Wearable devices ($n = 64$)	PD	HC
Age (Mean, SD (n))	66.98 ± 6.89 (56)	63.40 ± 13.04 (27)
Average % Male (Mean, SD (n))	60.69 ± 15.60 (53)	50.42 ± 18.02 (25)
Height (Mean, SD (n))	1.69 ± 0,04 (27)	1.69 ± 0,06 (14)
BMI (Mean, SD (n))	25,76 ± 1,42 (35)	25,49 ± 1,77 (17)
Disease duration (Mean, SD (n))	6.78 ± 5.38 (33)	NA
UPDRS III (Mean, SD (n))	29.46 ± 12.88 (35)	NA
Hoenh & Yard (Mean, SD (n))	2,28 ± 0,44 (39)	NA

			Gait Parameters			
Domain	Variable	Studies (n)	Units	Most frequent unit (n,%)	PD mean value (mean, SD (n))	HC mean value (mean, SD (n))
Ambulatory activity	Step count	12	number of steps, steps/day	number of steps (7, 53.85%)	NA	NA
	Gait Velocity	39	cm/sec, m/sec	m/sec (34, 87.18%)	1.01 ± 0.26 (32); 1.04 ± 0.19 (DT, 8)	1.19 ± 0.31 (17); 1.22 ± 0.1 (DT,3)
	Cadence	18	Hz, steps/min, steps/sec	steps/min (12, 66.67%)	106.68 ± 20.57 (11)	113.34 ± 7.55 (6)
Pace	Stride length	24	m, cm, % of the stature	meters (17, 70.83%)	1.14 ± 0.28 (18)	1.37 ± 0,08 (8)
	Stride velocity	2	seconds	NA	NA	NA
	Step length	15	cm, m	m (12, 80.00%)	0.55 ± 0.13 (13)	0.61 ± 0.21 (8)
	Step velocity	8	m/sec	m/sec (6, 75,00%)	1.18 ± 0.06 (6)	1.31 ± 0.07 (3)
	Stance phase	2	%	% (2, 100,00%)	60.25 ± 1.76 (2)	57.45 ± 2.75 (2)
	Swing phase	7	% gait cycle	% gait cycle (7, 100%)	36.95 ± 5.11 (7)	39.21 ± 3.62 (4)
	Double support phase	8	% gait cycle	% gait cycle (8, 100%)	29.03 ± 5.00 (8)	23.40 ± 5.83 (6)
Rhythm	Stride time	18	%, msec, seconds	seconds (14, 77.78%)	1.18 ± 0.18 (12)	1.09 ± 0.07 (9)
	Step time	14	msec, seconds	seconds (7, 50.00%)	0.55 ± 0.03 (7)	0.54 ± 0.02 (4)
	Stance time	9	seconds	seconds (5, 55.56%)	0.74 ± 0.07 (5)	0.71 ± 0.03 (3)
	Swing time	12	msec, seconds	seconds (6, 50.00%)	0.39 ± 0.03 (6)	0.39 ± 0.02 (4)
	Double support time	1	msec	NA	NA	NA
Variability	Stride time variability	14	%CV	% CV (12, 85.71%)	3.84 ± 2.94 (12)	2.18 ± 0.59 (9)
	Step length variability	6	m	m (4, 66,67%)	0.032 ± 0.012 (4)	NA
	Step time variability	13	%CV, msec, seconds	seconds (5, 38.46%)	0.030 ± 0.005 (5)	0.022 ± 0.004 (2)
	Step velocity variability	7	m/sec	m/sec (5, 71.43%)	0.057 ± 0.021 (5)	0.055 ± 0.015 (3)
	Stance time variability	8	%CV, seconds	seconds (4, 50.00%)	0.036 ± 0.015 (4)	0.024 ± 0.003 (2)
	Swing time variability	13	%CV, seconds	% CV (7, 53.85%)	4.714 ± 3.388 (7)	2.481 ± 0.624 (5)
	Double support variability	3	%, CV	% CV (3, 100.00%)	9.803 ± 4.617 (3)	6.552 ± 2.224 (3)
Asymetry	Stride time asymetry	1	% of stature	NA	NA	NA
	Step time asymetry	10	msec, sec	seconds (4, 40,00%)	0.021 ± 0.010 (4)	0.011 ± 0.010 (2)
	Stance time asymetry	7	seconds	seconds (4, 57.1%)	0.021 ± 0.010 (4)	0.011 ± 0.005 (2)
	Swing time asymetry	9	msec, seconds	seconds (4, 44.44%)	0.020 ± 0.009 (4)	0.012 ± 0.002 (2)
Postural control	Step length asymetry	8	m	m (6, 75,00%)	0.024 ± 0.011 (6)	0.010 ± 0.004 (3)
	Step width	2	m	m (2, 100.00%)	0.080 ± 0.014 (2)	NA

Other parameters
Ambulatory activity (walking bouts, total time, activity counts/day)
Arm swing amplitude, variability, asymmetry, jerk
Angular velocity of shanks, thighs, trunk and head
Range of head, trunk, shank, thigh and knee rotation
Entropy (measure of variability)
Energy, Power
Magnitude, Smoothness, Attenuation, Regularity, Symmetry, Harmonic ratio, Jerk
SPARC (measure of smoothness)

Uncorrected Author Proof

PD patients versus healthy controls

We were able to perform a forest plot analysis comparing the mean values of PD patients versus healthy controls (HC) for the following gait parameters: gait velocity, cadence, stride length, stride time, stride time variability, step length, step time, swing time, and double support time. All, except step time using WS, presented a statistically significant difference between groups. For gait velocity and stride length, a statistically significant difference between groups was found in WS assessment, but not in the assessment using NWS (Supplementary Material 2).

Wearable versus non-wearable sensors assessment

Comparison between the two types of devices was possible for gait velocity, stride, and step length. While gait velocity presented a statistically significant difference ($p=0.04$, $I^2=76.7\%$), there was no difference between WS and NWS in stride ($p=0.35$, $I^2=0\%$) or step length ($p=0.14$, $I^2=55\%$) (Supplementary Material 2).

Type of wearable sensor

The use of an accelerometer was compared with the use of other types of sensors for gait velocity. The subgroup analysis was not statistically significant ($p=0.18$ and $I^2=44.7\%$). Both groups showed a statistically significant difference between PD and HC ($p \leq 0.05$). The available data did not allow other comparisons for this topic (Supplementary Material 2).

Sensor location

The impact of sensor location (lower back versus feet versus other locations) was studied for gait velocity, stride time, and stride time variability. No differences between groups were registered. Heterogeneity (I^2) ranged between 0–52.9%. All the parameters, except for stride time variability, using the sensor in the lower back, showed a statistically significant difference between PD and HC ($p \leq 0.05$) (Supplementary Material 2).

Sample characteristics

Studies using non-wearable sensors

Eleven studies used a healthy control group. The mean age of PD patients was 67.1 ± 4.8 years ($n=29$ studies) and of 66.3 ± 5.7 years ($n=7$ studies) in HC. The mean percentage of male patients was 63.5 ± 16.0 % for PD ($n=22$ studies) and of 49.0 ± 11.2 for HC ($n=7$ studies). The mean disease duration of PD patients was 7.9 ± 2.3 years ($n=25$ studies). The mean Hoehn and Yahr (HY) score was 2.5 ± 0.4 (77.1%, $n=27$ studies), and the mean motor score for the Unified Parkinson's Disease Rating Scale (UPDRS III) was 28.9 ± 7.9 points (71.4%, $n=25$ studies) (Table 1).

Studies using wearable sensors

Twenty-nine studies used a healthy control group. The mean age of PD patients was 66.8 ± 6.8 years (82.3%, $n=51$ studies) and of 65.1 ± 11.3 in HC (35.5%, $n=22$ studies). The mean percentage of male patients was 60.4 ± 15.9 % for PD (77.4%, $n=48$ studies) and of 47.4 ± 16.2 for HC (30.6%, $n=19$ studies). The mean disease duration of PD patients was 6.7 ± 5.4 years (51.6%, $n=32$ studies). The mean HY score was 2.3 ± 0.4 (61.3%, $n=38$ studies), and the mean motor score for the UPDRS III was 30.0 ± 13.9 points (53.2%, $n=33$ studies) (Table 2).

General characteristics of technology-based gait analysis in PD

From the 95 included studies, according to the technology development phase classification: 24.2% of the studies ($n=23$) were in the preclinical development and testing phase, 31.6% ($n=30$) were in the clinical development and testing phase and 44.2% ($n=42$) belong to the clinical validation phase.

Preclinical development and testing phase

In 56.5% ($n=13$) of the 23 studies, gait assessment was performed in the laboratory, in 17.4% ($n=4$) it was performed in a free-living context, and in 26.1% ($n=6$) it was performed in both contexts.

In 87.0% ($n=20$) WS was used, while 13.0% ($n=3$) used both type of devices. The most common types of sensors were accelerometers (56.5%, $n=13$), accelerometers and gyroscopes (17.4%, $n=4$), only gyroscopes (8.7%, $n=2$) and smartphones (using an accelerometer and gyroscope, 8.7%, $n=2$).

The most common position for the sensor was on the lower back, between the second and fifth lumbar vertebras (43.5%, $n=10$ of the studies) (Table 3).

Clinical development and testing phase

In 83.3% ($n=25$) of the 30 studies, gait assessment was performed in the laboratory, while in 6.7%

Uncorrected Author Proof

Table 3
General characteristics of technology-based gait analysis in PD

	Preclinical development and testing	Clinical development and testing	Clinical validation	Total
N	23	30	42	95
Type of assessment				
Lab	13	25	40	78
FL	4	2	0	6
Both	6	3	2	11
Type of device				
Wearable	20	23	15	58
Non wearable	0	5	26	31
Both	3	2	1	6
Type of sensor				
Accelerometer	13	17	9	39
Accelerometer and gyroscope	4	2	3	9
Force-sensitive insoles	0	4	3	7
Accelerometer, gyroscope and magnetometer	1	2	0	3
Gyroscopes	2	0	0	2
Smartphone – Accelerometer and gyroscope	2	0	0	2
Pressure sensor	1	0	0	1
Magnetometers	0	0	1	1
Location of the sensor				
Lower back (L2–L5)	10	18	2	30
Ankles/Feet	3	4	3	10
Lower back and ankles/feet	2	2	5	9
4–6 sensors	3	0	1	4
Other	3	1	0	4
Lower back and wrists	0	0	1	1
Unknown	2	0	4	6
Medication state				
ON-phase medication	5	15	28	48
OFF-phase medication	1	1	5	7
ON- and OFF-phase medication	1	2	1	4
Not described	12	10	8	30
Not applicable (Free-living)	4	2	0	6

($n=2$) it was performed in a free-living context, and in 10.0% ($n=3$) it was performed in both contexts.

In 76.7% of the studies ($n=23$) a WS was used, 16.7% ($n=5$) used NWS and 6.7% ($n=2$) used both type of devices. Accelerometer (68.0%, $n=17$) and force-sensitive insoles (16.0%, $n=4$) were the most frequently used type of sensor. The most common position for the sensor was in the lower back, between the second and fifth lumbar vertebras (72.0%, $n=18$) (Table 3).

Clinical validation phase

The majority of the assessments were performed in the laboratory (95.2%, $n=40$). NWS was used in 61.9% ($n=26$) of the studies, a WS in 35.7% ($n=15$) and both devices in one study. Accelerometers (60.0%, $n=9$) were the most frequently used type of sensor. The most common position for the sensor was on the lower back and the feet/ankles (33.3%, $n=5$). (Table 3)

Protocol details

Table 4 shows the characteristics of the gait assessment protocol. The most frequently used distance in laboratory assessments was 10 meters ($n=23$), the shortest distance reported was 3 meters and the longest 500 meters. Table 5 compares PD patients' gait velocity using a gait assessment protocol with less than 10 meters, 10 meters and more than 10 meters. Due to the heterogeneity of the data, this comparison was only performed for gait velocity and a forest plot analysis was not possible.

The mean number of trials was 4.3 ± 2.9. In 46.1% of the studies ($n=41$), gait assessment was performed at a self-selected comfortable speed. In free-living assessments, the most common duration of data collection was 7 days (58.8%, $n=10$).

In 58.5% of studies ($n=48$), patients were in an "ON-state" during the assessment, in 7.4% ($n=7$) in an "OFF-state" and in 4.2% of the studies ($n=4$) the assessment was performed in both conditions

Uncorrected Author Proof

Table 4
Protocol details of laboratory and free-living gait assessments

Protocol details		
Laboratory assessment		
Distance		
	Median [Min, Max in meters]	10 [3,500]
	Mode (n, %)	10 (23, 24.2%)
Trials		
	Mean, SD	4,52 ± 2,98
Protocol		
	Self-selected comfortable speed	44
	Self-selected comfortable and dual task	8
	Self-selected comfortable, fast speed and dual task	6
	Self-selected comfortable and fast speed	5
	Self-selected comfortable and cueing	4
	Fast speed	2
	Fast, normal, and slow speed	2
	Other	7
	Unknown	11
Free-living assessment		
Duration		
	7 days	10
	3 days	3
	10 days	2

Table 5
Analysis of gait speed according to the distance covered in the gait protocol

	Wearable	Non-Wearable
Less than 10 meters (mean, SD (n))	0.9 ± 0.2 (5)	0.9 ± 0.3 (7)
10 meters (mean, SD (n))	1.0 ± 0.1 (7)	0.9 ± 0.4 (8)
More than 10 meters (mean, SD (n))	1.1 ± 0.3 (18)	NA

(Table 4). Table 6 compares the PD mean values with and without having into account the "ON/OFF" medication state. Due to the low number of studies assessing gait in "OFF" state medication ($n = 11$, 11.6%) and the heterogeneity of the data, this analysis was only possible to perform for some gait parameters and did not allow for a forest plot analysis. Except for stride time variability, all the mean values of the studies only including an "On" state medication assessment, were closer to those from the HC group.

DISCUSSION

The number of studies including a technology-based gait assessment is increasing (Fig. 1). Of the 95 studies included, the majority performed a laboratory assessment (82.1%, $n = 78$) and used WS (61.1%, $n = 58$). Accelerometers were the most frequently used type of sensor (67.2%, $n = 39$), usually on the lower back (51.7%, $n = 30$). The sample characteristics of the included studies were very similar, not allowing for subgroup analysis.

1) What should be measured?

The most frequently reported parameters in the included studies were gait velocity, stride and step length, and cadence. Compared to HC, PD patients had decreased velocity, reduced stride and step length, decreased swing time, increased stride time, stride time variability and dual support time ($p < 0.05$). These differences are in line with the usual description of PD gait impairments, i.e., a slow, short-stepped, shuffling, with a forward-stooped posture and asymmetrical arm swing [7, 12, 13].

Beyond this, a large number of different, or differently measured gait parameters, were found in the included studies. From a clinical point of view,

Table 6
Analysis of PD gait parameters according to the "ON/OFF" medication state during the gait assessment

	Wearable devices		
	All	"ON" State Medication	Healthy controls
Gait velocity	1.01 ± 0.26 (32)	1.06 ± 0.20 (29)	1.19 ± 0.31 (17)
Cadence	106.68 ± 20.57 (11)	112.33 ± 8.89 (10)	113.34 ± 7.55 (6)
Stride Length	1.14 ± 0.28 (18)	1.15 ± 0.26 (15)	1.37 ± 0,08 (8)
Stride Time	1.18 ± 0.17 (13)	1.18 ± 0.18 (12)	1.09 ± 0.07 (9)
Stride Time Var	3.84 ± 2.94 (12)	4.01 ± 3.02 (11)	2.18 ± 0.59 (9)
Double support phase	29.03 ± 5.00 (8)	29.22 ± 5.37 (7)	23.40 ± 5.83 (6)
	Non-wearable devices		
	All	"ON" State Medication	Healthy controls
Gait velocity	1.00 ± 0.25 (19)	1.01 ± 0.25 (18)	1.15 ± 0.32 (5)
Cadence	104.04 ± 9.57 (15)	105.75 ± 7.15 (14)	NA
Stride Length	0.77 ± 0.40 (19)	0.77 ± 0.43 (17)	1,20 ± 0.28 (4)
Step Length	0.54 ± 0.13 (17)	0.55 ± 0.13 (16)	0.64 ± 0.06 (6)

Uncorrected Author Proof

not every parameter that can be measured should be measured [6, 8]. The collection and interpretation of the data must lead to justified outcomes, i.e., those with an impact on activities of daily living, displayed in a visually intuitive format that covers the clinical information needs of the stakeholders (health professionals, patients, and caregivers) [6, 8]. For this, gait parameters should be correlated with robust measures of clinical meaningfulness, such as the MDS-UPDRS motor score or the Timed Up and Go Test (TUG). Once the most suitable parameters to measure PD gait impairments in different contexts are established, then the minimal clinically important differences should be addressed for each [6, 8]. Other measures emerging from the nonlinear analysis of human variability (e.g., entropy, fractals, and others) can give us a more accurate angle of patients' gait dynamics in a real-life environment. However, work is needed to make them more intuitive and clinically informative [6, 8].

Although currently, sensor-based gait analysis has demonstrated feasibility and applicability for objectively assess PD gait impairments, differences still exist measuring the same parameter, with different devices or devices from different manufacturers [3, 14, 15]. This highlights the difficulty of accurately measuring the spatiotemporal gait parameters and the need to continue developing valid and reliable mathematical algorithms. Despite the major technological advances and the current possibility of capturing and store extremely high amounts of data with TOMs, the ability to algorithmically analyze (eliminating the noise) and summarize the clinically relevant data to stakeholders remains limited. [3]

2) Which devices should be used?

The comparison between assessments using WS and NWS was investigated for gait velocity, stride and step length parameters. A statistically significant difference between groups was found in gait velocity ($p = 0.04$). Although it was the analysis with the highest number of studies ($n = 18$), due to the level of heterogeneity ($I^2 = 76.7\%$), the results should be interpreted with caution. We believe that the differences in the type of devices and in the assessment protocols of the included studies might have contributed to this result.

No statistically significant difference was found in the two other parameters (stride length – $p = 0.35$, step length – $p = 0.14$). Taking into account the low value for heterogeneity ($I^2 = 0\%, p < 0.001$), we believe that wearable sensors can be used in place of NWS (the gold standard of gait analysis).

WS have the added value of enabling the assessment of gait during activities of daily living in the patients' actual environment. However, more studies exploring how gait parameters behave in a real-world context are needed [4].

It was only possible to explore the impact of the type of WS for gait velocity. This was undertaken by comparing the use of accelerometer (used in 67.2% of the WS) with all other types of sensors.

Accelerometers allow the measurement of dynamic accelerations of a body, when submitted to an external force, and provide information about the device orientation related to gravity [3, 14, 15]. They are frequently combined with a gyroscope, which allow for the measurement of angular velocities [3, 14, 15]. In some devices, a 3D-magnetometer is also added for orientation purposes.

Since no difference was found in this subgroup analysis (accelerometer versus all other types of sensors) and both groups were able to detect a statistically significant difference between PD and HC, we believe that for an accurate assessment and monitorization of PD patients' gait impairments, the use of a single accelerometer is feasible. However, for the assessment of turns or of a more complex movement that requires the information captured by angular velocity, wearable devices including at least a gyroscope, seem more suitable.

In the included studies, only one study used an isolated magnetometer for gait analysis. Since magnetometers are very sensitive to magnetic changes (e.g., those produced by proximity with ferromagnetic objects) and therefore to many external interferences, they are more frequently used as a complement to accelerometers and gyroscopes, than as a single sensor [3, 14, 15].

3) Where to place the sensor?

Our results showed that in 46.9% ($n = 30$) of the studies using WS, the sensor was used on the lower back, between the second and the fifth lumbar vertebra. Although it was only possible to investigate the impact of sensor location for three parameters, it was limited to the comparison between lower back, feet and all other locations, the results consistently show no statistically significant difference between groups. Stride time variability measured with the sensor in the lower back was the only parameter that did not show a statistically significant difference between PD and

Uncorrected Manuscript

HC. However, a heterogeneity (I^2) of 82% was found, whereby these results should be interpreted carefully.

Several gait analyses protocols have been used. However, an optimal and standardized method remains for establishing [15]. The number and location of the sensors are key aspects for the success of assessments with TOMs, especially in a free-living context [8, 16]. To increase wearing compliance without hindering the precision of data collection the number of sensors should be kept to a minimum, and the least obtrusive devices preferred [8, 16]. Today, although the lower back is not considered the most comfortable and unobtrusive location, it has been shown that a single sensor (accelerometer) in this location is able to capture with precision, physical activity and gait parameters in a laboratory and free-living context [16, 17]. Recently, there has been a move toward using sensors on the wrist or embedded in smartphones. However, problems still exist when collecting data. Kim et al., 2019 [16] report that sensors used on the wrist tend to overestimate the number of steps and the time spent at different intensities of activity. Höchsmann et al., 2018 [18] compared the accuracy of step detection of a smartphone (placed in a trouser pocket, shoulder bag, and backpack) with a WS used on the wrist and waist. At a gait velocity of 4.8 km/h (shoulder bag and backpack) and 6.0 km/h (all positions), smartphones did not exceed a 1% error deviation from the gold standard (threshold to be considered an accurate measurement). However, for a gait velocity of 1.6 km/h, a 3% error was found. In a free-living context, smartphones underestimate the number of steps [18]. Another limitation of free-living assessment with smartphones is the place where it is used. While for men a trouser pocket is a commonly preferred position, for women it is more likely to be the purse or backpack [18]. In the search for a solution for a smartphone-based body location the magnetometer sensor will most certainly be a crucial sensor to consider when dealing with the device's orientation.

4) Which gait assessment protocol

The comparison between all the included studies and those that only used an assessment in "ON" state medication, revealed that PD gait parameters under the effect of the medication are closer to the HC. Only stride time variability did not follow this pattern. According to the literature [12], stride time variability is increased in PD patients and diminishes in response to dopaminergic medication. In our analysis, we found that the difference between PD on and HC increased when only studies assessing gait in "ON" state medication, were taking into account. However, this result should be interpreted with caution, since this was only a basic comparison of means and gait protocols differentiated substantially in the included studies.

The distance covered during gait analysis varied in the included studies. According to the analysis performed, the distance doesn't seem to have a high impact on gait velocity tested in a controlled environment. However, the data from the included studies doesn't allow us to conclude on this topic. More studies are needed to understand the implications of gait protocol length in PD gait parameters.

Almost half of the included studies (43.2%, $n = 41$) used only a self-selected comfortable speed, during gait assessment. Since some of the gait parameters, like stride length and cadence, are sensitive to velocity and to the presence of concurrent attention demands, gait assessment protocols should include different velocities and both single- and dual-task activities [19]. The most common duration of free-living assessment data collection was seven days, varying between three and ten days. Based on our results, we cannot conclude if this is the best option. These are challenging assessments due to the heterogeneity of ambulatory activity within habitual environments. We believe that the duration of data collection during free-living assessments should be a balance between not performing a burdensome assessment and the ability to collect enough and precise data to obtain a pattern of patients' performance during the day [8]. As a fluctuating disease, the duration applied in other research fields, may not be appropriate. This topic should be addressed in future studies.

Conclusion

Our results support previous descriptions of PD gait impairments when compared with HC. No statistically significant differences were found for the impact of different types of devices (WS vs NWS), or different types or locations of wearable sensors during assessments. Future studies should test the reported gait parameters against validated clinical meaningful outcome measures in PD to select those most suitable for evaluating and monitoring the progression of gait impairments in PD. More studies are also needed to explore gait parameter behavior in a free-living context, with more complex movements

Uncorrected Author Proof

frontiers in Neurology

ORIGINAL RESEARCH
published: 23 March 2021
doi: 10.3389/fneur.2021.637620

Kinematic and Clinical Outcomes to Evaluate the Efficacy of a Multidisciplinary Intervention on Functional Mobility in Parkinson's Disease

Raquel Bouça-Machado[1,2], Diogo Branco[3], Gustavo Fonseca[3], Raquel Fernandes[1], Daisy Abreu[1], Tiago Guerreiro[3], Joaquim J. Ferreira[1,2,4] and The CNS Physiotherapy Study Group*

[1] Instituto de Medicina Molecular João Lobo Antunes, Lisbon, Portugal, [2] CNS - Campus Neurológico, Torres Vedras, Portugal, [3] LASIGE, Faculdade de Ciências, Universidade de Lisboa, Lisbon, Portugal, [4] Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

OPEN ACCESS

Edited by:
Mayela Rodríguez-Violante, Manuel Velasco Suárez Instituto Nacional de Neurología y Neurocirugía, Mexico

Reviewed by:
Giovanni Mostile, University of Catania, Italy
Matteo Bologna, Sapienza University of Rome, Italy

***Correspondence:**
Joaquim J. Ferreira
joaquimjferreira@gmail.com

Specialty section:
This article was submitted to Movement Disorders, a section of the journal Frontiers in Neurology

Received: 03 December 2020
Accepted: 15 February 2021
Published: 23 March 2021

Citation:
Bouça-Machado R, Branco D, Fonseca G, Fernandes R, Abreu D, Guerreiro T, Ferreira JJ and The CNS Physiotherapy Study Group (2021) Kinematic and Clinical Outcomes to Evaluate the Efficacy of a Multidisciplinary Intervention on Functional Mobility in Parkinson's Disease. Front. Neurol. 12:637620. doi: 10.3389/fneur.2021.637620

Introduction: Functional mobility (FM) is a concept that incorporates the capacity of a person to move independently and safely to accomplish tasks. It has been proposed as a Parkinson's disease (PD) functional and global health outcome. In this study, we aimed to identify which kinematic and clinical outcomes changes better predict FM changes when PD patients are submitted to a specialized multidisciplinary program.

Methods: PD patients engaged in a pre-defined specialized multidisciplinary program were assessed at admission and discharge. Change from baseline was calculated for all kinematic and clinical outcomes, and Timed Up and Go (TUG) was defined as the primary outcome for FM. A stepwise multivariate linear regression was performed to identify which outcome measures better predict TUG changes.

Results: Twenty-four patients were included in the study. The changes in TUG Cognitive test, supervised step length, and free-living (FL) step time asymmetry were identified as the best predictors of TUG changes. The supervised step length and FL step time asymmetry were able to detect a small to moderate effect of the intervention (*d* values ranging from −0.26 to 0.42).

Conclusions: Our results support the use of kinematic outcome measures to evaluate the efficacy of multidisciplinary interventions on PD FM. The TUG Cognitive, step length, and FL step time asymmetry were identified as having the ability to predict TUG changes. More studies are needed to identify the minimal clinically important difference for step length and FL step time asymmetry in response to a multidisciplinary intervention for PD FM.

Keywords: Parkinson's disease, functional mobility, outcome measures, gait, sensors, digital health, wearable, technology

INTRODUCTION

Functional mobility (FM) in Parkinson's disease (PD) has been recently described as a person's physiological ability to move independently and safely in a variety of environments in order to accomplish functional activities or tasks and to participate in activities of daily living at home, at work, and in the community (1, 2). From the early disease stage, PD patients experience limitations in their FM. With disease progression, these limitations are usually a major cause of disability and loss of independence (1).

FM has been reported as a useful outcome measure to understand patients' overall health status, to address their daily needs related to mobility and social participation, and for monitoring, in a closer and more realistic fashion, the impact of disease progression and the effect of therapeutic interventions (2–4). The Timed Up and Go (TUG) test is a quick and easy-to-use test, specifically designed to measure FM that includes the three anchors of the concept, i.e., gait, balance, and postural transitions (2, 4, 5). Although it is the recommended tool for assessing FM in PD, other clinical tests are also used (2, 4, 5).

The development of technology-based objective measures (TOMs) and the possibility of using accurate and reliable quantitative information to evaluate PD patients' gait enable a more objective and ecological (i.e., closer to patients' real-life environment performance) perspective of patients' FM (6, 7). A recent systematic review on outcome measures for assessing FM in PD included nine studies using kinematic gait parameters (2). The authors emphasize the important role of TOMs in monitoring FM throughout disease progression. They also highlight that despite the capacity of current devices to capture large amounts of data and a great diversity of parameters, the best kinematic parameters for assessing FM in PD remain to be defined (2).

In this study, we aimed to identify which kinematic and clinical outcome measures better predict FM changes when PD patients are submitted to a specialized multidisciplinary intervention.

METHODS

Study Design

A pragmatic prospective clinical study was conducted.

Objective

The objective of this study is to identify the kinematic and clinical outcome measures that better predict FM changes when PD patients are submitted to a specialized multidisciplinary intervention.

Participants

Study participants were recruited from CNS—Campus Neurológico, a tertiary specialized movement disorders center in Portugal. Patients were eligible if they had a diagnosis of probable or clinically established PD (according to the International Parkinson and Movement Disorder Society criteria), had engaged in the specialized multidisciplinary program for parkinsonian patients at the CNS between January and September 2019, and if they agreed to participate. Exclusion criteria were the inability to adopt a standing position and/or to walk 3 m, postural instability compromising patient safety during the assessment, and the presence of cognitive deficits preventing understanding of the test instructions (according to a physiotherapist's best judgment). The study was undertaken with the understanding and written consent of each participant, with the approval from the CNS Ethics Committee (ref. 10/19), and in compliance with national legislation and the Declaration of Helsinki. Participants were required to agree to all aspects of the study and were able to leave the study at any time.

Therapeutic Intervention

The specialized multidisciplinary program combined pharmacological and non-pharmacological therapies, including up to 20 h per week of individually tailored neurorehabilitation sessions of physiotherapy, occupational therapy, speech therapy, and cognitive training, according to the patient's needs and rehabilitation goals. All rehabilitation sessions had a duration of 50 min.

The physiotherapy sessions aim to optimize independence, safety, and well-being, through movement rehabilitation, maximization of functionality, and minimization of secondary complications. The sessions focused on physical capacity training, gait, mobility, balance, sensorimotor coordination, and development, as well as teaching the patient and the usual caregivers adaptive strategies to enhance functionality.

Clinical Assessment Protocol

Patients were assessed in ON-state medication, by a trained health professional from each area, 48 h following admission and before discharge. The following parameters were collected:

- Demographic and clinical data;
- Disease severity: Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score and score from each sub-section (8), Hoehn and Yahr scale (8, 9), and Clinical and Patient Global Impression (CGI and PGI, respectively) of Severity and Change; (10)
- Motor function: The Timed Up and Go (TUG) test with and without a cognitive and manual dual-task (5, 11, 12), Mini-BESTest (5, 13, 14), Five times Sit-to-Stand test (5 STS) (15, 16), and Schwab and England scale (17).

Analysis of Kinematic Data

Kinematic gait parameters were collected during the supervised motor assessments and for 3 days at the end of each assessment, in a free-living (FL) context. Each participant wore a single tri-axial accelerometer-based body-worn monitor (Axivity AX3) on their lower back (L5), programmed to capture raw data at 100 Hz with a dynamic range of ±8 g. Each subject performed two trials of each assessment, on each visit, and wore the AX3 for 3 days after each assessment.

In the supervised motor assessment, the physiotherapist used a mobile application to mark the start and end of each trial, which was synced with the AX3 internal clock. Departing from the segmentation of test trials provided by the application, we

manually adjusted the start and end of each test to match with the exact start and end of the movement and removed reported periods of pause. To extract meaningful data from the raw accelerometer signal, we started by resampling data to 100 Hz using linear interpolation, to mitigate known fluctuations of the sample rate (18). Afterward, offset was removed as well as machine noise using a second-order Butterworth low pass filter of 17 Hz (19). We focused the kinematic gait analysis in the study of spatiotemporal gait parameters. To extract gait parameters, the process was divided into two steps. First, we identified the walking bouts as the 2-s moving windows where summed standard deviations of tri-axial accelerations were above 0.1 (20). Then, an algorithm to detect initial contact (IC)/final contact (FC) points was applied, from which we calculated the gait parameters (21). A concurrent validity analysis of the reported number of steps (by the physiotherapist observing the trial) and the automatic detection revealed an intra-class correlation above 0.85.

In the FL context, where walking bouts are not previously annotated, a conservative approach was followed, meaning that high precision was sought (seeking that all detected bouts are indeed bouts), even if at the cost of lower recall (i.e., not all bouts are detected). Pre-processing of FL raw data followed a similar approach as the controlled assessment (resample and filtering). To improve walking bout detection in FL, we estimated an optimized scale of the Gaussian continuous wavelet transform (22) ("gaus2") and considered only the segments with a duration above 5 s and at least five detected ICs. Additionally, the first and last detected steps of each bout were trimmed off, given their specific transition characteristics. All remaining bouts (and steps) were subjected to extraction of parameters. An average per subject of 285.3 (SD = 175.2, min = 17, max = 622) walking bouts were extracted at the period of admission, and an average of 270.4 (SD = 129.0, min = 32, max = 647) were detected at the period of discharge, in the 3-day period. Gait parameters were calculated from the detected bouts as in the supervised motor assessment (21). Following previously published evidence in FL assessment, gait parameters were categorized in bouts from 5 to 15 s, 15 to 30 s, 30 to 60 s, and longer than 60 s (21). Our implementation of the extraction of gait parameters from walking bouts is available and open-sourced (https://github.com/Gustavo-SF/gait_extractor).

Statistical Analysis

Descriptive statistics were used for demographic, clinical, and therapeutic data. Continuous outcomes were defined as change from baseline for all the previously mentioned outcome measures and presented as a mean ± standard deviation (SD).

Our main goal was to explore the best predictors of changes in TUG (the gold standard for evaluating FM in PD). To do this, stepwise multiple linear regression analyses were performed using different independent variables (clinical measures, gait parameter assessment during the 10-m walk test, and FL gait parameters analyzed in bouts longer than 60 s). To validate the analysis, the normal distribution of residuals and the absence of multicollinearity were ascertained.

Only the outcome measures able to detect an effect of the intervention were used in the main analysis. This required an assessment, before our main analysis, of the existence of an intervention effect and the ability of the included outcome measures to detect it. We started by studying normality, using the Kolmogorov–Smirnov and the Shapiro–Wilk tests, and applying the paired sample *T*-test and the Wilcoxon S-R test to each parameter to analyze the effects of the program (statistical significance was set at $p < 0.05$). Cohen's d was employed as a measure of effect size to assess small (0.20–0.49), medium (0.50–0.80), and large (>0.80) effects (23).

We also performed some exploratory analysis to better understand how the outcome measures, selected as best predictors of FM changes, behave if used as the primary outcome in a future study. Power analysis and sample size calculations were performed using G*Power software, to understand how many participants would be needed to enable statistically significant results (80% power) if the TUG test or one of the outcome measures able to detect at least a small effect size were used as the primary outcome in a clinical study. A significance level of $\alpha = 0.05$ and a power $= 1 - \beta = 0.80$ were assumed. To explore the variability of the different gait parameters, a power analysis assuming 10, 20, and 30% of change from baseline and using the mean SD of change from baseline was calculated for each parameter. The choice of the 30% magnitude of effect was based on the minimal clinically important difference (MCID) reported for the TUG test, the recommended measurement tool for assessing FM in PD. It also used a 20% magnitude of effect, based on MCID reported for spatial asymmetry in a previous study evaluating the effect of rehabilitation training on PD patients' gait parameters (25.76%) (24).

Additionally, and also as an exploratory analysis, we applied paired sample *t*-test and the Wilcoxon S-R test to the different bout lengths of FL assessment to investigate how the length of the bout contributes to the existence of a statistically significant difference between admission and the end of the program (significance was achieved with a p-value < 0.05).

RESULTS

Cohort Demographic and Clinical Data

Of the 54 PD patients who engaged in a CNS specialized multidisciplinary program between January and September 2019, a total of 24 participants were included in this study. The reasons for exclusion were lack of collaboration/missing data (27.8%, $n = 15$), motor inability to perform the assessments (18.5%, $n = 10$), and the presence of cognitive impairment and behavioral disturbances (9.3%, $n = 5$). Eight patients did not perform the FL assessment due to behavioral disturbances and refusal of the belt that supports the trunk sensor. Some of the included patients did not fulfill all the clinical assessment battery due to fatigue and lack of collaboration. The mean age of the participants was 73.0 ± 8.0 years, and 66.7% ($n = 16$) were men. At admission, the average disease duration was 8.0 ± 5.1 years, with a mean Hoehn and Yahr stage of 2.3 ± 0.9 and a mean MDS-UPDRS motor score of 39.4 ± 12.8. All patients were under antiparkinsonian treatment, and 50% ($n = 12$) had motor fluctuations.

TABLE 1 | Demographical and clinical characteristics of the sample.

Demographic features ($n = 24$)				
Age (Mean, SD)	73.04 ± 8.00			
Male sex [% (*n*)]	66.67% (16)			
Body mass index (BMI) (Mean, SD)	25.79 ± 3.90			
Time since diagnosis (Mean, SD)	8.04 ± 5.10			
Presence of motor fluctuations [% (*n*)]	50% (12)			
Clinical data [Mean (SD), (Range)]				
	Admission	**Discharge**	**Change**	***p*-value**
MDS-UPDRS I (range 0–52; $n = 19$; ↓)	13.95 ± 7.09	8.25 ± 4.90	−5.53 ± 6.81 (39.6%)	**0.002**
MDS-UPDRS II (range 0–52; $n = 19$; ↓)	17.18 ± 9.24	12.65 ± 7.04	−4.95 ± 10.02 (28.8%)	**0.045**
MDS-UPDRS III (range, 0–132; $n = 19$; ↓)	39.36 ± 12.77	32.20 ± 12.22	−8.52 ± 9.92 (21.7%)	**0.001**
MDS-UPDRS IV (range 0–24; $n = 19$; ↓)	1.95 ± 2.82	1.35 ± 2.16	−0.21 ± 2.53 (10.8%)	0.721
MDS-UPDRS Total (range 0–260; n = 19; ↓)	72.45 ± 25.75	54.45 ± 20.50	−19.26 ± 22.18 (26.6%)	**0.001**
Hoehn and Yahr stage (range 1–5; $n = 24$; ↓)	2.30 ± 0.93	2.35 ± 0.71	0.09 ± 0.68 (3.9%)	0.540
Schwab and England (range 0–100; $n = 24$; ↑)	73.75 ± 16.37	75.83 ± 15.86	2.08 ± 8.33 (2.8%)	0.225
TUG Normal ($n = 24$; ↓)	13.36 ± 7.27	11.68 ± 4.75	−1.69 ± 6.90 (12.7%)	0.243
TUG DT Cognitive ($n = 23$; ↓)	17.22 ± 10.42	14.10 ± 7.29	−2.80 ± 8.91 (16.3%)	0.146
TUG DT Manual ($n = 19$; ↓)	12.80±5.21	11.37±4.35	−0.92 ± 8.69 (7.2%)	0.417
Mini-best (range 0–28; $n = 19$; ↑)	20.19±3.97	20.70±4.59	0.63 ± 3.25 (3.1%)	0.408
5 Sit-to-Stand Normal ($n = 22$; ↓)	19.36 ± 6.99	14.29 ± 5.24	−4.31 ± 2.94 (22.3%)	**0.000**
5 Sit-to-Stand Fast ($n = 22$; ↓)	17.56 ± 4.91	13.25 ± 5.19	−5.07 ± 3.48 (28.9%)	**0.000**
	Severity (Baseline)		**Change (Discharge)**	
Clinical Global Impression ($n = 24$; ↓)	4.0 ± 0.83		2.83 ± 0.82	
Patient Global Impression ($n = 24$; ↓)	3.91 ± 1.02		2.50 ± 0.86	

↑ - a higher score means an improvement, ↓ - a lower score means an improvement. The paired-samples T-test and the Wilcoxon S-R tests were applied to investigate the existence of a statistically significant difference between admission and the end of the program. Significance was achieved with a p-value < 0.05. Bold values is to highlight the outcomes that reached statistical significance.

Patients' demographic and clinical characteristics at admission and discharge are summarized in **Table 1**. **Table 2** summarizes the changes in gait parameter values in both assessment conditions.

All the clinical and gait parameters from the supervised assessment showed an improvement, having reached statistical significance ($p \leq 0.05$) in the MDS-UPDRS parts I, II, III, and total score; in the 5 STS test; and the following gait parameters: gait velocity, stride and step velocity, step length, and swing time asymmetry (**Tables 1**, **2**). The improvement in the TUG test did not reach statistical significance, contrary to gait velocity, stride and step velocity, step length, and swing time asymmetry measured during the test. In FL conditions, an improvement was detected when the analysis was made using bouts of at least 30 s. Specifically, the following gait parameters have reached statistical significance ($p \leq 0.05$): cadence, step time, stance time, swing time, and double support time when data was analyzed in bouts of 30–60 s and stance, swing, and double support phases when bouts of more than 60 s were used in the analysis (**Table 2** and **Appendix 1**).

Prediction of FM Changes

The stepwise multivariate linear regression analysis, between TUG (dependent variable) and the clinical outcome measures able to detect an effect, indicated the TUG Cognitive as the best variable to predict TUG changes (adjusted $R^2 = 0.72$). The same analysis using supervised and FL kinematic gait parameters as independent variables identified step length (adjusted $R^2 = 0.53$) and step time asymmetry (adjusted $R^2 = 0.51$) as the best predictors of TUG changes for each assessment condition (**Table 3**).

Responsiveness to Intervention

The TUG test was able to detect a small effect size ($d = -0.24$) of the intervention (**Appendix 2**).

From the supervised assessment, the outcome measures able to detect a large effect size were the STS Normal ($d = -1.46$) and Fast ($d = -1.47$) and the MDS-UPDRS total score ($d = -0.87$).

From the FL assessment, the outcome parameters with higher sensitivity to the intervention were stance time asymmetry ($d = -0.38$), stride length ($d = 0.37$), double support time variability ($d = -0.37$), and step length ($d = 0.36$).

Sample Size Calculation

A power analysis was performed to understand how many participants would be needed to enable statistically significant results (80% power), if the TUG test or one of the outcome measures able to detect at least a small effect size was used as

TABLE 2 | Admission (i.e., baseline) and change from baseline values (i.e., mean post-pre assessment difference and respective percentage value) of gait parameters in the supervised and free-living assessments.

Gait parameters supervised assessment	Supervised assessment						Free-living assessment		
	TUG normal			10-meter walk test			Bouts longer than 60 s		
	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value
Gait velocity (m/s)	0.71 ± 0.19	0.06 ± 0.13 (8.5%)	**0.037**	0.82 ± 0.21	0.05 ± 0.18 (6.1%)	0.188	0.59 ± 0.14	0.04 ± 0.13 (6.8%)	0.209
Cadence (steps/min)	118.77 ± 12.00	1.94 ± 13.02 (1.6%)	0.472	119.92 ± 13.72	3.66 ± 12.95 (3.1%)	0.180	104.93 ± 10.33	−0.92 ± 9.17 (0.9%)	0.695
Stride length (m)	0.78 ± 0.18	0.06 ± 0.14 (7.7%)	0.057	0.89 ± 0.20	0.04 ± 0.17 (4.5%)	0.204	0.69 ± 0.16	0.05 ± 0.13 (7.2%)	0.160
Stride velocity (m/s)	0.71 ± 0.19	0.06 ± 0.13 (8.5%)	**0.033**	0.82 ± 0.21	0.05 ± 0.18 (6.1%)	0.225	0.59 ± 0.14	0.04 ± 0.13 (6.8%)	0.202
Step length (m)	0.39 ± 0.09	0.03 ± 0.07 (7.7%)	**0.049**	0.45 ± 0.10	0.02 ± 0.08 (4.4%)	0.230	0.34 ± 0.08	0.02 ± 0.06 (5.9%)	0.171
Step velocity (m/s)	0.72 ± 0.19	0.06 ± 0.13 (8.3%)	**0.037**	0.82 ± 0.21	0.05 ± 0.18 (6.1%)	0.182	0.60 ± 0.14	0.04 ± 0.13 (6.7%)	0.220
Stance phase (% of gait cycle)	75.26±1.36	−0.11 ± 1.35 (0.2%)	0.708	75.35 ± 0.49	−0.18 ± 1.32 (0.2%)	0.514	75.11 ± 0.55	0.20 ± 0.36 (0.3%)	**0.047**
Swing phase (% of gait cycle)	24.74 ± 1.36	0.11 ± 1.35 (0.5%)	0.708	24.65 ± 0.49	0.18 ± 1.32 (0.7%)	0.514	24.89 ± 0.55	−0.20 ± 0.36 (0.8%)	**0.047**
Double support phase (% of gait cycle)	25.33 ± 1.33	−0.13 ± 1.36 (0.5%)	0.643	25.34 ± 0.51	−0.19 ± 1.27 (0.8%)	0.476	25.11 ± 0.54	0.19 ± 0.36 (0.8%)	**0.050**
Step time (seconds)	0.56 ± 0.06	−0.02 ± 0.06 (3.6%)	0.893	0.55 ± 0.07	−0.01 ± 0.06 (1.8%)	0.525	0.60 ± 0.06	0.002 ± 0.06 (0.3%)	0.896
Stance time (seconds)	0.84 ± 0.09	−0.01 ± 0.09 (1.2%)	0.800	0.83 ± 0.10	−0.01 ± 0.09 (1.2%)	0.589	0.90 ± 0.09	0.004 ± 0.09 (0.4%)	0.845
Swing time (seconds)	0.28 ± 0.04	0.002 ± 0.04 (0.7%)	0.828	0.27 ± 0.03	−0.001 ± 0.03 (3.7%)	0.902	0.30 ± 0.03	−0.001 ± 0.03 (0.3%)	0.930
Double support time (seconds)	0.28 ± 0.03	−0.004 ± 0.03 (1.4%)	0.561	0.28 ± 0.03	−0.004 ± 0.03 (1.4%)	0.916	0.30 ± 0.03	0.004 ± 0.03 (1.3%)	0.583
Stride time variability (% CV)	0.07 ± 0.04	−0.004 ± 0.04 (5.7%)	0.636	0.04 ± 0.02	−0.001 ± 0.03 (2.5%)	0.880	0.12 ± 0.03	−0.01 ± 0.04 (8.3%)	0.393
Step length variability (% CV)	0.05 ± 0.02	−0.003 ± 0.03 (6%)	0.516	0.03 ± 0.01	0.004 ± 0.02 (13.3%)	0.260	0.06 ± 0.01	0.003 ± 0.02 (5%)	0.446
Step time variability (% CV)	0.05 ± 0.03	−0.002 ± 0.03 (4%)	0.730	0.03 ± 0.02	−0.0004 ± 0.02 (1.3%)	0.930	0.09 ± 0.02	−0.01 ± 0.03 (11.1%)	0.210
Step velocity variability (% CV)	0.11 ± 0.04	−0.008 ± 0.04 (7.3%)	0.352	0.06 ± 0.02	0.01 ± 0.04 (16.7%)	0.163	0.13 ± 0.03	0.004 ± 0.03 (3.1%)	0.657
Stance time variability (% CV)	0.06 ± 0.03	−0.005 ± 0.03 (8.3%)	0.384	0.03 ± 0.02	−0.002 ± 0.02 (6.7%)	0.665	0.10 ± 0.03	−0.01 ± 0.03 (10%)	0.340

(Continued)

TABLE 2 | Continued

Gait parameters supervised assessment	Supervised assessment						Free-living assessment		
	TUG normal			10-meter walk test			Bouts longer than 60 s		
	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value	Admission	Change from baseline	*p*-value
Swing time variability (% CV)	0.03 ± 0.02	−0.006 ± 0.02 (20%)	0.884	0.02 ± 0.01	0.001 ± 0.02 (20%)	0.862	0.05 ± 0.02	−0.01 ± 0.02 (20%)	0.216
Double support variability (% CV)	0.03 ± 0.02	−0.003 ± 0.02 (10%)	0.455	0.02 ± 0.01	0.00002 ± 0.01 (0.1%)	0.994	0.05 ± 0.02	−0.01 ± 0.02 (20%)	0.163
Stride time asymmetry (% CV)	0.01 ± 0.01	0.002 ± 0.02 (20%)	0.959	0.01 ± 0.01	−0.001 ± 0.01 (10%)	0.584	0.01 ± 0.004	−0.001 ± 0.01 (1%)	0.300
Step time asymmetry (% CV)	0.02 ± 0.02	0.005 ± 0.02 (25%)	0.262	0.03 ± 0.02	0.003 ± 0.02 (10%)	0.496	0.03 ± 0.02	−0.01 ± 0.02 (33.3%)	0.318
Stance time asymmetry (% CV)	0.02 ± 0.02	−0.003 ± 0.02 (15%)	0.622	0.02 ± 0.02	−0.003 ± 0.02 (15%)	0.420	0.02 ± 0.01	−0.01 ± 0.02 (50%)	0.153
Swing time asymmetry (% CV)	0.02 ± 0.01	0.008 ± 0.02 (40%)	**0.036**	0.02 ± 0.01	−0.003 ± 0.02 (15%)	0.423	0.02 ± 0.01	−0.01 ± 0.02 (50%)	0.195
Step length asymmetry (% CV)	0.03 ± 0.02	−0.002 ± 0.02 (6.7%)	0.605	0.02 ± 0.02	0.0002 ± 0.02 (1%)	0.959	0.02 ± 0.01	−0.002 ± 0.01 (10%)	0.504

The paired-samples T-test and the Wilcoxon S-R tests were applied for each parameter to investigate the existence of a statistically significant difference between admission and the end of the program (statistical significance was achieved with p-value <. 0.05). Bold values is to highlight the outcomes that reached statistical significance.

TABLE 3 | Stepwise multiple linear regression analysis with TUG as a dependent variable and (1) the clinical outcome measures, (2) gait parameters assessed during the 10-meter walk test, in supervised conditions, (3) gait parameters assessed in free-living conditions and analyzed in bouts longer than 60 s, as independent variables.

Dependent variable: TUG change from baseline	Predictors	R^2	Adjusted R^2	R^2 change	F	p-value	Unstandardized B	Standardized coefficients ß	Collinearity VIF
Independent variables: Clinical outcome measures	TUG cognitive	0.75	0.72	0.75	23.59	0.001	0.42	0.86	1.000
Independent variables: Kinematic outcome measures – Supervised assessment	Step length	0.55	0.53	0.55	27.11	0.000	−61.96	−0.74	1.000
Independent variables: Kinematic outcome measures – Free-living assessment	Step time asymmetry	0.55	0.51	0.55	16.79	0.001	104.88	0.74	1.000

a primary outcome in a clinical study. **Appendix 2** summarizes the sample size calculations assuming 10, 20, and 30% change from baseline.

DISCUSSION

Although this study was not designed to conclude on efficacy, the results obtained suggest an overall improvement (**Tables 1**, **2**). This enables us to identify the best predictors of FM changes when PD patients are submitted to a specialized multidisciplinary program. It also enables performing other exploratory analyses to better understand how the outcome measures behave if used as primary outcomes in future studies.

From the pool of outcome measures able to detect at least a small effect size of the intervention, those identified as the best predictors of TUG changes were the TUG Cognitive, step length, and step time asymmetry.

Clinical Assessment

The TUG Cognitive test was the clinical parameter with the best ability to predict TUG changes. This can be explained because the TUG Cognitive is a modified version of the TUG (i.e., it adds a cognitive task to the motor task) (25, 26). Since daily activities frequently require motor and cognitive tasks to be carried out simultaneously, this version of the test may give a more realistic perspective of the patients' FM. However, as it is only a modified version of the same test, some major limitations remain (e.g., it is limited to patients without significant postural instability and is subject to learning effects).

The Mini-BESTest test was not sensitive to the intervention, and the observed differences were not statistically significant. However, this is a very complete clinical test that includes the assessment of static and dynamic balance (i.e., biomechanical constraints, verticality/stability limits, anticipatory postural adjustments, postural responses, sensory orientation, and stability in gait) and the TUG Cognitive test itself (5, 13, 14). Although not formally validated to measure FM, this instrument provides a more complete approach to the three anchors of the concept, i.e., gait, balance, and postural transitions (5, 13, 14). We believe that future studies should clarify the Mini-BESTest's suitability to assess FM changes.

Clinical vs. Kinematic Assessment

Our results identified step length and step time asymmetry as the gait parameters with the best ability to predict TUG (and FM) changes, in supervised and FL conditions, respectively. Compared with the TUG, both showed higher responsiveness to change.

FM is a major source of disability for PD patients and requires an individualized and complex management approach that strongly depends on the information about the actual state of the patients in their daily lives (1). Although the TUG remains the gold standard for assessing PD FM, as is the case for all traditional clinical scales, it presents some limitations that can be overcome by the use of TOMs (27).

To optimize the accuracy of clinical evaluation, evidence suggests that patients should focus on the goal of the task asked and not on the movement required to achieve it. This is hampered when a reassessment using the TUG test takes place after a multidisciplinary program. During the physiotherapy sessions of the program, patients usually learn safety strategies to apply during walking and postural transitions that require being focused on the movement while doing it. Many of these strategies are applied during the TUG test, thereby hindering its ability to detect an improvement in patients' FM (27).

There is increasing evidence that TOMs may improve the sensitivity, accuracy, reproducibility, and feasibility of data capture, detecting improvements that the clinical tests are not able to find (6). Previous studies reported a greater sensitivity of TOMs, over the traditional clinical scales, in differentiating the gait and turning of PD patients from healthy controls (27).

The use of outcome measures of higher sensitivity and accuracy, which can predict TUG changes (step length and step time asymmetry), may help obtain a more complete and objective evaluation of patients' FM limitations and thereby favoring more personalized clinical decision making (6, 28). In the research field, the use of standardized outcome measures, with high responsiveness to change and low variability, not only enables better interpretation and discussion of research findings but also avoids unnecessary increases in complexity, duration, and financial expenses of studies (6).

Despite the benefits associated with the use of TOMs for assessing FM, from our experience, they also have some

limitations. The currently available sensors, although smaller and lighter, remain too intrusive, leading patients to reject their use. Also, in PD patients with behavioral changes, the use of sensors may not be possible. One of the patients was excluded from the FL analysis, after having thrown away the sensors during an episode of delirium.

Supervised vs. Free-Living Assessment

According to our results, the responsiveness of the outcomes and their ability to predict TUG changes differ depending on the type of assessment.

There is a growing awareness that, depending on the assessment conditions, the results related to gait and postural transitions can differ substantially, with a weak association between the results in both scenarios having been reported (28, 29). Many factors can contribute to these differences: (1) the clear and standardized environment in supervised assessment, in the absence of distractions, emphasizes a measure of someone's best, rather than their usual performance; (2) FL conditions, with narrow corridors, variable lighting, obstacles, etc., forces continuous gait adaptations, inducing large variability and asymmetry in walking patterns; (3) movements in a supervised assessment are triggered by instruction, while FL movements are usually self-initiated, goal-directed, and embedded in a rich behavioral environment; and (4) patients frequently improve their performance when they know that they are being evaluated (21, 28, 29).

In the FL context, gait parameters, and therefore FM, may be influenced not only by physical characteristics but also by ongoing environmental and cognitive challenges (29). Variability and asymmetry-related parameters are especially sensitive to behavioral and environmental factors, better reflecting patients' interaction with the context and their ability to adapt gait patterns (28, 29). We hypothesize that this may be one of the causes of step time asymmetry identified as the FL kinematic gait parameter, which better predicts TUG changes. Although it has only captured a small effect size of the intervention, having a high ecological validity, FL step time asymmetry seems to provide a more realistic picture of the impact of the disease in PD FM, whereby even small changes should be valued (27).

Length of Walking Bouts

We performed an exploratory analysis to understand how FL gait parameters behave when different bout lengths were used in the analysis. According to our results, there appears to be a link between the ability to capture an improvement and the length of the bout. The longer the walking bouts, the higher the velocity and length of stride/step and the lower the cadence, variability, and asymmetry.

A previous study exploring the impact of environment and bout length in PD patients' gait reached similar conclusions, i.e., the longer the bouts, the higher the increase in step velocity, step length and swing time variability and the lower the variability and asymmetry of gait. The authors also reported that the parameters analyzed in longer bouts were more similar to those measured in a supervised environment (21).

Walking bout length is influenced by the type of environment and activity patients are engaged in (21). Currently, the most suitable length of walking bouts used in FL analysis is not established (21). The majority of studies investigating gait characteristics in FL conditions use bouts longer than 60 s. However, it has been reported that PD patients in FL conditions more often perform a large number of very short bouts ($\leq$10 s) than prolonged bouts (21). According to the literature, bouts of 30–60 s usually represent indoor activities, while bouts $>$ 120 s correspond to walking outdoors. Only bouts with at least 30–60 s were able to discriminate PD patients from healthy controls (21).

Limitations

This study presents two major limitations: a small sample size ($n = 24$) and high heterogeneity in the included population. We believe that these aspects may overestimate the variability of the measurement tools, influencing the power calculations. We expect that future studies with a large and less heterogeneous population will need a smaller sample size. As an open non-controlled study, we hypothesize that in future larger, controlled trials, the detected effect size will be smaller. However, since this was not an efficacy study (due to the absence of a control group) and an improvement was observed, despite these limitations, we believe that our results are informative and important for the PD field. Also, we believe that the use of broad inclusion criteria in this study not only did not interfere with its aims but also better mimics the real scenario of the intervention and assessments, increasing its external validity. To minimize the impact, the study was conducted in a single tertiary care center.

According to our results, the TUG test did not achieve a statistically significant improvement. However, some of the gait parameters (including step length) not only reached a statistically significant result but also showed a higher sensitivity to change. Since all other results point to an improvement at the end of the program, we believe that this difference may be explained by the greater accuracy and sensitivity to change of TOMs when compared to the traditional clinical scales. A previous study has already highlighted this potential problem, highlighting that the validation of TOMs is often based on their correlation with validated clinical measures and that results may be undesirable, due to the superior capacity of TOMs for capturing the phenomena of interest (30).

CONCLUSION

Although we cannot attribute the observed improvements to the specialized multidisciplinary program, our results suggest a methodological approach for identifying outcome measures to assess FM changes, in response to a therapeutic intervention.

From all the outcome measures included in the study, only the TUG Cognitive, step length, and FL step time asymmetry were identified as having the ability to predict TUG changes. The kinematic parameters seem to present higher responsiveness to change when compared with the traditional clinical tests. According to our results, supported by published evidence, the longer the bouts, the higher the sensitivity of detecting an improvement.

Our results support the use of kinematic assessments in evaluating the effect of multidisciplinary interventions in PD FM. The FL step time asymmetry seems a very promising outcome measure to assess FM in PD. Nevertheless, there are some aspects of FL assessments that need to be improved, such as establishing the best data collection protocol and developing less intrusive sensors.

To improve the interpretation of results of responsiveness to change in a complex and fluctuating disease such as PD, it is necessary to clarify the variation of gait parameters in the absence of pharmacological and non-pharmacological therapeutic interventions. This requires repeating the assessment protocol in ON- and OFF-state medication and several times during a short period, thereby clarifying the effect of pharmacological interventions, permitting an understanding of the impact of motor fluctuations and minimizing the interference of disease progression. More studies are also needed to explore the cut-off points from which FM is considered to be affected and the smallest amount of change, in the identified parameters, considered important by the patient or clinician (i.e., the minimal clinically important difference).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CNS Ethics Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

RB-M and JF contributed to the conception and design of the study. The CNS physiotherapy study group contributed to the participants' recruitment and assessments. RB-M performed the assessments and performed the statistical analysis. DB, GF, and TG analyzed kinematic data. RB-M and JF drafted the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

FUNDING

The authors would like to acknowledge the support of Fundação para a Ciência e a Tecnologia (FCT) (SFRH/BD/120773/2016 to RB-M; SFRH/BD/144242/2019 to DB, UIDB/00408/2020 and UIDP/00408/2020 to LASIGE).

COLLABORATORS (CNS PHYSIOTHERAPY STUDY GROUP)

Daniela Guerreiro, Verónica Caniça, Francisco Queimado, Pedro Nunes, Alexandra Saúde, Laura Antunes, Joana Alves, Beatriz Santos, Inês Lousada, Maria A. Patriarca, Patrícia Costa, Raquel Nunes e Susana Dias.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.637620/full#supplementary-material

REFERENCES

1. Bouça-Machado R, Maetzler W, Ferreira JJ. What is functional mobility applied to Parkinson's disease? *J Parkinsons Dis.* (2018) 8:121–30. doi: 10.3233/JPD-171233
2. Bouça-Machado R, Duarte GS, Patriarca M, Castro Caldas A, Alarcão J, Fernandes RM, et al. measurement instruments to assess functional mobility in Parkinson's disease: a systematic review. *Movement Disord Clin Pract.* (2020) 7:129–39. doi: 10.1002/mdc3.12874
3. Bhidayasiri R, Martinez-Martin P. Clinical assessments in Parkinson's disease. *Int Rev Neurobiol.* (2017) 132:129–82. doi: 10.1016/bs.irn.2017.01.001
4. Verheyden G, Kampshoff CS, Burnett ME, Cashell J, Martinelli L, Nicholas A, et al. Psychometric properties of 3 functional mobility tests for people with Parkinson disease. *Phys Ther.* (2014) 94:230–9. doi: 10.2522/ptj.20130141
5. Bloem BR, Marinus J, Almeida Q, Dibble L, Nieuwboer A, Post B, et al. Measurement instruments to assess posture, gait, and balance in Parkinson's disease: critique and recommendations. *Mov Disord.* (2016) 31:1342–55. doi: 10.1002/mds.26572
6. Espay AJ, Bonato P, Nahab FB, Maetzler W, Dean JM, Klucken J, et al. Technology in Parkinson disease: challenges and opportunities. *Mov Disord.* (2016) 31:1272–82. doi: 10.1002/mds.26642
7. Muro-de-la-Herran A, García-Zapirain B, Méndez-Zorrilla A. Gait analysis methods: an overview of wearable and non-wearable systems, highlighting clinical applications. *Sensors.* (2014) 14:3362–94. doi: 10.3390/s140203362
8. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* (2008) 23:2129–70. doi: 10.1002/mds.22340
9. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. *Neurology.* (1967) 17:427–42. doi: 10.1212/WNL.17.5.427
10. Martínez-Martín P, Rojo-Abuin JM, Rodríguez-Violante M, Serrano-Dueñas M, Garretto N, Martínez-Castrillo JC, et al. Analysis of four scales for global severity evaluation in Parkinson's disease. *NPJ Park Dis.* (2016) 2:16007. doi: 10.1038/npjparkd.2016.7
11. Podsiadlo D, Richardson S. The timed "up & go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc.* (1991) 39:142–8. doi: 10.1111/j.1532-5415.1991.tb01616.x
12. Morris S, Morris ME, Iansek R. Reliability of measurements obtained with the timed 'up, & go' test in people with Parkinson disease. *Phys Ther.* (2001) 81:810–8. doi: 10.1093/ptj/81.2.810
13. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the balance evaluation systems test: the mini-BESTest. *J Rehabil Med.* (2013) 42:323–31. doi: 10.2340/16501977-0537
14. Leddy AL, Crowner BE, Earhart GM. Utility of the mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *J Neurol Phys Ther.* (2011) 35:90–7. doi: 10.1097/NPT.0b013e31821a620c

15. Mayhew T, Rothstein J. Measurement of muscle performance with instruments. *Percept Mot Skills.* (1995) 80:163–6. doi: 10.2466/pms.1995.80.1.163
16. Duncan RP, Leddy AL, Earhart GM. Five times sit-to-stand test performance in Parkinson's disease. *Arch Phys Med Rehabil.* (2011) 92:1431–6. doi: 10.1016/j.apmr.2011.04.008
17. Bjornestad A, Tysnes OB, Larsen JP, Alves G. Reliability of three disability scales for detection of independence loss in Parkinson's disease. *Parkinsons Dis.* (2016) 2016:1941034. doi: 10.1155/2016/1941034
18. Doherty A, Jackson D, Hammerla N, Plötz T, Olivier P, Granat MH, et al. Large scale population assessment of physical activity using wrist worn accelerometers: the UK biobank study. *PLoS ONE.* (2017) 12:e0169649. doi: 10.1371/journal.pone.0169649
19. Hickey A, Del Din S, Rochester L, Godfrey A. Detecting free-living steps and walking bouts: validating an algorithm for macro gait analysis. *Physiol Meas.* (2017) 38:N1–N15. doi: 10.1088/1361-6579/38/1/N1
20. Lyons GM, Culhane KM, Hilton D, Grace PA, Lyons D. A description of an accelerometer-based mobility monitoring technique. *Med Eng Phys.* (2005) 27:497–504. doi: 10.1016/j.medengphy.2004.11.006
21. Del Din S, Godfrey A, Galna B, Lord S, Rochester L. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. *J Neuroeng Rehabil.* (2016) 13:46. doi: 10.1186/s12984-016-0154-5
22. Pham MH, Elshehabi M, Haertner L, Del Din S, Srulijes K, Heger T, et al. Validation of a step detection algorithm during straight walking and turning in patients with Parkinson's disease and older adults using an inertial measurement unit at the lower back. *Front Neurol.* (2017) 8:1–9. doi: 10.3389/fneur.2017.00457
23. Aron, A. *Statistics for Psychology* (2003).
24. Serrao M, Chini G, Caramanico G, Bartolo M, Castiglia SF, Ranavolo A, et al. Prediction of responsiveness of gait variables to rehabilitation training in Parkinson's disease. *Front Neurol.* (2019) 10:826. doi: 10.3389/fneur.2019.00826
25. Campbell CM, Rowse JL, Ciol MA, Shumway-cook A. The effect of cognitive demand on timed up and go performance in older adults with and without Parkinson disease. *Neurol Rep.* (2003) 27:2–7. doi: 10.1097/01253086-200327010-00002
26. Hofheinz M, Schusterschitz C. Dual task interference in estimating the risk of falls and measuring change: a comparative, psychometric study of four measurements. *Clin Rehabil.* (2010) 24:831–42. doi: 10.1177/0269215510367993
27. Del Din S, Godfrey A, Mazzà C, Lord S, Rochester L. Free-living monitoring of Parkinson's disease: lessons from the field. *Mov Disord.* (2016) 31:1293–313. doi: 10.1002/mds.26718
28. Warmerdam E, Hausdorff JM, Atrsaei A, Zhou Y, Mirelman A, Aminian K, et al. Long-term unsupervised mobility assessment in movement disorders. *Lancet Neurol.* (2020) 19:462–70. doi: 10.1016/S1474-4422(19)30397-7
29. Rispens SM, Van Dieën JH, Van Schooten KS, Lizama LE, Daffertshofer A, Beek PJ, et al. Fall-related gait characteristics on the treadmill and in daily life. *J Neuroeng Rehabil.* (2016) 13:12. doi: 10.1186/s12984-016-0118-9
30. Artusi CA, Mishra M, Latimer P, Vizcarra JA, Lopiano L, Maetzler W, et al. Integration of technology-based outcome measures in clinical trials of Parkinson and other neurodegenerative diseases. *Park Relat Disord.* (2018) 46:S53–6. doi: 10.1016/j.parkreldis.2017.07.022

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Bouça-Machado, Branco, Fonseca, Fernandes, Abreu, Guerreiro, Ferreira and The CNS Physiotherapy Study Group. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.