Development and validation of gait digital outcomes as clinical endpoints in Parkinson's disease

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Abstract

A promising solution to the limited, clinical assessment of Parkinson's (PD), has emerged through quantification of real-world walking speed (RWS) from wearable devices. RWS can be remotely assessed across consecutive days, measuring change in aspects of quality of life that are of importance to patients which can complement the existing clinical assessment of PD. The aims of this thesis were to address several gaps in the literature and explore, validate, and characterise RWS as a digital mobility outcome (DMO), to understand what complementary information it can provide to enhance the existing clinical assessment of mobility in PD.

PD and older adults (OA) participants were recruited from two separate studies: the Incidence of Cognitive Impairment with Longitudinal Evaluation – GAIT (ICICLE-GAIT) and the Mobilise-D Technical Validation Study (TVS). Participants underwent mobility assessments in supervised and real-world environments over seven days, wearing a single lower-back wearable device. Algorithms were applied to estimate various macro and micro-level DMOs, including RWS within short, medium, and long walking bouts (WBs).

In comparison to OAs, RWS was significantly slower in PD cross-sectionally and declined more rapidly longitudinally. At medium WBs, RWS was significantly related with MDS-UPDRS III score. In contrast to PD, OAs appeared to modulate their RWS differently between indoor and outdoor locations. Walking modulation was further characterised as three selected walking speeds, modelled as the number of modes within the distribution. Within short WBs, a larger number of selected walking speeds were associated with larger medication dosage and FOG score.

This thesis provides evidence that digital assessment of RWS can provide novel complementary information about changes in gait that relate to real-world mobility and are of importance to patients. Inclusion of contextual data and novel statistical techniques can improve understanding of the impact of PD upon safe modulation of walking between different real-world scenarios and within a single bout of walking.

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Statement of work undertaken

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This thesis included participants recruited from the ICICLE-GAIT study, a nested study within ICICLE-PD. Professor David Burn and Professor Lynn Rochester were responsible for the study design and grant application of ICICLE-PD and ICICLE-GAIT respectively. Data was included from 18 month to 72-month assessment and was collected by the following individuals at different time points: Dr Sue Lord, Dr Brook Galna, Dadirayi Mhiripiri, Dr Tien K Khoo, Professor Alison Yarnall, Dr Gordon Duncan, Dr Rachael Lawson, Dr Joana Wilson, Dr Rosie Morris, Dr Lisa Alcock, Leanne Thompson, Victoria Foster & Phil Brown. The gait data of ICICLE-GAIT study was estimated in accordance with algorithms previously validated by Dr Silvia Del Din and colleagues.

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Awards publications and presentations arising from this thesis

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Publications

1. Del Din, S., **Kirk, C.,** Yarnall, A.J., Rochester, L., Hausdorff, J.M., 2021. Body-Worn Sensors for Remote Monitoring of Parkinson's Disease Motor Symptoms: Vision, State of the Art, and Challenges Ahead. J Parkinsons Dis 11, S35–S47.
2. **Kirk, C.,** Rehman, R. zia ur, Galna, B., Alcock, L., Ranciati, S., Palmerini, L., Garcia-Aymerich, J., Hansen, C., Schaeffer, E., Berg, D., Maetzler, W., Rochester, L., Din, S., Yarnall, A., 2023b. Can Digital Mobility Assessment Enhance the Clinical Assessment of Disease Severity in Parkinson's Disease? Journal of Parkinson's Disease 1–11.

Oral Presentations

1. Changes in real-world walking over 4.5 years in people with Parkinson's and older adults - *Association of Biomedical Engineers, Medical Engineers and Bioengineers (BioMedEng) Conference 2023, Swansea, UK,*
2. Changes in real-world walking speed over 4.5 years in people with Parkinson's and older adults – *ISPGR 2023, Brisbane, Australia,*
3. Modelling distributions of real-world walking speed in people with Parkinson's – *BioMedEng 2022, London, UK,*
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7. Game of thrones and Parkinson's Disease – *Three Minute Thesis 2021, Newcastle University*
8. Need for speed: remote monitoring of walking speed in Parkinson's disease matters – *INSIGHTS Public Lecture Series Final 2021, Newcastle University*
9. Exploring the relationship between real-world walking speed and motor disease severity in Parkinson's disease: insights from cross-sectional and longitudinal data – *BioMedEng 2021, Sheffield, UK.*

Poster presentations

1. Changes in real-world walking speed across 4.5 years in people with Parkinson's and Older adults – Newcastle University Translational and Clinical Research Institute (NUTCRI) *Live 2023, Newcastle University*
2. Unknown distributions: Modelling distributions of real-world walking speed in people with Parkinson's – *Newcastle University Centre of Research Excellence (NUCORE) 2022, Newcastle University*
3. Is real-world step length associated with motor disease severity in Parkinson's disease? – *ISPGR 2022, Montreal, Canada*
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Public Engagement

1. Why does measurement of real-world walking speed with wearable devices matter? – *Biomedical sciences seminar series 2021, Newcastle University*
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Awards, publications, and presentations arising from other work

Presentations

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Publications

1. Bate, G., **Kirk, C.,** Rehman, R. zia ur, Guan, Y., Yarnall, A., Din, S., Lawson, R., 2023. The Role of Wearable Sensors to Monitor Physical Activity and Sleep Patterns in Older Adult Inpatients: A Structured Review. Sensors (Basel, Switzerland) 23.
2. **Kirk, C.,** Kuederle, A., Micó-Amigo, M.E., Bonci, T., Paraschiv-Ionescu, A., Ullrich, M., Soltani, A., Gazit, E., Salis, F., Alcock, L., Aminian, K., Becker, C., Bertuletti, S., Brown, P., Buckley, E., Cantu, A., Carsin, A.-E., Caruso, M., Caulfield, B., Din, S., 2023. Estimating real-world walking speed from a single wearable device: analytical pipeline, results and lessons learnt from the Mobilise-D technical validation study.
3. Mazzà, C., Alcock, L., Aminian, K., Becker, C., Bertuletti, S., Bonci, T., Brown, P., Brozgol, M., Buckley, E., Carsin, A.-E., Caruso, M., Caulfield, B., Cereatti, A., Chiari, L., Chynkiamis, N., Ciravegna, F., Del Din, S., Eskofier, B., Evers, J., Garcia Aymerich, J., Gazit, E., Hansen, C., Hausdorff, J.M., Helbostad, J.L., Hiden, H., Hume, E., Paraschiv-Ionescu, A., Ireson, N., Keogh, A., **Kirk, C.,** Kluge, F., Koch, S., Küderle, A., Lanfranchi, V., Maetzler, W., Micó-Amigo, M.E.,

Mueller, A., Neatrour, I., Niessen, M., Palmerini, L., Pluimgraaff, L., Reggi, L., Salis, F., Schwickert, L., Scott, K., Sharrack, B., Sillen, H., Singleton, D., Soltani, A., Taraldsen, K., Ullrich, M., Van Gelder, L., Vereijken, B., Vogiatzis, I., Warmerdam, E., Yarnall, A., Rochester, L., 2021. Technical validation of real-world monitoring of gait: a multicentric observational study. BMJ Open 11, e050785.

4. Micó-Amigo, M.E., Bonci, T., Paraschiv-Ionescu, A., Ullrich, M., **Kirk, C.,** Soltani, A., Küderle, A., Gazit, E., Salis, F., Alcock, L., Aminian, K., Becker, C., Bertuletti, S., Brown, P., Buckley, E., Cantu, A., Carsin, A.-E., Caruso, M., Caulfield, B., Cereatti, A., Chiari, L., D'Ascanio, I., Eskofier, B., Fernstad, S., Froehlich, M., Garcia-Aymerich, J., Hansen, C., Hausdorff, J.M., Hiden, H., Hume, E., Keogh, A., Kluge, F., Koch, S., Maetzler, W., Megaritis, D., Mueller, A., Niessen, M., Palmerini, L., Schwickert, L., Scott, K., Sharrack, B., Sillén, H., Singleton, D., Vereijken, B., Vogiatzis, I., Yarnall, A.J., Rochester, L., Mazzà, C., Del Din, S., for the Mobilise-D consortium, 2023. Assessing real-world gait with digital technology? Validation, insights and recommendations from the Mobilise-D consortium. Journal of NeuroEngineering and Rehabilitation 20, 78.
5. Palmerini, L., Reggi, L., Bonci, T., Del Din, S., Micó-Amigo, M.E., Salis, F., Bertuletti, S., Caruso, M., Cereatti, A., Gazit, E., Paraschiv-Ionescu, A., Soltani, A., Kluge, F., Küderle, A., Ullrich, M., **Kirk, C.,** Hiden, H., D'Ascanio, I., Hansen, C., Rochester, L., Mazzà, C., Chiari, L., 2023. Mobility recorded by wearable devices and gold standards: the Mobilise-D procedure for data standardization. Sci Data 10, 38.
6. Polhemus, A., Ortiz, L.D., Brittain, G., Chynkiamis, N., Salis, F., Gaßner, H., Gross, **M., Kirk, C.,** Rossanigo, R., Taraldsen, K., Balta, D., Breuls, S., Buttery, S., Cardenas, G., Endress, C., Gugenhan, J., Keogh, A., Kluge, F., Koch, S., Micó-Amigo, M.E., Nerz, C., Sieber, C., Williams, P., Bergquist, R., de Basea, M.B., Buckley, E., Hansen, C., Mikolaizak, A.S., Schwickert, L., Scott, K., Stallforth, S., van Uem, J., Vereijken, B., Cereatti, A., Demeyer, H., Hopkinson, N., Maetzler, W., Troosters, T., Vogiatzis, I., Yarnall, A., Becker, C., Garcia-Aymerich, J., Leocani, L., Mazzà, C., Rochester, L., Sharrack, B., Frei, A., Puhan, M., 2021. Walking on common ground: a cross-disciplinary scoping review on the clinical utility of digital mobility outcomes. npj Digit. Med. 4, 1–14.
7. Rehman, R.Z.U., Buckley, C., Micó-Amigo, M.E., **Kirk, C.,** Dunne-Willows, M., Mazzà, C., Shi, J.Q., Alcock, L., Rochester, L., Del Din, S., 2020.

Accelerometry-Based Digital Gait Characteristics for Classification of Parkinson's Disease: What Counts? IEEE Open Journal of Engineering in Medicine and Biology 1, 65–73.

8. Salis, F., Bertuletti, S., Bonci, T., Caruso, M., Scott, K., Alcock, L., Buckley, E., Gazit, E., Hansen, C., Schwickert, L., Aminian, K., Becker, C., Brown, P., Carsin, A.-E., Caulfield, B., Chiari, L., D'Ascanio, I., Del Din, S., Eskofier, B.M., Garcia-Aymerich, J., Hausdorff, J.M., Hume, E.C., **Kirk, C.,** Kluge, F., Koch, S., Kuederle, A., Maetzler, W., Micó-Amigo, E.M., Mueller, A., Neatrour, I., Paraschiv-Ionescu, A., Palmerini, L., Yarnall, A.J., Rochester, L., Sharrack, B., Singleton, D., Vereijken, B., Vogiatzis, I., Della Croce, U., Mazzà, C., Cereatti, A., for the Mobilise-D consortium, 2023. A multi-sensor wearable system for the assessment of diseased gait in real-world conditions. Frontiers in Bioengineering and Biotechnology 11.
9. Scott, K., Bonci, T., Salis, F., Alcock, L., Buckley, E., Gazit, E., Hansen, C., Schwickert, L., Aminian, K., Bertuletti, S., Caruso, M., Chiari, L., Sharrack, B., Maetzler, W., Becker, C., Hausdorff, J.M., Vogiatzis, I., Brown, P., Del Din, S., Eskofier, B., Paraschiv-Ionescu, A., Keogh, A., **Kirk, C.,** Kluge, F., Micó-Amigo, E.M., Mueller, A., Neatrour, I., Niessen, M., Palmerini, L., Sillen, H., Singleton, D., Ullrich, M., Vereijken, B., Froehlich, M., Brittain, G., Caulfield, B., Koch, S., Carsin, A.-E., Garcia-Aymerich, J., Kuederle, A., Yarnall, A., Rochester, L., Cereatti, A., Mazzà, C., for the Mobilise-D consortium, 2022. Design and validation of a multi-task, multi-context protocol for real-world gait simulation. Journal of NeuroEngineering and Rehabilitation 19, 141.

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List of abbreviations

ABC = Activities balance confidence scale

BIC = Bayesian inference criterion

BMI = Body mass index

EM = Expectation maximisation

CAD = Cadence

CI = Confidence interval

COMT = Catechol-O-methyl transferase

CWT = Continuous wavelet transform

EQ-5D = EuroQol 5-dimensions

E-Sc = eScience central

DBS = Deep brain stimulation

DLS = Dual leg stance

DMO = Digital mobility outcome

FC = Final contact

FOG = Freezing of gait

GDS = Global depression scale

GSD = Gait sequence detection

GMM = Gaussian mixture model

GNNS = Global navigation satellite

GPS = Global positioning system

HY = Hoehn and Yahr stage

ICICLE-GAIT = Incidence of Cognitive Impairment with Longitudinal Evaluation – GAIT

ICICLE-PD = Incidence of Cognitive Impairment with Longitudinal Evaluation – Parkinson's disease

IC = Initial contact

ICD = Initial contact detection

IMU = Inertial measurement unit

L5 = Fifth lumbar vertebra

LEDD = Levodopa equivalent daily dosage

LEMs = Linear effects models

LLFDI = Late life function and disability index

MEMs = Mixed effects models

MDS = Movement disorder society

MDS-UPDRS = Movement Disorder Unified Parkinson's Disease Rating Scale

MFI = Multidimensional fatigue index

UPDRS = Unified Parkinson's Disease Rating Scale

MMSE = Mini-mental state exam

MoCA = Montreal cognitive assessment

NFOG = New freezing of gait questionnaire

OA = Older adult

OR = Odds Ratio

PD = Parkinson's disease

SD = Standard deviation

SF-36 = Physical functioning subscale

SL = Stride length

SLS = Single leg stance

TVS = Technical validation study

RQ = Research question

RWS = Real-world walking speed

WB = Walking bout

Chapter 1. How could digital mobility outcomes improve the clinical assessment of mobility in Parkinson's?

1.1 Parkinson's disease

1.1.1 Epidemiology

Parkinson's disease (PD) is a progressive neurological disorder, which affects an estimated 10 million people globally (European Parkinson's disease Association, 2020), and 145,000 people in the UK (Parkinson's UK, 2020). The majority of people with PD are above the age of 50 and due to an ageing population, it is estimated that 170,000 people will be living with PD by 2030 in the UK (Parkinson's UK, 2020), and 13 million people, globally, by 2040 (Deuschl et al., 2020).

1.1.2 Pathology, Cause and Risk Factors

Pathologically, PD is typified by the loss of dopaminergic neurones within the substantia nigra region of the brain, with formation of Lewy bodies and Lewy neurites (Braak and Braak, 2000; Dauer and Przedborski, 2003). PD is viewed as a slowly progressive condition, that begins years before diagnosis and affects multiple neuroanatomical areas (Kalia and Lang, 2015). The mechanisms underpinning the dopaminergic cell loss which cause PD are still not widely understood, however it is thought to result from a complex interplay between genetic and environmental features (Kalia and Lang, 2015). Age is the greatest risk factor for PD, with prevalence and incidence peaking after 80 years of age. Gender is another risk factor as there is a higher incidence rate in males compared to females (Pringsheim et al., 2014). While there is some insight from genetic research that has identified specific genetic mutations associated with a higher incidence of PD, these genetic factors are relatively rare and account only for a small percentage of cases (Kalia and Lang, 2015). A meta-analysis by Noyce et al., 2012 identified environmental factors that significantly increased risk of PD such as: pesticide exposure, prior head injury, beta-blocker use, agricultural occupation, and well-water drinking. Significant factors associated with a decreased risk of PD included tobacco smoking, coffee drinking, non-steroidal anti-inflammatory use, calcium channel blocker use and alcohol consumption.

1.1.3 Motor symptoms

The resulting dopamine deficiency within the basal ganglia leads to motor dysfunction, defined by the cardinal motor symptoms of tremor, rigidity and bradykinesia (Braak and

Braak, 2000; Jankovic, 2008). Progression of PD is characterised by worsening of these motor symptoms. These motor symptoms propagate to balance, gait and postural control impairments, some of which are present in the early stages of PD and get worse over time alongside increasing progression in motor symptom severity (Galna et al., 2015; Pistacchi et al., 2017; Raccagni et al., 2020).

1.1.3.1 Gait disturbance

Gait impairments represent a manifestation of motor symptoms that are of most detriment to independence and quality of life (Deane et al., 2014). Gait is defined as a human's method of walking, that relies on kinetic and kinematic motion primarily of the lower limbs to move the centre of mass through space, with the arms and trunk moving synchronously to provide stability (Richards et al., 2022). Gait, is a complex task that requires integration between several motor and cognitive pathways where it is regulated by locomotor centres, the cerebral cortex and cerebellum within the brain and the spinal cord (Pirker and Katzenschlager, 2017; Richards et al., 2022). Therefore, changes in gait have been shown to reflect changes in cognitive, systemic and motor function (Middleton et al., 2015).

Parkinsonian gait has been divided into two categories (i) continuous and (ii) episodic (Giladi et al., 2013; Hausdorff, 2009). Continuous gait deficits are defined as changes in the gait pattern that appear to be consistent from one step to the next. For example, it has been found that people with PD walk with reduced step length and walking speed, alongside increased double support time and cadence in comparison to aged-matched older adults (OAs) (Zanardi et al., 2021). In contrast, episodic gait impairments are unpredictable, occurring randomly and thus are difficult to replicate in a measurement setting. Episodic gait disturbances can include festination, defined as short, rapid steps, which attempt to keep center of gravity between feet while trunk involuntary leans forward (Giladi et al., 2001). Other episodic gait disturbances include difficulties with gait initiation and freezing of gait symptoms (FOG). FOG is defined as an episodic inability to generate effective stepping, in the absence of any known cause other than PD (Zhang et al., 2021). FOG symptoms are one of the more prominent risk factors for increased falls risk in PD, where there is a larger a risk of sustaining a fall and fracture in PD, in comparison to OAs, that increases from 40 years of age (Kalilani et al., 2016). Falls are one of the most significant events that can occur with either episodic or continuous gait difficulties, as the consequences of sustaining a fall and

fracture can cause disability that has a devasting impact upon independence and quality of life in PD (Pelicioni et al., 2019).

1.1.4 Non-motor symptoms

PD also includes the occurrence of non-motor symptoms, which may include cognitive dysfunction and decline, depression, sleep disorders and fatigue (Poewe, 2008). Non-motor symptoms may be present in the early stage of PD, potentially even earlier than presence of motor symptoms (Kalia and Lang, 2015). Not all symptoms are experienced in PD. An overview of some of the motor and non-motor symptoms can be viewed in (Table 1-1).

Table 1-1. Motor and non-motor symptoms of Parkinson's (Moustafa et al., 2016; Poewe, 2008).

Motor symptom	**Description**
Tremor	Tremors can occur in a resting state (resting tremor), during voluntary movements (action/kinetic tremor) and postural tremor (inability to maintain stable posture against gravity)
Bradykinesia	Slowness of movement
Rigidity	Stiff or inflexible muscles
Postural instability	Reduced ability to maintain equilibrium under dynamic and static conditions
Akinesia	Difficulty initiating movements, loss of voluntary muscle control
Dyskinesia	Difficulty controlling movements, increased involuntary muscle control
Gait disturbance	Gait disturbances can be classified as episodic (freezing of gait, gait festination, difficulty with gait initiation) and continuous (walking with reduced step length and walking speed)
Speech impairments	Increased dysarthria, largely appearing in the later stages of PD
Non-motor symptom	**Description**
Cognitive dysfunction	Dysfunction affecting memory, attention, and other cognitive functions
Depression and anxiety	Increased depression and anxiety
Sleep disorders	Insomnia, restless leg syndrome and sleep apnea
Fatigue	General feelings of fatigue and weakness
Pain	Pain maybe present in muscles, joints, or bones
Visual disturbance	Complications such as blurred vision, double vision or difficulty tracking moving objects

1.1.5 Diagnosis and clinical features

Bradykinesia, rigidity and resting tremor form the diagnostic criteria of PD (Kalia and Lang, 2015). The UK PD Brain Bank criteria is primarily used for clinical diagnosis (Table 1-2) (Hughes, 1992), and more recently also the Movement Disorder Society (MDS) clinical diagnostic criteria (Appendix 1) (Postuma et al., 2015).

Table 1-2. The UK Parkinson's disease Society Brain Bank clinical diagnostic criteria (Hughes, 1992).

Step 1. Diagnosis of Parkinson's
Bradykinesia plus one or more of the following features: • Muscular rigidity • 4-6 Hertz (Hz) rest tremor • Postural instability, not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
Step 2. Exclusion criteria for Parkinson's
One or more of the following suggests a different diagnosis: • History of repeated strokes with stepwise progression of parkinsonian features • History of repeated head injury • History of definite encephalitis Neuroleptic treatment at onset of symptoms • 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure • Negative response to large doses of levodopa (if malabsorption excluded) • More than one affected relative • Sustained remission • Strictly unilateral features after 3 years • Early severe autonomic involvement • Early severe dementia with disturbances of memory, language, and praxis • Oculogyric crises • Supranuclear gaze palsy • Babinski sign • Cerebellar signs • Presence of a cerebral tumour or communicating hydrocephalus on CT scan or MRI
Step 3. Supportive prospective positive criteria for Parkinson's
Three or more of the following features are required for diagnosis of definite Parkinson's: • Unilateral onset • Rest tremor present • Progressive disorder • Persistent asymmetry affecting the side of onset most • Excellent response (70–100%) to levodopa • Severe levodopa-induced chorea • Levodopa response for 5 years or more • Clinical course of 10 years or more

Diagnosis of PD remains a challenge and can only be confirmed with post-mortem assessment, where the heterogeneity of symptoms increases the misdiagnosis rate (Postuma et al., 2015). Between 75% and 95% of individuals with PD have their

diagnosis confirmed upon autopsy (Postuma et al., 2015). Furthermore, studies have shown that experienced movement disorder specialists can diagnose PD with greater accuracy (Hughes et al., 2001). In the early stages misdiagnosis is increased due to the similar profile in symptoms of early PD to other neurodegenerative conditions such as multiple system atrophy, progressive supranuclear palsy, subcortical arteriosclerotic etc. (Postuma et al., 2015). There has been an extensive focus upon developing biomarkers that can diagnose PD in the early stages, as early diagnosis would allow for accurate treatment and prognosis.

1.1.6 Management

Dopaminergic medications used to manage motor symptoms in PD (Bryant et al., 2011; Galna et al., 2015; Lord et al., 2011a) and are designed to replace or increase the availability of dopamine to maintain motor control (Zahoor et al., 2018). Such medications include levodopa, dopamine agonists, monoamine oxidase type B (MAO-I B) inhibitors and catechol-O-methyl transferase (COMT) inhibitors (Fujikawa et al., 2022; Sigurdsson et al., 2021). According to the NICE guidelines for management of PD (Rogers et al., 2017) alongside pharmacological treatment, individuals can also receive input from a multidisciplinary team including physiotherapy (PT), to deliver specific intervention for balance or motor function problems. Physical rehabilitation of motor function in PD can be achieved through various exercise programmes (Mak and Wong-Yu, 2019; Pang, 2021; Uhrbrand et al., 2015). Recent work has demonstrated that aerobic exercise leads to increased cognitive function and stabilizes disease progression of the corticostriatal sensorimotor network (Johansson et al., 2022). Occupational therapy may help improve activities of daily living, and speech and language therapy and referral for a dietician may also be recommended (Rogers et al., 2017).

1.1.7 Motor complications

Medications targeting specific symptoms improve quality of life in PD (Deane et al., 2014), however they've been shown to have no disease modifying effect (Verschuur et al., 2019). Medication is effective at improving motor symptoms, particularly in the early stages where the beneficial response is maintained by intermittent dosing in waking hours (Aradi and Hauser, 2020). However, prolonged medication usage can lead to motor complications, including motor fluctuations which are defined as transitions between ON and OFF medication stages, which can be sudden and unpredictable and have no relationship with the response time of levodopa (Jankovic,

2005). Additional complications may include increased frequency of dyskinesias, the wearing-off phenomenon and unpredictable off episodes (Aradi and Hauser, 2020). Dyskinesias are defined as uncontrolled, involuntary movements, the incidence of which increase with prolonged levodopa usage (Aradi and Hauser, 2020). Increasing number of fluctuations and medication usage and advanced PD duration increase the incidence of FOG symptoms (Zhang et al., 2021).

1.1.8 Clinical assessment

One of the key challenges for delivering effective management and treatment of PD motor symptoms, is ultimately focused upon extension of quality of life. The effectiveness of management and treatment methods upon motor and non-motor symptoms of PD are currently evaluated within supervised environments (ie., hospital or laboratory), through the use of questionnaire-based assessments, such as the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008). The MDS-UPDRS is a four-part rating scale, parts I and II assesses non-motor and motor experiences of daily living respectively, and part IV assesses motor complications. MDS-UPDRS part III assesses motor symptom severity, through evaluating the individual across a wide range of upper and lower body motor signs assessed clinically. The MDS-UPDRS III remains the most widely used method to evaluate motor symptom severity, however, it has limitations. The score is based upon subjective visual interpretation, and the assessment is currently accessible to those physically capable of travelling into a clinic, which increases the burden upon patient, clinician, and carer. Furthermore, the assessment is conducted within a controlled, supervised setting which does not reflect how symptoms manifest in the daily lives of people with PD, providing clinicians with an incomplete perspective of how symptoms truly impact upon quality of life. Most fundamentally, assessments such as the MDS-UPDRS III does directly assess the impact of symptoms upon aspects of quality of life that are of most importance to patients, such as preservation of their physical mobility in their day to day lives (Deane et al., 2014; Port et al., 2021).

1.2 Physical mobility

The presence of motor and non-symptoms in PD, translate to impairments in their physical mobility. Mobility impairments are also termed *Mobility disability*, which is defined as the inability to repeatedly perform activities of daily living (Rochester et al., 2020; Viceconti et al., 2022). Mobility is a broad concept, and has been defined as the

ability to move freely and easily without a vehicle (Viceconti et al., 2022), where the ability to walk through the home and community independently and safely represents one of the most functionally relevant concepts of mobility. Thus, one of the most substantial and disruptive causes of mobility disability is the gait disturbances experienced by people with PD (see - 1.1.3.1). People with PD consider their gait, as one of the most important aspects of mobility (Deane et al., 2014; Delgado-Ortiz et al., 2023; Keogh et al., 2021; Port et al., 2021), however current clinical assessment does not objectively measure how gait is affected in the daily-lives of people with PD, which limits selection of optimal treatment methods that target and protect the aspects of quality of life that people with PD care about the most.

1.2.1 Mobility assessment

Mobility assessment is multi-faceted and can be objectively measured in supervised and real-world environments with assessments of an individual's *mobility capacity,* and *mobility performance* (Table 1-3) (Rochester et al., 2020; Viceconti et al., 2022).

Table 1-3. Definitions of mobility concepts (Viceconti et al., 2022)

Mobility concept	**Definition**
Mobility	The ability to move freely and easily without a vehicle
Mobility capacity	Intensity of which an individual can perform a specific motor task, in a clinical or research setting
Mobility performance	Mobility that has been assessed in the real-world over a sufficiently long period of time.
Mobility disability	Inability to repeatedly perform activities of daily living (bathing and grooming, dressing and undressing, meal preparation and feeding, functional transfers, safe toilet use and maintaining continence and ambulation)

1.2.2 Supervised assessment of mobility capacity

Mobility capacity is typically assessed by the intensity of which individuals can perform specific motor tasks. The MDS-UPDRS III assesses capacity in a clinical context, as outlined in section 1.1.8, it evaluates motor symptom severity and does not direct assess mobility. In a research setting, capacity is assessed through use of brief functional walking tasks (10 metre straight walk, timed up and go test etc.,) in supervised environments (Bloem et al., 2016). Supervised environments are standardised and free from obstructions, changes in lighting and other distractions that are present in the real-world. Supervised assessment is limited as scrutiny from researchers and clinicians, may create measurement effects such as the Hawthorne effect, which is the alteration of behaviour by the participants of a study due to awareness of being observed (Sedgwick and Greenwood, 2015). Furthermore, these brief assessments only provide a snapshot insight into how individual's motor symptoms can manifest during testing in optimal, supervised conditions. Participants are typically assessed 'ON' medication, so this does not capture the full extent of symptoms which may fluctuate widely in PD. For these reasons, supervised assessment only provides an insight into an individual's *mobility capacity* under optimal conditions (Rochester et al., 2020; Viceconti et al., 2022; Warmerdam et al., 2020).

1.2.3 Real-world assessment of mobility performance

Mobility performance is assessed in real-world settings over extended periods of time. Real-world is defined as the context that walking takes place, where real-world assessment is unsupervised, uncontrolled and non-standardised (Kluge et al., 2021). In the real-world, mobility may be influenced by variation in various confounding factors such as terrain (Kowalsky et al., 2021), weather (Kim and Brown, 2022), and specific types of indoor and outdoor environments (Toda et al., 2020). Furthermore, real-world mobility takes place over multi-task scenarios, such as walking and talking, or using a smartphone. The presence of partners or caregivers may also influence real-world mobility (Warmerdam et al., 2020). Thus, real-world environments are more challenging, which is reflected by findings that assessments of mobility capacity in supervised settings, might overestimate real-world mobility performance (Corrà et al., 2021; Del Din et al., 2016a; Hillel et al., 2019). People with PD also experience fluctuations in symptoms and medication state which are difficult to replicate during supervised capacity assessments.

1.2.4 Mobility outcomes

An individual's mobility capacity or performance is quantified through mobility outcomes (Viceconti et al., 2022). At present existing mobility outcome measures in PD are only based upon assessments of supervised mobility capacity such as the EuroQol 5-dimensions (EQ-5D) and Short Form 36 Physical Functioning Subscale (SF-36) (Jaeger et al., 2022). However, the current use of these outcome measures as surrogate markers of an individual's real-world mobility disability does not predict behaviours in real-world settings (ie., ecological validity) and lacks sensitivity and granularity in detecting the discrete changes that occur during repeated activities of daily living. This incomplete assessment of mobility limits therapeutic development and clinical management (Warmerdam et al., 2020).

1.3 Digital mobility outcomes

Due to technological limitations, it was not previously possible to continuously assess an individual's mobility perfomance in the real-world, thus there are currently no tools widely used in clinical research or clinical care (Jaeger et al., 2022). An emerging solution exists in the quantification of Digital Mobility Outcomes (DMOs) (Del Din et al., 2021; Rochester et al., 2020). DMOs are mobility outcomes are obtained through the quantified assessment of gait, which enable the extraction of a plethora of clinically relevant features that can directly assess an individual's mobility. Perseveration of gait is important to people with PD, (Deane et al., 2014; Delgado-Ortiz et al., 2023; Keogh et al., 2021; Port et al., 2021) where walking is a fundamental aspect of mobility. Thus, DMOs quantified from gait assessment are able to assess the efficacy of management and treatment of symptoms that relate to aspects of mobility that are of most importance to people with PD, being relevant to both patient and clinician. DMOs can be evaluated in both supervised and real-world settings providing concurrent insight into both mobility capacity and mobility performance.

1.3.1 Tools for quantification of DMOs

An overview of some of the existing measurement devices for quantifying DMOs, along with their respective advantages and disadvantages can be found below (Table 1-4).

Table 1-4. Advantages and disadvantages of measurement instruments that can quantitatively assess digital mobility outcomes (Buckley et al., 2019)

Traditional		
Instrument	**Advantages**	**Disadvantages**
Video cameras	• Low-cost • Minimal setup time • Portable • Non-invasive • No training required	• Subjective • Low resolution data • Gait cannot directly be quantified • Low inter-researcher reliability
Stopwatch	• Non-invasive • Minimal setup time • No training required	• Subjective • Prone to various sources of measurement error • Extremely low granularity
3D motion capture	• Considered gold standard • High accuracy and precision • High resolution data • Non-invasive	• Expensive • Requires extensive training and expertise • Misplacement of markers is subjective and prone to error • Markers prone to soft tissue artefact • Preparation of participant can be time consuming • Assessment confined to supervised environments
Instrumented walkways	• Fast processing time • High accuracy and precision • Non-invasive • Fast setup	• Expensive • Measurement volume limited by mat dimensions • Requires large enough space to accommodate mat dimensions • Prone to errors in misidentification of gait sequences from shuffling feet • Assessment confined to supervised environments

Force plates	• Considered gold standard for measuring ground reaction forces and COP • Non-invasive • Minimal space required • Minimal participant preparation time • High resolution data	• High cost • Requires technical expertise • Requires purpose built dedicated space

Wearables		
Instrument	**Advantages**	**Disadvantages**
Pressure insoles	• Can accurately and reliably measure real-world gait • Considered wearable 'silver standard' • Can be applied as a reference system to validate algorithms in real-world settings	• Difficult to equip • High battery consumption • Expensive, bespoke made devices
Smartphones	• High availability • Excellent measurement potential • Non-invasive • Lightweight • Opportunity for remote monitoring	• Data not readily available • Proprietary 'black box' algorithms applied to data • Battery life
Inertial measurement units	• Low cost • Lightweight • Capable of continuously monitoring across consecutive days in real-world settings • Opportunity for remote monitoring • Minimal preparation time	• Algorithms are often validated in their performance in controlled, supervised environments, limited their reliability upon data collected in more complex real-world settings • Requires complex algorithms and specialist expertise to extract key features

		• Battery life
Wearable camera	• Lightweight • Minimal preparation time • Provides more contextual insight	• Battery life • Low resolution • Automatic solution to analyse the hours' worth of collected videos.

1.3.2 Traditional tools

Traditionally DMOs have been quantitatively assessed across clinical assessments of mobility capacity through use of researcher operator stopwatches (Polhemus et al., 2021). However due to the development of more sophisticated equipment such as 3D motion capture it is possible to more accurately and reliably quantify a wide range of gait characteristics, (Del Din et al., 2016b; Lord et al., 2013a). Despite the high accuracy and precision of 3D motion capture, the widespread adoption within clinical analysis is limited, due to its high cost, and the expert training required to operate the system. Furthermore, the placement of the reflective markers is time consuming requiring extensive knowledge of human anatomy, as small misplacement of the markers can create crosstalk between joint angles (Piazza and Cavanagh, 2000). The markers themselves may impede movement and soft tissue artefact can be caused by the skin underlying the marker (Mündermann et al., 2006). Instrumented walkways can be set up with relative ease in comparison to motion capture systems, however such systems are also expensive and may only capture gait sequences across short distances. Furthermore, inaccuracies in gait detection may be produced through shuffling of the feet, which is common in PD (Del Din et al., 2016b). Gold standard technologies such as these, are confined to assessing participants in supervised settings, and they are only able to assess mobility capacity and only accessible to those individuals fortunate to live in close geographical proximity, or able to travel to assessment. Access to the clinician's and researchers experienced in interpreting these values are not widely available for NHS use.

1.3.3 Wearable devices

More recent technological advances have led to the development of wearable devices, which can offer a lightweight and low-cost alternative to gold standard technologies for assessment of DMOs. Wearable devices are comprised of various inertial measurement units (IMUs) such as accelerometers, gyroscopes, magnetometers, barometers, temperature sensors and global positioning satellite (GPS) receivers (Lu

et al., 2020) (Table 1-5). These devices are designed to be worn on the body and can be equipped with relatively low preparation times. Wearables can be worn in both clinical and real-world settings, enabling concurrent evaluation of traditional and novel measures DMOs (Buckley et al., 2019). Their extended battery life offers a feasible and non-invasive solution to objectively and continuously measuring real-world mobility performance across extended periods of time.

Table 1-5. Different inertial measurement units that can be incorporated into wearable devices, to quantify digital mobility outcomes.

Sensor	Measure
Accelerometer	Tri-axial gravitational accelerations (g) of a moving body.
Gyroscope	Tri-axial angular velocity, or rotations (degrees per second).
Magnetometer	Position relative to earth's magnetic core (T)
Barometer	Atmospheric pressure (bar), can be applied to quantify real-world activity more robustly, in terms of stair decent and incline walking
Temperature sensor	Body temperature in Celsius or Fahrenheit. Particularly useful in determining wear times of the device
Global position satellite (GPS) receivers	Latitude and longitude coordinates that can be processed to understand spatial behaviour

While wearable devices are not without their limitations (Table 1-4), the inclusion of real-world DMOs, may provide a more data-driven and detailed insight, that may help complement in the diagnosis and management of PD.

1.3.4 Quantification of DMOs from wearable devices

DMOs can be objectively measured with a single wearable device. In general, a larger number of sensors results in better accuracy of DMOs, however this reduces usability and comfort for the participant (Keogh et al., 2023) and increases the likelihood of

missing and incorrect data through accidental misplacement of the sensors (Czech et al., 2020). A single sensor has sufficient accuracy, alongside maintaining maximum device adherence. While the sensor can be worn is a variety of locations, the lower back (fifth lumbar vertebrae) is most favourable as it can be can be worn via an elasticated strap unobtrusively for seven days, and is capable to measure gait events, and due to its positioning close to the centre of mass it can reflect the overall movement pattern of the right and left limbs (Yang and Hsu, 2010).

Algorithms can be applied to the raw sensor data to calculate walking speed and a battery of DMOs (Rochester et al., 2020). These algorithms, draw upon biomechanical (Zijlstra and Hof, 2003), signals processing (Paraschiv-Ionescu et al., 2020) and machine learning techniques (Ullrich et al., 2021) and are highly adaptable, enabling an almost infinite number of gait features to be calculated. Quantification of real-world DMOs with wearable devices, is first reliant upon the accurate segmentation of periods of walking activity from non-walking activity (lying, sitting, sedentary behaviour and travelling in vehicles) (Figure 1-1A). Within each identified walking sequence, individual gait events are then detected, which then enable estimation of step/stride time and length and subsequently the estimation of DMOs across multiple gait cycles (Del Din et al., 2016b). A single gait cycle may also be defined as a stride, as it consisted of two consecutive steps of either foot. A gait cycle is comprised of both the stance and swing phase, where the stance phase is when the foot is in contact with the ground and makes up 60% of the cycle and the swing phase when the foot is in flight and is the remaining 40% (Richards et al., 2022) (Figure 1-1B). Lord et al., 2013a, conceptualised a gait model in older adults and PD, that identified 16 clinically relevant gait outcomes, from five different domains namely pace, rhythm, variability, asymmetry and postural instability (Figure 1-1D). This model was developed with data collected from an instrumented walkway in supervised settings, however it has since been replicated with DMOs estimated from wearable devices (Morris et al., 2017a).

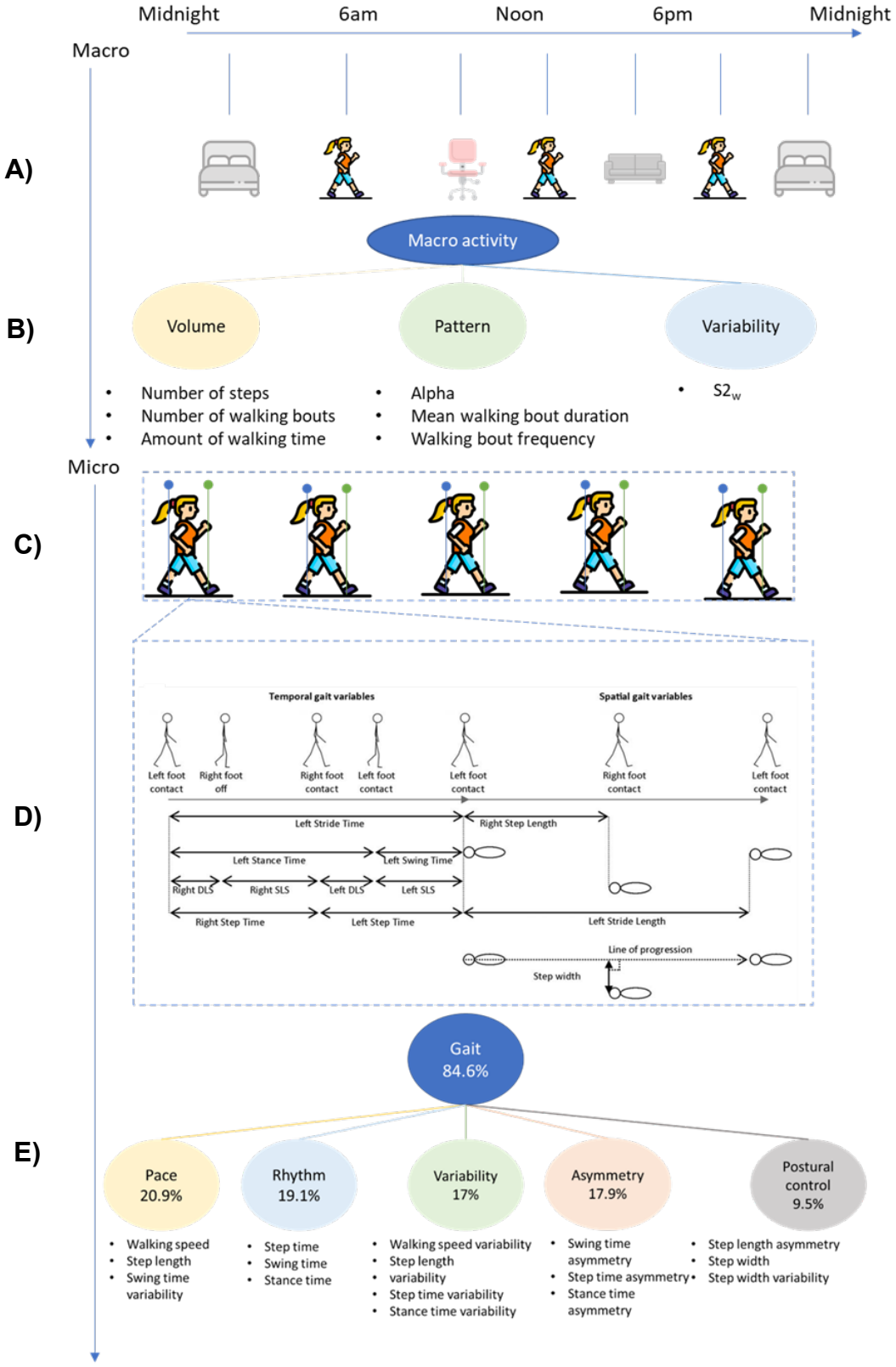


Figure 1-1. Estimation of digital mobility outcomes (DMOs) adapted from (Lord et al., 2013a). 1A) Periods of walking activity are segmented from periods of non-walking activity (lying, sitting, sedentary behaviour. 1B) Estimation of the volume, pattern, and variability of walking activity. 1C) Within each detected walking sequence, individual gait events are detected, which in turn enable estimated of step/stride durations and

cadence. 1D) Within each identified gait cycle, spatial-temporal DMOs are estimated. Dual leg stance (DLS) meaning both feet in contact with the ground and single leg stance (SLS) refers to a single foot in contact with the ground. 1E) DMOs can then be estimated from any of the spatial-temporal domains of gait (Lord et al., 2013b).

1.3.5 Characterisation of DMOs in PD

Real-world DMOs, offer further mobility insight as DMOs to provide insight into ambulatory behaviour, alongside measurement of spatial-temporal gait characteristics. Considering a more refined and standardized approach, real-world DMOs can conceptualised at a macro and microstructural level (Lord et al., 2013a).

1.3.6 Macrostructural DMOs

Macrostructural DMOs refers to quantification of volume (i.e., step count, number of walking bouts (WB), amount of walking time), patterns (ie. frequency of WBs and variability of ambulatory behaviour. People with PD typically have less volume and reduced variability of macro gait activity which is prevalent even in early PD (Chastin et al., 2010; Lord et al., 2013c). Maintaining physical activity with ageing presents a significant challenge, even more so for people with PD. The benefits of physical activity are far reaching and in PD may extend to reducing deterioration in gait and balance (Tsukita et al., 2022), to help mitigate loss of quality of life and independence. Thus, quantification of DMOs on a *macrostructural* level is useful, as it can provide insights into behavioural patterns, such as reduced physical activity, which could propagate to increased mobility impairment. This would allow specific recommendations or interventions can be made to ensure that physical activity and exercise is maintained to mitigate the effects of ageing upon quality of life and independence.

1.3.7 Microstructural DMOs

Microlevel DMOs have been characterised in PD in supervised and real-world settings. In a supervised setting, a variety of micro gait DMOs, such as stride length, stride time, walking speed, were significantly lower and cadence and double support time significantly higher in PD in comparison to OAs (Schlachetzki et al., 2017), which is consistent with previous findings made with gold standard technologies (Zanardi et al., 2021). Furthermore, walking speed has been demonstrated to reduce significantly overtime, however no difference in the rate of change in walking speed between PD and OA could be found (Wilson et al., 2020). Step length on the other hand was found

to deteriorate more rapidly over time in PD, suggesting this is a more sensitive measure of PD progression when assessed in a supervised setting.

In the real-world, researchers have made similar findings to supervised research, in that people with PD have reduced walking speed and step length (Del Din et al., 2016a). When understanding whether any influence of environment exists upon DMOs, researchers have demonstrated that irrespective of cohort, people with PD walked with decreased pace and increased rhythm, variability and asymmetry in the real-world when compared to the laboratory (Del Din et al., 2016a). Furthermore, in comparison to the gold standard (instrumented walkway), they found higher values of variability and asymmetry metrics quantified from the wearable device, which suggests that it's a more sensitive tool in measuring gait characteristics from those domains (Del Din et al., 2016b). Where other studies have demonstrated people with PD walk with more variability and asymmetry of the upper and lower limbs (Mirelman et al., 2019; Zanardi et al., 2021) and changes in the pace and rhythm domains of gait have been demonstrated to be evident in early PD, even with optimal medications (Galna et al., 2015). This suggests that measuring DMOs in a real-world setting may provide more sensitive surrogate markers of PD pathology compared to laboratory based DMOs, and provide different insights of mobility, in comparison to mobility capacity. There is a lack of studies that have explored whether progression in PD translates to changes in real-world DMOs, which makes for an interesting area of analysis.

1.3.8 Real-world walking speed

A plethora of DMOs can be estimated at micro and macro levels to provide insight into different aspects of mobility. However, walking speed could be applied as a single outcome measure to gain into an individual's global mobility performance. Walking speed reflects a composite outcome measure of gait, as it combines spatial-temporal measures, specifically calculated through the ratio of step/stride length to step/stride duration (Del Din et al., 2016b). Walking speed specifically, has been cited as the sixth vital sign of health (Middleton et al., 2015), where there is a wealth of evidence demonstrating associations between reductions in walking speed with ageing (Hollman et al., 2011; Wilson et al., 2020), cognitive decline (Iansek et al., 2013; Morris et al., 2016), falls risk (Jehu et al., 2021; Kyrdalen et al., 2019) and PD (Del Din et al., 2016a; Mirelman et al., 2019; Wilson et al., 2020; Zanardi et al., 2021). Walking speed was significantly slower in the real-world in contrast to supervised settings in PD, where

real-world walking speed (RWS) was more sensitive to discriminating between PD and age-matched control participants (Del Din et al., 2016a).

Digital assessment of mobility, through quantification of RWS with wearable devices could be remotely deployed in the future to monitor aspects of health that is not captured through the existing clinical assessment (Del Din et al., 2021). This would extend availability of assessment to individuals not physically capable of travelling into the clinic and allow clinicians to target and manage aspects of PD that are of most importance to people with PD. However, for this to be achieved a number of challenges must be overcome.

1.4 Barriers to the clinical adoption of DMOs

DMOs, such as RWS are yet to gain adoption in clinical trials and clinical care. In order for this to be achieved a number of critical steps and challenges must be overcome, including comprehensive technical and clinical validations (Goldsack et al., 2020; Rochester et al., 2020; Viceconti et al., 2020).

1.4.1 Technical validity

Technical validation concerns the evaluation of algorithms to convert sample-level sensor measurements in DMOs and evaluate their performance with respect to gold or silver standard technology. Large multi-centric efforts, such as the Mobilise-D project (Mazzà et al., 2021; Rochester et al., 2020) have undertaken a highly comprehensive validation that has ensured that RWS can be estimated accurately and reliably across a range of environments, cohorts and contextual factors (Kirk et al., 2023b; Micó-Amigo et al., 2023).

1.4.2 Clinical validity

Clinical validation is typically undertaken to demonstrate that it is related to something relevant to the patient, clinician or health service and measures or predicts the clinical, biological, function state, or experience in the context of use (in this instance RWS as a measure of mobility in PD) (Goldsack et al., 2020). Clinical validity for RWS can specifically be demonstrated as outlined below (Table 1-6) (Rochester et al., 2020; Viceconti et al., 2020).

Table 1-6. Criteria for demonstrating clinical validity of digital mobility outcomes (Rochester et al., 2020; Viceconti et al., 2020)

Concept	Description
Convergent validity	The extent to which the DMO correlates with measures that should be theoretically related to each other
Discriminant validity	The extent to which the DMO does not correlate with measures of attributes that are different from the attribute the DMO is intended to assess
Known group validity	The extent to which the DMO demonstrates significant differences between groups who are known to differ on that specific construct
Predictive validity	The extent of which a DMO is able to predict future clinical outcomes
Responsiveness to intervention	Whether the DMO, is sensitive to changes that occur in a clinical intervention trial
Ecological validity	The extent of which the DMO can be generalised to real-world settings

DMO = Digital mobility outcome

A large scoping review (Polhemus et al., 2021), mapped a large body of existing evidence of studies in a supervised setting that have demonstrated the clinical validity of DMOs including walking speed in PD. However, it's known that DMOs estimated from supervised assessments lack ecological validity in being representative of real-world mobility. Whilst real-world DMOs weren't included in their review, this represents an essential first step in understanding why there is a lack of evidence and where the specific gaps in clinical validity lie. Further challenges need to be addressed in understanding the optimal methods of data aggregation and statistical summary for real-world DMOs.

1.4.3 The context of real-world mobility

RWS is assessed over seven consecutive days encapsulates a rich and vast dataset of mobility that has been undertaken across various WBs, which differ in their length, duration, and context. The majority of research of research summarises RWS through averaging across the entire week. More recently other researchers have started to explore more subtle approaches that consider the duration or length or length of WBs, termed aggregation. This involves the aggregation of RWS within specific WB thresholds, based upon their duration (ie., length in seconds), or the number of steps within each bout (Del Din et al., 2016a; Rehman et al., 2022; Shah et al., 2020a). An overview of the different duration thresholds that have typically been applied to categorise WBs can be viewed below (Table 1-7).

Table 1-7. Different walking bout duration thresholds that are typically applied in real-world studies (Del Din et al., 2016a)

WB duration	Activity
All WBs	Contains all real-world information
< 10 seconds	Very short WBs, most challenging to estimate gait from, often excluded from real-world mobility analysis
10 to 30 second	Short WBs, may capture essential household activities (making a drink, etc.,)
30 to 60 seconds	Medium length WBs containing prolonged periods of house-hold activity, or intermittent periods of outdoor walking (shopping, walking in parks etc.,)
> 60 seconds	Long WBs, that are speculated to take place in outdoor spaces, where individuals may achieve their real-world capacity and fastest RWS

WB = Walking bout. RWS = Real-world walking speed

Most WBs are very short (< 10 seconds) (Del Din et al., 2016a; Rehman et al., 2022; Shah et al., 2020a), however these WBs often contain non-gait related activities (transitions, sharp turns, gait initiation and termination), as such this duration provides

the greatest challenge to algorithm performance (Kirk et al., 2023b; Micó-Amigo et al., 2023). Furthermore, DMOs estimated at < 10 seconds, do not discriminate between PD and OAs (Del Din et al., 2016a). For these reasons < 10 seconds can be excluded from real-world analysis. RWS within short WBs (10 to 30 seconds), are speculated to take place indoors (specifically in the household) and may encapsulate the largest number of motor fluctuations, as essential activities as this duration are completed irrespective of medication state (Del Din et al., 2016a; Lord et al., 2013c). In contrast, longer WBs would likely take place within more open outdoor spaces, where individuals would achieve steady-state walking and their fastest RWS, the lowest numbers of data are contained within longer durations (Del Din et al., 2016a). Previous research that demonstrated RWS encapsulated within medium to long WBs was significantly slower in PD in comparison to OAs (Del Din et al., 2016a). This demonstrates how WB duration helps to further sensitise the information reflected by RWS.

1.4.3.1 Environmental location

Real-world mobility may also fluctuate between environments. At present, direct measurement of environmental information is not typically included by researchers and instead this information is inferred based upon the WB duration (ie., short WBs take place indoors and long WBs outdoors) (Corrà et al., 2021; Del Din et al., 2016a; Shah et al., 2020a). The importance of understanding environmental context and its influence upon mobility is gaining traction within health-care research, as an increasing number of studies have suggested the context of the places of which people work, live and socialise are associated with health-related behaviours and outcomes (Rainham et al., 2008). Real-world environments can be broadly categorised as indoor or outdoor, and both types of environments could pose their own specific challenges to mobility. Indoor or outdoor location in real-world settings can be quantified through GPS and Global Navigation Satellite (GNSS) Systems, which have had promising applications toward quantifying real-world physical activity behaviour (Jankowska et al., 2015; Schipperijn et al., 2014). However, no study has directly compared differences in RWS between indoor and outdoor locations. GPS data coupled with RWS measurements from wearable devices, has potential to provide more specific insight into how the ability of individuals to adapt their walking through modulation of their RWS to safely navigate the demands of each real-world context they find themselves within.

1.4.4 Real-world gait modulations

RWS may need to be modulated to account for different changes in environment and WB duration. Individuals may modulate their RWS through different phases of acceleration, steady-state, and deceleration. They must also adapt to contextual challenges like changes in surface (Osaba et al., 2020), obstacles, fatigue (Zhang et al., 2022), and multitasking. Moreover, PD could disrupt gait initiation and cause inconsistent patterns in RWS due to episodic gait disturbances such as festination (Giladi et al., 2001), or FOG symptoms (Mancini et al., 2021; Zhang et al., 2021) and motor fluctuations. Objective quantification of modulations within a walking bout can provide a comprehensive understanding of walking dynamics and functional capabilities, especially in PD. This information can inform decision-making, therapeutic management, and personalized interventions to improve mobility and quality of life. Traditional mean values for RWS may not capture clinically important patterns and frequencies but analysing DMOs, through more novel techniques could offer valuable insights into adaptability of walking across various real-world contexts, alongside the fluctuating nature of PD (Figure 1-2) (Goodier, 2007).

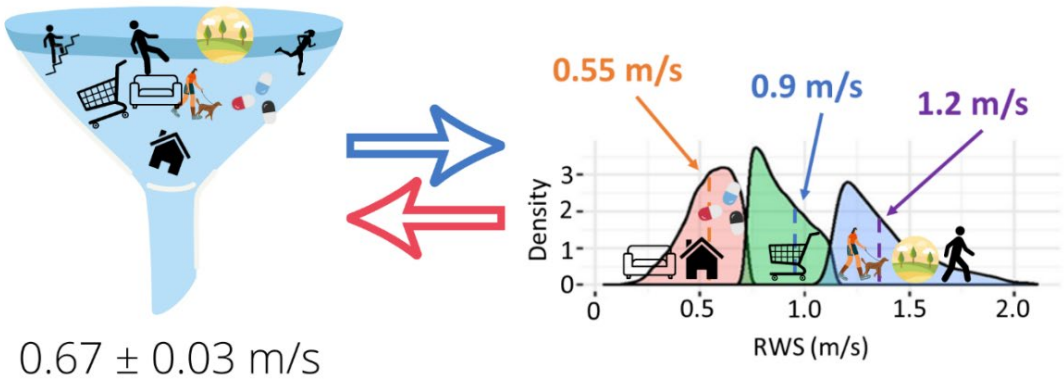


Figure 1-2. Condensing information from real-world walking speed (RWS) assessed over seven days**:** standard statistics (mean and standard deviation) versus exploring the number of modulations that occur within RWS.

1.5 Thesis aims

This thesis aimed to understand whether digital assessment of mobility, through quantification of RWS has value as a clinical mobility endpoint to provide a more complete and objective, remote evaluation of mobility. There was a particular focus

upon understanding whether novel methods of data aggregation or statistical summary were able to further extract the point of which RWS has the most clinical relevance. The specific aims of the thesis are addressed across the chapters outlined below:

Chapter 2: Mapping the existing evidence of the clinical validity of real-world digital mobility outcomes: a systematic review

This chapter contains a systematic review, which mapped the existing literature that has sought to clinically validate DMOs estimated from unsupervised and continuous assessments, to understand what they are telling us about real-world mobility.

Aims:

To explore the existing literature, to understand what information is reflected by real-world DMOs, with the following specific aims:

- Ecological validity: Identify existing studies that have sought to explore the influence of supervised and real-world assessment upon DMOs;
- Known groups differences: Explore the existing literature that has quantified differences in real-world DMOs between PD and OAs, and specific clinical groups within PD;
- Convergent validity: Map body of literature that has explored relationships between real-world DMOs an clinical scales;
- Predictive capacity: Identify studies that have explored longitudinal relationships between real-world DMOs and clinical outcomes.

Chapter 3: General methods

This chapter provides an overview of the general methods within this thesis, including detailed descriptions of the two datasets; Incidence of Cognitive Impairment with Longitudinal Evaluation – GAIT (ICICLE-GAIT) study and Mobilise-D Technical Validation Study (TVS).

Chapter 4: Can real-world walking speed add value to assessment of disease severity in Parkinson's disease?

This chapter undertook a comprehensive exploration of RWS to understand what information it is providing. Specifically, whether RWS can assess real-world mobility impairment, through exploring cross-sectional and longitudinal differences between

PD and OA participants, before exploring cross-sectional and longitudinal associations with MDS-UPDRS III

Aims

- Explore whether RWS corresponds to known group differences in RWS in PD and compare to OAs, cross-sectionally
- Explore whether RWS corresponds to known group differences in changes in RWS in PD and compare to OAs, longitudinally
- Determine the convergent validity between RWS and MDS-UPDRS-III
- Explore the relationship between change in RWS with change in MDS-UPDRS III

Hypotheses

- RWS would be slower in PD across a range of WB durations
- Longitudinally, RWS would reduce more rapidly in PD
- RWS would show a weak to moderate relationship with the MDS-UPDRS III, dependent upon WB duration
- Changes in RWS would not be related to changes in the MDS-UPDRS III.

Chapter 5: Enhancing the understanding of real-world walking speed in Parkinson's and aging: Influence of Indoor and Outdoor location

This chapter aimed to understand whether inclusion of environment contextual data (indoor and outdoor location), alongside the WB duration is able to improve interpretation of RWS and provide further insight into what factors may influence real-world mobility.

Aims

- Explore whether the volume of real-world walking is larger within indoor or outdoor locations, in different WB duration thresholds in PD and OA participants;
- Determine if volume of walking within indoor and outdoor locations is significantly different between PD and OAs;
- Explore whether mean RWS is significantly different between indoor and outdoor locations in different thresholds of WB duration for PD and OA participants;

- Determine whether RWS within indoor and outdoor locations is significantly different between PD and OAs.

Hypotheses

- The majority of real-world walking will take place indoors for both cohorts; with the largest proportion of indoor walking being comprised of short WBs and conversely largest proportion of outdoor walking being comprised of longer WB durations;
- PD will have a significantly larger proportion of indoor walking activity in comparison to OAs;
- Mean RWS would be significantly slower within indoor environments compared to outdoor settings for both cohorts across each WB duration;
- Mean RWS would be significantly slower in PD participants in comparison to OAs across each environment, and WB duration threshold.

Chapter 6: Gait adaptation in the real-world: Quantification of modulations within real-world walking speed in people with Parkinson's and older adults

This chapter described an exploratory study of the utility of a novel method of characterising the number of modulations that occur within RWS across WBs, real-world locations and assessment contexts, and whether these modulations are different between PD and OAs

Aims

- Determine of the number of selected walking speeds (defined by the number of modes) in real-world and laboratory settings in PD and OAs
- Explore whether selected walking speeds are modulated differently between WB duration thresholds and assessment context (laboratory vs real-world)

Hypotheses

- In the real-world, selected walking speeds would be dependent upon the WB duration, as mean RWS has been previously shown to differ between WBs (Del Din et al., 2016a). PD participants would be characterised by fewer selected walking speeds in comparison to OAs, demonstrating a reduced ability to adapt RWS (Lord et al., 2013c).

- Both groups would have a larger number of selected walking speeds in the real-world, in comparison to the laboratory, due to the need to adapt walking to a more complex environment.

Chapter 7: **Unravelling the clinical implications of real-world walking speed adaptations: A key to understanding real-world behaviour in Parkinson's?**

This chapter undertook an explanatory analysis to understand the number of selected walking speeds correspond to. It was also explored whether the number of selected walking speeds changed as time progressed was explored.

Aims

- Undertake an explanatory analysis to understand what information is reflected by a larger or smaller number of selected walking speeds, across different WB durations in in PD and OAs
- Characterise longitudinal differences in the number of selected walking speeds between PD and OAs

Hypotheses

- The number of selected walking speeds would reflect different clinical, demographic or gait-related factors dependent upon the WB duration
- Longitudinal changes in modulations of selected walking speeds would occur more rapidly in PD, in comparison to OAs.

Chapter 8: Thesis overview and conclusions

This chapter provides a final overall summary of all chapters. It will outline key findings and the clinical implications of the thesis, along with discussion of limitations and recommendations for future research.

Chapter 2. Mapping the existing evidence of the clinical validity of real-world digital mobility outcomes: a systematic review

This chapter contains a systematic review, which mapped the existing literature that has sought to clinically validate DMOs estimated from unsupervised and continuous assessments, to understand what they are telling us about real-world mobility.

2.1 Introduction

While there is large body of evidence that provides insight into the clinical measures that are reflected by DMOs assessed in a supervised setting (Polhemus et al., 2021), the existing literature exploring what clinical information is reflected by DMOs estimated from unsupervised and continuous real-world assessments has not been widely explored (Polhemus et al., 2021). Thus, the overarching aim of this chapter was to conduct a systematic review to address this gap and map the existing evidence of studies seeking to understand what real-world DMOs tell us about mobility. Furthermore, literature needs to be reviewed to establish similarities and differences in DMOs assessed in supervised and real-world environments, to understand the influence of environmental context upon the clinical utility of DMOs. It was hoped this review would also identify application of studies exploring the impact of real-world contexts and novel methods of statistical summary upon the construct validity of DMOs.

2.1.1 Aims

Aims:

To explore the existing literature, to understand what information is reflected by real-world DMOs, with the following specific aims:

- Ecological validity: Identify existing studies that have sought to explore the influence of supervised and real-world assessment upon DMOs;
- Known groups differences: Explore the existing literature that has quantified differences in real-world DMOs between PD and OAs, and specific clinical groups within PD;
- Convergent validity: Map body of literature that has explored relationships between real-world DMOs an clinical scales;

- Predictive capacity: Identify studies that have explored longitudinal relationships between real-world DMOs and clinical outcomes.

2.2 Methods

2.2.1 Search strategy

Systematic searches were conducted in 11 databases for peer-review and grey literature (ie., Master's and doctorate theses) MEDLINE, EMBASE, CINAHL, Cochrane Library, Scopus, Web of Science, IEEE Xplore, ACM Digital Library, ProQuest Dissertations, OpenGrey, National Information Centre's Projects in Progress Database. Criteria was limited to studies prior to October 2021, which was the date of the searches, where the lower limit was set to studies published during or after 1999. The search strategy can be observed in Appendix 2.

2.2.2 Study selection

For an article to be eligible, it must have reported an original analysis that addressed one of the RQs, with respect to an included DMO (Figure 1-1).

Eligibility of articles was assessed through abstract and full text screening. All reviewers (CK, MM and HB) received training on review conduct prior to abstract screening and piloted eligibility criteria on a random set of 50 abstracts to ensure consistency. Four reviewers independently screened the abstracts, where the lead reviewer (CK) monitored consistency between reviewers throughout the abstract screening stage. Articles were included in the full-text screening if a single reviewer deemed an abstract eligible; articles were excluded if two reviewers opted for rejection. For the abstract screening, study design, review conduct, records of duplication, reference exclusion on an individual author contribution were managed in Rayyan (Cambridge, Massachusetts, USA). Initially, references were compiled in Zotero (George Mason University, Virginia, USA) and the final review libraries in Mendeley (Elsevier B.V., Amsterdam, The Netherlands), an open access reference management software. Any Duplicate studies were excluded, based upon comparing titles, authors, publication years and abstracts.

Two reviewers (CK, MM) screened each full-text and extracted data if eligible, where all the data extraction items from the review can also be viewed in Appendix 3. Following data-extraction, disagreements were resolved through discussion. Data extraction forms were developed, and data extraction was conducted in Microsoft Excel (Microsoft, Washington, USA). Customised risk of bias and quality assessment

was developed, which assessed the external and internal validity of the included full text articles and is defined below (see - 2.2.4). This was completed alongside data extraction and reporting quality of bias is presented through narrative analysis and table summaries.

2.2.3 Data analysis

Data was extracted and analysed to provide a descriptive summary for each research question (RQ)

1. Ecological validity: studies that recorded statistically significant differences between DMOs assessed in both supervised, and real-world assessments, in people with PD were documented.
2. Known group differences: report the proportion of analyses that recorded statistically significantly differences in DMOs between groups (people with PD vs. OAs) or stratified differences between sub-groups of PD participants, such as comparison between:

    - Hoehn and Yahr stage (Goetz et al., 2008)
    - Freezing of gait symptoms, as recorded by the New Freezing of Gait Questionnaire (NFOG) (Nieuwboer et al., 2009)
    - Fall status, as recorded by falls diaries, or other means reported by the study

Studies were identified that explored whether known group differences were stronger in supervised or real-world settings, so those studies were reported separately.

3. Convergent validity: report the proportion of analyses that reported statistically significant associations between DMOs and included clinical measures such as:

- The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) total score, or MDS-UPDRS Part II, or MDS-UPDRS Part III and the MDS-UPDRS part III-Gait assessment (Goetz et al., 2008)

4. Predictive validity: Determine whether there were literature exploring longitudinal associations between DMOs and clinical outcomes such as falls risk, FOG symptoms or motor severity.

2.2.4 Quality assessment

The quality of studies within a review, is usually conducted with respect to standardised guidelines. However, those standardised guidelines focus on healthcare interventions

such as randomised control trials. As such, a customised quality of appraisal form was developed, based upon the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies (Zeng et al., 2015) which was assessed by two reviewers (CK and MM). Risk of bias/quality assessment relative to each research question and is summarised below (Table 2-1).

Table 2-1. Quality appraisal assessment

Category	Aspect of quality
External validity	• Was the study population clearly specified and defined? (age/gender/condition) • Were inclusion and exclusion criteria for participants defined? • Was the research question or objective in this paper clearly stated?
Internal validity	• Were the main outcomes clearly described in the methods/introduction. • Could it be replicated? • Validated measures (criterion/convergent/discriminant validity) and implemented consistently across all study participants? • Devices for a data acquisition clearly reported? • Protocol clearly described • Sensor attachment reported? • Length of real-world assessment clearly described? • > 3 days of collected data controlled for? • Appropriate ethics and consent?
Analysis	• Were the statistical tests used to assess the main outcomes appropriate (i.e. parametric vs. non-parametric)? • Probability values reported (e.g. 0.026 rather than <0.05) for the main outcomes. • Were key potential confounding variables measured and adjusted statistically for their impact on the outcome(s)? • Was reporting of results adequate (i.e. no selective reporting)

The reviewer scored one if they felt the study has addressed that aspect of quality, and a zero if they believed the study has insufficient quality. The total score across

all aspects of quality was deemed as the quality score for that study. The average of the two scores between both reviewers was deemed as the final quality score. The classification of each quality score can be found below (Table 2-2).

Table 2-2. Category of quality rating with their respective score range (Zeng et al., 2015)

Quality rating	Score
Poor	0 to 3
Moderate	4 to 7
Good	8 to 11
Excellent	> 12

2.3 Results

2.3.1 Characteristics of included studies

The initial search identified 3518 articles, where 60 articles were eligible for the full-text review. Seventeen articles that were eligible for all RQ; five of which were eligible for ecological validity, nine for known group differences, ten for convergent validity; and none for predictive capacity. An overview of the population characteristics for all eligible studies.

Table 2-3. Population characteristics identified across the included articles. All variables reported as median and range.

Population characteristics	PD	OAs
Number of participants	47 (27, 106)	20 (17, 35)
Age (years)	68.02 (66.6, 69.3)	67.9 (66.85, 69.8)
MDS-UPDRS III (points)	32.95 (28.63, 34.69)	-
Hoehn and Yahr stage	2.07 (2, 2.45)	-
Disease duration (years)	6.45 (5.21, 7.60)	-
LEDD (mmhg)	470.46 (425.42, 532.75)	-

PD = Parkinson's. OA = Older adults. MDS-UPDRS III = Movement disorder society unified Parkinson's disease rating scale Part III. LEDD = levodopa equivalent daily dosage.

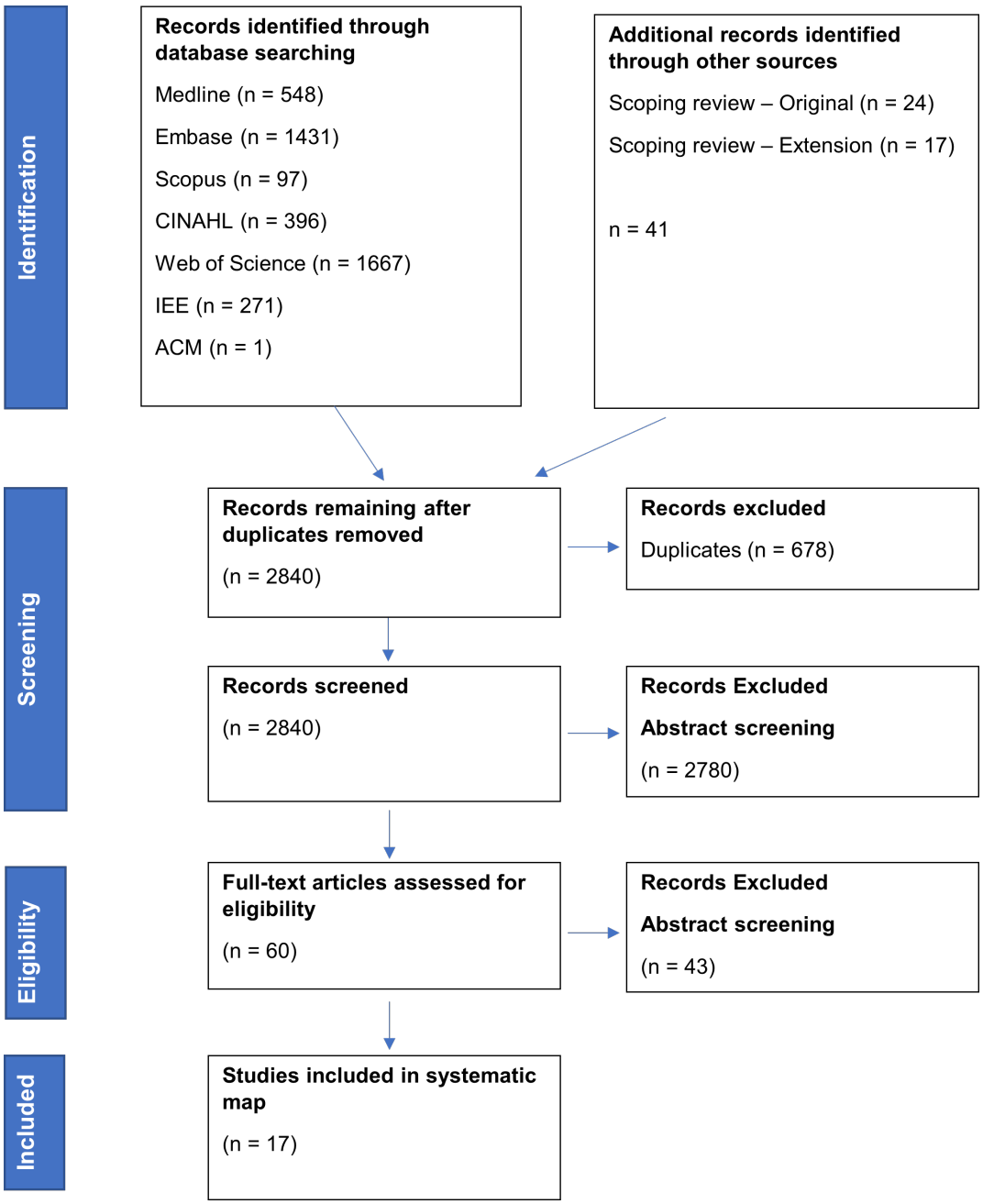


Figure 2-1. From identification to inclusion: number of articles identified, screened, and extracted for each stage of this systematic review.

Across all of the 17 eligible studies, construct validity was explored across 114 analyses. Known groups validity was the most widely explored aspect of construct validity (number of validations = 52), followed by ecological validity (n=22) and convergent validity (n=17).

DMOs belonging from the pace domain had the largest number of analyses for their construct validity (Figure 2-2). In terms of individual DMOs, construct validity was most widely explored for walking speed (n = 17), step/stride length (n=9) and step/stride time (n=9).

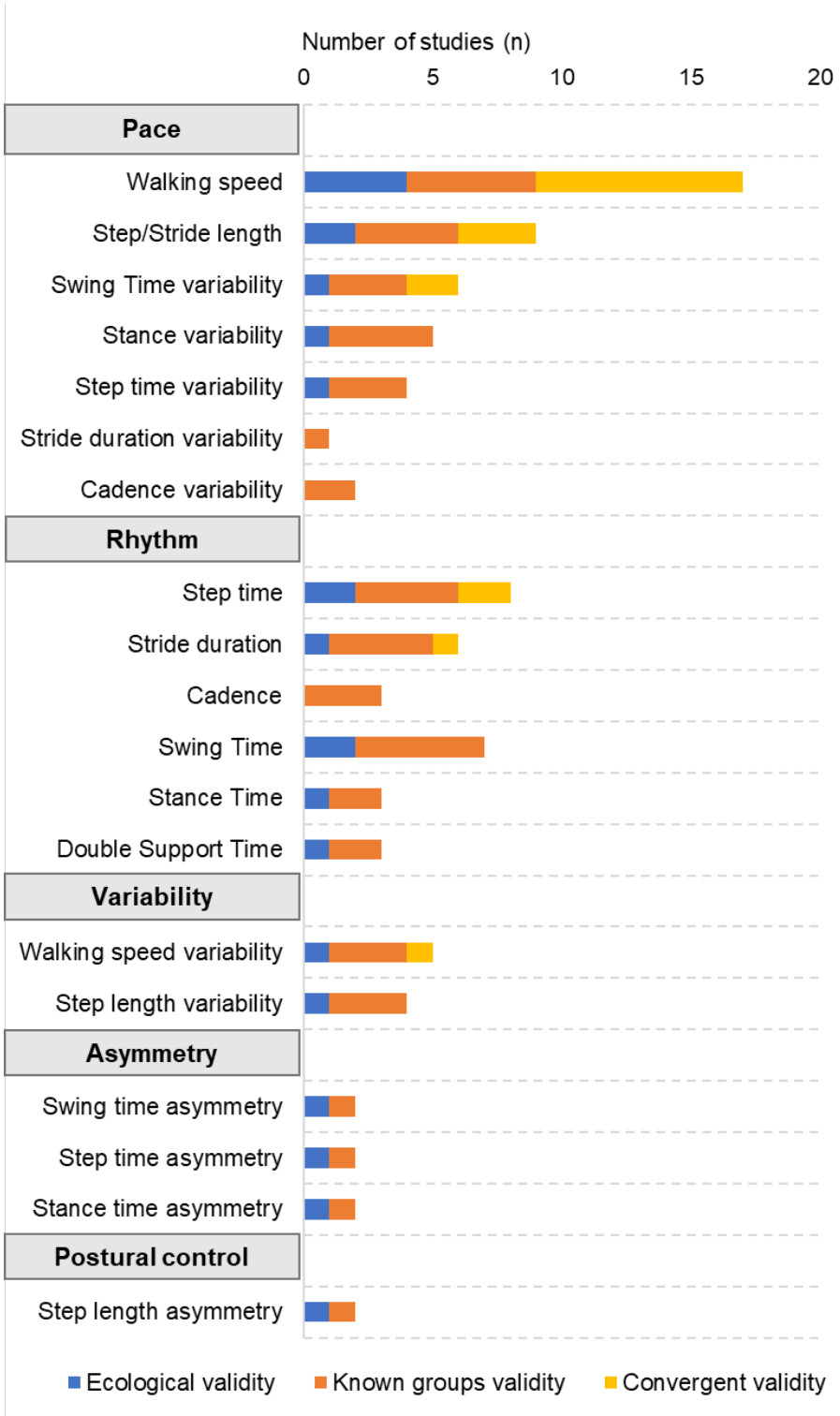


Figure 2-2. The number of digital mobility outcomes identified across all studies and aspects of validity, grouped by gait model domain. (Lord et al., 2013b).

For all studies heterogeneity in measurement methods was found with respect to instrument; sensor attachment; length of assessment; and WB duration from which each DMO was estimated (Table 2-4). Measurement methods of supervised studies can be viewed in Appendix 4.

Table 2-4. Measurement methodologies applied within real-world studies.

Instrument	Number (%)
Wearable device (Lower back and feet)	6 (35%)
Wearable device (Lower back)	6 (35%)
Wearable device (Lower back)	6 (35%)
Sensor attachment	**Number (%)**
Unreported	8 (47%)
Velcro belt	4 (23%)
Adhesive and bandage	3 (17%)
Worn in pocket	1 (1%)
Instrumented socks and elastic belt	1 (1%)
Length of assessment	**Number (%)**
7 days	9 (52%)
1 day	4 (23%)
3 days	3 (17%)
12 days	1 (6%)
Walking bout (WB) duration	**Number (%)**
Unreported	5 (29%)
All WBs > 3 s	4 (23%)
All WBs > 1 minute	4 (23%)
All WBs > 10s	2 (11%)
15 to 30 seconds	2 (11%)
20 to 30 seconds	2 (11%)
30 to 60 seconds	2 (11%)
WBs > 120 seconds	2 (11%)
30 to 60 seconds	2 (11%)
All WBs	1 (6%)
All WBs > 15s	1 (6%)
60 to 120 seconds	1 (6%)
WBs < 10 seconds	1 (6%)

WB = Walking bout.

2.3.2 Ecological validity

Across five studies, 22 explorations of the influence of real-world and supervised assessment upon DMOs was identified (Atrsaei et al., 2021; Corrà et al., 2021; Del Din et al., 2016a; Shah et al., 2020a; Toosizadeh et al., 2015). The majority of studies, reported DMOs that were significantly different between real-world and supervised assessments, excluding one article which demonstrated no differences in step time, stride length and stride duration (Shah et al., 2020c) (Figure 2-3).

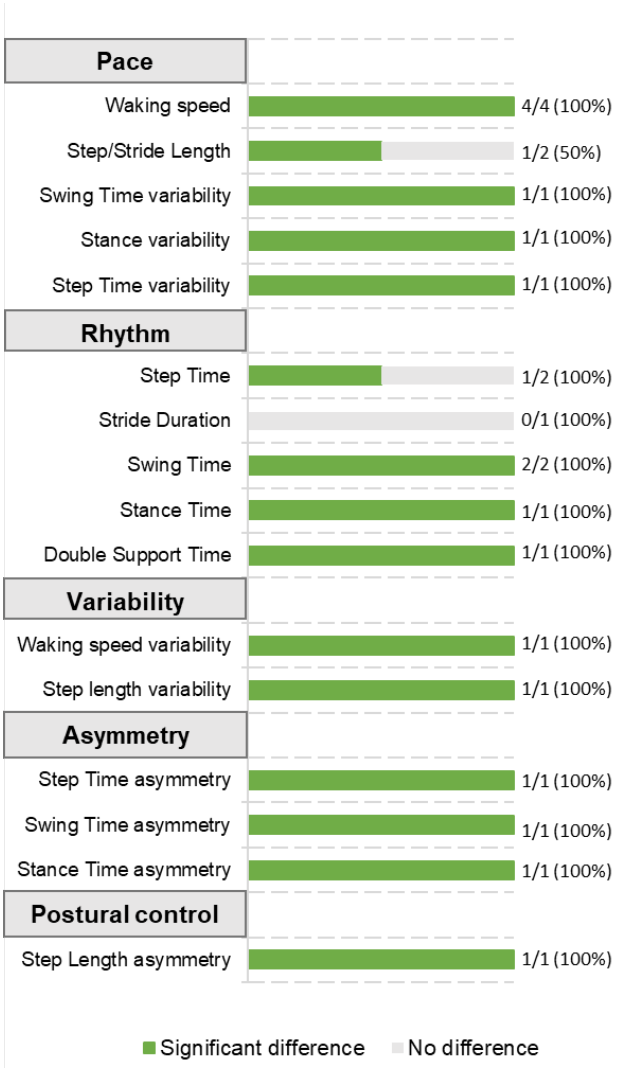


Figure 2-3. Ecological validity: number and proportion of studies that reported significant differences or no differences between digital mobility outcomes assessed in real-world and supervised assessments.

2.3.3 Known group differences

Within the nine studies, 52 analyses were extracted exploring whether DMOs were significantly different between PD and OAs (Corrà et al., 2021; Del Din et al., 2019, 2016a; Shah et al., 2020d, 2020b, 2020c; Terashi et al., 2020, 2013; Toosizadeh et al., 2015). The DMOs that were significantly different between PD and OAs in the largest proportion of analyses were swing time and step length asymmetry (100% of analyses), step length (75% of analyses), step length variability (66% of analyses), swing time variability (66% of analyses) and walking speed (60% of analyses). Known group differences were not reported for stride duration variability, stride time, double support time and step/stance time asymmetry (Figure 2-4).

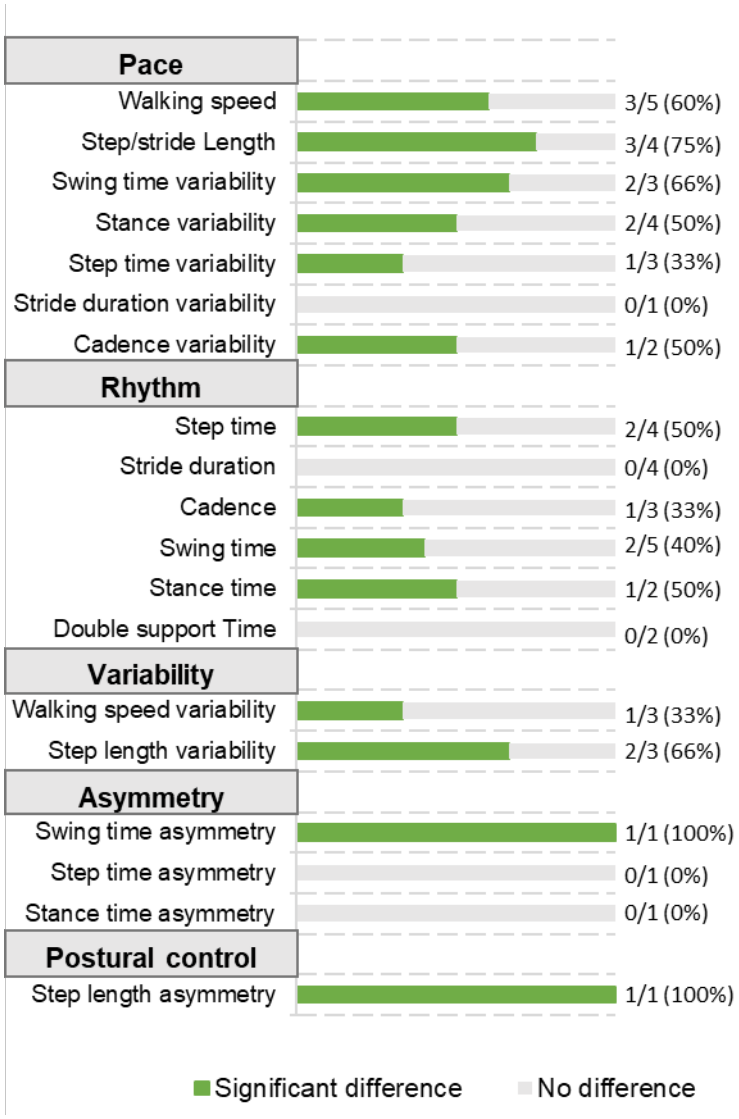


Figure 2-4. Known group differences: number and proportion of studies that reported significant differences in digital mobility outcomes between Parkinson's and control participants assessed in the real-world assessments.

Twenty-three analyses identified within three studies explored whether DMOs estimated from real-world assessments were more sensitive to differences between PD and OAs in comparison to those assessed under supervised conditions (Del Din et al., 2016a; Shah et al., 2020c; Toosizadeh et al., 2015). In the pace domain, walking speed was significantly different between groups in the same proportion of analyses (33%). In contrast, step/stride length was more consistently different when assessed in real-world settings. From the other domains, only swing time and step length asymmetry when assessed in the real-world were significantly different between PD and OA (Figure 2-5).

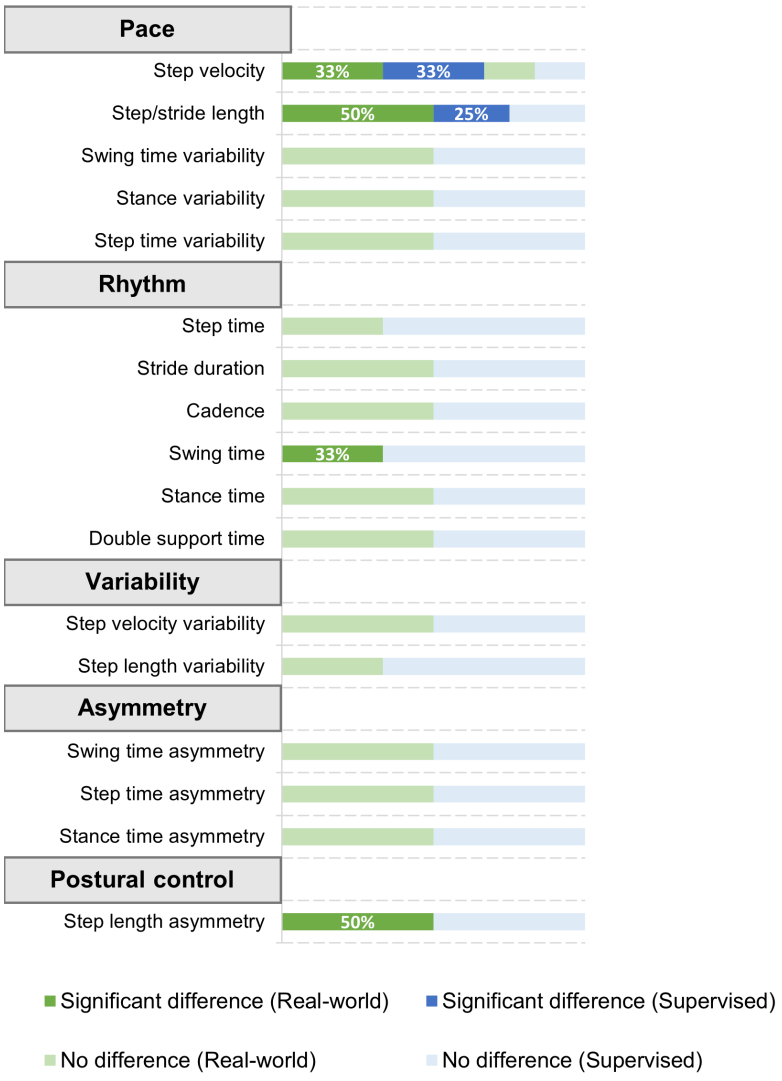


Figure 2-5. Known group differences: number and proportion of studies that reported significant differences or no differences in digital mobility outcomes between Parkinson's and control participants assessed in either real world or supervised conditions. Only solid fill colour reported significant differences.

Ten analyses across five studies explored whether DMOs can discriminate between known clinical groups (Del Din et al., 2019; Mancini et al., 2021; Terashi et al., 2013; Weiss et al., 2015, 2014). Walking speed, step length and walking speed variability were able to discriminate fallers from non-fallers and differed between Hoehn and Yahr stages. However, walking speed and step time were unable to distinguish FOG from non-FOG (Figure 2-6).

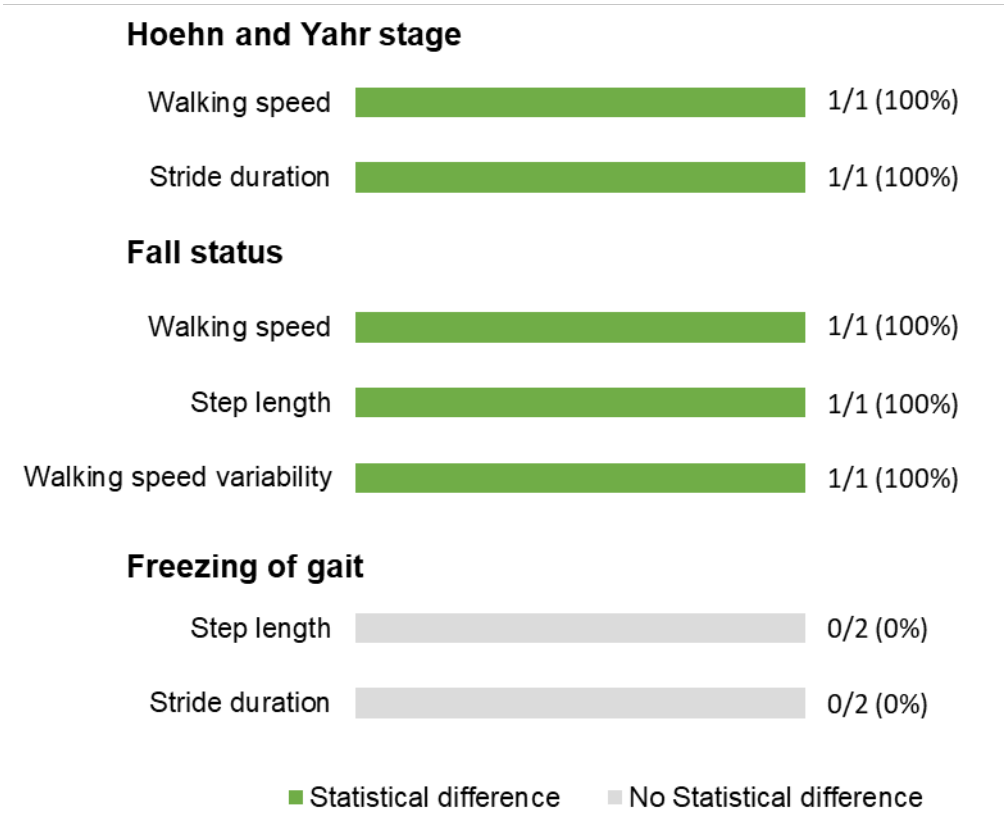


Figure 2-6. Stratified differences between groups: number and proportion of studies reporting statistical differences or no statistical difference in digital mobility outcomes between different Parkinson's groups.

2.3.4 Convergent validity

Within 10 studies, 17 analyses were identified exploring the convergent validity of DMOs (Corrà et al., 2021; Galperin et al., 2019; Mancini et al., 2021; Shah et al., 2020d; Terashi et al., 2020, 2013; Weiss et al., 2015, 2014). Walking speed was not associated with any component of the MDS-UPDRS total score and parts II & III. However, two analyses recorded associations with the MDS-UPDRS III gait-item (Corrà et al., 2021). One study found step length and swing time variability was associated with PIGD sub score (Shah et al., 2020d) (Figure 2-7).

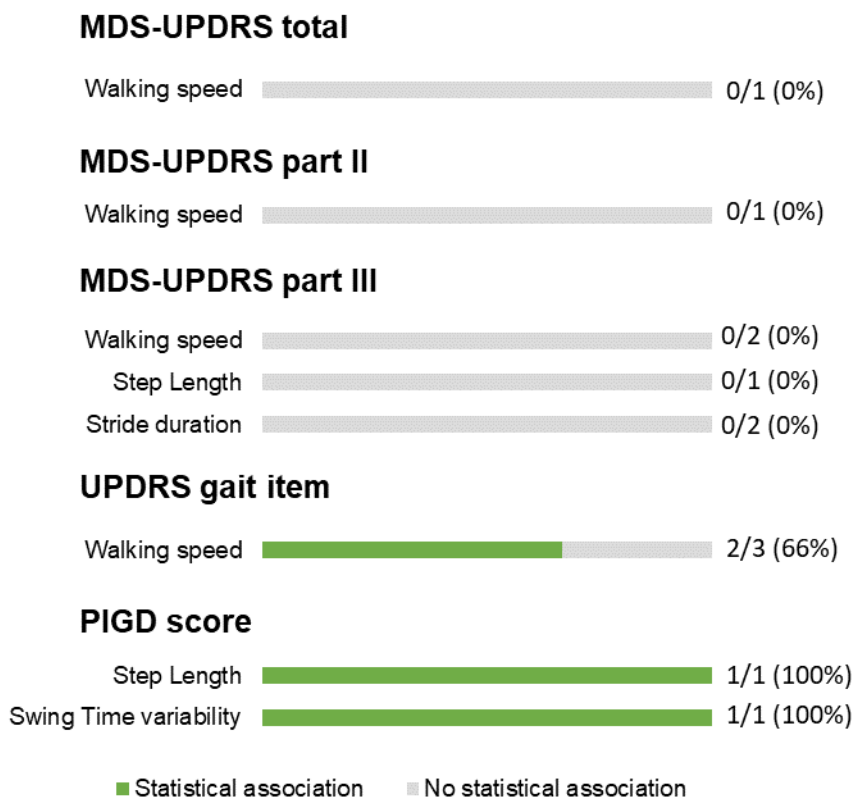


Figure 2-7. Convergent validity: number and proportion of studies reporting statistical associations or no statistical association between digital mobility outcomes and Parkinson's clinical scales.

2.3.5 Predictive capacity

No studies explored the predictive capacity of real-world DMOs.

2.3.6 Quality assessment

Overall, the quality of studies was moderate [median = 11, IQR = 9, Range = 8:13]

2.4 Discussion

The overarching aim of this review was to map the existing evidence exploring the construct validity of real-world DMOs. From 3518 articles identified from the initial search, only 17 articles were eligible for data extraction. This is substantially fewer than the 307 articles identified in a similar review of only supervised-based DMOs (Polhemus et al., 2021). Real-world mobility monitoring is technically challenging because algorithm performance may differ across WB duration and is also influenced by various contextual factors such as terrain (Kowalsky et al., 2021), weather (Kim and Brown, 2022), and specific types of environments (Del Din et al., 2016a; Mazzà et al., 2021; Shah et al., 2020a). Furthermore, there was no common consensus about how to contextualise RWS, as differences in which WB duration thresholds to apply to

estimate DMOs from was observed, which limits comparison. Seven articles (40%) recorded data for less than three days, where it has previously been demonstrated that more than three days of assessment is necessary to obtain reliable data (Czech et al., 2020). In terms of sensor location and number, less than half of the included studies (n = 6, 35%) positioned a single wearable device on the lower back, which has been shown to provide reliable measurements, whilst also accounting for the usability needs of the participant (Del Din et al., 2016b; Keogh et al., 2023; Soltani et al., 2021). The lack of literature, combined with methodological heterogeneity identifies the need for a common consensus and robust technical validation that maximises the accuracy, reliability, and validity of real-world DMOs.

2.4.1 Are DMOs different between context of assessment?

The majority of studies reported that DMOs were significantly different between supervised and real-world assessments (Atrsaei et al., 2021; Corrà et al., 2021; Del Din et al., 2016a; Shah et al., 2020c; Toosizadeh et al., 2015). For a DMO to be considered ecologically valid, it must be demonstrated that it's measurement can be generalized to real-world environments. The difference between supervised and real-world assessments of mobility have previously been well described (see - 1.2.2 to 1.2.3). *S*upervised assessment provides insight into an individual's *mobility capacity* under optimal conditions, where real-world assessment provides insight into *mobility performance* (Rochester et al., 2020; Viceconti et al., 2022). The current assessment of PD mobility typically only includes an assessment of capacity, which is then generalised to their real-world performance. However, these findings further strengthen the argument that real-world and supervised mobility is different, thus supporting the inclusion of real-world data, to capture information not captured by existing clinical assessment.

Real-world environments posed more of a challenge to mobility (see – 1.2.3), which is reflected by the majority of DMOs being lower when assessed in the real-world (Atrsaei et al., 2021; Del Din et al., 2016a; Shah et al., 2020c; Toosizadeh et al., 2015). One study however reported no difference in stride length between assessment settings (Shah et al., 2020c). This was surprising given that step/stride length is a gait disturbance that has been consistently associated with PD in both supervised and real-world settings (Del Din et al., 2016a; Zanardi et al., 2021). Despite finding no difference in stride length, Shah et al., 2020c, found that walking speed was significantly slower in the real-world, this suggests that in their cohort participants modulated their real-

world mobility through adaptation of their overall walking speed, rather than underlying gait.

Corrà et al., 2021, explored the influence of medication state upon the ecological validity of walking speed. Despite finding no association between the mean value of walking speed, they did find associations between supervised and real-world walking speeds when the participant was ON-medication and when RWS was estimated from the upper, percentiles in its distribution, representing its fastest real-world speeds. This demonstrates the context of which it's possible for an individual to achieve their capacity in the real-world. These associations may not have been found if walking speed was summarised with the mean value and demonstrate that real-world DMOs reflect different aspects of mobility, dependent upon the region of the distribution they are extracted from.

Real-world DMOs are more complex, and condensing of DMOs into singular values (mean, median etc.,) may exclude potentially clinically important patterns that exist inside the datasets. Atrsaei et al., 2021 included a novel method of summarising walking speed based upon different regions, or modes, within its distribution. They found only the median walking speed estimated from the individuals 'fastest' or 'highest' mode reflected their supervised-walking speed. Furthermore, they demonstrated a link between a slower 'lowest' mode, with an increased number of levodopa intakes. However, they only collected data across one day, and the sample size was small (n = 27), and motor symptom severity was low (MDS-UPDRS III = 25). Furthermore, they fitted the same bi-modal distribution to all participants, which assumes each individual had the same number of modes. Further findings in a larger cohort, that have been assessed across a larger number of days in the real-world is required to confirm these findings. However, this is promising and demonstrates how novel methods of statistical summary can provide an objective measure of the impact of fluctuations in symptoms and medication state upon real-world mobility, which cannot easily be replicated in a supervised setting.

2.4.2 Do DMOs discriminate between PD and OAs?

Within the real-world studies, the majority of DMOs were significantly different between PD and OA participants (Del Din et al., 2019, 2016a; Shah et al., 2020d, 2020d, 2020b; Toosizadeh et al., 2015). PD participants were largely in the early stages and mild to moderate in their motor symptom severity (MDS-UPDRS III across all studies mean = 32.95, range = (28.63, 34.69). This demonstrates how real-world DMOs are sensitive

to detecting real-world mobility impairments in PD. Despite walking speed being the most widely studied DMO, reduced step length and increased step length variability were more consistently identified as significantly different between groups. A slower walking speed is seen as age increases (Wilson et al., 2020; Zanardi et al., 2021), whereas reduced step length was more typically associated with PD (Morris et al., 1996; Zanardi et al., 2021). One study found step length asymmetry was significantly larger in PD compared to OAs (Del Din et al., 2016a), which is not surprising, given that an asymmetrical walking pattern has typically been observed in PD (Del Din et al., 2016a), where gait asymmetry maybe related to asymmetric neural degeneration within the basal ganglia (Peterson and Horak, 2016). However, in that study differences in DMOs were largely dependent upon the real-world context, or WB duration, that the DMO was estimated from.

Real-world walking is comprised of various WBs, which may reflect different activities dependent upon the WB duration threshold that DMO is estimated from (see – 1.4.3). Del Din et al., 2016a, was the only study to explore the influence of WB duration upon differences in DMOs between PD and OAs. They found no group differences, when the DMO was estimated from very short WBs (< 10 seconds). Activity within very short WBs < 10 seconds is noisy and is does not contain activities that directly relate to gait (Micó-Amigo et al., 2023). In contrast, they found that DMOs from the pace domain were lower in PD in comparison to OAs as the WB duration increased. Differences in rhythm (step, swing, and stance times), and asymmetry were only present in medium length WBs. While measurement of environment is not typically included in real-world protocols, it is inferred that short WBs take place within the home environment, in contrast to long WBs (> 60 seconds), that could likely only be accommodated within open outdoor spaces, encapsulated steady state gait, where fastest walking speeds may be achieved. DMOs estimated from these faster WBs, may reflect closer to an individual's mobility capacity, which is already assessed within a supervised setting. In contrast, short to medium length WBs may contain a larger proportion of essential activities of daily living, which provide a more functionally relevant mobility insight, reflecting an individual's real-world mobility performance. This work demonstrates why real-world contexts are critical to interpretation of real-world mobility.

Three studies explored whether differences between PD and OAs in DMOs were greater in the real-world, in comparison to supervised settings (Del Din et al., 2016a; Shah et al., 2020c; Toosizadeh et al., 2015). Differences in walking speed were similar

when assessed in either real-world or supervised settings (33% of analyses reporting significant differences); one study found group differences in walking speed only existed in supervised assessment (Toosizadeh et al., 2015). However, they only assessed gait over 24 hours (Buckley et al., 2020) and did not aggregate walking speed within WB thresholds. In contrast to walking speed, some aspects of step length discriminated between people with PD and controls more consistently in the real-world rather than supervised settings, where differences in step length asymmetry were only present in the real-world (Del Din et al., 2016a). Due to the more challenging nature of real-world environments (navigation of furniture, obstacles, human traffic etc.,), this would've propagated to a more asymmetrical walking pattern in PD, as they are unable to regulate their real-world gait to account for environmental challenges as well as OAs. These findings further support the need for ecological valid DMOs to be applied as mobility outcomes to provide a more complete insight.

2.4.3 Do DMOs discriminate between clinical groups in PD?

Seven analyses explored whether DMOs can stratify differences between freezers, fall status and Hoehn and Yahr stage (Del Din et al., 2019; Mancini et al., 2021; Terashi et al., 2013; Weiss et al., 2015, 2014). Lower walking speed and stride length, and increased walking speed variability were consistently able to distinguish fall status in PD (Del Din et al., 2019; Weiss et al., 2014). However, no difference in walking speed and step time were found between individuals with and without freezing of gait symptoms (Mancini et al., 2021; Weiss et al., 2015). Gait freezing is speculated to be contextually sensitive (Nieuwboer et al., 2009), and may typically occur during shorter periods of walking undertaken in more confined home-based environments, which involve sharp turns (Mancini et al., 2018). Both studies exploring DMOs in individuals with FOG symptoms, did not aggregate based upon WB duration. HY stage measures functional disability and is scored from 0 (unilateral involvement only usually with minimal or no functional disability) to 5 (confinement to a wheelchair). A slower walking speed and increased stride duration were associated with a larger HY stage (Terashi et al., 2013; Toosizadeh et al., 2015), demonstrating how real-world mobility impairments correspond to clinicians rating of progression in functional disability.

2.4.4 Do DMOs relate to clinical measurements of PD severity?

In comparison to the other RQs, there was a limited number of analyses that explored the convergent validity of real-world DMOs with traditional clinical scales (n=17). The most widely explored relationship was with the MDS-UPDRS III (number of analyses

= 5), however no relationship with any DMO and total score was identified. The MDS-UPDRS III is a large composite score, which despite including a gait item in its assessment, is also comprised of many upper and lower body items not directly related to gait. The PIGD score (J. Jankovic, 1990) was calculated from the gait-related items of the MDS-UPDRS III, where Shah et al., 2020d found stride length to be associated with PIGD score. This is logical given than during the gait-item of the MDS-UPDRS III raters are advised to observe step/stride lengths specifically (Goetz et al., 2008).

Corrà et al., 2021, explored whether walking speed was related to only the gait item of the MDS-UPDRS III. Despite finding no association with the mean walking speed, they did find associations with the MDS-UPDRS III gait item from the 90^{th} percentile of walking speed when ON medication, and the 25^{th} percentile of walking speed when OFF medication. The MDS-UPDRS III, is a capacity measure so an association with the 90^{th} of RWS assessed in an optimal medication state (ON) (representing real-world capacity), is not surprising. When mobility was assessed in an OFF state, they observed associations with the lowest percentiles of RWS with the MDS-UPDRS III-gait item (also assessed in OFF). This demonstrates how only the lowest real-world mobility was related to lowest measurements in a capacity setting. However, they didn't include WBs < 15 seconds, which potentially excluded the slowest real-world WBs. No study had systematically explored whether estimation of DMOs within each WB duration threshold, influences its convergent validity, this makes for an essential next study.

2.4.5 Are DMOs able to predict clinically important outcomes?

It was not possible to identify any studies which explored whether DMOs were able to predict clinical important outcomes (such as falls risk, motor severity, hospitalization etc.,). This finding was expected given that a similar previous review identified limited evidence exploring the predictive capacity of supervised DMOs (Polhemus et al., 2021), and given that there is a limited number of longitudinal studies with wearable data. A lack of evidence may stem from several technical challenges that need to be addressed, which limits the confidence of researchers to collect longitudinal data. Furthermore, there is a limited consensus on what the best statistical approach toward modelling complex interplay between real-world DMOs and clinical outcomes. In order to understand whether DMOs can predict important clinical outcomes, such as motor disease progression or falls risk, this is an essential gap that must be addressed in the literature (Polhemus et al., 2021; Rochester et al., 2020; Viceconti et al., 2020).

2.5 Limitations

A large number of articles from a comprehensive search strategy were identified, which following a rigorous screening process reduced the data for extraction to just 17 articles. Despite only including spatial-temporal DMOs in the eligibility criteria, there several studies that explored the clinical utility of DMOs at a macro level only, which would've increased the number of studies and scope of the review. Additionally, DMOs related to turning were not included, which may have had stronger clinical relationships particularly in the instance of Shah, et al. 2020 and Mancini, et al. 2021, who both found strongest relationships with freezing of gait symptoms with turning measures. More complex DMOs based upon machine learning, deep learning and signals processing paradigms have been quantified using real-world data (spectral density, signal magnitude, signal regularity, single complexity) (Coates et al., 2020; Rehman et al., 2020), and explored with respect to their clinical validity. Although not included within this review, perhaps a future research direction in PD, could be whether more complex DMOs have stronger clinical validity than spatial-temporal DMOs. However, spatial-temporal DMOs are advantageous when considering interpretability to clinicians and patients. The body of real-world literature will rapidly expand over the next few years so it's vital for similar reviews as the present study to be updated.

2.6 Conclusions

Overall, this review identified that there was limited evidence to support the clinical validity of real-world DMOs and therefore understand their potential utility to inform research and clinical practice. This was particularly true for predictive capacity, where no evidence was identified, which highlights the need for collection and analysis of longitudinal real-world datasets. Some differences in DMOs were dependent upon the environment they were assessed within, which highlights the importance of including real-world measurements to ensure DMOs are ecological valid. Real-world environments are complex and variable, and a more granular approach to understanding real-world data would be to explore how specific types of environments (indoor or outdoor) influence the aspect of mobility that is being assessed by RWS. Strongest findings were observed with studies that aggregated DMOs within specific WB durations or that used novel summary statistics based upon extreme values in the distribution.

Chapter 3. General methods

This chapter provides an overview of the general methods within this thesis, including detailed descriptions of the two datasets of participants included in this thesis; Incidence of Cognitive Impairment with Longitudinal Evaluation – GAIT (ICICLE-GAIT) study and Mobilise-D Technical Validation Study (TVS). In the original thesis proposal submitted to the University during my first year, it was intended to include the TVS dataset only. However, due to impact of the COVID-19 pandemic the availability of the TVS dataset was extensively delayed, so permission was granted to include participants from the ICICLE-GAIT study to continue progression of this thesis whilst awaiting availability of the TVS data. As such, the analysis of ***Chapters 4 & 7*** was conducted with ICICLE-GAIT and ***Chapter 5 & 6*** with the TVS-dataset. I was not involved with the data collection process of ICICLE-GAIT, as the study took place prior to the start of my PhD. For Mobilise-D, I trained to assist in the face-to-face data collection, however due to COVID-19, there was a need to limit footfall in the laboratory, as such I did not have a role in data collection.

3.1 ICICLE Dataset

Participants were recruited from the ICICLE-GAIT study (Del Din et al., 2016a; Rochester et al., 2014; Wilson et al., 2020; Yarnall et al., 2014). The main objective of ICICLE-GAIT was to examine the utility of gait, as a surrogate marker of cognitive decline and falls in early PD. Recruitment took place between June 2009 and December 2011. Participants were diagnosed with idiopathic PD according to the UK Parkinson's Disease Brain Bank criteria (Hughes, 1992) by a movement disorders specialist and diagnosis was confirmed at each follow-up visit. Baseline exclusion criteria comprised: significant memory impairment (Mini-Mental State Exam (MMSE) <24) or a diagnosis of Parkinson's disease dementia (Emre et al., 2007); dementia with Lewy bodies; drug-induced parkinsonism; ''vascular'' parkinsonism; atypical parkinsonian disorders; poor command of English; or presence of any neurological (other than idiopathic PD), orthopaedic, or cardiovascular conditions that severely impacted mobility. OAs had to be at least 60 years of age, walk independently without a walking aid and have no substantial cognitive impairment, mood or movement disorder. Participants underwent clinical and real-world assessment at 18-, 36-, 54- and 72-months following baseline assessment. Across all time points, 88 individual PD participants, from a total of 120 and 111 people from 184 OAs for whom data was

available were included. ICICLE-GAIT was undertaken in accordance with the Declaration of Helsinki and was granted ethical approval from the Newcastle and North Tyneside Research Ethics Committee (Ref: 09/H0906/82). All participants provided written informed consent prior to assessment.

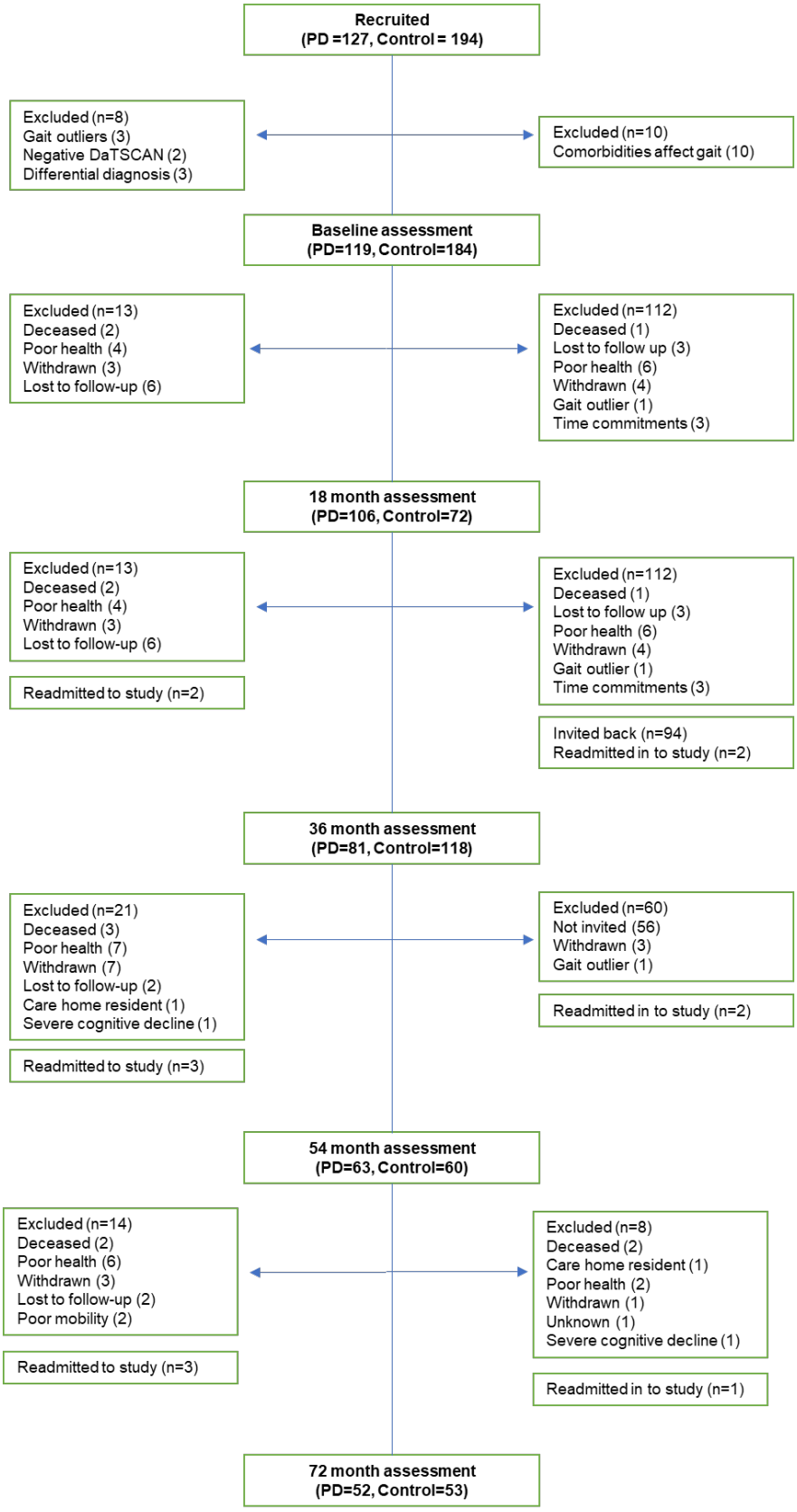


Figure 3-1. Recruitment and deviation diagram for the ICICLE-GAIT study

3.2 Demographical and clinical measures

Participants underwent clinical and real-world assessment at baseline, 18-, 36-, 54- and 72-months following baseline assessment. For clinical and demographic assessment, participants were tested 'ON' medication, defined as within hour after PD medication. Participants were assessed with the MDS-UPDRS (Goetz et al., 2008) (score min to max 0-199). The MDS-UPDRS III consists of four parts, however only MDS-UPDRS part II and part III were investigated in this thesis, and the majority of ICICLE. MDS-UPDRS II assesses motor experiences of daily living (score min to max 0-52), where MDS-UPDRS III assesses motor symptom severity (score min to max 0-108), alongside the Hoehn and Yahr stage (0-5). Incidence of gait-freezing was assessed with the New Freezing of Gait Questionnaire (NFOG) (Hulzinga et al., 2020) (score min to max 0-25), and Levodopa Equivalent Daily Dosage (LEDD) was calculated in accordance with previously defined methods (Tomlinson et al., 2010).

3.3 Real-world gait assessment protocol

Participants were asked to wear a wearable sensor (Axivity AX3, York, UK) (23.0×32.5×7.6 mm; weight: 11 grams, data collected at 100 Hz, range ± 8 g). The sensor was attached over the fifth lumbar vertebra (L5) with a hydrogel adhesive (PALStickies, PAL Technologies, Glasgow, UK) and covered with Hypafix™ bandage upon their lower back. They were subsequently monitored during their everyday activities for 7-continuous day and were asked to continue their normal routine. After seven days, participants removed the device and posted it back to the researcher (Del Din et al., 2016a).

3.4 Data processing & DMO estimation

All *macro* and *micro* level DMOs, were processed from the tri-axial raw accelerometer data, using bespoke validated algorithms implemented in MATLAB® R2018a (Mathworks, California, United States) (Del Din et al., 2016b; Hickey et al., 2016).

3.5 Walking bout detection (Macro)

First, periods of walking were segmented from non-walking. The detection and segmentation algorithm employed a logical heuristics paradigm, as defined in a previous work (Hickey et al., 2016). Periods of upright signal were analysed by a

moving window, based upon the combined SD of accelerations and mean of vertical acceleration. A conservative approach was adopted and used a threshold of three steps (minimum bout length) to define a WB with a minimum resting period of 2.5 s between bouts (Del Din et al., 2016b). The algorithm was validated and demonstrated excellent relative and absolute agreement with gold standard (wearable camera) (Hickey et al., 2016). Pattern of ambulatory behaviour was assessed through estimation of Alpha and Variability.

- Alpha is defined as the distribution of WBs, a lower alpha indicates that a greater proportion of the individuals Macro activity is derived from longer WBs (Lord et al., 2013c). Alpha has been previously defined in PD and OA participants (Chastin et al., 2010; Lord et al., 2011b).
- Variability is defined as the within participant variability in WB duration (Lord et al., 2013c). Variability is calculated from maximum likelihood estimation, as distribution of bout length is log normally distributed (Rochester et al., 2012). A higher variability score indicates a more varied pattern of walking.

3.6 RWS estimation (Micro)

The accelerometer data was transformed into a horizontal-vertical coordinate system and filtered with a fourth-order Butterworth filter at 20 Hz. First, the algorithm estimated Initial contact (IC) and final contact (FC) gait events from a continuous wavelet transformation (CWT). The IC were detected as the local minima of the CWT. A further differentiation with the Gaussian CWT resulted in the local maxima being defined as the FC events. IC and FC events were then used to estimate step, stride, stance, and swing times. To estimate step length, the algorithm adopted the inverted pendulum model, as described in a previous work (Zijlstra and Hof, 2003). Where h refers to the change in height of the device, derived using the double integration of the vertical acceleration signal and l is the pendulum length (height of the sensor from the ground).

$$Step\ Length = 2\sqrt{2lh - h^2}$$

Walking speed was estimated as the ratio of step length to step time:

Walking speed = Step length / step time

This algorithm was validated in a previous work, with excellent relative and absolute agreement when compared to a gold-standard instrumented walkway (Del Din et al., 2016b). This method was applied to estimate the mean, variability (SD of steps) and

asymmetry ($Average_{Left}$ – $Average_{Right}$), of all 15 DMOs from each domain in the conceptual model of gait (Figure 1-1D)

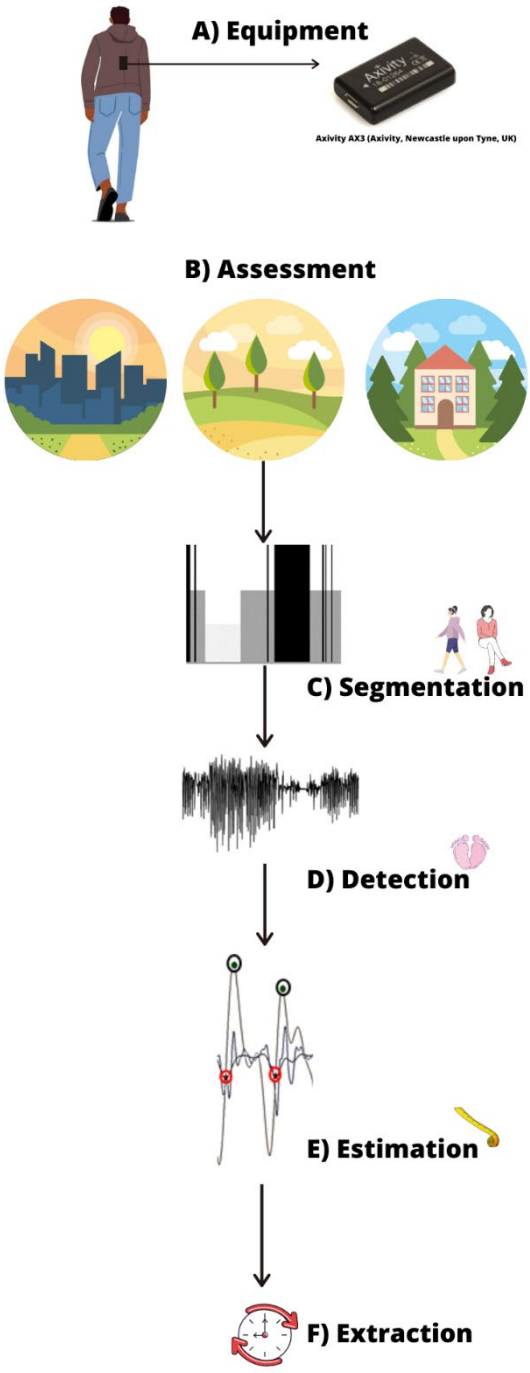


Figure 3-2. Protocol and data extraction for real-world gait assessment. A) Axivity AX3 sensor is attached to the lower back with a hydrogel adhesive (PALStickies, PAL Technologies, Glasgow, UK) and covered with Hypafix™ bandage. B) Participant continues their normal weekly activities, whilst the device monitors their mobility over seven-consecutive days. C) Segment periods of walking from non-walking (Hickey et al., 2016). D) Detection of initial contact gait events within WBs (Del Din et al., 2016b).

E) Estimation of step length based upon the inverted pendulum model (Zijlstra and Hof, 2003). F) Extraction of real-world walking speed and battery of digital mobility outcomes.

3.7 Mobilise-D technical validation study dataset

The Mobilise-D TVS, was cross-sectional study, conducted as the first phase of the Mobilise-D project (Mazzà et al., 2021; Rochester et al., 2020). Mobilise-D is a public-private partnership, that represents the combined efforts of 34 global academic and industrial research partners, aiming to deliver a solution for the remote digital assessment of mobility (Rochester et al., 2020). This thesis only includes data from the TVS, as it was the only data that became available during my PhD studentship. The primary objective of the TVS was to produce and extensively validate a single-sensor algorithm combination in its ability to estimate DMOs across a variety of cohorts and environments, before establishing participants and assessors' opinions on the usability and acceptability of the devices (Mazzà et al., 2021). Recruitment took place between August 2020 and December 2021 where the consortium targeting a convenience sample of 20 participants to be recruited from each of the cohorts defined in Section 3.2. This thesis includes only the PD and OAs cohorts. inclusion and exclusion criteria is defined below (Table 3-1).

Table 3-1. Inclusion and exclusion criteria for the Parkinson's and older adult cohorts of Mobilise-D.

Group	Inclusion criteria	Exclusion criteria
Both groups	• Able to walk 4 metres independently with or without walking aids • Able to give informed consent • Willingness to wear the sensor setups during the study • Shoe size 36 EU (3 UK), or above • Able to read and write in first language of the respective country • Montreal Cognitive Assessment score > 15 (Nasreddine et al., 2005) • Available for home / office visit during study period	• Occurrence of any of the following 3 months prior to inclusion: myocardial infarction, hospitalisation for unstable angina, stroke, coronary artery bypass graft, percutaneous coronary intervention, implantation of a cardiac resynchronisation therapy device • Current medical condition that could interfere with the patient's compliance
PD	• Aged 18+ years • Diagnosis of PD according to the Movement Disorders Society criteria (Postuma et al., 2015)	• Impaired mobility related to non-PD causes as judged by the investigator
OA	• Aged 65+ years	

Twenty PD and 20 OA participants were recruited across four sites: Tel Aviv Sourasky Medical Centre, Israel (ethics approval granted by the Helsinki Committee, Tel Aviv Sourasky Medical Centre, Tel Aviv, Israel, 0551-19TLV), Robert Bosch Foundation for Medical Research, Germany (ethics approval granted by the ethical committee of the medical faculty of The University of Tübingen, 647/2019BO2), University of Kiel, Germany (ethics approval granted by the ethical committee of the medical faculty of Kiel University, D438/18) and The Newcastle upon Tyne Hospitals NHS Foundation Trust, UK (ethics approval granted by London—Bloomsbury Research Ethics committee, 19/LO/1507). As per the study register (ISRCTN, 12246987). The study commenced in April 2020, however due to COVID-19 the study began in August 2020 and concluded in April 2022.

3.8 Demographic and clinical measures

All the demographic and clinical variables assessed within participants of the TVS can be viewed in Table 3-2.

Table 3-2. Demographic and clinical information assessed within the TVS.

Category	Variable
Descriptive	• Age • Sex • Living arrangements • Education
Anthropometric	• Height • Mass • Shoe size • Waist width
Clinical status	• Comorbidities • Number of falls and injuries in the 12 months prior to assessment • Walking aid usage • Current medication • Montreal Cognitive Assessment (Nasreddine et al., 2005) (score min to max 0-30) • Visual Analogue Scale (Campbell and Lewis, 1990) (score min to max 0-100) • Late-Life Function and Disability instrument (Jette et al., 2002) (score min to max 0-100).
Motor disease severity	• MDS-UPDRS III (Goetz et al., 2008), (score min to max 0-108)

MDS-UPDRS III: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part III

3.9 Protocol

Participants were assessed in the laboratory and the real-world. Mobility data was collected with a wearable device (McRoberts Dynaport MM+) (sampling frequency 100 Hz, triaxial acceleration range: ±8 g / resolution: 1 mg, triaxial gyroscope range: ±2000 degrees per second (dps)/ resolution: 70 mdps), secured to their lower back with a Velcro belt.

3.9.1 Laboratory protocol

Participants were asked to complete seven tasks with increasing complexity: straight walking, timed up and go, L-test, surface test, hallway test and simulated daily activities. Each task was designed to assess various elements associated with real-world walking including a range of walking speeds, incline/steps, surface, path shape, turns and specific motor tasks to simulate of typical real-world transitions (Mazzà et al., 2021; Scott et al., 2022).

3.9.2 Real-world protocol

The participants were equipped the wearable device and asked to carry a Samsung Galaxy S9 (Samsung, Seoul, South Korea) smartphone, with the AEQORA application (Ciravegna et al., 2019) installed, which enables the measurement of contextual confounding factors that are defined below. Participants were instructed to go about their normal activities and asked to always wear the DynaPort MM+, excluding during water-based activities, continuously over seven days.

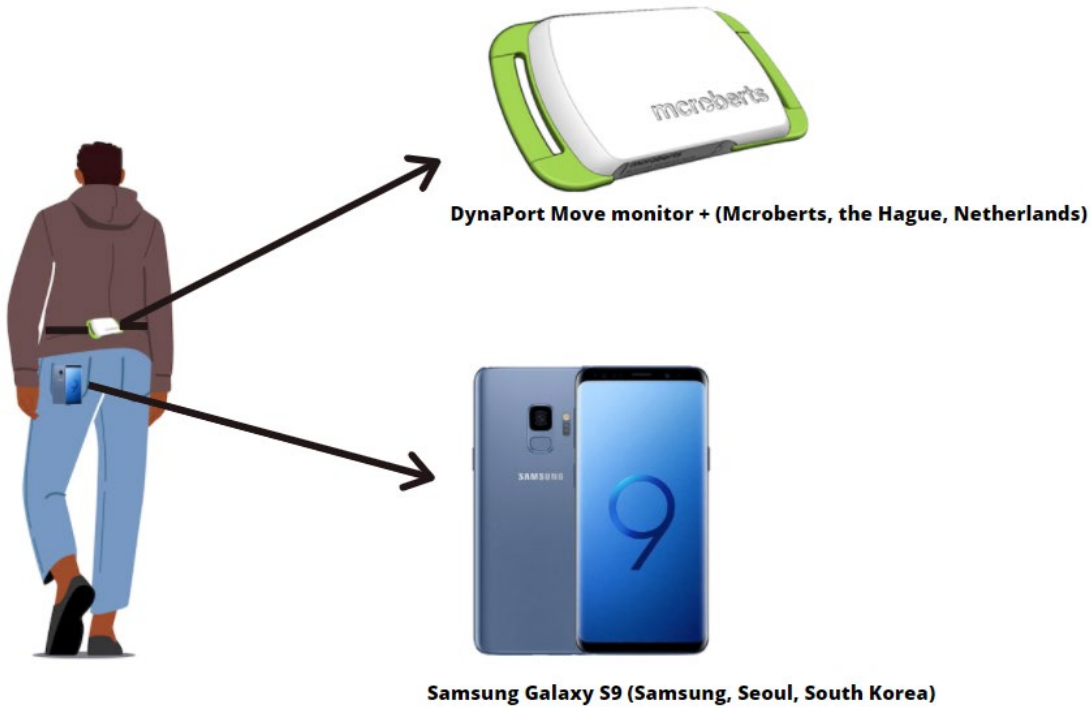


Figure 3-3. Equipment worn by the participant to assess mobility during the real-world gait protocol.

3.10 Data processing & DMO estimation

3.10.1 Algorithm selection (pre-technical validation study)

The pre-technical validation study (pre-TVS) was conducted prior to the TVS with the purpose of identifying, optimising, and comparing the performance of many algorithms for each block of the processing pipeline (Figure 3-4). Initially, researchers conducted an extensive review of the literature to identify algorithms that have been applied to extract gait features from a single device. These algorithms underwent optimisation and development in accordance with definitions identified from a consensus-based framework for digital mobility monitoring (Kluge et al., 2021), in software packages such as MATLAB® (Mathworks, California, United States) and Python® (Python Software Foundation, Delaware, USA). All of the algorithms were uploaded onto a GitLab repository, before packaging to be run on the e-Science Central platform (e-SC) (Hiden et al., 2013).

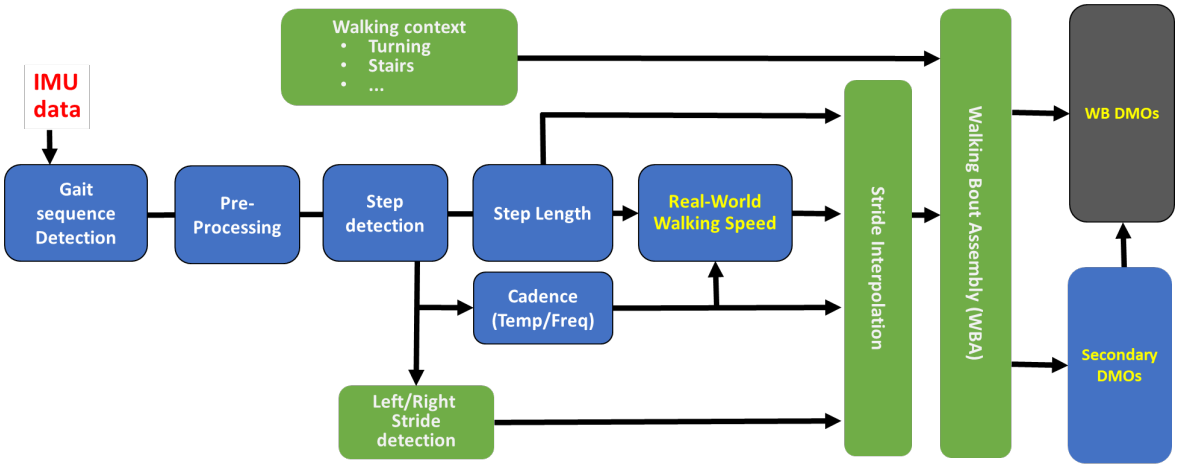


Figure 3-4. The Mobilise-D pipeline for digital mobility outcome estimation.

Due to the complexity and size of the data required in the Mobilise-D project, the e-SC platform was employed (Hiden et al., 2013), to avoid high computational cost, and delayed processing times caused by data-processing by individual researchers, and allow storage of large datasets. e-SC is a cloud-based application, which enables the processing and manipulation of data through an in-browser window editor, providing users with the ability to build workflows by dragging services and connecting them. Algorithms were packaged onto the e-SC platform from GitLab utilising Docker Containers, which enables to code from MATLAB or Python to run in a separated environment (comprising a docker container), in the same workflow. Thus, all of the

algorithms to be evaluated within a specific block of the processing pipeline can be processed en-masse with a single click (Figure 3-5).

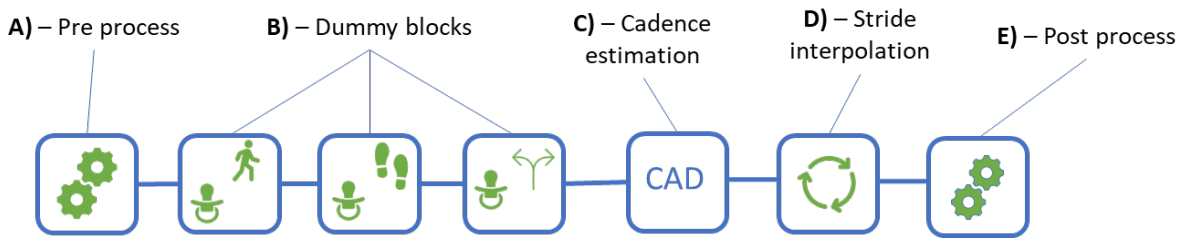


Figure 3-5. Graphical representation of the Cadence workflow, the input data was the raw inertial measurement unit data, which was passed through the following steps: A) Pre-process; extracts naming and time-zone information. B) Dummy blocks; applies the same 'dummy' algorithm from the gold standard in either laboratory or free-living conditions, to estimate fake/dummy outputs needed for individual evaluation of each cadence block. Dummy algorithms for cadence estimation include gait sequence detection, stride detection, and left right estimation. C) Cadence estimation; can select any of the 20 cadence algorithms under evaluation, which can be combined within the same workflow (Figure 3-9). D) Stride interpolation; defines output files on a per second and per stride level. E) Post process; ensures correct naming and saving of each results file.

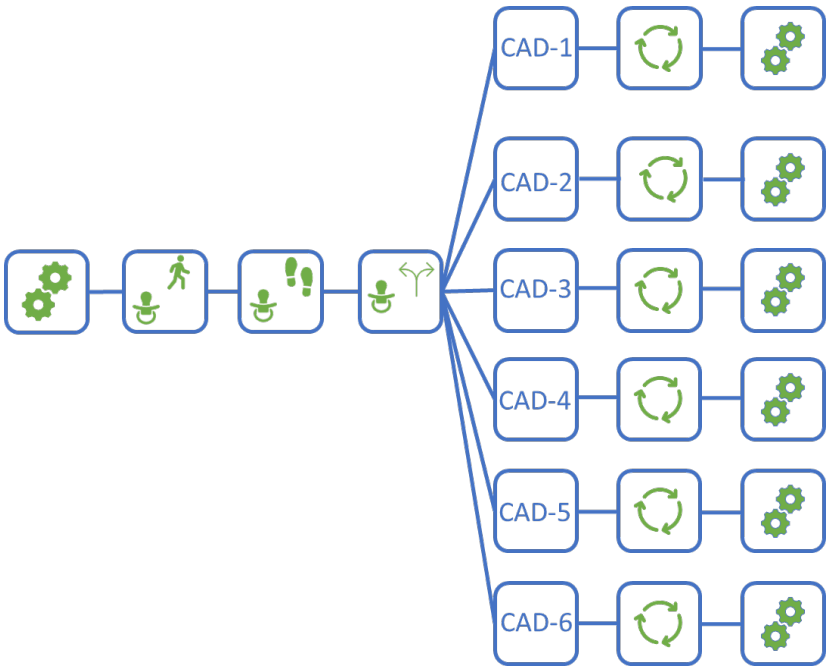


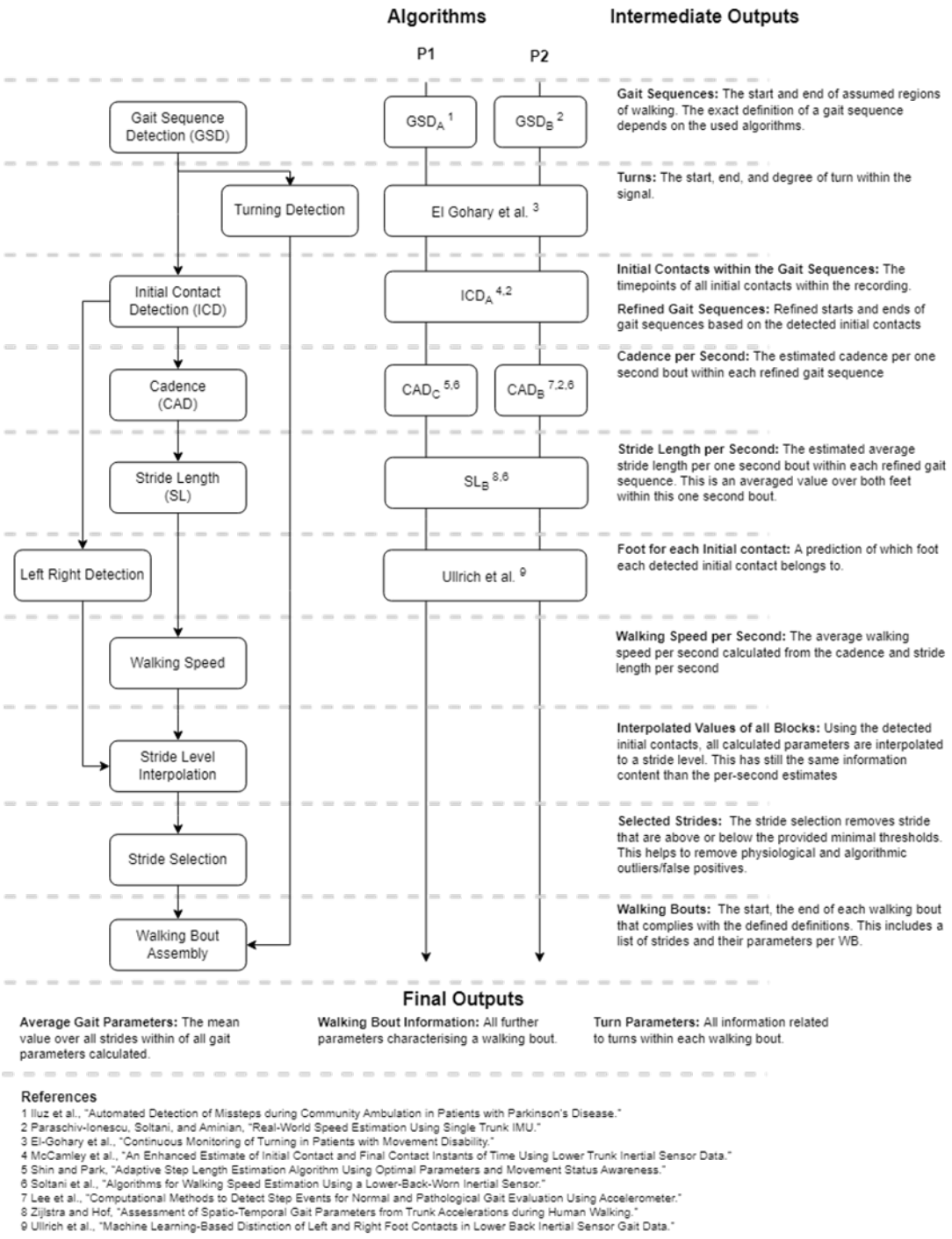
Figure 3-6. Example cadence workflow, containing six of the 20 cadence algorithms, for graphical representation.

In the pre-TVS, algorithms was concurrently validated, as defined by Bonci et al., 2020. This validation was performed upon previously existing dataset that were provided by consortium partners and stored upon the e-SC platform. The best performing algorithms upon these datasets underwent further optimisation, before undergoing validation upon the data collected from the TVS protocol.

3.10.2 Algorithm selection (Technical validation study)

Algorithms were ranked based upon their performance upon TVS dataset, where the best performing algorithm for each block of the DMO pipeline (Micó-Amigo et al., 2023) was identified (Figure 3-7). As algorithms were applied upon the data of the PD and OA cohorts separately, both cohorts differed in their best ranked algorithm for GSD and cadence blocks. As a result, two pipelines; *P1* and *P2* were created for OA and PD cohorts respectively, below the technical description of each block of the DMO pipeline is detailed (Figure 3-7). The pipelines to estimate RWS have been extensively validated by Kirk et al., 2023b. For all types of evaluations various statistical/comparison measures were evaluated to quantify the walking speed estimation error for the sensitivity analysis:

- Intra Class Correlation Coefficient ($ICC_{(2,1)}$) was calculated to assess the association between the DMOs of the two systems. Based on ICC estimates, values < 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and > 0.90 were deemed to be indicative of poor, moderate, good, and excellent reliability, respectively.
- Absolute agreement was assessed by quantifying (i) the accuracy/mean absolute error (MAE), (ii) bias/mean error and (iii) precision/limits of agreements (LoA) between walking speed estimates of both systems.
- Mean relative errors (MRE) and mean absolute relative error (MARE) were estimated as the ratio between the (absolute) errors per WB and the corresponding estimates from the reference system, expressed as a percentage.



References
1 Iluz et al., "Automated Detection of Missteps during Community Ambulation in Patients with Parkinson's Disease."
2 Paraschiv-Ionescu, Soltani, and Aminian, "Real-World Speed Estimation Using Single Trunk IMU."
3 El-Gohary et al., "Continuous Monitoring of Turning in Patients with Movement Disability."
4 McCamley et al., "An Enhanced Estimate of Initial Contact and Final Contact Instants of Time Using Lower Trunk Inertial Sensor Data."
5 Shin and Park, "Adaptive Step Length Estimation Algorithm Using Optimal Parameters and Movement Status Awareness."
6 Soltani et al., "Algorithms for Walking Speed Estimation Using a Lower-Back-Worn Inertial Sensor."
7 Lee et al., "Computational Methods to Detect Step Events for Normal and Pathological Gait Evaluation Using Accelerometer."
8 Zijlstra and Hof, "Assessment of Spatio-Temporal Gait Parameters from Trunk Accelerations during Human Walking."
9 Ullrich et al., "Machine Learning-Based Distinction of Left and Right Foot Contacts in Lower Back Inertial Sensor Gait Data."

Figure 3-7. Overview over the different algorithmic steps of the gait analysis pipeline with short explanations of the intermediate and final outputs of each of the algorithmic blocks. The algorithm column in indicates the used algorithms for the two pipelines P1 (PD) and P2 (OA). Algorithms include, gait sequence detection (GSD), turning detection, initial contact detection (ICD), cadence estimation (CAD) and stride length estimation (SL). Short citations for the algorithms are provided below the figure. For more details see Kirk et al., 2023b.

3.10.3 Indoor or outdoor estimation

GPS data needed to estimate the contextual factors under assessment in the TVS were captured from the AEQORA application installed on the Smart Phones that participants were asked to wear during the real-world protocol of the TVS (Ciravegna et al., 2019). The only contextual factor investigated in this thesis, was whether the participant was indoor or outdoor, which was estimated from staypoint information. A staypoint is defined as a location where a participant spends a significant amount of time. There are two methods to estimate these locations:

Method (i) If the phone does not attempt to acquire GPS data, it determines that it is stationary. In this period, it can be assumed that the participant is positioned at the last recorded GPS location, however this is prone to error as the participant may not be at last GPS location due to their phone running out of battery, or lost GPS signal.

Method (ii) The second method utilises the proximate consecutive GPS locations to indicate the participant has stopped at a given location. Here, a staypoint is defined by a minimum threshold of time at a given location, where a location is defined by a maximum threshold of distance. Staypoints are then clustered to determine the actual staypoints using HDBSCAN, a density-based clustering algorithm. Location semantics, such as the nearest building or area of land, are derived from the relevant area of the OpenStreetMap (OSM) (https://www.openstreetmap.org), over which the GPS coordinates overlap. The data from OSM are used to identify the land use associated with each staypoint (parks, forests, urban), as well as whether the participant is indoor or outdoor.

3.11 Statistical analysis

Continuous variables were visually inspected for their distribution and outliers through use of histograms, scatterplots, and boxplots. All statistical analysis was completed in R (R Foundation for statistical computing, V4.02, Austria). Other statistical methods will be described as they are applied within the thesis.

Chapter 4. Can real-world walking speed add value to the clinical assessment of disease severity in Parkinson's disease?

In ***Chapter 2***, there was an overall lack of comprehensive studies that have sought to establish what clinically useful information real-world DMOs are able to provide, particularly with longitudinal data and across different WB durations. The main aim of this chapter was to address these gaps and comprehensively explore whether RWS was able to discriminate between groups, sensitive to detecting changes over time, related to motor symptom severity and changes in motor symptom severity. This chapter has been published in the Journal of Parkinson' disease (Kirk et al., 2023a).

4.1 Introduction

DMOs, such as RWS have been proposed as ecologically valid measures of real-world mobility performance. These tools could be used to complement the existing clinical assessment of motor symptom severity in PD (Holden et al., 2018; Morris et al., 2017b), addressing some of the limitations of existing scales (Rochester et al., 2020), such as the MDS-UPDRS III (Goetz et al., 2008). The MDS-UPDRS III is the clinical standard to rate motor severity in PD, however it does have limitations. The assessment is conducted episodically in person, it is time consuming to administer which increases patient and clinician burden and may not reflect the fluctuating nature of PD, as participants are typically assessed 'ON' medication. Interest in remotely monitoring PD using digital tools is increasing to address some of these limitations (see - 1.3.8).

Despite the promise, widespread adoption of real-world gait as a clinical mobility endpoint has not yet reached the clinic or clinical trials. To achieve this, comprehensive clinical validation is required (Del Din et al., 2021; Rochester et al., 2020) to explore what information RWS (or other DMOs) can provide that can complement the existing clinical assessment. This can be achieved through undertaking explorations of the clinical validity of RWS and demonstrate it measures what it's claimed to measure (ie., real-world mobility perfomance), something relevant to the patient, clinician, or health service, and is able to monitor changes in patient characteristics over time. Despite showcasing in ***Chapter 2***, that some studies have demonstrated the clinical validity of real-world DMOs, there was an overall lack of evidence. Furthermore, there was no common consensus on methodological approach, as studies differed in their choice of

device location, number of devices, WB duration and number of days collected, which limits comparison between results. There was also no literature that included analysis of relationships between DMOs and clinical outcomes, longitudinally.

This study aimed to address these gaps and explore whether RWS is sensitive to monitoring the presence and progression of PD, with respect to ageing in general (Wilson et al., 2020). While walking speed is related to motor disease severity in controlled testing (Galperin et al., 2019; Hill et al., 2021; Polhemus et al., 2021; Raccagni et al., 2018; Schlachetzki et al., 2017), the relationship between RWS and MDS-UPDRS III is yet to be explored (Polhemus et al., 2021).

4.1.1 Aims and hypotheses

Aims

- Explore whether RWS corresponds to known group differences in RWS in PD and compare to OAs, cross-sectionally
- Explore whether RWS corresponds to known group differences in changes in RWS in PD and compare to OAs, longitudinally
- Determine the convergent validity between RWS and MDS-UPDRS-III
- Explore the relationship between change in RWS with change in MDS-UPDRS III

Hypotheses

- RWS would be slower in PD across a range of WB durations
- Longitudinally, RWS would reduce more rapidly in PD
- RWS would show a weak to moderate relationship with the MDS-UPDRS III, dependent upon WB duration
- Changes in RWS would not be related to changes in the MDS-UPDRS III.

4.2 Methods

4.2.1 Participants

4.2.2 ICICLE-GAIT

Participants with PD were included from the 18-, 36-, 54- and 72-month time points of the ICICLE-GAIT study, with recruitment and diagnosis as described in **Chapter 3.**

4.2.3 Demographical and clinical measures

Motor symptom severity was evaluated using the MDS-UPDRS part III (0-108) and Hoehn and Yahr (H&Y) stage (0-5). Participants were tested 'ON' medication, defined as within 1 hour after PD medication.

4.2.4 Real-world gait assessment protocol

Participants were monitored during their everyday activities over seven consecutive days at each assessment. Data from the 36-month assessment was chosen for the cross-sectional analysis as it provided the largest sample size (Table 4-1). Longitudinal analysis included data from all time points. Each participant wore a tri-axial device (Axivity AX3, York, UK).

A conservative approach was adopted and used a threshold of three steps (minimum bout length) to define a WB with a minimum resting period of 2.5 seconds between bouts (Del Din et al., 2016b). This approach was selected as the majority of WBs are short, so by adopting no threshold, a larger percentage of WBs were included in this analysis (Del Din et al., 2016a; Hickey et al., 2016). Furthermore, all WBs < 10 seconds from any analysis. This is because activity within these durations does not always reflect gait and previous research has shown that DMOs evaluated in shorter bouts are less accurate (Micó-Amigo et al., 2023) and show less discriminate ability between PD and OAs (Del Din et al., 2016a).

4.2.5 Real-world walking speed estimation

RWS was calculated from the tri-axial raw accelerometer data from both devices using bespoke validated algorithms in MATLAB® R2018a (MathWorks, California, United States) (Del Din et al., 2016a). The accelerometer data was first segmented into WBs as detailed in previous work (Del Din et al., 2016a), where RWS was calculated from step time and step length (Del Din et al., 2016b). RWS was quantified as the weekly mean, where it was first calculated mean RWS within each WB and then calculated the mean RWS from all bouts (Del Din et al., 2016a).

4.2.6 Statistical analysis

The data was analysed using R (R Foundation for statistical computing, V4.02, Austria). The demographic and clinical variables of the ICICLE-GAIT cohort at 36 months were compared to OAs using two-sampled T tests.

4.2.6.1 Does RWS discriminate between PD and OAs?

RWS within each WB duration threshold underwent assessment for normality, utilising Shapiro-Wilkes's testing. Subsequently, either the T-test (parametric), or Wilcoxon-H test (non-parametric) was applied to determine whether the mean RWS at each WB duration, was significantly different between 62 PD participants and 94 OAs (Figure 3-1).

4.2.6.2 Does RWS change differently in PD or OAs?

Mixed effects linear models (MEMs) ('lmer' function in 'lme4' package) (Bates, 2020) were used to investigate change in 186 RWS and MDS-UPDRS III measures in 88 PD participants, and change in 240 RWS measures within 111 OAs that were assessed at consecutive timepoints (ICICLE-GAIT) (Figure 3-1). MEMs allow flexibility when dealing with the missing data and are in accordance with the Food and Drug Administration guidelines for dealing with missing data (Garcia and Marder, 2017). The assessment timepoint, alongside sex and baseline age were included as fixed effects, where HY stage was included as an additional fixed effect for PD, to ensure differences in RWS controlled for motor disability. To establish whether the annual rate of change in RWS, across the study duration, differed between OAs and PD participants a group and time point of assessment interaction term was modelled, alongside sex, and baseline age, also modelling a random intercept for the participant. Performance was assessed by calculating conditional R^2, marginal R^2 and confidence intervals. Conditional R^2 considers the combined explanatory power of both fixed and random effects. Goodness of fit for the models was achieved by reviewing residuals, Q-Q plots with tests of dispersion, distribution and outliers, and residual vs predicted plots.

4.2.7 Is RWS related to clinical measurements of motor severity (MDS-UPDRS-III)?

Bivariate correlations and linear effects models (LEMs) ('lm' function in 'lme4' R package) (Pinheiro, 2020) were applied to investigate the cross-sectional relationship between RWS with MDS-UPDRS III score. In the LEMs, sex and age were included as fixed effects. Model performance was assessed by adjusted R^2 and confidence intervals. Diagnosis of goodness of fit for the LEMs was achieved by reviewing residuals vs fitted, Q-Q, scale location and Cook's distance plots. An outlier was identified in the analysis, through observation of a substantially slower RWS of a participant on a scatter plot. The analysis was replicated with and without the outlier

and it did not impact the findings, so the data was included. Finally, a secondary analysis was performed on discrete thresholds of WB duration in both datasets (10 to 30 seconds, 30 to 60 seconds, > 60 seconds) as defined in previous research (Del Din et al., 2016a; Mc Ardle et al., 2021). The comparison of WB duration, was not adjusted for multiple comparisons, due to the exploratory nature of the analysis.

4.2.8 Are changes in RWS associated with changes in motor severity (MDS-UPDRS III)?

MEMs were applied with data from 88 PD participants to investigate the relationship between change in RWS and change in MDS-UPDRS III score. For the fixed effects, an RWS*assessment time point interaction term was included, alongside RWS, HY stage, sex, and baseline age. A random intercept for the participants was also modelled. Model performance was assessed as per the characterising change in RWS analysis.

4.3 Results

Demographic and clinical data, as well as RWS aggregated across all bouts, are shown in Table 4-1. Clinical and demographic information of the ICICLE-GAIT cohort at 18-, 36-, 54- and 72-months assessment timepoints.

Table 4-1. Clinical and demographic information of the ICICLE-GAIT cohort at 18-, 36-, 54- and 72-months assessment timepoints

	18 months		36 months		54 months		72 months	
Group	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
n	43	51	62	94	59	49	49	43
Age (yrs)	69.1 ± 10.7	70.8 ± 7.1	69.3 ± 9.5	72.5 ± 6.5	**68.8 ± 9.4**	**73.0 ± 7.6**	71.3 ± 9.5	72.8 ± 6.5
Sex (Male / Female, n)	31 / 12	27 / 24	**40 / 22**	**44 / 50**	39 / 20	28 / 24	35 / 14	26 / 17
Height (metres)	1.69 ± 0.88	1.69 ± 0.08	1.69 ± 0.08	1.68 ± 0.09	1.68 ± 0.8	1.70 ± 0.09	1.67 ± 0.09	1.70 ± 0.08
Body Mass (kg)	79 ± 15	81 ± 15	79 ± 17	77 ± 13	76 ± 15	81 ± 13	77 ± 14	84 ± 13
MDS-UPDRS II (points)	11 ± 6	-	13 ± 4	-	14 ± 5	-	16 ± 5	-
MDS-UPDRS III (points)	33 ± 11	-	38 ± 12.4	-	39.1 ± 12.6	-	40.9 ± 13.8	-
Disease duration (years)	7.90 ± 4.69	-	8.77 ± 4.02	-	10.36 ± 4.31	-	12.01 ± 4.5	-
Hoehn and Yahr Stage								
I, n (%)	5 (11%)	-	1 (1%)	-	1 (2%)	-	0 (0%)	-
II, n (%)	40 (85%)	-	57 (90%)	-	51 (86%)	-	35 (70%)	-
III, n (%)	2 (4%)	-	6 (9%)	-	7 (12%)	-	12 (24%)	-
IV, n (%)	0 (0%)	-	0 (0%)	-	0 (0%)	-	3 (6%)	-
NFOG (points)	1.16 ± 4.57		2.17 ± 5.33		1.65 ± 4.73		2.21 ± 5.04	
LEDD (mg/day)	395 ± 206	-	515 ± 256	-	663 ± 294	-	720 ± 312	-

Data presented as mean and standard deviation (SD). Bold highlight indicates significant difference at <0.05 significance level between (i) between PD and OAs at specific time point. '-'describes an empty field, due to data availability. MDS-UPDRS III = Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III. LEDD = Levodopa equivalent daily dosage. Independent data set compared to 36 months ICICLE-GAIT data.

4.3.1 Does RWS discriminate between PD and OAs?

RWS was significantly different between PD and OAs at each time point and WB duration, excluding > 60 seconds at the 54-month time point. For both cohorts the largest number of available WBs for analysis existed in short durations (10 to 30 seconds) and the lowest number of WBs were within long WB durations (> 60 seconds). Differences between PD and OAs in the number of WBs undertaken per day, was dependent upon the time point and WB duration (Table 4-2).

Table 4-2. Characterisation of real-world walking speed (RWS) and the number of walking bouts recorded per day across the study duration in people with Parkinson's and older adults. *36 months RWS data was utilised used as time point for cross-sectional analysis. For longitudinal analysis, RWS data was included from all time points (18 to 72 months)

RWS (m/s)								
WB duration	**18 months**		***36 months**		**54 months**		**72 months**	
(seconds)	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
All > 10	**1.03 ± 0.09**	**1.10 ± 0.09**	**1.10 ± 0.09**	**1.04 ± 0.09**	**1.02 ± 0.09**	**1.07 ± 0.07**	**0.99 ± 0.07**	**1.06 ± 0.07**
10 to 30	**1.00 ± 0.08**	**1.05 ± 0.06**	**1.05 ± 0.66**	**0.99 ± 0.77**	**0.97 ± 0.07**	**1.02 ± 0.06**	**0.96 ± 0.07**	**1.02 ± 0.06**
30 to 60	**1.04 ± 0.08**	**1.10 ± 0.08**	**1.08 ± 0.07**	**1.03 ± 0.76**	**1.02 ± 0.08**	**1.07 ± 0.06**	**1.00 ± 0.07**	**1.07 ± 0.06**
> 60	**1.05 ± 0.12**	**1.16 ± 0.15**	**1.15 ± 0.13**	**1.07 ± 0.12**	**1.09 ± 0.12**	**1.13 ± 0.11**	**1.04 ± 0.11**	**1.11 ± 0.13**
Walking bouts per day (number)								
WB duration	**18 months**		**36 months**		**54 months**		**72 months**	
(seconds)	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
All > 10	583 ± 202	617 ± 208	625 ± 225	629 ± 189	574 ± 195	622 ± 195	600 ± 199	609 ± 183
10 to 30	183 ± 71	206 ± 71	**192 ± 72**	**208 ± 66**	**174 ± 65**	**203 ± 68**	190 ± 67	205 ± 65
30 to 60	**34 ± 16**	**45 ± 2**	**38 ± 20**	**45 ± 18**	**33 ± 17**	**44 ± 18**	**37 ± 19**	**47 ± 19**
> 60	19 ± 12	24 ± 13	**21 ± 14**	**24 ± 12**	**19 ± 12**	**2 ± 12**	18 ± 1	22 ± 11

PD = Parkinson's. OA = Older adults. RWS = Real-world walking speed. WB = Walking bout. The mean and standard deviation (SD), is reported for both RWS and walking bouts per day across each time point of the study duration in people with PD and OAs. If value highlighted in bold, indicates statistically significant difference between PD and OA at that time point at < 0.01 level.

Cross-sectionally at 36-months, RWS was significantly lower (P = 0.007) in PD (1.035 m/s) comparison to OAs (1.097 m/s) at all WBs and within each WB duration threshold (Figure 4-1).

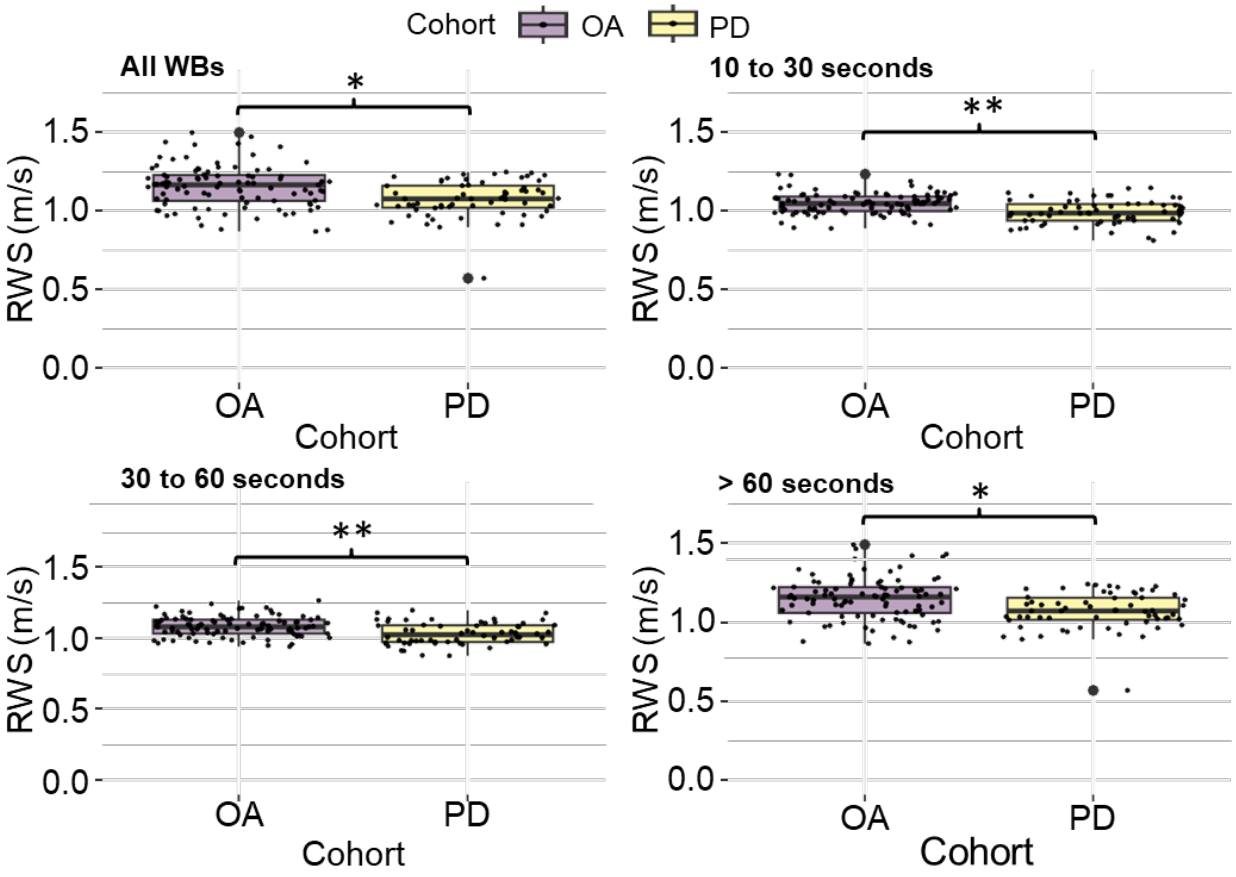


Figure 4-1. Mean real-world walking speed (RWS) for Parkinson's (PD) and older adult (OA) participants, estimated at each WB duration. '*' denotes P = < 0.05, where '**' indicates P = < 0.01. Datapoints represent an individual's RWS averaged across the seven days, within that specific WB. Line represents median values of RWS.

4.3.2 Does RWS change differently in PD or OAs?

Longitudinally, RWS significantly slowed in PD by 0.02 m/s (or 2 cm/s) per year and in OAs by 0.01 m/s (or 1 cm/s) per year, when aggregated at WBs > 10 seconds (Table 4-3). When aggregating within WB thresholds, RWS slowed significantly at each WB duration, excluding long WBs (> 60 seconds) in PD (Table 4-3). Rate of decline in RWS was larger in PD in comparison to OAs, at each WB duration threshold, excluding > 60 seconds where no difference with OAs was observed (Table 4-3).

Table 4-3. Annual decline in real-world walking speed recorded in Parkinson's and older adults and the difference in annual decline between cohorts across the study duration, from 18 months to 72 months

	Annual Decline of RWS		Difference in annual decline of RWS
WB duration (seconds)	**OA (β, 95% CI, *P*, R^2)**	**PD (β, 95% CI, *P*, R^2)**	**(β, 95% CI, *P*, R^2)**
All > 10	-0.011, -0.017, -0.006 m/s, **<0.001**, 72%	-0.021, -0.037, -0.004 m/s, **0.014,** 55%	-0.017, -0.030, -0.005 m/s, **0.006***, 39%
10 to 30	-0.008, -0.013, -0.003 m/s, **0.001**, 69%	-0.013, -0.020, -0.006 m/s, **<0.001,** 71%	-0.007, -0.013, -0.000 m/s, **0.036***, 67%
30 to 60	-0.009, -0.015, -0.004 m/s, **0.001**, 61%	-0.014, -0.021, -0.008 m/s, **<0.001**, 76%	-0.007, -0.014, -0.001 m/s, **0.035***, 64%
> 60	-0.013, -0.021, -0.005 m/s, **0.001**, 73%	-0.004, -0.014, 0.006 m/s, 0.466, 71%	-0.000, (-0.011, 0.011 m/s, 0.938, 69%

PD = Parkinson's. OA = Older adults. RWS = Real-world walking speed. WB = Walking bout. Estimated from a mixed linear regression model including 186 RWS measures from 85 PD participants and 240 RWS measures from 111 OA participants with age, sex and HY stage (in PD only), as covariates. Subject also a random effect to account for the correlation of measures of the same subject and a interaction term between follow up time (in years) and group (PD or OA). ''' – indicates significant difference in annual decline of RWS between PD and OAs.*

4.3.3 Is RWS related to clinical measurements of MDS-UPDRS-III?

At the 36-month time point of the ICICLE-GAIT dataset, there was no significant association between MDS-UPDRS III score with RWS at all WBs (β = 1.25 [95% CI = -4.29, 1.78] points, P = 0.412). However, when aggregating RWS within specific WB thresholds, a significant negative association was found with the MDS-UPDRS III at WBs between 30 to 60 seconds (β = -3.94, [95% CI = -7.83, -0.05] points, P = 0.047) (Figure 4-2).

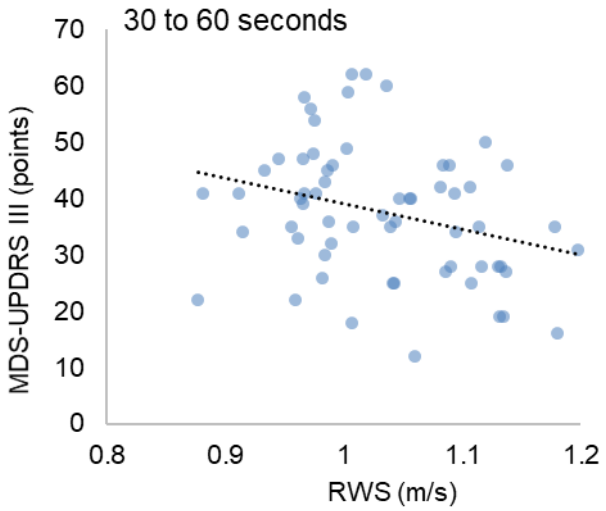


Figure 4-2. Cross-sectional relationship between MDS-UPDRS III and RWS for walking bouts between 30 and 60 seconds.

4.3.4 Are changes in RWS associated with changes in MDS-UPDRS III?

MDS-UPDRS III scores significantly increased by 1.86 [95% CI = 1.11, 2.61] points per year across the study duration. However, there was no association between change in RWS with change in MDS-UPDRS III at all WBs and each other WB duration threshold (Table 4-4).

Table 4-4. Relationship between decline in real-world walking speed and change in MDS-UPDRS III score in Parkinson's participants for all walking bouts (WB) pooled and for each WB threshold. Adjusted for age, sex and Hoehn and Yahr stage, according to WB duration.

WB duration (seconds)	Association of change in RWS with change in MDS-UPDRS III (β, 95% CI, *P, Cd.* R^2)
WBs > 10	0.323, (-0.203, 0.850), 0.229, 70%
10 to 30	-0.223, (-1.121, 0.764), 0.657, 69%
30 to 60	-0.076, (-1.046, 0.888) 0.872**,** 69%
> 60	0.141, (-0.506, 0.789), 0.668, 71%

Estimated from a mixed linear regression model including 186 RWS measures from 85 PD participants with age, sex and HY stage as covariates, subject as a random effect to account for the correlation of measures of the same subject and an interaction term between follow up time (in years) and RWS. MDS-UPDRS III scores increased by 1.84 points per year in the cohort.

4.4 Discussion

This chapter aimed to address to gaps identified in the review of ***Chapter 2*** and provide a comprehensive exploration of whether RWS can provide information that is complementary to the clinical assessment of mobility, motor disease severity and progression in PD. Cross-sectionally, RWS was significantly slower in PD compared to OAs across a range of different WBs. Across the study duration, RWS decreased annually in both cohorts, however the reduction was generally more rapid in PD, compared to OAs. Significant associations between motor disease severity (MDS-UPDRS III) and RWS were seen for medium length WBs in the ICICLE-GAIT dataset. MDS-UPDRS III scores increased annually; however, change scores were not associated with change in RWS longitudinally. These findings highlight that remote monitoring may add complimentary information to improve the clinical assessment of PD.

4.4.1 Does RWS discriminate between PD and OAs?

RWS was significantly slower in PD in comparison to OAs, which is in agreement with previous research in the same cohort (Del Din et al., 2016a), plus with work of others (Shah et al., 2020c). This finding further validates how a slower RWS corresponds to real-world mobility impairments that occur in PD and are separate to, or interact with, age-related changes. The challenges of modulating RWS, to safely navigate complex real-world environments are likely exacerbated by presence of motor symptoms and fluctuations. Thus, real-world mobility measures such as RWS have potential to capture novel insights in PD, in comparison to supervised assessments of capacity

(Warmerdam et al., 2020). RWS reflects a complex measure of real-world mobility that has been assessed across a wide variety of WBs that differ in their duration, context, and purpose. For example, short WBs capture more demanding activities such as obstacle negotiation, change in direction, gait initiation and termination. In contrast, longer WBs which may reflect steady-state gait and a more consistent gait pattern. This finding, along with (Del Din et al., 2016a), that RWS was slower in PD across a variety WB duration, demonstrates how RWS was slower in PD when assessed across a variety of contexts and activities.

4.4.2 Does RWS change differently in PD or OAs?

Over the six-year study duration, RWS reduced annually in both PD and OAs. RWS significantly reduced by 0.02 m/s more per year (all WBs) in PD compared to OAs. Whilst there is lack of agreement of what constitutes a clinically meaningful difference in real-world DMOs, a change in supervised walking speed of 0.06 m/s has been shown to be a meaningful change in PD (Hass et al., 2014). However, meaningful changes in RWS would be expected to be more discrete and be dependent upon WB duration (Corrà et al., 2021; Del Din et al., 2016a; Hillel et al., 2019). These findings were in contrast to previous work in the same cohort in a laboratory setting (Wilson et al., 2020) where walking speed declined in both OAs and PD, but with no difference in the rate of decline. Thus, supervised assessment (or mobility capacity) (Viceconti et al., 2022), may be a less sensitive measure of detecting the more rapid PD specific deterioration that occurs in an individual's real-world mobility, reflected by differences in RWS. Interestingly, differences in rate of decline in RWS were not observed when aggregated at long WBs. As time (and disease severity) progressed, the ability to walk for extended periods becomes more challenging and the number of longer walking bouts decreased. Long WBs reflect more optimal walking, where individuals may achieve performance close to their laboratory capacity, so this further supports the view that assessment of capacity may be less sensitive to discrete changes in mobility that occur over time. This is in agreement with previous research that found only the maximum values of RWS correlated with supervised walking speed (Corrà et al., 2021), and further demonstrates how RWS can provide novel information to existing mobility assessment.

4.4.3 Is RWS related to clinical measurements of motor severity (MDS-UPDRS-III)?

When considering all WBs > 10 seconds, no cross-sectional association between RWS and MDS-UPDRS III was found. This is in contrast to previous studies that found associations of the MDS-UPDRS III with supervised walking speed (Galperin et al., 2019; Hill et al., 2021; Raccagni et al., 2018; Schlachetzki et al., 2017). The MDS-UPDRS III score is large and captures a wide range of diverse signs (including upper limb function, tremor), that have been assessed over a brief clinical visit. In contrast, RWS is a complex measure that reflects different contexts of mobility dependent upon the WB duration that it is estimated from. This is supported by the finding that RWS encapsulated within short to medium length WBs (30-60s duration) was associated with greater motor disease severity, in contrast to other WB durations. Short to medium length WBs may contain prolonged periods of navigating the household environment, or perhaps intermittent periods of outdoor walking which provide the optimal balance between periods of straight walking, whilst maintaining some challenge to motor control. These, additional explorations of WBs are helpful as they may represent different contexts of mobility, and thus WB duration may moderate the relationship with RWS and disease severity (Galperin et al., 2019; Shah et al., 2020a). From the results, a faster RWS of 0.1m/s was associated with less severe motor disease (four points on the MDS UPDRS III), which is between the range of minimally and moderate important difference of 2.7 to 5.2 points that has previously reported (Shulman, 2010).

4.4.4 Are changes in RWS associated with changes in motor severity (MDS-UPDRS III)?

MDS-UPDRS III scores increased by 1.86 points per year, which suggests that after two years the cohort experienced a change above the threshold of minimally clinically important change (Shulman, 2010), although note the reference was using a previous version of the UPDRS III (rated out of 108). Alongside increasing MDS-UPDRS III scores, RWS increased per year; however, no association was found between the two measures. This is not necessarily surprising, given that changes in RWS, a complex measure of real-world mobility, were compared with changes in the MDS-UPDRS III, a large composite score that assesses many upper and lower body signs, some of which are not directly related to gait (tremor, speech, etc.,). Previous studies conducted in supervised, laboratory setting have found associations between walking speed and MDS-UPDRS III (Hass et al., 2014; Hobert et al., 2019). Interestingly, Hass et al., 2014

found that a 0.02 m/s change in walking speed was associated with the minimally important change in MDS-UPDRS III score as reported by Shulman, 2010. However, they assessed walking speed across a short distance and duration, and participants were optimally medicated. MDS-UPDRS III scores have been demonstrated to reflect slower rates of progression within unmedicated compared to medicated groups (Holden et al., 2018). Thus, RWS may only be associated with motor severity when assessed in a similar medication state (Corrà et al., 2021). Despite the lack of statistical association, both MDS-UPDRS III and RWS changed independently over time, which suggests that RWS may be able to capture additional insights into the impact of progression upon real-world mobility, that is not currently captured by the MDS-UPDRS III.

4.4.5 Clinical implications and future research

People with PD walked significantly slower in the real-world, cross-sectionally. Longitudinally despite RWS reducing in both PD and OAs, the reduction was more rapid for PD. Despite the lack of association with changes in the MDS-UPDRS III, this was expected given the differences in nature of assessment between real-world and supervised measures. However, the fact that RWS declined alongside increasing MDS-UPDRS III scores demonstrates that RWS captures some progressive aspect of PD that can complement the progressive aspect of PD that is assessed by changes in the MDS-UPDRS III. Thus, digital assessment of mobility, through quantification of RWS offers a reliable and sensitive complementary aid to existing clinical assessment of progression in motor severity. From the literature it was found that a change in supervised walking speed of 0.06 m/s constitutes a clinically important difference, however there is no research for what change in RWS is clinically meaningful, which represents an essential area of future research.

Capturing longitudinal real-world data presents a number of technical and logistical challenges which are being addressed. Efforts are ongoing to improve the validity of outcomes, with more advanced wearable devices that contain gyroscope sensors, which enable the enhanced validity of measurement and repeat analyses, in larger cohorts (Mikolaizak et al., 2022). In addition, the methods of data aggregation and summary metrics explored in this study offer a starting point, where future research could explore the optimal combination of aggregation values and summary metrics to capture RWS (such as extreme values etc.). Assessment of RWS in independent cohort studies would corroborate these findings.

Finally, continuous real-world gait outcomes such as RWS also may capture important additional information relating to fluctuating nature of disease, and further work is warranted to explore this topic. Further work is also required to establish whether relationships exist between RWS and additional clinical measures, such as MDS-UPDRS Part II or falls status and to establish the influence of changes in medication and cognition upon RWS. Real-world context is critical to the interpretation of RWS, as in the present study context was inferred based upon only the WB duration. Specific types of real-world environments could also influence RWS, where inclusion of environmental data would improve understanding of real-world data.

4.4.6 Limitations

Due to a lack of variation in H&Y stages, analysis of H&Y was not included in this study (the majority were H&Y stage II); future work with a greater variability in H&Y stages would be helpful to determine generalisability across disease stage and assess known groups' validity. Medication intake, cognition and depression were not controlled for and further work should understand the influence of other characteristics on validity of RWS. Compared to laboratory-based research, this study was relatively low in number (36). The possibility of a type two error and statistical power was not directly explored, and this should be addressed in future studies. PD motor disease symptoms are associated with gait abnormalities such as an reduced stride length and step time, alongside a slower walking speed (Zanardi et al., 2021). It could be speculated that these gait variables may present more sensitive representations of motor disease severity; therefore, other real-world gait outcomes could be evaluated in future research. Future research should also explore additional analysis of changes in RWS that can address more prognostic questions such as prediction of clinical outcomes including falls, freezing of gait symptoms or increased fluctuations and dyskinesias.

4.5 Conclusion

Assessment of real-world mobility using real-world walking speed as an exemplar shows potential to compliment monitoring of mobility in PD, which is an important feature with consequent clinical and research utility (Deane et al., 2014; Port et al., 2021). Ongoing multidisciplinary efforts (Mobilise-D) between academic, industrial and clinical partners are underway to address challenges and move tools towards wide scale adoption of real-world mobility monitoring (Rochester et al., 2020). Such is the

vast nature of real-world dataset, further work is needed to how more granular real-world contexts, such as the environment, influence real-world mobility.

Chapter 5. Enhancing the understanding of real-world walking speed in people with Parkinson's and older adults with contextual factors

This chapter aimed to understand whether interpretation of real-world walking is improved by exploration of indoor and outdoor walking alongside the WB duration. Specifically, it was characterised whether real-world walking predominantly takes place within indoor or outdoor locations in PD and OAs. This chapter also explored whether RWS is modulated differently to account for different challenges, by understanding whether the RWS of people with PD and OAs is different when assessed indoors or outdoors.

5.1 Introduction

Building upon the findings of ***Chapter 4,*** it is important to explore RWS in more depth and understand what additional insights into real-world mobility it is able to provide. The majority of real-world walking takes place within short WBs (Corrà et al., 2021; Del Din et al., 2016a; Shah et al., 2020a), which are primarily speculated to take place indoors, within the home environment (Hickey et al., 2016). While previous research has demonstrated volume of real-world walking activity is reduced in PD (Adams et al., 2021; Del Din et al., 2020; Lord et al., 2013c; Pradhan and Kelly, 2019; Toosizadeh et al., 2015), no study has explored whether people with PD walk less within indoor or outdoor locations. Understanding the context of real-world walking volume is important, as reduced physical activity and out-of-home mobility is associated with prolonged sedentary behaviour, increased falls risk and an increased reliance on carers to complete daily activities (Milanović et al., 2013). One the other hand, reduced volume of indoor walking may imply that individuals are unable to independently complete essential activities of daily living within the home setting.

Indoor environments are enclosed spaces within buildings and may include homes, workplaces, shops, banks, and public exhibition centres. These spaces create challenges such as including sharp turns, navigation of tight spaces, avoidance of obstacles. In contrast, outdoor environments are defined as open spaces outside of buildings, including parks, gardens, residential streets, high streets, and recreational

areas. Outdoor mobility may be affected by changes in the walking surface, by weather (ice, rain etc.,) (Kim and Brown, 2022; Toda et al., 2020), or variations in terrain (pot holes, incline, decline, curbs etc.,) (Kowalsky et al., 2021). Furthermore, people may feel more unsafe outdoors as they may navigate other pedestrians and traffic crossings. In both indoor and outdoor public spaces, psychological factors such as reduced feelings of privacy and security may contribute to increased anxiety, which negatively influences mobility (Kandola et al., 2018; Zimmermann et al., 2020). For people with PD, episodic gait disturbances (e.g. FOG) (Zhang et al., 2021) or motor fluctuations may be more apparent within indoor WBs, rather than outdoor WBs as individuals may only leave the house when ON medication (Del Din et al., 2016a; Lord et al., 2013c).

Due to challenging and ever-changing nature of indoor and outdoor environments, continued adjustment to the persons walking is required, such as changes in speed and direction. An inability to adapt RWS to meet specific real-world demands could lead to increased falls and injury risk (Brodie et al., 2017; Silva-Batista et al., 2018), as most falls have been shown to be due to trips, slips or misplaced strides (Ashburn et al., 2008; Hyndman et al., 2002; Talbot et al., 2005), suggesting that falls occur from an inability to adapt walking. People with PD have significantly reduced foot clearance during gait which is potentially related to reduced walking speed and stride length (Alcock et al., 2018, 2016). Evidently, it is important to explore how RWS is adapted for different real-world demands, however the influence of context has not been widely assessed within the literature.

At present, context is often inferred indirecly by the duration of a WB (ie., short and long WBs take place indoors and outdoors, respectively) (Corrà et al., 2021; Del Din et al., 2016a; Shah et al., 2020a). Measurement of environmental information through GPS and GNSS systems allows context to be directly captured. These systems can be imbedded into specialised wearable devices, or smart phone technologies and enable measurement of environmental location than can be synchronously captured with wearable data (Breasail et al., 2021; Schipperijn et al., 2014). There is a growing body of evidence in health research that has sought to quantify environmental and spatial behaviour in order to understand whether a link exists with physical mobility (Rainham et al., 2008; Schipperijn et al., 2014; Suri et al., 2023). RWS has been quantified separately for in-home (Chung et al., 2022; Stone et al., 2015) and out of home respectively (Wettstein et al., 2015, 2013). For in-home 97% of RWS was

reported to be less than 0.1 m/s (Chung et al., 2022), where another study, reported average RWS in-home was less than 0.57 m/s (Stone et al., 2015). In contrast, studies characterising out of home speeds found RWS to be between 1.03 to 1.09 m/s (Wettstein et al., 2015, 2013), which appears to be higher than the home. These findings collectively show that RWS assessed within the home is potentially slower than RWS assessed outdoors, however none of these studies explored differences between indoor and outdoor locations within the same study. All of these studies were explored in OA participants; however they did not include people with PD.

5.1.1 Aims and hypotheses

Aims

- Explore whether the volume of real-world walking is larger within indoor or outdoor locations, in different WB duration thresholds in PD and OA participants;
- Determine if volume of walking within indoor and outdoor locations is significantly different between PD and OAs;
- Explore whether mean RWS is significantly different between indoor and outdoor locations in different thresholds of WB duration for PD and OA participants;
- Determine whether RWS within indoor and outdoor locations is significantly different between PD and OAs.

Hypotheses

- The majority of real-world walking will take place indoors for both cohorts; with the largest proportion of indoor walking being comprised of short WBs and conversely largest proportion of outdoor walking being comprised of longer WB durations;
- PD will have a significantly larger proportion of indoor walking activity in comparison to OAs;
- Mean RWS would be significantly slower within indoor environments compared to outdoor settings for both cohorts across each WB duration;
- Mean RWS would be significantly slower in PD participants in comparison to OAs across each environment, and WB duration threshold.

5.2 Methods

5.2.1 Participants

Nineteen PD participants and 20 OA participants were included from the Mobilise-D TVS (Mazzà et al., 2021) with recruitment process and inclusion and exclusion criteria described in ***Chapter 3.*** Only 12 PD participants and 18 OA participants were included in this study, as GPS data was not collected from some participants, due to technical difficulties with the smartphones.

5.2.2 Real-world protocol

The participants were continuously monitored over seven days in their habitual environment, whilst wearing a Dynaport Move Monitor +.

5.2.3 RWS estimation

RWS was estimated per stride from the wearable data, through application of P1 and P2 algorithm pipelines for the PD and OA cohorts respectively, that were determined in the TVS (Micó-Amigo et al., 2023). Both pipelines are defined in ***Chapter 3*** and extensively validated in Kirk et al., 2023b***.***

5.2.4 Estimation of indoor and outdoor location

The GPS information needed to estimate whether the participant was indoor or outdoor was captured via AEQORA application (Ciravegna et al., 2019) installed on the smartphone that participants were asked to carry. An algorithm (more extensively defined in ***Chapter 3***) was applied to estimate the probability that RWS was assessed within indoor or outdoor settings, the probability ranged from 0 (outdoor walking) to 100 (indoor walking). A conservative threshold and classified a probability of < 30% as outdoor and > 70% as indoor walking (Debelle et al., 2023) and excluded RWS not captured within these thresholds. There is no consensus upon which threshold to apply, however an iterative approach was adopted, testing different thresholds to ensure a sufficient number of datapoints, whilst maximising a greater likelihood of being indoor/outdoor. For PD participants, this filtering removed 459 WBs (7% of total WBs) and for OAs this excluded 580 WBs (8% of total WBs).

5.2.5 Walking bout duration

Once real-world walking had been classified within environment, it was subsequently aggregated at specific WB thresholds (All WBs, 10 to 30 seconds, 30 to 60 seconds,

> 60 seconds). In the analysis of RWS all WBs < 10 seconds were excluded, as RWS cannot be quantified accurately at this duration (Kirk et al., 2023b; Micó-Amigo et al., 2023). For PD participants, this filtering subsequently removed 1363 WBs (25% of total WBs), for OAs this removed 1146 WBs (18% of total WBs). All participants had > 3 days of collected data (Buckley et al., 2020).

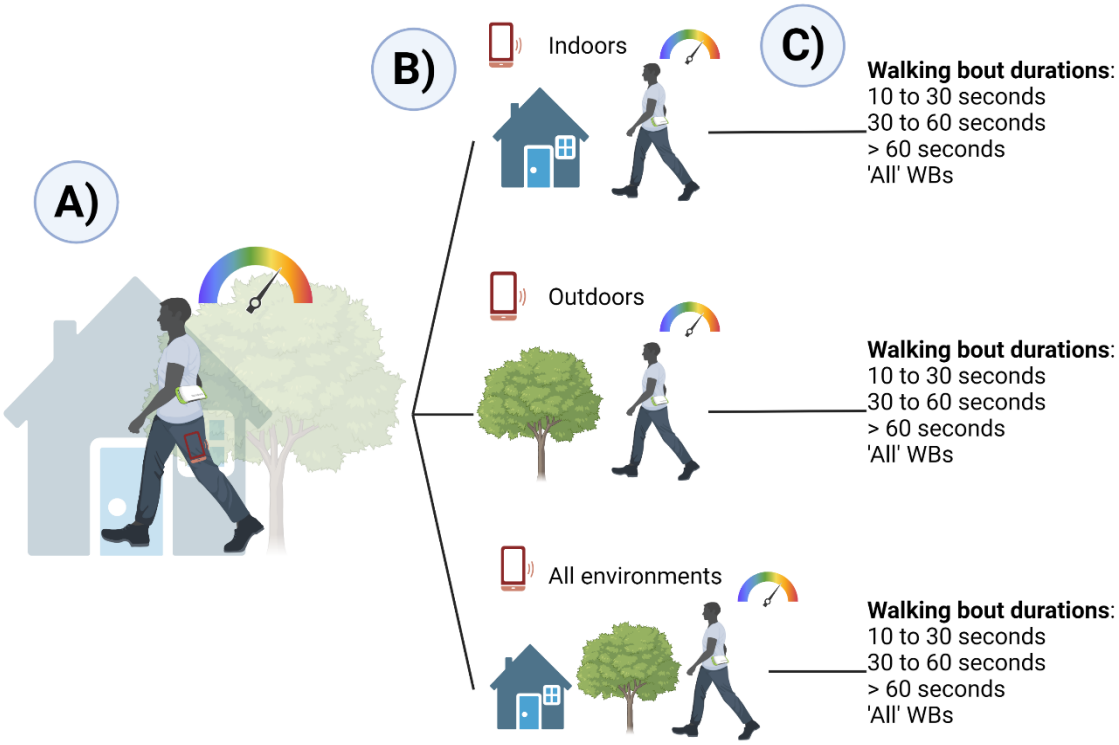


Figure 5-1. Aggregation of real-world walking speed (RWS) from the technical validation study protocol (Mazzà et al., 2021). A) Participant completes 7-days of mobility assessment, equipped with the Dynaport MM+ to assess RWS and the smartphone to assess indoor/outdoor global positioning system (GPS) information. B) From the GPS data, thresholds were applied to filter each stride and RWS into separate datasets for indoors, outdoors and all environments. C) Within each environment RWS is further aggregated into specific walking bout durations

5.2.6 Statistical analysis

Demographic variables were checked for normality through use of Shapiro-Wilkes's test, before applying either an independent T test (parametric) or a Mann-Whitney test (non-parametric).

5.2.7 Characterisation of indoor and outdoor walking volumes

The number of WBs and strides averaged across the week and per-day, was calculated within indoor and outdoor locations for each duration threshold of WB duration for PD and OAs. All of the below comparisons were made with paired-t test (parametric) or Wilcoxon-H test (non-parametric).

Within cohort

- Compared the number of WBs and the number of strides (weekly and daily average) between indoor and outdoor locations within each cohort

Between cohort

- Compared the number of WBs and the number of strides (weekly and daily average) estimated within indoor and outdoor environments between cohorts.

5.2.8 Influence of indoor and outdoor environments upon RWS

The mean RWS was compared between indoor and outdoor environments for each WB duration threshold, before comparing indoor and outdoor RWS between PD and OA. All of the below comparisons were made with paired-t test (parametric) or Wilcoxon-H test (non-parametric).

Within cohort

- Compared the mean RWS assessed across all, indoor and outdoor locations within each WB duration threshold, for both cohorts separately.

Between cohort

- Explored whether the mean RWS estimated from all indoor and outdoor locations was significantly different between PD and OA participants within each WB duration threshold.

5.3 Results

A summary of all participants demographic and clinical information can be viewed below (Table 5-1). PD participants were low disease severity (MDS-UPDRS III = 24.75 points). The PD cohort had a significantly larger proportion of males to females in comparison to OAs, otherwise no significant differences in descriptive statistics between PD and OAs were found (P = > 0.05).

Table 5-1. Demographic and clinical information for the Parkinson's and older adult cohorts of the technical validation study.

Group	PD	OA
n	12	18
Age (yrs)	66 ± 7	71 ± 6
Sex (Male / Female, n)	10/2	9/9
Height (metres)	1.75 ± 1.50	1.66 ± 1.05
Body Mass (kg)	79.6 ± 14.52	74.32 ± 11.47
BMI (kg/m^2)	25.87 ± 3.96	27.04 ± 3.79
Number of Walking bouts	5016 ± 209	7814 ± 163
Real-world walking speed (m/s)	1.01 ± 0.08	1.02 ± 0.12
MDS-UPDRS III	24.75 ± 10.32	-
Hoehn and Yahr Stage		
I, n (%)	3 (25%)	-
II, n (%)	7 (58%)	-
III, n (%)	2 (16%)	-
IV, n (%)	0	-

'-'describes an empty field, due to data availability. BMI = Body Mass Index. MDS-UPDRS III = Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III.

A summary of the all the PD participants excluded and included due to availability of indoor and outdoor data can be viewed in Appendix 5. The excluded participants (n=7), were significantly older (mean age = 74 years), had significantly larger MDS-UPDRS III scores (mean = 27.57 points), and significantly lower RWS (mean = 0.85 m/s) in comparison to the included participants (Table 5-1).

5.3.1 Characterisation of indoor and outdoor walking

For both cohorts the majority of WBs were undertaken indoors in comparison to outdoors. Within specific WB duration thresholds, differences between indoor and outdoor walking volume were not observed for PD participants within WBs between 10 to 30 seconds and 30 to 60 seconds, however at these durations OA participants undertook a significantly larger number of WBs and strides indoors in comparison to outdoors. In contrast, long WBs primarily took place outdoors, where both groups of

participants had a significantly larger volume of strides and daily average number of strides outdoors (P = < 0.01) (Table 5-2) (Figure 5-2).

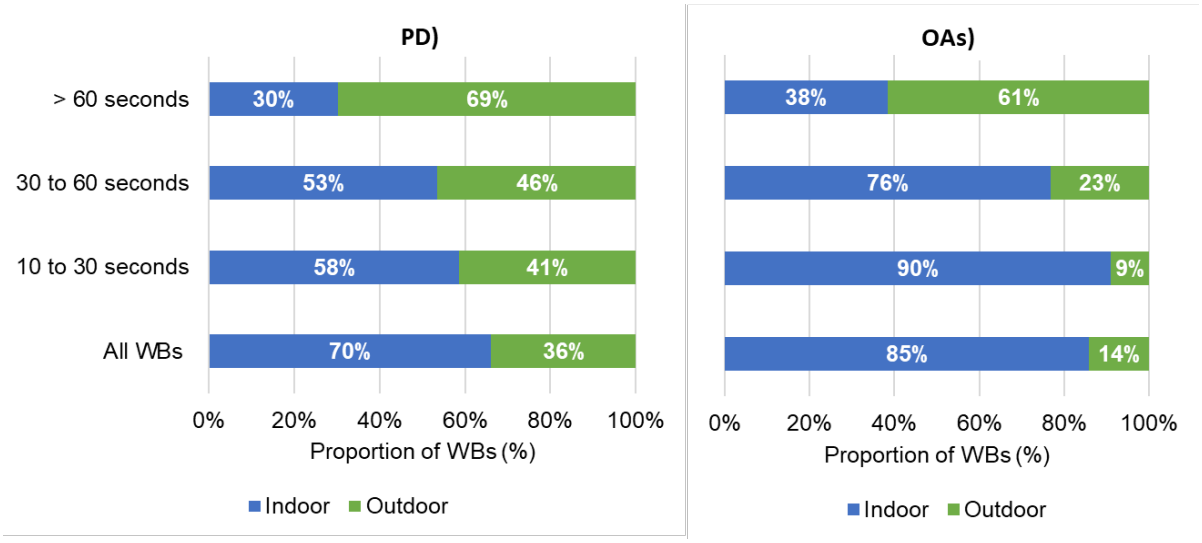


Figure 5-2. Proportion of walking bouts (WBs) that occurred in either environmental context for Parkinson's (PD) or older adults (OAs). Data are shown grouped by different thresholds of WB duration.

When comparing cohorts, across all real-world locations combined, OAs had a significantly larger stride count and number of daily strides in comparison to PD for All WBs and WBs > 60 seconds (P = < 0.05) (Table 5-2). Within outdoor locations, the number of WBs and the daily average number of WBs were significantly larger in PD participants in comparison to OAs. No significant differences between cohorts in outdoor walking volumes were observed at any additional WB duration threshold. In contrast, OAs had a significantly larger number of walking bouts, daily WBs, stride count and daily stride count in indoor environments, for each WB duration (Table 5-2).

Table 5-2. Volume of walking bouts and strides assessed indoors and outdoors for Parkinson's and older adult participants.

All WBs						
	All locations		Indoor		Outdoor	
Variable	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
Total WBs (n)[a,b]	1616 ± 948	1894 ± 702	**932 ± 549****	**1667 ± 716****	423 ± 509	238 ± 234
Daily average WBs (n)[a,b]	245 ± 150	270 ± 100	**138 ± 81****	**246 ± 99****	62 ± 72	34 ± 33
Total strides (n)	**39466 ± 25129***	**68866 ± 38117***	**13977 ± 8642****	**30148 ± 13487****	18259 ± 17835	38543 ± 36519
Daily average strides (n)	**5958 ± 3773***	**9838 ± 5445***	**2076 ± 1300****	**447 ± 1852****	2706 ± 2603	5507 ± 5216
RWS (m/s)	1.10 ± 0.17	1.14 ± 0.18	1.03 ± 0.10	0.97 0.11	1.16 ± 0.28	1.19 ± 0.22
WBs 10 to 30 seconds						
	All locations		**Indoor**		**Outdoor**	
Variable	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
Total WBs (n)[b]	512 ± 284	646 ± 253	**222 ± 182****	**590 ± 244****	89 ± 189	35 ± 67
Daily average WBs (n)[b]	73 ± 40	95 ± 36	**35 ± 26****	**83 ± 34****	20 ± 27	10 ± 11
Total strides (n)[b]	11107± 6358	13836 ± 5467	**4410 ± 3835****	**12563 ± 5152****	1900 ± 4256	807 ± 1640
Daily average strides (n)[b]	1583 ± 908	2036 ± 801	**741 ± 547****	**1765 ± 736****	478 ± 608	244 ± 273
RWS (m/s)	0.93 0.07	0.93 ± 0.09	**1.01 ± 0.08***	**0.82 ± 0.34***	0.92 ± 0.09	0.98 ± 0.15
WBs 30 to 60 seconds						
	All locations		**Indoor**		**Outdoor**	
Variable	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
Total WBs (n)[b]	85 ± 70	100 ± 51	**21 ± 26****	**39 ± 48****	25 ± 48	13 ± 27
Daily average WBs (n)[b]	12 ± 10	14 ± 7	**4 ± 4****	**12 ± 10****	6 ± 7	4 ± 5
Total strides (n)[b]	5026 ± 4122	5837 ± 3146	**1244 ± 1387****	**3741 ± 2609****	1514 ± 3027	834 ± 1718
Daily average strides[b]	744 ± 595	833 ± 449	**268 ± 231****	**687 ± 614****	373 ± 432	258 ± 286
RWS (m/s)	1.11 **±** 0.16	1.07 **±** 0.11	1.05 ± 0.35	1.08 ± 0.24	1.04 ± 0.11	1.01 ± 0.32
WBs > 60 seconds						
	All locations		**Indoor**		**Outdoor**	
Variable	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
Total WBs (n)	56 ± 48	80 ± 63	**9 ± 9***	**18 ± 21***	16 ± 39	36 ± 60
Daily average WBs (n)	9 ± 8	11 ± 9	**2 ± 2***	**4 ± 3***	5 ± 6	8 ± 9
Total strides (n)[a,b]	**15834 ± 12134***	**41268 ± 35174***	**1385 ± 1802****	**4417 ± 4214****	8336 ± 10087	31944 ± 35317
Daily average Strides (n)[a,b]	**2587 ± 2056***	**5895 ± 5024***	**335 ± 315****	**836 ± 598****	1660 ± 1658	5038 ± 5045
RWS (m/s)	1.28 **±** 0.19	1.25 **±** 0.17	1.07 ± 0.52	1.25 ± 0.22	1.14 ± 0.32	1.25 ± 0.37

Total WBs/Strides = total number across the week. RWS = Real-world walking speed. WB = Walking bouts. All variables reported as median across the week. a = significantly different between indoor and outdoor for PD, b = significantly different between indoor and outdoor for OA. Bold = Significantly different between PD and OAs. '*' – P = < 0.05, '**' = P < 0.01

5.3.2 Comparison of RWS between indoor and outdoor environments

For people with PD, RWS was not significantly different between indoor and outdoor environments for any WB duration threshold. In contrast, in OAs mean RWS was significantly slower in indoor environments for all WBs combined (P = < 0.001), and WBs between 30 to 60 seconds (P = 0.018) (Figure 5-3).

When comparing cohorts, differences in RWS where only observed for short indoor WBs where RWS was significantly faster in PD by 8% (1.01 ± 0.08 m/s) in comparison to OAs (0.92 ± 0.09 m/s) (*P* = 0.01).

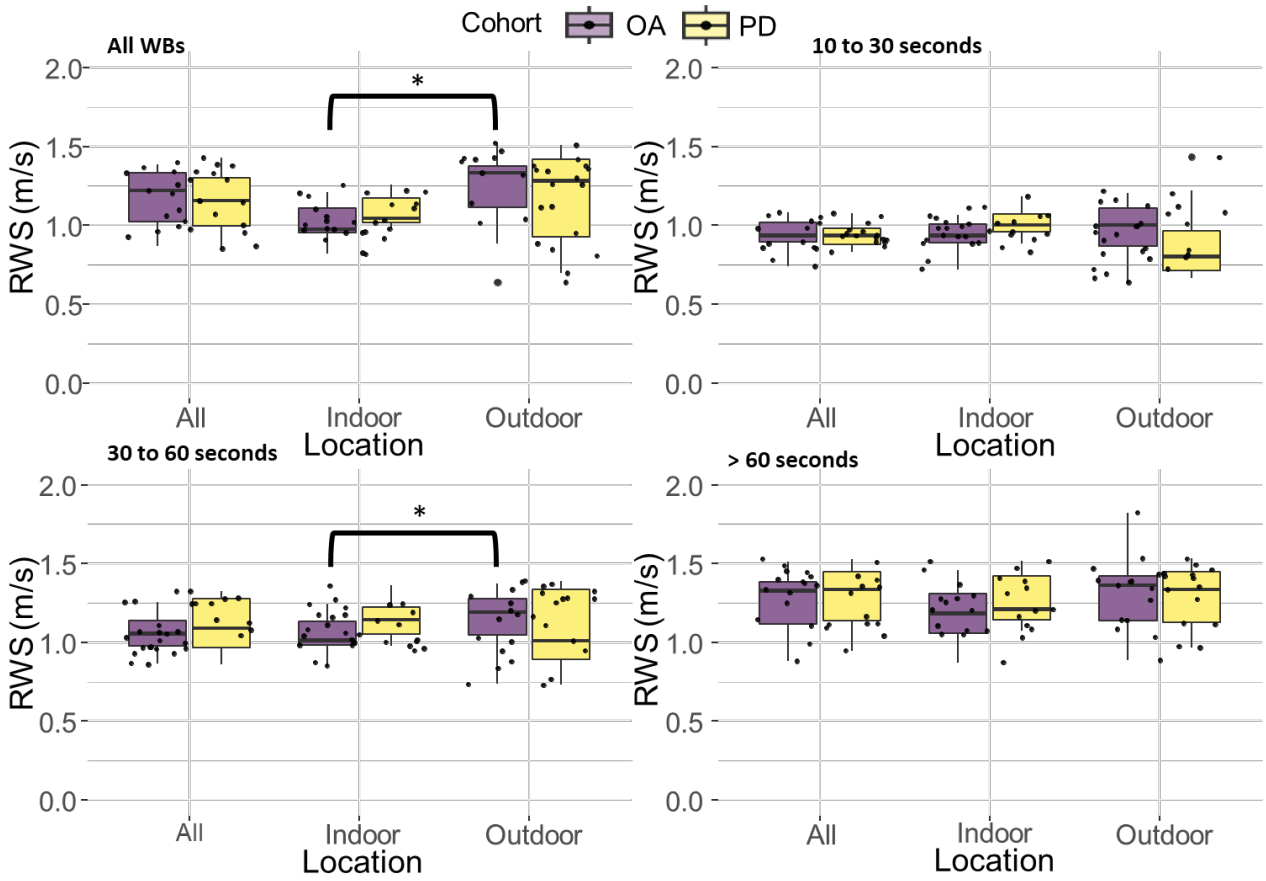


Figure 5-3. Comparison of mean RWS recorded across all, indoor and outdoor locations, across different walking bout (WB) thresholds. Datapoints represent an individual's RWS averaged across the seven days, within that specific WB and environment. *Indicates statistically significant difference (P = < 0.05) in RWS between indoor and outdoor location. Line represents median values of RWS.

5.4 Discussion

The overarching aim of this chapter was to understand whether exploration of real-world walking within indoor and outdoor locations is able to improve interpretation of real-world behaviour. Both cohorts undertook the largest volume of walking within indoor locations, where the majority of short WBs also took place indoors and the majority of longer WBs primarily took place outdoors. When comparing cohorts, no differences in outdoor walking volume was observed, however OAs had a significantly larger volume of indoor WBs and strides at each WB duration threshold in comparison to PD. Significant differences in RWS between indoor and outdoor locations were only observed for the OA cohort, within specific WB thresholds. When comparing cohorts, RWS was significantly slower in short duration indoor WBs in OAs compared to PD, showing that OAs are able to safely adjust their walking to meet demands of specific contexts in comparison to PD. Below the meaning of these findings is discussed and provide recommendations on the future use of GPS data in real-world mobility analysis.

5.4.1 Characterisation of indoor and outdoor walking volume

The first aim of this chapter was to understand in which location (indoor or outdoor) does most real-world walking takes place, and if the pattern of WB duration that relates to locations is different. Across all WBs, the largest proportion of WBs took place indoors, in keeping with hypothesis. This finding is not surprising given that previous self-reported surveys have determined humans spend 90% of their time indoors (Diffey, 2011). Within specific thresholds, short WBs (10 to 30 seconds) primarily took place within indoor locations, which is in agreement with previous speculation (Hickey et al., 2016). Despite not defining specific types of indoor locations, it's speculated that short WBs largely take place within the individual's home and thus RWS in short WBs could reflect performance of essential activities of daily life. In contrast, long WBs (> 60 seconds), were predominantly outdoors, which is expected given that prolonged periods of walking may only be accommodated within open, outdoor spaces. These findings should be interpreted with caution as assessment was undertaken during COVID-19 where many indoor public spaces were closed and individuals were instructed to remain at home (Ammar et al., 2020; "Coronavirus," 2020). Furthermore, participants were asked to place the smartphone on a Bluetooth always charging dock when in the home. This increased the probability of participants forgetting to re-equip the device and may have resulted in misclassification of outdoor WBs as indoor.

5.4.2 Is indoor and outdoor walking volume different between PD and OAs?

At all WBs and across all locations, the number of strides were significantly less for PD participants in contrast to OA participants, which is consistent with previous studies that have shown similar findings with the number of steps (Adams et al., 2021; Del Din et al., 2020; Lord et al., 2013c; Pradhan and Kelly, 2019; Toosizadeh et al., 2015). However, no literature had explored whether the volume of real-world walking is different between each location. Interestingly, no differences between cohorts in outdoor walking volume was observed, however PD participants recorded a significantly lower proportion and volume of indoor walking across each WB duration threshold in comparison to OAs, where these differences were stronger than all locations combined. Thus, these findings build upon existing literature and suggest that it is indoor, rather than outdoor walking volume, that is different between cohorts. Indoor walking is speculated to primarily take place within the home-environment, so this could be interpreted as OAs being more independently able to complete household activities in comparison to PD. In the present study participants' motor severity can be considered mild (MDS-UPDRS III score = 24.75 points), and mean age was similar between PD and OAs. At all WBs indoors PD had 53% fewer steps than OAs, which is larger than the than the 30% and 43% fewer steps reported in early-stage and mildly impaired PD participants reported in previous studies (Lord et al., 2013c; Pradhan and Kelly, 2019). This suggests that a reduction within indoor real-world walking volume potentially exists even in early stage PD, however further findings in larger samples are needed to confirm this.

While 10,000 strides per day is a popular recommendation of an active life style (Cavanaugh et al., 2012; Choi et al., 2007), there is no consensus on whether a higher/lower volume of indoor or outdoor walking activity reflects a healthy pattern in walking activity. While distributions between environmental walking has not been explored, across all real-world data combined, PD walking has been shown to be primarily comprised of a larger proportion of short WBs to long WBs, in comparison to OAs through estimation of Alpha (Lord et al., 2013c). Chung et al., 2022, have estimated other GPS measures and found relationships between proportion of time spent > 1000 ft from house with increased functional fitness (Nagi score) (Masala and Petretto, 2008). While it was not possible to quantify such metrics in this study, GPS data can be further analyzed to calculate life and activity spaces (Hirsch et al., 2014;

Liddle et al., 2014). These spaces reflect the geographical area of which an individual conducts their activity and their patterns of mobility within the community and activity space specifically can serve as a dynamic measure of ambulation in the community and surrounding neighbourhood. Associations have been made between smaller activity/life spaces in PD in comparison to OAs (Hirsch et al., 2014), while other research in community dwelling OAs has found associations between larger volume of physical activity with increased activity space (Suri et al., 2023). Future research could expand upon the present study to understand whether activity and life-space metrics can improve interpretation of real-world mobility.

5.4.3 Was RWS different between indoor and outdoor environments?

In PD participants, no significant difference in RWS between indoor and outdoor locations was found, across any WB duration threshold, which contrasts with the hypothesis. This hypothesis was partially based upon existing literature that has quantified separately for in-home (Chung et al., 2022; Stone et al., 2015) and out of home respectively (Wettstein et al., 2015, 2013). Previous studies quantified in-home RWS as <1m/s (Chung et al., 2022), and <0.57 m/s (Stone et al., 2015). Liu et al., 2022 quantified in-home RWS through use of radio waves found a mean RWS of 0.71 m/s for people with PD and 0.91 m/s for individuals without PD. In contrast to those studies, in the present chapter all real-world indoor locations were explored, rather than exclusively the home environment, however RWS captured within short WBs is speculated to primarily reflect in-home activity which was recorded to be 1.01 m/s, which is larger than the ranges reported in the existing literature. A possible explanation for this, could be the exclusion of WBs < 10 seconds in the present study, where there is not mention of filtering this threshold, or any other threshold in the existing studies. Furthermore, the PD participants in (Liu et al., 2022), had a larger disease severity (MDS-UPDRS III = 30 points), in comparison to the present cohort which could explain the slower RWS.

For outdoor RWS, other studies included OA participants (Mean age range 70 to 72 years) with and without cognitive impairment have reported average ranges of RWS to be between 1.03 to 1.09 m/s (Wettstein et al., 2015, 2013), however they did not explore differences between WB duration thresholds. Outdoor RWS in the present study was largely dependent upon WB threshold and reported between 0.92 to 1.14 m/s, with the fastest speeds recorded during long WBs. Comparison of the findings of the present study with the existing literature is limited, as studies have quantified RWS

with different technologies (GPS, Microsoft Kinect or radio waves), explored only in-home RWS rather than all indoor real-world locations, not explored differences in PD participants and most fundamentally not compared differences between indoor and outdoor RWS in the same study (Chung et al., 2022; Stone et al., 2015; Wettstein et al., 2015, 2013).

In contrast to PD, for OAs RWS was significantly slower when measured indoors across all real-world data (all WBs). This supports the hypothesis which was based upon previous research (Chung et al., 2022; Stone et al., 2015; Wettstein et al., 2015, 2013), but also upon the speculation that the different challenges of each type of location would require a different adaptation of RWS to safely navigate. At all WBs, RWS was lower for OAs when assessed indoors (1.17 m/s), as these environments represent more confined spaces, in comparison to outdoor environments that have longer pathways and more open spaces allowing for greater modulation of RWS speed, particularly at higher walking speeds (mean RWS of 1.23 m/s). The mean outdoor RWS at all WBs for OAs was substantially larger than the ranges reported by previous studies (1.03 to 1.09 m/s) (Wettstein et al., 2015, 2013), however those studies estimated RWS with a different measurement device, real-world assessment was completed across a shorter time frame, and they didn't exclude WBs < 10 seconds from their analysis.

Also, for OAs, within medium length WBs, RWS was significantly faster indoors (1.08 m/s) in comparison to outdoors (1.01 m/s). One possible explanation is that medium outdoor WBs could reflect intermittent periods of walking in urban settings that have the need to navigate traffic crossings and other obstacles, requiring slower speed to navigate these challenges, which could have reduced RWS. In comparison medium length indoor WBs could include shops, places of work, or other large public spaces. However, these interpretations remain speculative, and further highlights and the challenges and importance of understanding the context of real-world mobility. A more granular approach would be built upon promising methods and characterise specific types of indoor and outdoor environments (Bayat et al., 2020), or explore differences in RWS between individual's living in rural or urban areas.

5.4.3.1 Is indoor and outdoor RWS different between PD and OAs?

The indoor and outdoor RWS across each WB duration threshold, was compared between PD and OAs. The only significant differences were observed within RWS

assessed during short WBs undertaken indoors, where RWS was significantly slower in OAs in comparison to PD. This contrasts with previous findings made in ***Chapter 4***, that demonstrated, irrespective of location, RWS in short WBs was significantly slower in PD (0.99 m/s) in comparison to OAs (1.05 m/s). In the present study, the fact that RWS was significantly slower indoors in comparison to outdoors, only in OA participants, demonstrates that they can modulate their walking pattern in comparison to people with PD. Within confined indoor locations, a slower RWS reflects a safer gait modulation as individuals would want to avoid tripping over furniture, or safely navigate other obstacles. This finding, along with the potential inability of PD to adapt walking speeds could suggest an 'inflexibility' to safely adapt their mobility for specific environments or WB durations.

5.4.4 Limitations

A primary limitation of this study was in the data collection and estimation of GPS information to quantify indoor and outdoor location. Future studies utilising specialist GPS devices, with more standardised placement is needed, as previous research studies have demonstrated a difference in accuracy between not only the type of GPS device, but also differences in estimation of GPS information when the device is worn on different locations (Schipperijn et al., 2014; Taoum et al., 2021). Differences in accuracy is also reduced within indoor environment using urban locations with high rise buildings (urban canyons) (Kerr et al., 2011; Webber and Porter, 2009) and increased foot traffic or in spring and summer seasons where trees have greater foliage which blocks the satellite signal, reducing accuracy (Duncan et al., 2013; Rainham et al., 2008). The sample size for both cohorts was small, and further reduced by some participants not recording GPS information. As the study was conducted during COVID-19, this could have had a negative influence upon the confidence of participants to leave the house, restricting their out of home activities (Falla et al., 2021; Knapik et al., 2021; Luis-Martínez et al., 2021). Future studies in a larger sample, with more varied motor symptom severity, that is not confounded by COVID-19 is needed. Such as the nature of the TVS, a large amount of clinical information was not collected. This is an essential area of future analysis, which should be completed in cohorts with wide ranges in disease severity, medication intakes and symptoms.

5.4.5 Clinical implications & future directions

The importance of understanding environmental context and its influence upon mobility is gaining traction within health-care research, as this would substantially enhance interpretation of complex real-world datasets. These findings suggest that indoor walking volume, rather than outdoor walking volume, is significantly affected in PD, which potentially enables the design of simple interventions and practical recommendations to be made for people with PD and their carers such as ensuring they continue to independently complete as many home-based activities as possible. RWS was only modulated differently between different real-world locations for OA rather than PD participants within specific WB duration thresholds. This inability to adapt RWS could propagate to reduced foot clearance and increased risk of tripping, slipping or misplacing strides and subsequently sustaining a fall (Ashburn et al., 2008; Hyndman et al., 2002; Talbot et al., 2005). Evaluation of RWS adaptability could improve detection of falls and assist in the development of fall prevention strategies. While previous studies in supervised settings have found associations between walking adaptability and prospective fallers (Geerse et al., 2019), associations between adaptability of RWS between real-world locations and increased falls-risk are yet to explored.

Despite this exploratory work and the exciting potential of GPS data in general, current methods of capturing GPS are confounded by several limitations which question their accuracy and precision as clinical tools. Liu et al., 2022 has pioneered an innovative method of accurately estimating in-home RWS through use of radio waves emitted by a Wi-Fi device, however such method is limited to in-home environments only. Several technical steps must be addressed, including determining optimal algorithms, type of device and the optimal position for device to be worn among others. While no study has explored indoor physical activity in PD, other clinical measurements related to ageing such as the late life function and disability index (LLFDI) (Jette et al., 2002), or the MDS-UPDRS II (self-reported experiences of daily living), could perhaps explain the reduced volume of indoor walking activity in PD. Previous studies have also suggested a potential link between reduced volumes of walking activity with greater cognitive impairment in PD (Mc Ardle et al., 2022), which would make for an interesting area for future work.

5.4.6 Conclusion

Digital examination of mobility, through assessment of RWS assesses an individual across many different environments, WB durations and contexts, offering a method of enhancing the richness and depth of clinical mobility monitoring, alongside existing methods. Specifically, it provided greater understanding of specific factors that drive real-world mobility and whether mobility is modulated differently between indoor and outdoor environments. Here the potential of environmental data into future wearable research has been demonstrated. Further technical validation work is needed to optimise collection and analysis of GPS data, before application upon a larger sample of participants presenting with more varied stage of PD. Despite characterising RWS as the mean value between environment, an additional way to explore this would be to understand how RWS is modulated within a single WB.

Chapter 6. Gait adaptation in the real-world: Quantification of modulations within real-world walking speed in people with Parkinson's and older adults

Understanding how RWS is modulated within a single WB could provide insight into the ability of individuals to adapt their walking to safely navigate real-world demands. While there is no widely accepted method of modelling the number of modulations, this chapter explores one potential method of achieving this by quantifying the number of modes, or selected walking speeds, within the distribution of RWS.

6.1 Introduction

Real-world walking is complex, as mobility may be challenged by the different demands of different contexts, such as the type of location (indoor or outdoor) (Kim and Brown, 2022; Toda et al., 2020). In ***Chapter 5***, no difference in mean RWS between indoor and outdoor locations for people with PD, which suggested that there is inability to modulate RWS between environments within PD. This which may lead to negative consequences such as increased falls and injury risk (Brodie et al., 2017; Silva-Batista et al., 2018), or reduced quality of life through avoidance of walking which could limit mobility and social participation (Delgado-Ortiz et al., 2023; Merchant et al., 2020). While this method was able to provide insight into the broader patterns and trends that exist within RWS, an additional way to explore walking adaptations would be to understand how RWS is modulated within a single bout of walking, which is not represented by the singular values averaged across the entire assessment period in the previous chapter.

Within a single WB, an individual may modulate their RWS with separate acceleration, steady-state, and deceleration phases. Furthermore, an individual may need to adapt their walking to account for several contextual challenges they may encounter during the WB such as changes in the walking surface (Osaba et al., 2020) obstacle negotiation**,** fatigue (Zhang et al., 2022). Cognitive impairment may also influence adaptability of gait, due to the need to complete more cognitively demanding dual-tasks (Rochester et al., 2014). Specifically in PD, episodic gait disturbances such as festination (Giladi et al., 2001), or FOG (Zhang et al., 2021), can cause inconsistencies with acceleration and gait initiation (Plotnik et al., 2008). Medication fluctuations and dyskinesias can also cause inconsistent gait patterns, which may be reflected in step

length and RWS, which have been shown to be more dopa-responsive DMOs (Corrà et al., 2021; Curtze et al., 2015; Rochester et al., 2011). These, in turn could create more variability within gait modulation (Jankovic, 2005). Additionally, deficits in balance, postural control (Raccagni et al., 2020), muscle function (Pääsuke et al., 2004), and rapid force production (Pelicioni et al., 2021), also occur in PD and may negatively affect the ability to quickly adapt walking. Thus, objectively quantifying the number of modulations that occur within a WB could provide a comprehensive understanding of an individual's walking dynamics and functional capabilities and assist decision making, therapeutic management and personalised intervention strategies.

While there is no widely accepted method of modelling modulations in RWS within WBs, one potential solution exists through modelling the number of modes within the distribution. A distribution is a function that shows the possible values for a variable and how often they occur, where a mode is described as a frequently occurring value within the distribution. On the surface, the distribution of RWS may be described with one mode, however it may include several modes (Figure 1-2). Each mode within the distribution could represent a ‘selected walking speed’, existing within RWS, where the ‘slowest’ or ‘lowest’ selected walking speed could reflect different aspects of mobility versus the ‘fastest’ or ‘highest’ mode in the distribution. It could be hypothesised in the most complex real-world scenarios an individual may have to adapt their speed several times, resulting in a larger number of selected walking speeds. Thus, a reduced number of selected walking speeds could reflect limited capability for adapting gait across environments and WB durations (Lord et al., 2013c). Alternatively, specific WB durations and environments, medication fluctuations, dyskinesias and gait-freezing could drive a larger pattern in selected walking speeds (Atrsaei et al., 2021; Mancini et al., 2018).

It is not currently understood how many selected walking speeds exist within the distribution. Previously in OAs and PD, researchers have fitted a distribution with a fixed number of two selected walking speeds to all assuming that there is a bimodal distribution within their RWS (Atrsaei et al., 2021; Brodie et al., 2017; Van Ancum et al., 2019). One study fitted a fixed number of five selected walking speeds (Baroudi et al., 2022), however their participants were young adult athletes. All of those previous studies did not model whether a more optimal number of selected walking speeds better fitted the distribution of RWS. While no widely adopted method toward modelling

the number of selected walking speeds within RWS exists, one approach is based upon unsupervised machine learning clustering algorithm and is implemented within the 'Mclust' package (Scrucca et al., 2016) in R (R Foundation for statistical computing, V4.02, Austria). While Mclust has had applications in a broad range of fields (Foley et al., 2020; Nadif et al., 2020; Villafaña et al., 2020), it was yet to applied upon continuous real-world gait data.

6.1.1 Aims and hypotheses

Aims

- Determine of the number of selected walking speeds (defined by the number of modes) in real-world and laboratory settings in PD and OAs
- Explore whether selected walking speeds are modulated differently between WB duration thresholds and assessment context (laboratory vs real-world)

Hypotheses

- In the real-world, selected walking speeds would be dependent upon the WB duration, as mean RWS has been previously shown to differ between WBs (Del Din et al., 2016a)**.** PD participants would be characterised by fewer selected walking speeds in comparison to OAs, demonstrating a reduced ability to adapt RWS (Lord et al., 2013c).
- Both groups would have a larger number of selected walking speeds in the real-world, in comparison to the laboratory, due to the need to adapt walking to a more complex environment.

6.2 Methods

6.2.1 Participants

Nineteen PD participants and 20 OA participants were included from the Mobilise-D TVS (Mazzà et al., 2021) with recruitment process and inclusion and exclusion criteria described in ***Chapter 3.***

6.2.2 Laboratory protocol

Participants completed seven tasks: straight walking, timed up and go, l-test, surface test, hallway test and simulated daily activities. Each task was considered as a single WB, where walking speed was aggregated across all laboratory tasks.

6.2.3 Real-world protocol

The participants were continuously monitored over seven days in their habitual environment, whilst wearing a Dynaport Move Monitor.

6.2.4 RWS estimation

RWS was estimated per stride from the wearable data, through application of P1 and P2 algorithm pipelines for the PD and OA cohorts respectively, that were determined in the TVS (Kirk et al., 2023b; Micó-Amigo et al., 2023). Both pipelines are defined in ***Chapter 3.***

6.2.5 Characterisation of selected walking speeds

A distribution may also be termed a 'Gaussian Mixture Model (GMM) (Reynolds, 2009). A GMM can be fitted with any fixed number of modes, or selected walking speeds, where each selected speed is defined by mean and covariance parameters. GMMs were employed to identify the number of modes, or selected walking speeds existing in the distribution underlying RWS for PD and OA participants. GMMs were fitted utilizing the 'Mclust' function in the 'Mclust' package (Scrucca et al., 2016) in R (R Foundation for statistical computing, V4.02, Austria). Mclust applies probabilistic, unsupervised machine learning algorithms, through utilizing a soft-clustering approach that identifies the probability that each data-point belongs to a specific mode or selected-walking speed.

Conceptually, a GMM is defined by several modes, or selected walking speeds identified by $k\{1, \dots, K\}$, where K is the number of selected-walking speeds within this dataset (each selected speed K in the mixture is comprised of a mean μ that defines the centre, a covariance $\sum$ that defines its width, and a mixing probability π that defines how big or small the gaussian function would be.

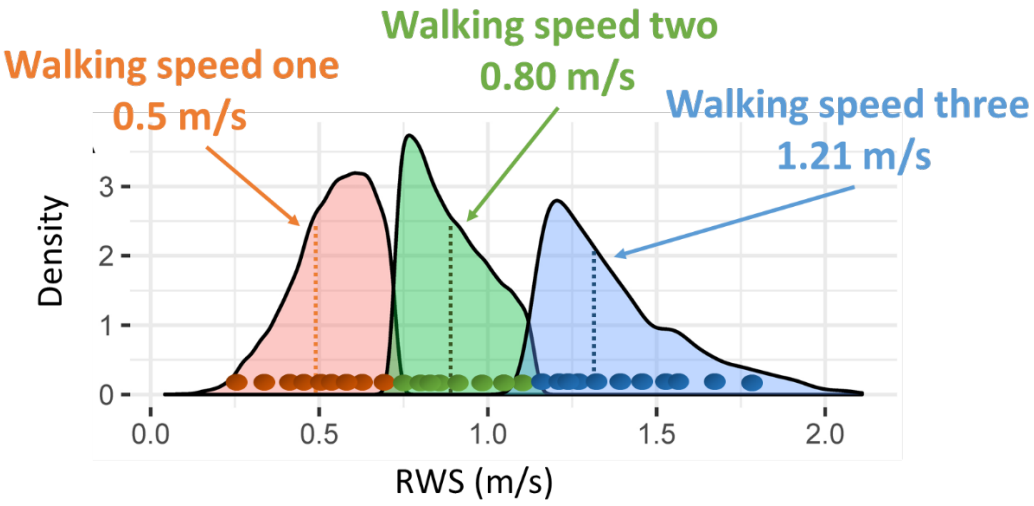


Figure 6-1. Gaussian mixture model containing three modes, or selected walking-speeds. Datapoints represent an example of an individual's real-world walking speed collected across seven-days, which consisted of thousands of datapoints.

Mclust was first applied to estimate the number of selected walking speeds K existing within the distribution of RWS. In this study, models were fitted containing different numbers of selected walking-speeds, ranging from one to nine, to each individual's RWS assessed over the 7-days, or their laboratory walking speed aggregated across all tasks. To determine which model, defined by the number of selected walking speeds, was the optimal fit, the Bayesian information criterion (BIC) as utilised as a method to correct for over-fitting. Where the model that had the largest BIC value was determined as the optimal fit.

6.2.6 Estimation of selected walking-speed parameters

Once the optimal number of modes was determined, or selected walking speeds within RWS, Mclust then applies an expectation-maximisation algorithm to fit the location and width of each selected-walking speed to the individual's distribution. Given that GMMs are an unsupervised learning algorithm, the selected walking-speed of which data point of RWS belongs to is unknown and is considered a 'latent variable'. Traditional techniques to estimate parameters of each mode, or selected walking-speed, such as maximum likelihood estimation, is not possible with the presence of latent variables, thus Mclust employs and Expectation-maximisation (E-M) algorithm approach to achieve this (Scrucca et al., 2016).

EM algorithms are defined by an '*E-step'* which estimated the expected value for each selected walking-speed within the mixture and an '*M-step'* that optimized the

parameters (mean and variance) of the distribution using maximum likelihood. Specifically, EM algorithms, assumes random modes that are randomly centered upon data points of walking speed and computed for each observation, the probability that it was generated by each selected walking speed of the model. The algorithm adjusted the mean and covariance parameters (μ, $\sum$) to maximize the likelihood of the data given those assignments, the EM algorithm repeats this process until convergence is observed in the likelihood value. An overview of this process can be viewed below (Figure 6-2).

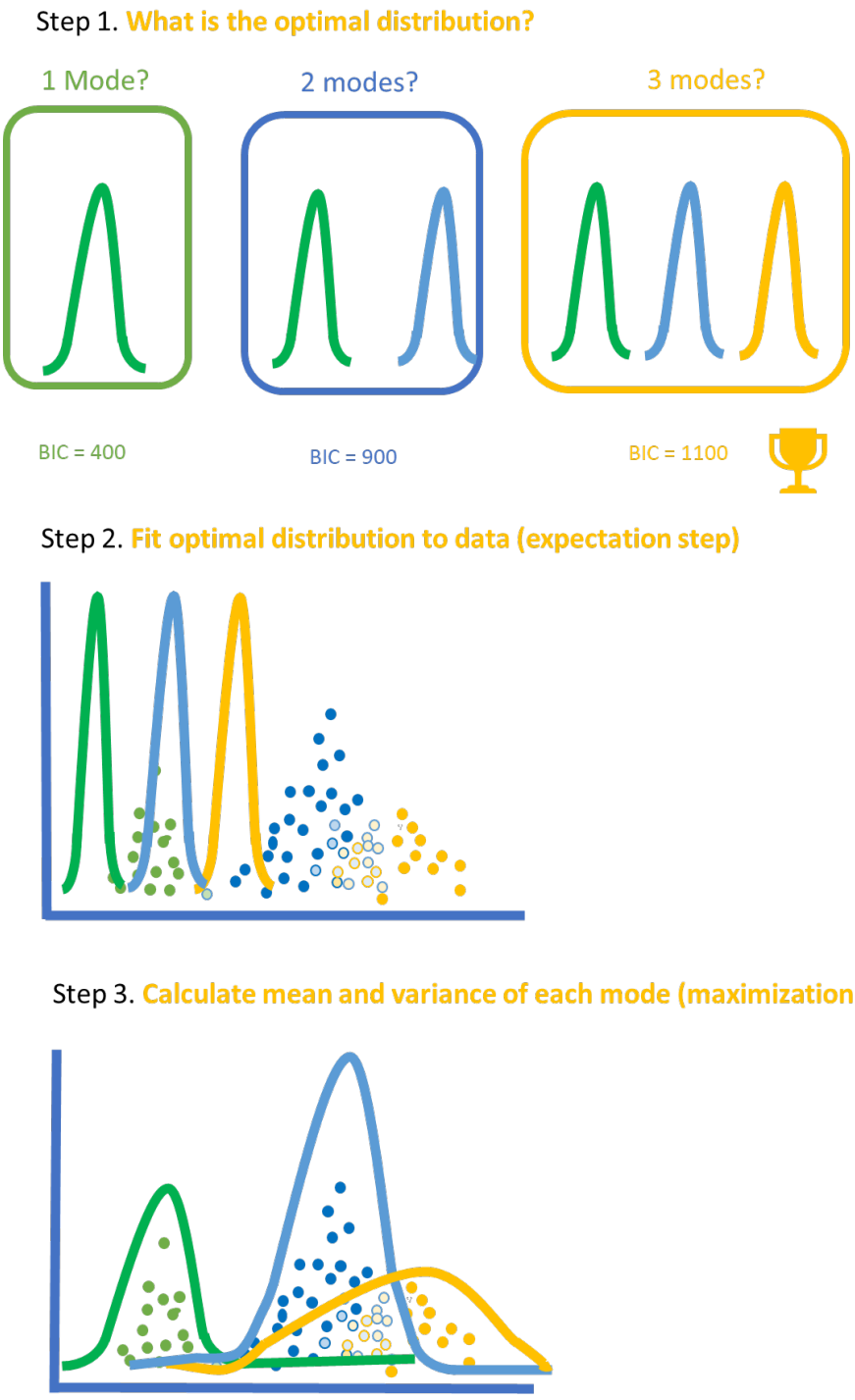


Figure 6-2. Modelling the optimal distribution within real-world walking speed (RWS). Step 1) quantification of the number of selected walking speeds existing within the distribution, in this method nine models were fitted, however here only include 3 for graphical representation. The model that maximises the Bayesian inference criterion is chosen as the optimal fit. Step 2) The algorithm randomly positions the three selected walking speeds at some random area of the distribution of RWS. Step 3) Algorithm optimises fit of each selected walking speed by re-fitting around its mean and variance.

Following these steps, the algorithm produced an output for everyone containing the optimal number of selected walking-speeds within the distribution of RWS and

laboratory walking speed process was repeated for RWS within each WB duration (10 to 30 seconds, 30 to 60 seconds, > 60 seconds and all WBs), in both PD and OA cohorts.

The median and ranges of the number of selected walking speeds were calculated to summarize the results across each WB duration, and assessment context. The weights were calculated based upon the proportion of participants in each number of selected walking speeds, with the number selected walking speeds assigned to a larger proportion of participants having a higher weight.

Ordinal Logistic regression (Polr function in R statistical software) was employed to explore whether the number of selected walking speeds were significantly different between PD and OA participants. All models were adjusted for sex, age. The number of strides each individual has undertaken was controlled for, to ensure that any differences were dependent upon the characteristics of the cohort, rather than individual's recording a larger volume of strides.

6.3 Results

A summary of all participants demographic and clinical information can be viewed below (Table 6-1). There were no significant differences in general characteristics between PD and OAs (P = > 0.05).

Table 6-1. Demographic and clinical information for PD and OA participants.

Group	PD	OA
n	19	19
Age (yrs)	69 ± 8	71 ± 6
Sex (Male / Female, n)	15/4	9 / 10
Height (metres)	1.74 ± 0.66	1.67 ± 0.10
Body Mass (kg)	79.1 ± 13.46	74.4 ± 12.11
BMI	25.9 ± 4.2	27.12 ± 3.6
Real-world walking speed (m/s)	1.05 ± 0.21	1.17 ± 0.16
MDS-UPDRS III	25.78 ± 14.16	-
Hoehn and Yahr Stage		
I, n (%)	4 (21%)	-
II, n (%)	11 (47%)	-
III, n (%)	4 (21%)	-
IV, n (%)	0	-

'-'describes an empty field, due to data availability. BMI = Body Mass Index. MDS-UPDRS III = Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III.

6.3.1 Estimation of selected walking speeds within the distribution of RWS

An example of the number of selected walking speeds that were identified within RWS assessed from PD participants can be viewed in Figure 6-3.

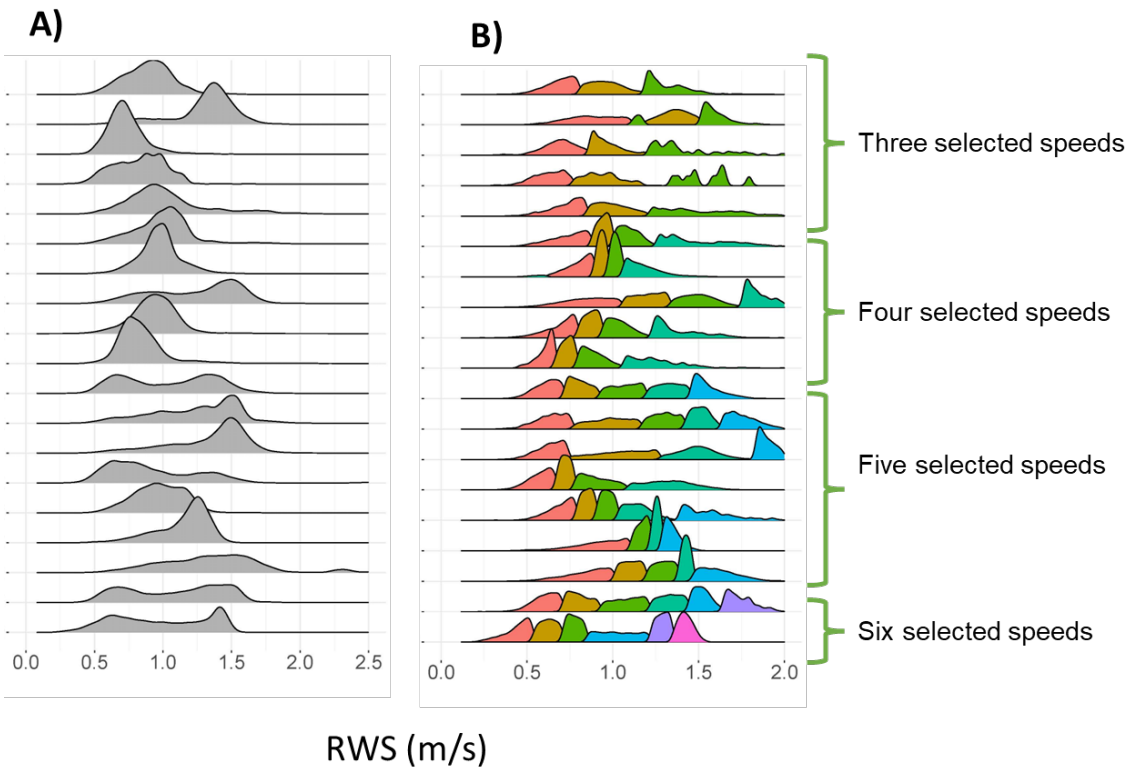


Figure 6-3. Illustration of selected walking speeds within real-world walking speed (RWS) at all walking bout in Parkinson's. A) Raw distribution of RWS assessed across seven days. B) The distribution, defined by number of selected walking speeds identified by the algorithm (number of participants = 19).

6.3.2 Were selected walking speeds modulated differently between WBs?

The weighted averages of the optimal number of selected walking speeds at each WB duration are presented below (Table 6-2).

Table 6-2. Weighted averages and ranges of selected walking speeds estimated in Parkinson's and older adult participants.

WB duration threshold	PD (Weighted average, range)	OA (Weighted average, range)
All WBs	4, 3:7	5, 3:9
10 to 30 seconds	4, 2:7	4, 3:7
30 to 60 seconds	4, 2:9	3, 2:6
> 60 seconds	3, 2:6	4, 2:9

At all WBs, both cohorts were characterised by selected walking speeds ranging from three to nine (Figure 6-4). Across each WB duration threshold, the largest proportion

of PD participants were characterised by four selected walking speeds, excluding > 60 seconds in PD, where the largest proportion had three (Figure 6-4).

When comparing cohorts, the number of selected walking speeds was significantly larger in PD for WBs between 30 to 60 seconds in comparison to OA (Odds Ratio = 4.75, 95% CI [1.14, 22.20], P = 0.05).

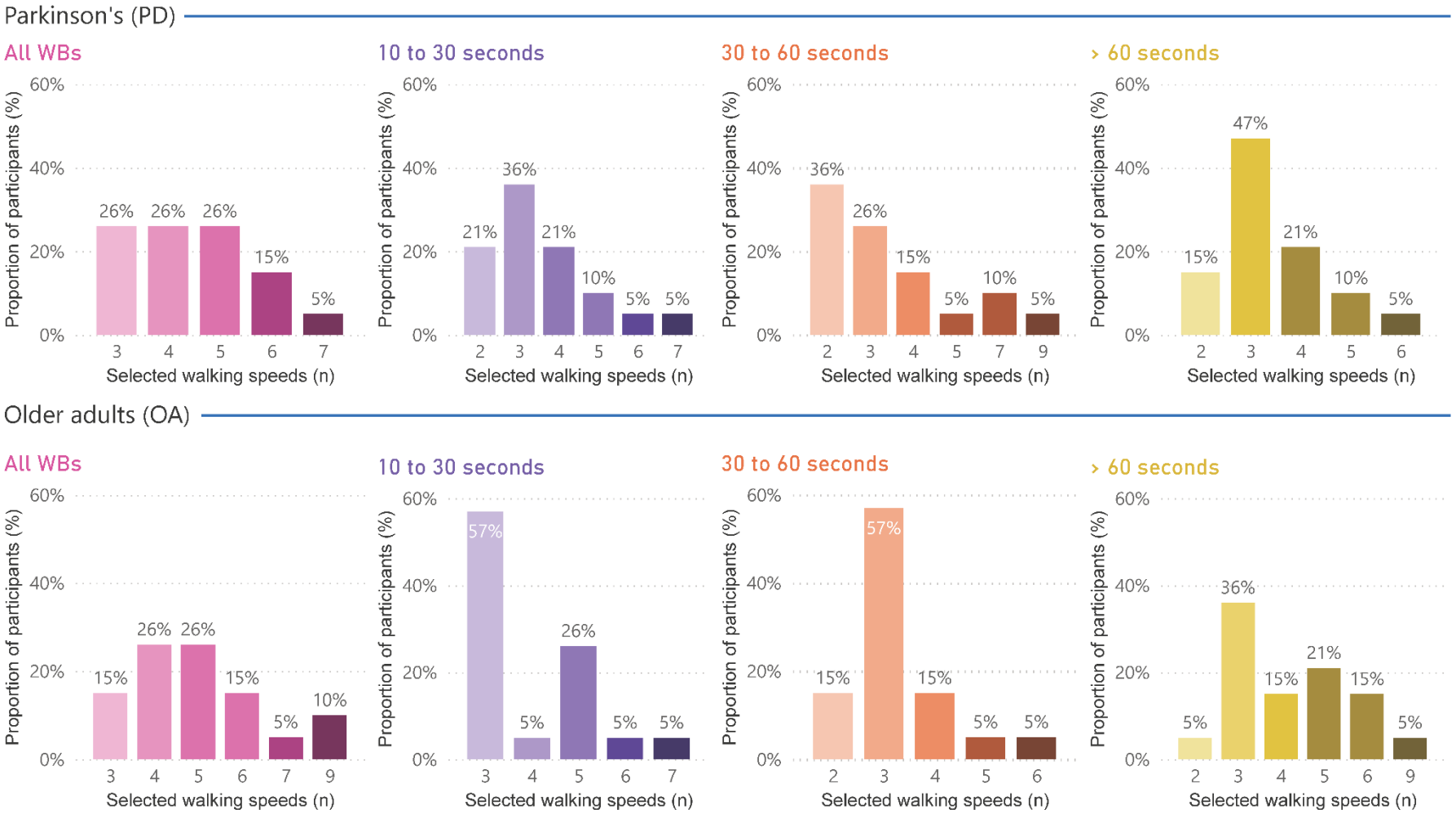


Figure 6-4. Number of selected walking speeds within real-world walking speed for Parkinson's and older adult participants assessed at walking bout (WB) durations; all WBs, 10 to 30 seconds, 30 to 60 seconds, > 60 seconds.

6.3.3 Were selected walking speeds different between assessment?

Across all laboratory tasks aggregated together, the largest proportion of PD participants were characterised by one selected walking speed. In contrast, the largest proportion of OAs had two speeds (Figure 6-5).

The number of selected walking speeds in the laboratory was significantly different between PD and OA participants (Fisher's exact test $P = 0.04$).

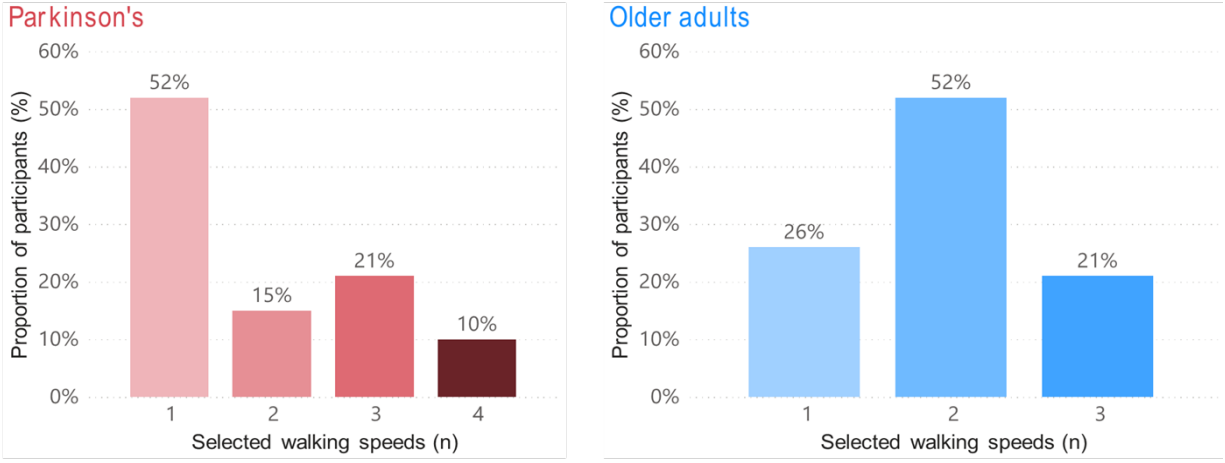


Figure 6-5. Characterisation of the number of selected walking speeds estimated from all laboratory tasks together in Parkinson's and older adults.

For both cohorts, significantly fewer selected walking speeds in laboratory assessments were observed in comparison to the real-world across each WB duration for both cohorts ($P = < 0.05$).

6.4 Discussion

Understanding of how RWS is modulated within a single WB could provide important insight into real-world walking adaptability. This chapter aimed to explore whether the number of selected walking speeds was able to provide insight into how RWS is modulated across individuals, cohorts, WB durations, and assessment settings. In the real-world, participants were largely characterised by three, four and five selected walking speeds. While variation across WB duration thresholds was evident, it was difficult to draw any definitive conclusions on the exact influence each context had upon modulations. In a laboratory setting, participants were characterised by one or two selected walking speeds for PD and OAs, respectively, which was significantly less than in the real-world, demonstrating the different challenges each assessment environment poses to RWS modulation strategies. Here the utility of a novel application

of the ‘Mclust’ (Scrucca et al., 2016) algorithm is discussed and selected walking speeds in their ability to reflect modulations within RWS, whilst also highlighting limitations and identifying areas of future work.

6.4.1 Real-world characterisation of selected walking speeds

Participants exhibited three, four, or five selected walking speeds, indicating different strategies for modulating RWS. Within a single WB, RWS was expected to demonstrate three distinct phases: acceleration, steady-state, and deceleration, with additional variability to adapt to real-world demands. These findings support the hypothesis and expand upon previous knowledge about the number of selected speeds in RWS (Atrsaei et al., 2021; Brodie et al., 2017; Van Ancum et al., 2019). Prior studies in OAs (Van Ancum et al., 2019) and PD (Atrsaei et al., 2021), fitted a GMM with two modes to RWS, assuming the existence of two selected walking speeds (faster and slower). They assessed goodness of fit using Ashman's D (Ashman et al., 1994), where a score of ≥2 indicates bimodality. However, Ashman's D does not quantify the optimal number of selected speeds. A more recent study by Baroudi et al., 2022 employed a multi-level modelling approach, which was more similar to the approach in this chapter and identified an optimal number of five selected walking speeds across all individuals. However, comparisons are limited as their population consisted of young athletes who were assessed across 14 days. In contrast, in PD participants, Atrsaei et al., 2021 identified a bimodal distribution based on data from a single day, capturing a smaller number of walking modulations and potentially resulting in fewer selected speeds. The results showed differences in selected walking speeds across individuals, which suggests the need to estimate the number of selected walking speeds individually, rather than assuming all participants have the same uniform number.

6.4.2 Were selected walking speeds modulated differently between WBs?

Based on ***Chapter 4*** and previous literature (Del Din et al., 2016a; Shah et al., 2020a), it was hypothesized that selected walking speeds would be modulated differently to adapt RWS to various activities inferred from different WB duration thresholds. These findings partially support this hypothesis, as variation in the number of selected walking speeds was observed across WB durations (Figure 6-4). However, it was difficult to draw definitive patterns or trends from the results to understand the precise influence of each WB duration threshold on RWS modulations. The weighted averages of

selected walking speeds appeared to show more variability between WB durations in the OA cohort compared to the PD cohort (Table 6-2), although no significant differences were observed between the cohorts. This finding is inconsistent with the hypothesis, as gait modulation was expected to differ more significantly in PD. This hypothesis was based on previous research that explored patterns of ambulatory behaviour in PD and OA participants using metrics such as "Variability" (Lord et al., 2013c). Variability refers to within-subject variability in WB duration, and previous studies have shown reduced variability in PD, suggesting a more "inflexible" pattern of walking activity (Lord et al., 2013c). Therefore, differences in the number of speeds would suggest inflexibility in adapting RWS, but this was not evident within the real-world results.

This study represents the first investigation into the differences in modulation of selected walking speeds across various WB durations and indoor/outdoor locations in individuals with PD and OAs. Despite these initial findings, there is still a limited understanding of what information is reflected by the number of selected walking speeds. Despite only fitting a distribution with two selected walking speeds, Atrsaei et al., 2021, estimated a fixed number of selected walking speeds from all WBs > 15 seconds and found a correlation between increased variability of the ‘slowest’ or ‘lowest’ selected walking speed with an increased dopaminergic medication intake throughout the day. which suggests a possible link between medication fluctuations. In PD, completing such tasks indoors may be independent of ON/OFF medication states, where FOG symptoms are more likely to occur during short intermittent periods of indoor walking (Mancini et al., 2018; Nieuwboer and Giladi, 2013). These factors could contribute to fluctuations in RWS modulations and result in greater variation in the pattern of selected walking speeds across individuals (Atrsaei et al., 2021; Smulders et al., 2016). However, in the present study, motor disease severity of participants was relatively low, therefore the majority of participants may not experience FOG events.

Balance and postural control deficits are commonly associated with PD (Raccagni et al., 2020), and may all influence the ability for people with PD to modulate gait. Reduced muscle function is one of the symptoms experienced by individual’s with PD (Pääsuke et al., 2004), where deficits in force modulation and production may also occur (Park and Stelmach, 2007). Previous research has shown that PD affects the capacity to produce maximal and rapid force (Pelicioni et al., 2021), which could negatively affect the ability to quickly recover stepping to avoid tripping and

subsequently sustaining a fall. Additionally fatigue is a debilitating non-motor symptom experienced by individual's with PD (Friedman and Friedman, 1993), where previous research has found that people with PD with increased fatigue had slower acceleration and walking speed and shorter (Tanaka et al., 2014). Thus, fatigue could influence the ability to modulate walking, particularly during prolonged WBs. Increased cognitive impairment is another non-motor symptom associated with PD, which could also affect an individual's ability to safely modulate their walking within complex environments (Mc Ardle et al., 2022), however this is yet to be explored.

A reduced number of selected walking speeds could also imply reduced between-walk adaptability, implying a reduced ability to avoid obstacles and quickly adapt and recover whilst a trip or slip occurs (Brodie et al., 2017). While no study has explored associations between falls risk and the number of selected speeds with RWS, Brodie et al., 2017 assessed cadence across seven days and found participants with a larger distribution, characterized by two modes (bimodal) had a lower risk of falls than individuals with a cadence distribution better modelled by a single mode. While this was not explored in the present chapter, different walking modulation strategies maybe more evident in the spatial (step length) or temporal (step time) DMOs that RWS is estimated from. Reduced step length is a continuous gait deficit that is commonly experienced by people with PD (Del Din et al., 2016a; Zanardi et al., 2021), where it's been previously demonstrated that people with PD increase their cadence to account for reduced step/stride length in order to maintain their walking speed (Morris et al., 1996, 1994). Thus, an interesting area of future research would be to characterise the distributions across a range of additional DMOs, which could in turn reveal more sensitive markers of gait modulation across environments and WB durations in comparison to RWS.

Understanding the relationship between selected walking speed modulations and environments is complex due to the influence of environmental constraints. Factors such as changes in walking surfaces caused by weather conditions (e.g., ice, rain) (Kim and Brown, 2022; Toda et al., 2020), variations in terrain (e.g., potholes, inclines, declines, curbs) (Kowalsky et al., 2021), increased anxiety levels (Kandola et al., 2018; Zimmermann et al., 2020), lighting conditions (Bicket et al., 2020), noise levels, and the presence of other individuals can contribute to differences in gait modulation strategies. Although these specific environmental factors were not captured in the present study, it would be valuable for future research to include metrics related to

environmental and spatial behaviour, such as the life-space assessment (Liddle et al., 2014), GPS measures of activity space (Hirsch et al., 2014), or the quantification of travel patterns and engagement with different environments (Bayat et al., 2020). Investigating the influence of these factors on the number of modulations in selected walking speeds may provide further insights into whether the ability of people with PD to adapt gait affects physical activity and limits out-of-home mobility, which is associated with increased sedentary behaviour, fall risk and heightened independence on carers to assist in completion of their day to day activities (Milanović et al., 2013; Suri et al., 2023).

6.4.3 Were selected walking speeds different between assessment?

In the laboratory setting, participants with PD and OAs exhibited primarily one or two selected walking speeds, which is fewer compared to real-world conditions. This outcome was expected due to the differences in complexity between unsupervised real-world assessments (most complex) and supervised laboratory settings (least complex) (Warmerdam et al., 2020). Previous studies have consistently shown disparities in DMOs (including walking speed) when assessed in laboratory versus real-world environments (***Chapter 2*** and (Atrsaei et al., 2021; Corrà et al., 2021; Del Din et al., 2016a; Shah et al., 2020c; Toosizadeh et al., 2015)). Despite this, the laboratory protocol in this study was designed to replicate the range of walking speeds observed in real-world scenarios by incorporating varying levels of complexity (Mazzà et al., 2021; Scott et al., 2022). In the same cohort, Scott et al., 2022 reported a visually similar distribution of walking speeds between laboratory and real-world tasks, indicating successful replication of real-world complexity. However, their real-world assessment period was limited to 2.5 hours, in contrast to the seven-day duration of the present study. Additionally, their analysis involved visual inspection of walking speeds without quantitative modelling of optimal distributions for each participant individually. Consequently, the fact that OAs demonstrated a larger number of selected walking speeds suggests they had a greater ability to adapt their gait to safely navigate the challenges presented by each task, as compared to individuals with PD. Other literature has quantified a fixed number of two selected walking speeds in a laboratory setting, suggesting that a similar number of modulations occur within walking speed between assessment setting (Atrsaei et al., 2021; Van Ancum et al., 2019). While not exploring differences in the number of selected walking speed, Van Ancum et al., 2019 found low to negligible correlations between the median value from each selected

walking speed. Atrsaei et al., 2021 demonstrated higher variability within the lowest or slowest selected walking speed in the real-world, in comparison to the lab, which supports the argument that real-world environments are more challenging.

6.4.4 Limitations

The application of 'Mclust' was computationally heavy, where it was not explored whether a more efficient method exists. The sample size for both cohorts was small and the PD cohort had a mild to moderate disease severity and thus the results may not be generalisable to the PD population as a whole. As the study was conducted during COVID-19, this could have had a negative influence upon the confidence of participants to leave the house, restricting their out of home activities (Falla et al., 2021; Knapik et al., 2021; Luis-Martínez et al., 2021). Future studies in a larger sample, with more varied motor symptom severity, that is not confounded by COVID-19 is needed. Such as the nature of the TVS, a large amount of clinical information was not collected, so it was not possible to explore in detail whether the number of selected-walking speeds corresponds to clinical characteristics, such as gait freezing and medication. This is an essential area of future analysis, which should be completed in cohorts with wide ranges in disease severity, medication intakes and symptoms.

6.4.5 Clinical implications & future directions

At present there is limited understanding of whether a larger or smaller number of selected walking speeds can provide objective measures of real-world walking adaptability, or whether they can provide clinical insight into the impact of PD upon an individual's mobility. A reduced number of selected walking speeds within RWS could imply reduce ability to avoid obstacles, or reduced ability to rapidly adapt stepping to recover balance when a slip or trip occurs and avoid sustaining a fall (Brodie et al., 2017). People with PD are at more risk of sustaining a fall in comparison to OAs (Del Din et al., 2020; Kalilani et al., 2016), where FOG symptoms are one of the most prominent falls risk factors after sustaining a previous fall. Conversely, a larger number of selected walking speeds could be associated with increased motor fluctuations, or FOG which could create a more inconsistent gait pattern, particularly within the initiation and acceleration phases of gait (Plotnik et al., 2008). If an association between a larger number of selected walking speeds and motor fluctuations were found, this may represent an endpoint target in an interventional trial.

6.4.6 Conclusion

Understanding of how RWS is modulated within a single WB could have several advantages for the clinical assessment of PD, such as insight the ability of individuals to safely adapt walking in different environmental settings to avoid sustaining a fall, which could lead to targeted interventions to improve real-world adaptability. The number of modulations within RWS, could be quantified through estimation of the number of modes, or selected walking speeds, within the distribution. While there is no 'gold standard' method to achieve this, the 'Mclust' algorithm (Scrucca et al., 2016) offers a more comprehensive and data-driven approach in comparison to previous methods (Atrsaei et al., 2021; Brodie et al., 2017; Van Ancum et al., 2019). The findings demonstrate the importance of modelling, rather than assuming a given number of modes exist within the data. It was difficult to draw may be definitive conclusions of what the number of selected walking speeds corresponds to. There is a need to further validate this method in a larger cohort with a more diverse range of PD participants. The findings of this study lay a framework for future research and in the next chapter of this thesis, an explanatory analysis will be undertaken to understand whether a higher or lower number of selected walking speeds is associated with real-world adaptability or specific aspects of PD.

Chapter 7. Unravelling the clinical implications of real-world selected walking speeds: A key to understanding real-world behaviour in Parkinson's?

The primary aim of this chapter was to undertake an explanatory analysis to understand whether a smaller or larger number of selected walking speeds corresponds to clinically useful information.

7.1 Introduction

In ***Chapter 6***, the number of modulations within RWS, were modelled as selected walking speeds. The results demonstrated that the number of selected walking speeds appeared to differ across environments and WB durations, however it was difficult to draw any conclusive patterns of trends to understand exactly how selected walking speeds are modulated differently. There is no understanding of whether a larger or smaller number of selected walking speeds corresponds to clinically meaningful outcomes. For example, a reduced number of selected walking speeds could reflect reduced control of stepping and increased loss of postural control (Brodie et al., 2017), which could be associated with increased impairment to muscle force production (Pelicioni et al., 2021), balance (Raccagni et al., 2020) and fatigue (Friedman and Friedman, 1993; Rochester et al., 2006; Tanaka et al., 2014) that occurs in PD. Conversely, FOG symptoms or fluctuations in mobility between ON/OFF medication states could cause a more inconsistent gait pattern in PD, which could result in a larger number of selected walking speeds (Jankovic, 2005; Kalilani et al., 2016). Longitudinally, selected walking speeds could also reflect changes in dynamic balance control of gait with respect to time, which has been shown to decrease with ageing (Boripuntakul et al., 2014; Gehlsen and Whaley, 1990). Alternatively, longitudinal changes in RWS modulations could increase alongside increasing severity of FOG symptoms (Zhang et al., 2021) and incidence of medication fluctuations and dyskinesias (Aradi and Hauser, 2020). Thus, the primary aim of this chapter was to understand which personal or clinical characteristics affect an individual's ability to modulate their gait, through selected walking speeds.

7.1.1 Aims and hypotheses

Aims

- Undertake an explanatory analysis to understand what information is reflected by a larger or smaller number of selected walking speeds, across different WB durations in in PD and OAs
- Characterise longitudinal differences in the number of selected walking speeds between PD and OAs

Hypotheses

- The number of selected walking speeds would reflect different clinical, demographic or gait-related factors dependent upon the WB duration
- Longitudinal changes in modulations of selected walking speeds would occur more rapidly in PD, in comparison to OAs.

7.2 Methods

7.2.1 Participants

Participants with PD and OAs were included from the 18-, 36-, 54- and 72-month time points of the ICICLE-GAIT study (Del Din et al., 2016a; Rochester et al., 2014; Yarnall et al., 2014), with recruitment and diagnosis as described in ***Chapter 3.*** Global cognition was assessed through the Montreal Cognitive Assessment (MoCA) score (Nasreddine et al., 2005) and depression symptoms were evaluated with the Geriatric Depression Scale-15 score (GDS-15) (Sheikh and Yesavage, 1986).

For PD participants, motor experiences of daily living and motor symptom severity were evaluated using the MDS-UPDRS parts II (0-65) & III (0-108) (Goetz et al., 2008) , respectively, and Hoehn and Yahr (H&Y) stage (0-5). Participants were tested 'ON' medication, defined as within 1 hour after PD medication. Freezing of gait was assessed with the New Freezing of Gait Questionnaire (NFOG) (Hulzinga et al., 2020) (score min to max 0-25), where Levodopa Equivalent Daily Dosage (LEDD) mg/day was calculated in accordance with previously defined methods (Tomlinson et al., 2010).

7.2.2 Real-world protocol

The participants were continuously monitored over seven days in their habitual environment, whilst equipped with an Axivity AX3 sensor, that was attached to the fifth

lumbar vertebra with a hydrogel adhesive (PALStickies, PAL Technologies, Glasgow, UK) and covered with Hypafix™ bandage. Data from the 36-month assessment was chosen for the cross-sectional analysis as it provided the largest sample size. After seven days, participants removed the device and posted it back to the researcher (Del Din et al., 2016a).

RWS was estimated per-step from the wearable data, using validated algorithms (Del Din et al., 2016b; Hickey et al., 2016). RWS was aggregated into specific WB thresholds (10 to 30 seconds, 30 to 60 seconds, > 60 seconds). All WBs < 10 seconds were excluded and only participants with > 3 days were included in any analysis.

7.2.3 Statistical analysis

7.2.4 Characterisation of selected walking speeds

GMMs were employed to estimate the number of modes, or selected walking speeds, existing in the distribution underlying RWS. GMMs were fitted utilizing the 'Mclust' function in the 'Mclust' package (Scrucca et al., 2016) in R (R Foundation for statistical computing, V4.02, Austria). The method has previously been defined in ***Chapter 6.*** In short, everyone's RWS assessed per each step over the 7-days is inputted into the algorithm, where Mclust fitted models containing different numbers of selected walking-speeds, ranging from one to nine. The model that has the largest BIC value, was determined as the optimal number of selected walking speeds. The algorithm then estimates the probability of each data point of RWS belonging to each mode, or selected speed and subsequently re-estimates the mean and variance parameters to optimise the fit upon the distribution.

Following these steps, for everyone's RWS across WBs; 10 to 30 seconds, 30 to 60 seconds, > 60 seconds and all WBs the following variables were estimated: (i) the optimal number of selected walking-speeds within the distribution of RWS and (ii) the mean and covariance of each selected walking-speed.

7.2.5 What information is reflected by the number of selected walking speeds?

This cross-sectional, explanatory analysis was performed at the 36-month time point of ICICLE-GAIT, as it contained the largest number of observations in comparison to the other time points. An overview of the explanatory analysis can be viewed in Figure 7-1 and is more extensively defined in the following sections.

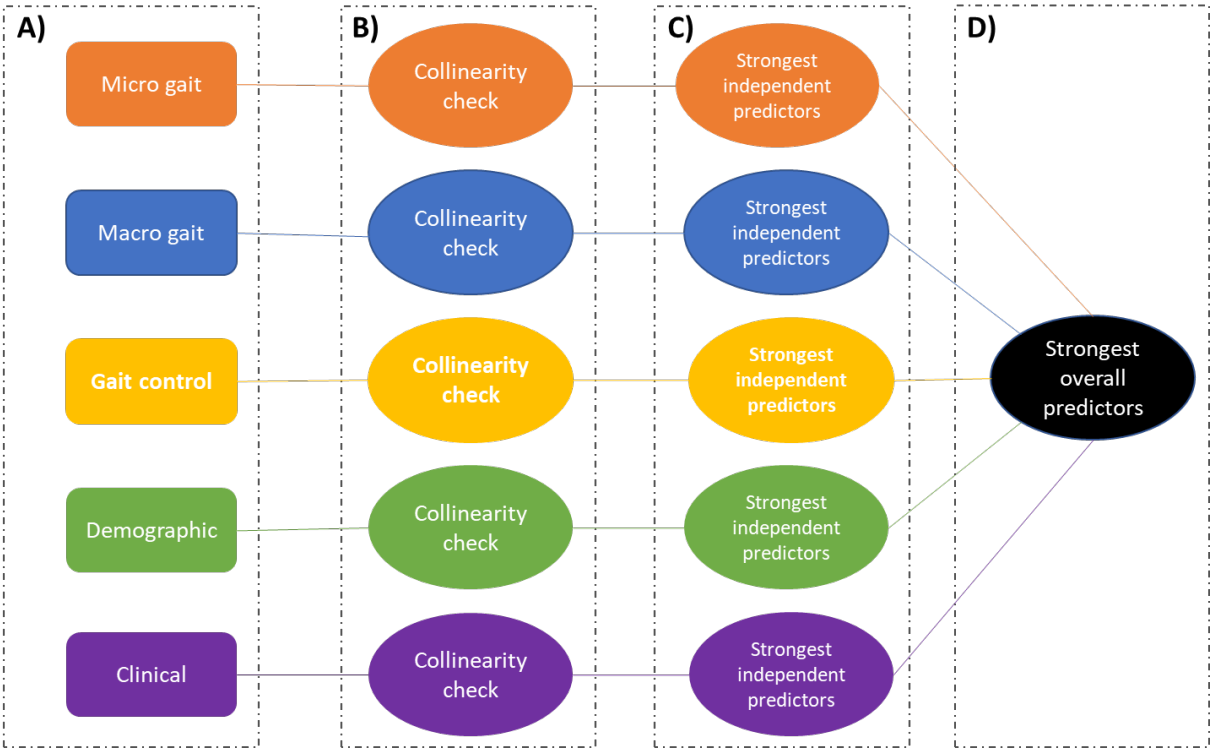


Figure 7-1. Process of identifying the strongest independent predictors of the number of selected walking speeds within each category of variable. This was repeated at each walking bout duration threshold.

7.2.5.1 Ordinal regression

Ordinal logistic regression was employed to explore which independent predictors have the strongest association with the number of selected walking speeds, at each WB duration threshold. In this instance, odds ratios represent the constant effect of a predictor x on the likelihood of having a larger or smaller number of selected walking speeds. An odds ratio of < 1 can be interpreted as, an increase in the predictor variable reduces the likelihood of having a larger number of selected walking speeds. In contrast an odds ratio of > 1 is interpreted as an increased likelihood of having a larger number of selected walking speeds. Below, the odds ratios have also been converted to probabilities, which is more intuitive, and easier to interpret.

7.2.5.2 Predictor selection (Figure 7-1A)

Potential predictor variables that might be associated with the number of selected walking speeds were identified from different categories of interest, namely, macro and micro gait outcomes, variables related to the control of gait, clinical and demographic information. Specifically, within the macro-gait outcomes category predictors related to

the volume, pattern and variability in macro-gait activity (Lord et al., 2013c). For micro gait outcomes 15 potential predictors were included related to the pace, rhythm, variability, asymmetry and postural control five domains of gait (Lord et al., 2013a). Micro gait and macro-gait predictors were estimated in accordance with methods defined in ***Chapter 3*** through application of previously validated algorithms (Del Din et al., 2016b; Lord et al., 2013c) and were aggregated within the WB durations defined above. The gait control category included (i) balance (as measured by Activities Balance Confidence Scale (ABC)) (Powell and Myers, 1995), (ii) lower extremity function, as measured by time (seconds) to complete five repetitions of the sit to stand test, and (iii) Fatigue as measured by multi-dimensional fatigue index (MFI), a 20-item questionnaire that assesses (Smets et al., 1995) total fatigue, physical fatigue and general fatigue, where a larger scores indicate higher fatigue. For the clinical category, medication dosage (LEDD) (Tomlinson et al., 2010) perception of motor experiences of daily living (MDS-UPDRS II), Motor symptom severity (MDS-UPDRS III) (Goetz et al., 2008), motor disability (H&Y stage) (Goetz et al., 2008) and Incidence of FOG events (NFOG) score (Hulzinga et al., 2020) were included. The demographic category included mass, height, and cognition (MoCA). All models were controlled for sex, age and depression (GDS). A list of all variables included in the backwards regression for each category can be viewed in Table 7-1.

Table 7-1. Selected independent predictors from each category that were assessed for any association with the number of selected walking speeds.

Category	Predictor
Clinical (PD only)	• *Medication dosage (LEDD)* • *Motor experiences of daily living (MDS-UPDRS II)* • *Motor symptom severity (MDS-UPDRS III)* • *Incidence of freezing of gait events (NFOG)* • *PD motor disability (H&Y stage)*
Demographics	• *Demographics (height, sex, mass, BMI and age)* • *Depression (GDS)* • *Cognition (MoCA)*
Gait control	• *General fatigue, physical fatigue and total fatigue (*multi-dimensional fatigue index) • *Balance (ABC scale)* • *Lower extremity function (five times sit to stand time)*
Micro gait	• *Stance Time* • *Stance time SD* • *Stance time asymmetry* • *Step time* • *Step time SD* • *Step time asymmetry* • *Step length* • *Step length SD* • *Step length asymmetry* • *Swing time* • *Swing time SD* • *Swing time asymmetry* • *RWS* • *RWS SD*
Macro gait	• *Alpha* • *Variability* • *Step count* • *Total WBs (per WB duration)* • *Walking Seconds* • *Walking % per day*

LEDD = Levodopa Equivalent Daily Dosage. MDS-UPDRS = Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part II or III. NFOG = New freezing of gait questionnaire. H&Y stage = Hoehn and Yahr stage. BMI = Body mass index. GDS = Global depression scale. MoCA = Montreal cognitive assessment. ABC scale = Activities balance confidence scale. SD = Standard deviation. RWS = real-world walking speed. WB = Walking bout.

7.2.5.3 Collinearity check (Figure 7-1B)

This was achieved by estimating Pearson's correlations between all predictors within each category separately. If two predictors were highly correlated with eachother, (R > 0.75) (Mukaka, 2012), then only the predictor that had the highest correlation with the number of selected speeds was bought forward into the backwards ordinal regressions.

7.2.5.4 Strongest independent predictors (Figure 7-1C)

To identify the strongest independent predictors of the number of selected walking speeds within each category or variables, a series of backwards ordinal regression models were carried out in R ('polr' function in the 'MASS' package) (Ripley et al., 2022).

Within each category, all potential predictors that remained following the collinearity check were inputted as predictors into the same ordinal regression model and assessed for their association with the number of selected walking speeds. All predictors that were not significantly associated with the number of speeds (*P = > 0.05),* were removed from the model. This process was repeated until the model contained only variables that were significantly associated with the number of selected walking speeds, or until there were no significant predictors left in the model.

7.2.5.5 Strongest overall predictors (Figure 7-1D)

Similar to the previous step, only the variables that still had a significant association with the number of selected walking speeds were selected as the independent predictors that best explained what the number of speeds corresponds to across all categories and WB durations. Only the predictor variables that remained following this process are reported, along with the proportion of variance explained (R^2 Nagelkerke) by each model across each WB duration.

All numerical predictor variables were re-scaled by their mean and SD, to ensure robustness of comparison. Each model was adjusted for sex and age, where the Odds ratios, 95% CIs, P values and R^2 Nagelkerke were reported.

7.2.6 Characterisation of longitudinal change in selected walking speeds

Ordinal logistic regression was used to investigate whether the probability that the number of selected walking speeds within RWS changed over time, in 88 PD participants and 111 OAs. The time point, sex, and baseline age were included as fixed

effects. For the random effects, a random intercept for participant was modelled. Performance was assessed by calculating conditional R^2, marginal R^2 and confidence intervals. This was repeated with the number of selected walking speeds estimated from each WB duration.

7.3 Results

A summary of all participants demographic and clinical information can be viewed below (Table 7-2), a summary table of all real-world information can be observed in Appendix 7. Motor severity of the PD participants at baseline was low (MDS-UPDRS = 33 points). At 18 months, 12% of individuals had already experienced FOG events, by 72 months 19% of individuals were experiencing FOG. 94% of participants were taking dopaminergic medication at 18 months, by 72-months 100% of participants were taking dopaminergic medication and LEDD had increased by an average of 314.49 ± 240.68 across all participants who were assessed across both 18 and 72 months. Baseline gait characteristics have been previously defined in detail (Galna et al., 2015; Morris et al., 2017b).

Table 7-2. Clinical and demographic information of the ICICLE-GAIT cohort at 18-, 36-, 54- and 72-months assessment timepoints.

	18 months		36 months		54 months		72 months	
Group	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**	**PD**	**OA**
n	43	51	62	94	59	49	49	43
Age (yrs)	69.1 ± 10.7	70.8 ± 7.1	69.3 ± 9.5	72.5 ± 6.5	**68.8 ± 9.4**	**73.0 ± 7.6**	71.3 ± 9.5	72.8 ± 6.5
Sex (Male / Female, n)	31 / 12	27 / 24	**40 / 22**	**44 / 50**	39 / 20	28 / 24	35 / 14	26 / 17
Height (metres)	1.69 ± 0.88	1.69 ± 0.08	1.69 ± 0.08	1.68 ± 0.09	1.68 ± 0.8	1.70 ± 0.09	1.67 ± 0.09	1.70 ± 0.08
Body Mass (kg)	79 ± 15	81 ± 15	79 ± 17	77 ± 13	76 ± 15	81 ± 13	77 ± 14	84 ± 13
GDS	2.65 ± 2.78	1.17 ± 1.95	2.80 ± 2.40	1.41 ± 2.43	2.77 ± 2.54	1.36 ± 2.14	3.35 ± 3	1.26 ± 2
MoCA	25.93 ± 3.6	27.5 ± 2.3	26.2 ± 3.5	27.4 ± 2.3	26.1 ± 3.5	26.1 ± 3.31	24.7 ± 4.6	26.6 ± 3.3
MDS-UPDRS II (points)	11 ± 6	-	13 ± 4	-	14 ± 5	-	16 ± 5	-
MDS-UPDRS III (points)	33 ± 11	-	38 ± 12.4	-	39.1 ± 12.6	-	40.9 ± 13.8	-
Disease duration (years)	7.90 ± 4.69	-	8.77 ± 4.02	-	10.36 ± 4.31	-	12.01 ± 4.5	-
Hoehn and Yahr Stage								
I, n (%)	5 (11%)	-	1 (1%)	-	1 (2%)	-	0 (0%)	-
II, n (%)	40 (85%)	-	57 (90%)	-	51 (86%)	-	35 (70%)	-
III, n (%)	2 (4%)	-	6 (9%)	-	7 (12%)	-	12 (24%)	-
IV, n (%)	0 (0%)	-	0 (0%)	-	0 (0%)	-	3 (6%)	-
NFOG (points)	1.16 ± 4.57		2.17 ± 5.33		1.65 ± 4.73		2.21 ± 5.04	
LEDD (mg/day)	395 ± 206	-	515 ± 256	-	663 ± 294	-	720 ± 312	-

Data presented as mean and standard deviation (SD). Bold highlight indicates significant difference at <0.05 significance level between (i) between PD and OAs at specific time point or (ii) independent dataset and 36 month of ICICLE-GAIT dataset. '-'describes an empty field, due to data availability. MDS-UPDRS III = Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III. LEDD = Levodopa equivalent daily dosage. Independent data set compared to 36 months ICICLE-GAIT data.

7.3.1 Characterisation of selected walking walking-speeds within RWS

The largest proportion of participants from both cohorts were characterised by three or four selected walking speeds, across the majority of WB durations (Table 7-3) (Appendix 6).

Table 7-3. The median and range of the number of selected walking speeds estimated in people with PD and OAs, across each WB duration at the 36-month time point.

WB duration	PD	OA
All WBs	4 [3 , 7]	4 [3 , 7]
10 to 30 seconds	3 [2 , 5]	3 [2 , 5]
30 to 60 seconds	3 [2 , 5]	3 [2 , 6]
> 60 seconds	3 [2 , 9]	4 [2 , 7]

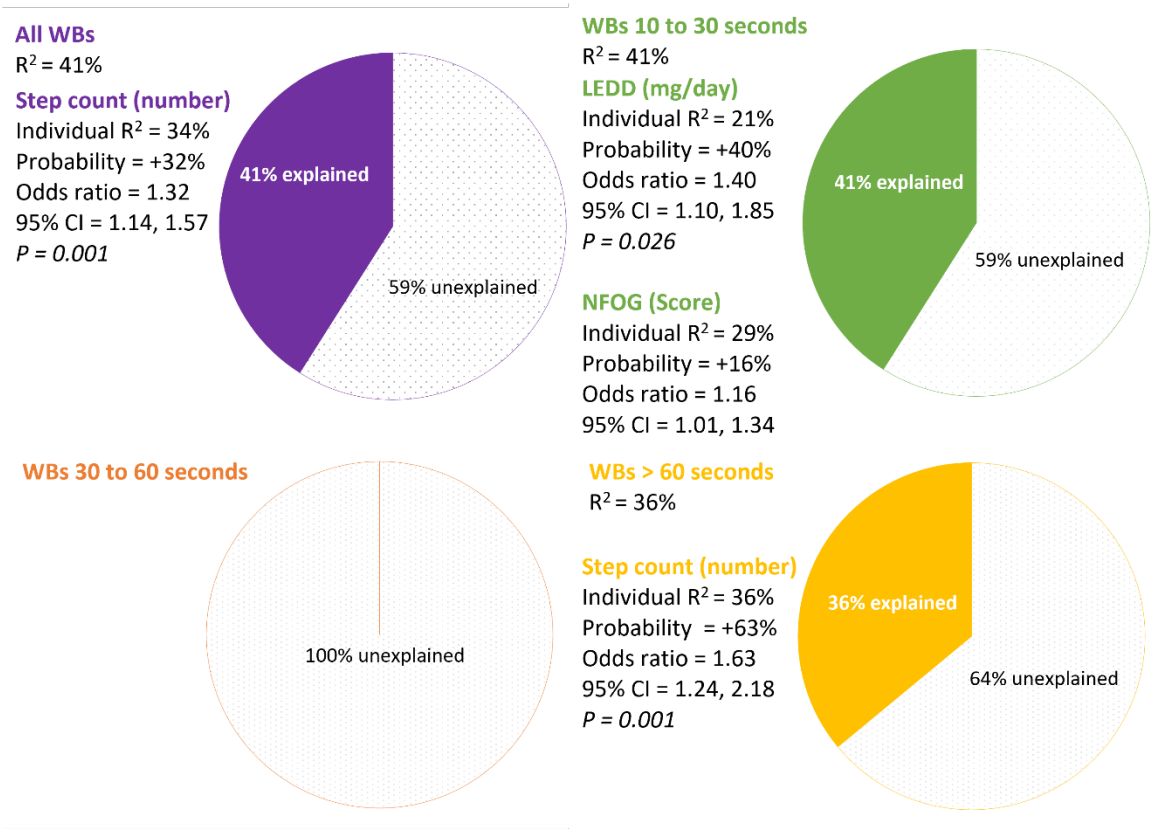
7.3.2 What information is reflected by the number of selected walking speeds?

An overview of the strongest independent predictors of the number of selected walking speeds within each category can be viewed in Appendix 8. For both cohorts, the information reflected by the number of selected walking speeds was dependent upon the WB duration.

7.3.2.1 PD

For PD participants at all WBs and WBs > 60 seconds, increased step count was the only significant independent predictor of the number of selected walking speeds (Figure 7-2). Specifically, an increase in weekly step count of 10,000 steps was associated with a 32% or 62% increased likelihood of greater number of selected walking speeds for all WBs and long WBs respectively.

For WBs between 10 to 30 seconds, increasing LEDD and NFOG scores significantly predicted a larger number of selected walking speeds (Figure 7-2). An increase in LEDD of 100 mg/day was associated with a 40% increased likelihood of someone having a larger number of selected walking speeds. An increase in NFOG score of 10 points had a 16% increased the likelihood of having a larger number of selected walking speeds.



Step count probability reported as increased likelihood of larger number of speeds per 10,000 steps. LEDD probability reported as increased likelihood per 100mmhg increase NFOG probability reported as increased likelihood for one point increase. '+' refers to probability of an increased number of selected speeds.

Figure 7-2. Strongest independent predictors of the number of selected walking speeds within each walking bout duration for the Parkinson's

7.3.2.2 OAs

At all WBs, an increased step count and increased walking time in minutes were the only significant predictors of a larger number of selected walking speeds. Specifically, a larger step count (by 10,000 steps) and larger walking time (by 166 minutes) was associated with a 311% increased likelihood of a larger number of selected walking speeds. In contrast, a larger walking time by 166 minutes was associated with a 74% increased likelihood of having a lower number of selected walking speeds.

Within both WBs between 10 to 30 seconds, and WBs > 60 seconds, a greater step length asymmetry by 0.01m was associated with a reduced 44% (10 to 30 seconds) and 88% (> 60 seconds) likelihood of having a smaller number of selected walking speeds. Similar to PD, no significant predictors were identified at WBs 30 to 60 seconds (Figure 7-3).

Step count and walking seconds probability reported as increased likelihood of larger number of speeds per 10,000 steps, or 10,000 seconds of walking respectively. Step length asymmetry probability reported as increased likelihood per 0.01m increase. '+' refers to probability of an increased number of selected speeds. '-'refers to probability of a reduced number of selected speeds.

Figure 7-3. Strongest independent predictors of the number of selected walking speeds within each walking bout duration for older adults.

7.3.3 Does the number of selected walking speeds change longitudinally?

The number of selected walking speeds estimated at each time point can be observed in Appendix 9. Significant change in the number of selected walking speeds was only observed within the PD cohort, at WBs 10 to 30 seconds, where the likelihood of an increased number of selected walking speeds increased by 41% more per year (Table 7-4).

Furthermore, when comparing the change between PD and OA cohorts, differences were only observed in WBs between 10 to 30 seconds, where the likelihood of an increase in the number of selected walking speeds was 35% larger for people with PD (Table 7-4).

Table 7-4. Annual change in the number of selected walking speeds recorded in Parkinson's and older adults and the difference in annual change between cohorts across the study duration, from 18 months to 72 months

	Annual change in selected walking speeds		**Difference in change of selected walking speeds**
WB duration (seconds)	**OA (Probability, odds ratios, 95% CI, *P, R^2*)**	**PD (Probability, odds ratios, 95% CI, *P, R^2*)**	**(Probability, odds ratios, 95% CI, *P, R^2*)**
All > 10	-25%, 0.85, (0.30, 2.42), 0.056, 6%	-21%, 0.89, (0.48, 1.64), 0.245, 4%	+3%, 1.03, (0.11, 9.04), 0.795, 5%
10 to 30	+3%, 1.03, (0.62, 1.70), 0.719, <1%	**+41%, 1.41, (0.89, 2.24), 0.001, 6%**	**+35%, 1.35, (0.13, 14.11), 0.030, 8%**
30 to 60	+2%, 1.02, (0.61, 1.70), 0.231, 2%	+13%, 1.13, (0.68, 1.87), 0.250, 1%	+6%, 1.06, (0.07, 15.85), 0.634, 2%
> 60	-9%, 0.91, (0.35, 2.36), 0.275, 10%	-1%, 0.99, (0.34, 2.83), 0.937, 9%	+6%, 1.06, (0.12, 9.58), 0.628, 11%

PD = Parkinson's. OA = Older adults. RWS = Real-world walking speed. WB = Walking bout. Estimated from a mixed linear regression model including 194 selected walking speed measures from 88 PD participants and 221 selected walking speed measures from 111 OA participants with age, sex and HY stage (in PD only), as covariates. Subject also a random effect to account for the correlation of measures of the same subject and a interaction term between follow up time (in years) and group (PD or OA).
'+' refers to probability of an increased number of selected speeds. '-' refers to probability of a reduced number of selected speeds.

7.4 Discussion

The primary aim of this chapter was to undertake an explanatory analysis to understand whether the number of selected walking speeds can provide meaningful insight into real-world behaviour. The findings were largely dependent upon the cohort and WB duration. For PD participants in short WBs, a larger number of selected walking speeds was driven by larger LEDD and NFOG score, highlighting that individual on higher dopaminergic medication doses and FOG symptoms had more variation within their ability to modulate their walking in short, primarily home-based WBs. In contrast, modulations of selected walking speeds at longer WBs, were driven by larger step volume. An individual with a larger step count would interact with a wider number of different real-world environments, thus required greater adaptations in their RWS to account for the greater variety of contextual challenges they face. Longitudinally, the number of selected walking speeds only changed within WBs 10 to 30 seconds in PD, and the rate of change was larger in PD compared to OAs.

7.4.1 Cross-sectional characterisation of selected walking speeds

The number of selected walking speeds was estimated in a larger number of participants (n=156), in comparison to ***Chapter 6*** (n=29). In the present chapter, individuals were largely characterised by three or four selected speeds, where variation was observed across individuals and WB durations. These findings collectively further emphasise that the distribution within RWS is not best modelled as a uniform number across all participants as previously suggested (Atrsaei et al., 2021; Baroudi et al., 2022; Brodie et al., 2017; Van Ancum et al., 2019). This has important implications for researchers seeking to quantify the number of modulations that occur within RWS, with estimation of selected walking speeds, in that it demonstrates that individuals modulate their gait differently in the real-world. Thus, it can be recommended that the number of selected walking speeds should be modelled for each individual separately.

7.4.2 What information is reflected by selected walking speeds in PD?

The strongest predictors of the number of selected walking speeds depended on the WB duration and cohort. In PD, greater LEDD and higher NFOG score were the only significant predictors of increased selected walking speeds within short WBs (10 to 30 seconds). Despite excluding WBs < 10 seconds, In ***Chapter 5,*** the majority of short WBs took place within indoor settings, which is speculated to predominantly be the home environment. RWS within short WBs would reflect essential household activities

(ie., getting a drink of water, going to the toilet etc.,). Thus, individuals may complete essential tasks such as these, irrespective of ON/OFF medication state, which could cause more variability in RWS (Corrà et al., 2021; Smulders et al., 2016) and impact upon the number of modulations (Atrsaei et al., 2021). A higher LEDD pertains to longer disease duration and severity, resulting in greater variability in walking speed between ON/OFF states. Medication fluctuations, alongside the type of activity within this WB duration (turning, obstacle negotiation etc.), would increase risk of gait freezing events (Mancini et al., 2018; Smulders et al., 2016). A greater NFOG score, is likely to have led to inconsistencies in acceleration and gait initiation, contributing to greater variability in selected walking speeds. These findings imply how medication and FOG symptoms are more likely to influence gait modulations within short WBs (Corrà et al., 2021; Mancini et al., 2018). Despite this, participants at the 36-month time point of ICICLE-GAIT were relatively early in their motor symptom severity (MDS-UPDRS III = 38 points), and some would not have experienced any medication fluctuations, with only 17% of individuals experiencing FOG events.

At a macro level, variability and alpha (proportion of the number of short WBs in comparison to long WBs) did not emerge as significant predictors of the number of selected walking speeds at any WB duration threshold. This was surprising given that previous research in the same cohort had found reduced variability, suggesting an ‘inflexible walking pattern’, in PD (Lord et al., 2013c). Another study found that individual’s that received deep brain stimulation surgery (DBS) had a significantly more variable and flexible walking pattern (Rochester et al., 2012), however the cohort of the present chapter did not include any individual’s that had DBS. Instead, at longer WBs (> 60 seconds) and all WBs, a larger weekly step count was identified as one of the strongest predictors of a larger number of selected walking speeds. This is logical given an individual with an increased step count, would have been more active across a wider range of contexts in comparison to an individual with fewer steps, which reflected the need to adapt their gait across a wider range of environments.

For both cohorts, the number of selected walking speeds showed no significant relationship with fatigue. Fatigue levels were assessed using the MFI scale, where a score of 20 indicates the highest level of fatigue within a specific category. Among the PD participants, their median scores for general and physical fatigue were 12 and 10, respectively, whereas the OA participants reported lower scores (general fatigue = 9, physical fatigue = 7). Previous studies have also highlighted a connection between

reduced acceleration, walking speed, and step length with increased fatigue in PD (Tanaka et al., 2014). Consequently, it was anticipated that during the longest WBs, greater fatigue would influence their ability to modulate their RWS and may limit their capacity to engage in a wider variety of activities outside their homes (Herlofson and Larsen, 2003), thereby resulting in a narrower range of selected walking speeds due to their adaptation to a more restricted set of circumstances. Surprisingly, there was no observable association between fatigue and selected walking speeds, potentially due to the participants reporting only moderate fatigue scores. It's important to note that motor symptom severity in PD is a significant contributing factor to increased fatigue. Therefore, the relatively low MDS-UPDRS III scores may explain why participants with more severe fatigue symptoms were not captured (Havlikova et al., 2008).

No association was found between perception of the individual's balance capabilities, as measured by ABC with selected walking speeds. Balance impairment in the cohort was not substantial, as median ABC scores for PD and OA participants was 77% and 95%, indicating moderate and high levels of functioning (Powell and Myers, 1995). An additional way to explore balance would be to quantify sway velocity, sway jerkiness (Mancini et al., 2012, 2011) and sway frequency estimated from accelerometers worn during > 30 seconds of a quiet stance task (Horak and Mancini, 2013). Additionally, estimation of postural responses such as number of steps and time to equilibrium quantified assessed from the push and release test (El-Gohary et al., 2017), can measure ineffective stepping response in a supervised setting. It would be interesting to explore whether these metrics are related to the number of selected walking speeds. Impairment to lower body function was relatively low, as time to complete five sit to stand repetitions recorded to be 16.8 seconds for PD participants, which is lower than the mean sit to stand time recorded for individual's with H&Y stage 2 impairment (21.3 seconds) (Duncan et al., 2011). This could explain a lack of association with the number of selected walking speeds, however perhaps modulations are more related to rapid force production, which increases the ability to rapidly adapt walking within a single WB (Pelicioni et al., 2021), which warrants further exploration.

7.4.3 What information is reflected by selected walking speeds in OAs?

Similar to people with PD, for OA participants, an increased step count was associated with a higher likelihood of having a larger number of selected walking speeds at All WBs. OAs had a significantly higher number of weekly steps at All WBs, which

explained why they also had a larger number of selected walking speeds. However, step count did not predict the number of speeds in WBs longer than 60 seconds, where no significant predictors were found. The reason behind OAs having a larger number of selected walking speed modulations within long WBs is unclear. While longer WBs mainly occur outdoors, in contrast to short WBs that primarily take place indoors (***Chapter 5***), it is possible that the increased variability in environmental location during longer WBs contributes to more modulations in walking speeds. However, based on previous findings, this seems unlikely. Future studies could explore metrics related to environmental and spatial behaviour, such as life-space assessment (Liddle et al., 2014; Stalvey et al., 1999), or GPS measures of activity space (Hirsch et al., 2014), to determine if they influence the number of modulations in walking speeds during longer WBs. It is possible that OAs have larger life or activity spaces and engage with a wider range of environments compared to PD, resulting in more modulations in walking speeds.

For OAs at WBs 10 to 30 seconds and > 60 seconds, a larger step length asymmetry was associated with an increased likelihood of having fewer selected walking speeds. Previous real-world research in the same cohort has demonstrated that step length asymmetry was significantly higher in PD compared to OAs indicating a less symmetrical walking pattern in PD, indicating potentially an inability to modulate RWS, which could propagate an increased falls risk (Del Din et al., 2016a). Additional research found that step length variability, not asymmetry was higher in PD fallers in comparison to non-fallers (Del Din et al., 2019). While step length asymmetry did not emerge as a significant predictor of PD, these findings demonstrate that within short and long WBs, OAs with a less symmetrical gait are unable to modulate their RWS to adapt their walking for to the type of environment that individual's encounter within short WBs (primarily household) and longer WBs (primarily outdoors), which present their own respective challenges.

7.4.4 Did selected walking speeds change longitudinally?

Significant increases in the number of selected walking speeds across the study duration was only observed for PD participants, with RWS assessed in short WBs, where no change in selected walking speeds was observed for OA participants with respect to time. Interestingly, the explanatory analysis revealed that both LEDD and NFOG were significant predictors of a larger number of modulations in selected walking speeds within short bouts. PD participants in the present study had increased

incidence of FOG events and increased motor symptom severity at the end of the study duration. To manage these worsening symptoms LEDD increased across all participants by a mean of 323 ± 390 mg/day across the study duration. However, the effectiveness of the medication diminishes over time, which could've lead to more severe motor fluctuations (Aradi and Hauser, 2020; Jankovic, 2005). Thus, the progression in symptom severity, medication usage, and the negative consequences of prolonged medication usage on motor fluctuations could drive greater variability within RWS between WBs and explain why changes in selected walking speeds were only observed within PD participants in short WBs. Increases in selected walking speeds, may lead to difficulties with gait initiation, and differences in selected walking speed modulations over time (Aradi and Hauser, 2020).

7.4.5 Clinical implications & future directions

A larger number of selected walking speeds was associated with higher dosages of medication and FOG scores, only within short WBs. Furthermore, short WBs were the only duration threshold where selected walking speeds changed across the study duration. Short WBs likely take place in a home setting, so in a clinical setting if an individual with PD that has experienced increases in their medication dosage and FOG score, report that they are having difficulty navigating the home environment, leading to reduced ability to independently carry out daily activities, this could be the result of increased variability and inconsistency in the ability to safely modulate gait. Subsequently, this could lead to adjustment of treatment methods, or specific training such as virtual-reality interventions (Mirelman et al., 2016; Pazzaglia et al., 2020). While such interventions can improve balance outcomes or walking adaptability as measured in a controlled clinical setting, there is limited evidence that they improve walking adaptability in a real-world setting. Therefore, reduction in selected walking speeds could act as an ecological valid, positive outcome for these interventions, which should be explored in the future. Additionally, modulations within RWS may reflect the interaction between several motor, perceptual and behavioural processes such as anxiety and fear (Toby J. Ellmers et al., 2022; Toby J Ellmers et al., 2022), and associations could be explored in future studies. From an environment perspective, simple recommendations can be made to ensure the optimisation of safe indoor environments to reduce the risk of slipping or tripping, sustaining a fall and subsequently a suffering a debilitating injury, due to changes in involuntary and

voluntary control of movement resultant from medication fluctuations and FOG symptoms.

7.4.1 Limitations

Despite exploring associations with LEDD, future research is needed to explore relationships between the number of selected walking speeds and the number of ON/OFF medication states. Due to a lack of variation in Hoehn and Yahr stage, it was not included as a predictor variable of the number of selected walking speeds, future research with greater variability in Hoehn and Yahr stage should explore this. Additionally, explorations of relationships between falls risk, measures of peak force and rate of force development estimated from maximum knee isometric contractions (Pelicioni et al., 2021), balance as quantified from wearable sensor data (sway velocity, sway jerkiness and sway frequency (Mancini et al., 2012, 2011)), anxiety and fear with the number of selected walking speeds could identify further predictors.

7.4.2 Conclusions

The clinical assessment of PD is often based upon one-off assessments of many motor items, or perhaps one-time assessments of balance, gait, and other fall risk factors. Due to their brief nature, these approaches do not capture the impact of PD motor symptoms and gait disturbances upon how walking is modulated across different real-world contexts. Selected walking speeds may objectively quantify modulations, where a larger number of speeds corresponded to different outcomes dependent upon the WB duration. A larger number of selected walking speeds corresponds to greater levels of physical activity at longer WBs and conversely increased medication dosage and FOG scores within short WBs. Furthermore, the number of selected speeds only increased within short WBs for PD. This information could improve insight of risk factors for reduced independence, quality of life and potentially future risk of falls in PD, and potentially be applied as a future endpoint if the goal is to improve individual's real-world adaptability.

Chapter 8. Thesis overview and conclusions

This thesis aimed to explore, validate and characterise RWS as a DMO, to understand what complementary information it can provide to enhance the assessment of mobility in PD. The current assessment is based upon brief testing which may only provide a snapshot insight into an individual's mobility capacity under optimal conditions (Rochester et al., 2020; Viceconti et al., 2022; Warmerdam et al., 2020). Furthermore, it does not directly assess aspects of quality of life that are of most importance to patients, such as preservation of their ability to walk independently and safely in their daily lives (Deane et al., 2014; Delgado-Ortiz et al., 2023; Port et al., 2021). While no tools that can continuously assess real-world mobility are adopted for clinical use, one potential solution is within the continuous measurement of DMOs, such as RWS, with wearable devices. Specifically, RWS can be remotely assessed across consecutive days, offering an objective measure of real-world mobility performance, providing data driven and detailed insight that can complement existing the diagnosis and management of PD and measure change in aspects of quality of life that are of importance to patients.

Despite the promise, there is a need to undertake explorations of clinical validity, to understand exactly what insight of mobility DMOs, such as RWS, are able to provide in PD. The clinical validity of DMOs assessed in a supervised setting has received a relatively large amount of attention (Polhemus et al., 2021). However, the systematic review conducted in ***Chapter 2****,* found an overall lack of studies that have sought to objectively understand what information is provided by real-world DMOs, which confirmed the hypothesis. RWS was the most widely explored DMO, where studies exploring whether DMOs were able to different between PD and OAs had the largest body of evidence. No real-world studies that included longitudinal data were found, which is an essential gap, as tools that can track the progressive nature of PD not captured by existing assessment would be clinically useful. Additionally, a small number of studies demonstrated how aggregating DMOs into different WB duration thresholds (Del Din et al., 2016a; Shah et al., 2020a), or novel methods of statistically summarising RWS based upon its distribution (Atrsaei et al., 2021; Corrà et al., 2021), are able to add further insight into the fluctuating nature of real-world mobility that could complement existing clinical assessment.

In ***Chapter 4****,* a comprehensive study was undertaken to address the gaps identified in the review, including longitudinal data and aggregation of RWS into different WB durations thresholds. Cross-sectionally, RWS was slower in PD in comparison to OAs, across a range of WB durations. Furthermore, RWS declined in both PD and OAs across the six-year study duration, however this was more rapid in PD by 0.02 m/s more per year. Previous research in the same cohort in a supervised setting found no difference in the rate of decline in walking speed (Wilson et al., 2020), suggesting that real-world mobility measures are more sensitive to detecting PD-specific deterioration in real-world mobility. RWS was not related to motor severity (MDS-UPDRS III) when aggregated at all WBs, but a significant relationship did exist with RWS when aggregated within medium length WBs. Longitudinally, MDS-UPDRS III scores increased overtime, however this was not associated with the annual decline in RWS. The score of the MDS-UPDRS III assesses a range of upper and lower body symptoms not all of which relate to gait, so a lack of association is not necessarily surprising. Despite this, the fact that RWS changed overtime, it does suggest it is able to assess some progressive aspect of PD, that is not captured by existing clinical assessment. These findings collectively, demonstrate that RWS can provide novel complementary information about changes in gait that relate to real-world mobility and are of importance to patients (Deane et al., 2014; Delgado-Ortiz et al., 2023; Port et al., 2021).

Real-world walking takes place across different indoor and outdoor locations, both of which present their own specific challenge to walking adaptability. In ***Chapter 5***, the location in which the majority of real-world walking takes place was determined and then explored whether OA and PD participants adapted their RWS differently between indoor and outdoor locations. The majority of walking activity took place within indoor environments for both cohorts. While the amount of outdoor walking was not different between cohorts, PD participants had significantly less indoor walking in comparison to OAs, suggesting that is indoor rather than outdoor activities that differ between cohorts. No difference in the mean value of RWS was found between any environment in PD, where RWS was slower in OAs within indoor environments at all WBs and WBs 30 to 60 seconds. Furthermore, RWS was faster in PD in comparison to OAs within short WBs undertaken indoors. These findings suggest that OAs are able to better adapt their RWS to safely navigate different real-world settings in contrast to PD participants, which may lead to negative consequences, such as increased injury risk

(Brodie et al., 2017; Silva-Batista et al., 2018), and reduced quality of life (Merchant et al., 2020). An additional way to understand walking adaptations would be to understand how RWS is modified within a single WB as the individual responds to their changing circumstances. This is not captured by the use of singular mean values.

RWS maybe modulated several times within a single WB, due to the need to accelerate and decelerate to safely navigate different real-world challenges. The presence of PD may negatively influence how gait is modulated, through the presence of fluctuating symptoms, medication states, fatigue and deficits in balance and postural control. In ***Chapter 6***, the number of walking modulations were modelled, as modes, or selected walking speeds, within the distribution of RWS. The number of selected walking speeds were estimated in PD and OA participants, in RWS across different WB durations and assessments (lab vs real-world). In the real-world, most individuals were characterised by three selected walking speeds and variation across each WB duration was observed. It was difficult to drawer any conclusive patterns to understand whether modulations were different between PD and OA participants. Selected walking speeds were significantly larger in the real-world in contrast to the laboratory, which suggests that more complex real-world environments require a larger number of modulations in selected walking speeds, in order to account for the greater depth of various contextual and environmental challenges individual's face. There was also needed to conduct an explanatory analysis in larger cohort with more available clinical and demographic data.

In ***Chapter 7***, the findings demonstrated the information reflected by a larger number of selected walking speeds was largely dependent upon the cohort and WB duration. Larger number of selected walking speeds provides different insight dependent upon the WB duration. Within long WBs, which capture real-world capacity, a larger number of selected walking speeds was associated with greater levels of physical activity, as indicated by a higher step volume. This implies that more physical active individuals may complete a wider variety of out of home activities, promoting more adaptations within their RWS. In contrast, at short WBs a larger number of selected walking speeds were associated with increased medication dosage and FOG score. In an additional, longitudinal analysis selected walking speeds significantly increased within short WBs only in PD. This information could serve to identify mechanisms responsible for reducing in-home independence and potentially future risk of falls and reduced independence.

Overall, this thesis has provided evidence that digital mobility assessment, through quantification of RWS has potential to provide a more data-driven remote monitoring complementary aid to the existing clinical assessment of PD. Specifically that RWS can distinguish people with PD from OAs cross-sectionally, and RWS is also responsive to measuring changes in progressive aspects of PD that could complement the aspect of changes measured by the MDS-UPDRS III. This thesis also sought to characterise RWS at a more granular level, to understand what specific contexts may drive real-world mobility. These findings demonstrate that people with PD potentially have an inability to modulate their walking activity to safely navigate different real-word locations. This research also piloted novel distribution-based methods of characterising the number of selected walking speeds, to model the number of modulations within RWS. Potential links between increased medication dosage and FOG symptoms upon causing greater inconsistency within RWS in short WBs were demonstrated. Where the number of selected walking speeds only increased longitudinally within short WBs for the PD cohort. Moving toward acceptance of RWS as a clinical mobility measure, this thesis will inform the work of large multi-centric clinical validations (Mikolaizak et al., 2022).

8.1 Clinical implications

RWS could be deployed to remotely monitor aspects of PD which are not currently captured in routine clinical assessments. Such information would allow clinicians to target and manage aspects of mobility disability that are of utmost importance to people with PD, such as preservation of their walking ability (Deane et al., 2014; Delgado-Ortiz et al., 2023; Port et al., 2021). The ability to objectively evaluate patients remotely has significant advantages for both clinical research and clinical management. We anticipated that the relationship between RWS and the MDS-UPDRS III would be moderate at best due to the diverse nature of the clinical scale. The results support this, but also demonstrate that RWS is sensitive to change over time and thus may offer a supportive tool to monitor motor function remotely in PD. Walking in particular is challenging to manage and highlighted as of key importance by people with PD. The ability to detect change over time therefore makes this an important complimentary feature.

Context is key to the clinical interpretation of real-world mobility, justifying the need to characterise RWS in a range of different real-world contexts, to understand what

specific mobility insight is provided. Specifically supporting the use of tradiational approaches to aggregating RWS within different WB durations (all WBs, short, medium and long) (Del Din et al., 2016a). Longer WBs contain faster periods of walking, which may reflect real-world mobility capacity, thus already measuring what is observed in the laboratory. In contrast, short and medium length WBs may capture the majority of PD symptoms. Differences in mean RWS between indoor and outdoor locations were evident for OA participants, however not observed within individuals with PD. Previous research has shown that people with PD have significantly reduced foot clearance during gait which is related to reduced walking speed and step length (Alcock et al., 2018, 2016). Thus, this inability for PD to adapt RWS could reduce foot clearance and increase the risk of slipping, mis-stepping, and sustaining a fall and serious injury (Ashburn et al., 2008; Hyndman et al., 2002; Talbot et al., 2005). Therefore, evaluation of RWS adaptability could improve detection of falls and assist in the development of fall prevention strategies and effective interventions.

Alongside mean values, estimation of selected walking speeds within RWS can provide further insight into how gait is modulated within a single bout of walking. In this thesis, larger medication dosages and FOG scores were associated with a larger number of selected walking speeds, which could cause an increased number of mis-steps and increase falls risk (Ashburn et al., 2008; Hyndman et al., 2002; Talbot et al., 2005). Such information cannot be easily captured within a clinical setting, so selected walking speeds could facilitate personalised treatment planning, as it provides insight into individual walking patterns and adaptability, where reduced selected walking speeds could become an ecologically valid outcome measure for VR interventions that seek to improve real-world adaptability.

Assessment of RWS, through use of wearable devices offers the opportunity to remotely monitor mobility, which would enhance accessibility of assessment to individual's living in more isolated or underserved communities. The future of digital mobility assessment, as outlined in (Del Din et al., 2021), could involve every year, individual's over a certain age receiving a device in the post, which they would continuously wear across the week. The device could then be posted back, and the data would be uploaded to a cloud, before being automatically summarized in visually intuitive and clinically meaningful figures. This would provide clinician's with a detailed map of the patients mobility disability and could compare any changes in RWS to their previous assessment, providing insight into any changes in their mobility disability

before they even enter the clinic Widespread adoption would provide a more complete and objective examination of mobility, reduce waiting times for assessment and treatment, and revolutionise the personalised nature of clinical care (Del Din et al., 2021; Rochester et al., 2020; Viceconti et al., 2020). However, for this to be vision to be realised, several unique challenges must be overcome.

8.2 Strengths, limitations, and recommendations for future research

A key strength of this thesis is the analysis of RWS with both cross-sectional and longitudinal data, which has enabled us to address several of the gaps in the literature identified in the review of ***Chapter 2***. Despite largely only quantifying RWS within this analysis, there are other DMOs alongside RWS that could provide more insightful findings. For example, reduced stride/step length has typically been more associated with PD, rather than RWS (Wilson et al., 2020; Zanardi et al., 2021). However, it's been demonstrated that stride length remains the most challenging DMO to estimate from a technical perspective (Micó-Amigo et al., 2023). Expanding upon exploration of additional DMOs, researchers could explore what additional information is added by more complex DMOs based upon machine learning, deep learning and signals processing paradigms have been quantified upon real-world data (Spectral density, signal magnitude, signal regularity, single complexity) (Coates et al., 2020; Rehman et al., 2020). Additionally, exploration of change in macro-gait level variables could reveal important changes that occur within ambulatory behaviour, which would have strong clinical utility as maintaining physical activity is vital for maintaining quality of life and slowing disease progression. Despite the promise of wearable technology, it does have limitations which have been previously outlined in Table 1-4.

The pipeline to estimate walking speed from ICICLE-GAIT had excellent performance across PD and OA cohorts, finding lower Mean absolute error (MAE) and stronger ICCs (OA: MAE = 0.009 m/s, ICC = 0.95; PD: MAE = 0.055 m/s, ICC = 0.92) (Del Din et al., 2016b) than the Mobilise-D pipelines (P1 HA: MAE = 0.08 m/s, ICC = 0.86; P2 PD: MAE = 0.11 m/s, ICC = 0.79) (Kirk et al., 2023b). However, these differences are not surprising given that the ICICLE-GAIT pipeline was validated in its performance based upon simple-straight walking laboratory assessments, in contrast to the Mobilise-D pipelines which were validated across a wide variety of gait-tasks and walking speeds. Overall, the Mobilise-D pipeline is advantageous as it includes several additional filtering and CWT methods, alongside machine-learning models to train the

stride length estimation algorithm. While further validation of the results in this thesis would be required to understand the true impact of these differences, both pipelines have demonstrated that they can provide measurement of walking speed to acceptable accuracy and reliability. Furthermore, the number of selected walking speeds did not visibly differ when estimated from the difference methods of walking speed. While this approach was unavoidable in this case, it demonstrates the importance of adopting a common methodological approach to collecting and analysing real-world mobility data both within and between studies.

Contextualization of real-world data remains a significant challenge. In this thesis, the environment and activity was largely inferred based upon the WB without objectively measuring. As outlined in ***Chapter 5*** the method of estimating indoor or outdoor location needs to be further validated. Accuracy of GPS is dependent upon many factors that need to be taken into consideration (Kerr et al., 2011), such as the optimal device, wear location, number of satellites and even more granular factors such as the number of leaves on the trees that can block the signal. Future studies considering including GPS data, should adapt an approach to technical validation like the TVS, before moving onto clinical application. It would be fascinating to expand upon previous research that has quantified the specific types of indoor and outdoor environments (Bayat et al., 2020) and quantifying more specific environmental characteristics (life/activity spaces, walkability score etc..,) (Hirsch et al., 2014; Liddle et al., 2014) could also provide further clinically relevant insight into how individuals are able to respond to specific real-world situations or environment cues. Furthermore, from a research perspective it would be useful to undertake a study to understand the a 'ground truth' of the context that activity occurs within. Perhaps this could be achieved through video-based data that has been collected from a wearable go-pro camera and worn continuously across the week. This would be challenging; due to the sensitive nature of the data this would provide.

The method of estimating selected walking speeds within RWS, showed potential, however this is just one of the many additional methods of statistical summary that can be applied upon the continuous real-world data to reveal interesting patterns. This work can provide further motivation for future researcher's looking to develop novel methods of exploring data. Selected walking speeds are complex and may also be driven by characteristics relating to real-world environments and spatial activity that were not captured in the studies explored in this thesis. Perhaps individuals with larger life-

space or activity space diameters (Hirsch et al., 2014; Liddle et al., 2014) may have a greater number of modulations within RWS that would need to be more widely explored. Additionally, the Mclust algorithm estimates sigma squared, median and variance of each selected walking speed, future research could determine whether these values can provide additional clinical insights. In future participants could also be grouped in clusters with individuals that have the same number of selected walking speeds, this would potentially lead to the identification of novel patient subgroups (ie., Individuals grouped by the highest number of selected walking speeds have larger medication dosage). Future validation work is required in additional cohorts is required before more comprehensive conclusions can be drawn, where they may exist other methods than Mclust, which can more efficiently model optimal numbers of selected walking speeds. Future studies containing more detailed medication data, would also to validate whether it reflect fluctuations that occur within short WBs. Perhaps future work could validate these additional methods in larger sample sizes. Here, the number of selected walking speeds were included as a measure, due to complexity. However, future studies should explore what other variables related to the distribution can be estimated.

One of the most significant research questions arising from this thesis is the determination of what constitutes a clinically important change within RWS. In ***Chapter 4,*** RWS showed a significant decline of 0.02 m/s per year in PD. However, the clinical importance of this change remains unclear. Previous research in a supervised setting suggests that a clinically important change in walking speed is 0.06 m/s (Hass et al., 2014). However, I anticipate real-world changes to be lower and more discrete. This requires attention in larger cohorts. Additionally, further analysis could include exploration of other non-linear methods of analysing RWS, such as entropy, autocorrelation, and harmonic ratio. Notably, previous work in the ICICLE-GAIT cohort (Coates et al., 2020) found that increased entropy (indicating greater variability) is significantly associated with larger medication dosage (LEDD). This strengthens the connection between increased inconsistencies in walking patterns and heightened motor fluctuations. While fluctuations were not objectively measured in the ICICLE-GAIT dataset, ongoing studies (Debelle et al., 2023) are now capturing such information. This presents an intriguing area for future analysis.

8.3 Conclusions

This thesis provides evidence that digital mobility assessment, through quantification of RWS can provide novel complementary information about changes in gait that relate to real-world mobility and are of importance to patients. Additionally, inclusion of contextual data and novel statistical techniques are able to improve understanding of the impact of PD upon safe modulation of walking between different real-world scenarios and within a single bout of walking.

Key conclusions of this thesis are:

1. A systematic review demonstrated an overall lack of studies that have sought to characterise real-world DMOs, such as RWS in depth to understand what specific clinical insights they are able to provide, particularly in the exploration of longitudinal data.
2. People with PD walking slower in the real-world in comparison to OAs, across a range of different WB duration thresholds
3. RWS declined more rapidly in PD compared to OA over time showing sensitivity to change and reflecting PD specific change.
4. The relationship of RWS to motor severity was only apparent at selected WB duration. The influence and importance of data aggregation upon the information reflected by RWS needs further exploration to understand the best methods to aggregate real-world data for use as a clinical outcome.
5. Changes in RWS were not associated with changes in MDS-UPDRS III. However, the fact they both changed overtime does suggest that RWS is related to some progressive aspect of PD, not captured by the existing assessment.
6. When characterising RWS in greater contextual depth, RWS was significantly different between indoor and outdoor real-world locations, only in OAs which demonstrates a potential inability for PD to adapt their walking, however further findings in larger sample sizes are needed
7. Use of GPS data offers exciting potential in healthcare research, however further, robust validation efforts are required before this can be achieved with acceptable reliability and accuracy
8. Understanding how gait is modulated within a single WB, may provide valuable understanding of individual-level strategies to adapting RWS to account for the different contextual demands of the real-world and the real-world behaviour of

PD. The utility of one method to quantify modulation was explored, through quantification of selected walking speeds.

9. While selected walking speeds were not modulated differently between WB durations, the findings suggested a possible difference in RWS modulations between real-world locations in PD and OA participants
10. Selected walking speeds were also associated with larger medication dosage and NFOG score within short WBs, indicating the impact of medication and specific PD symptoms on gait modulations, which could reflect an increased risk of falls of reduced independence in PD
11. Longitudinally, selected walking speeds only changed significantly for the PD cohort within short WBs, suggesting an association between PD progression and greater inconsistency within RWS modulations.

Chapter 9. Appendices

Appendix 1. Movement Disorder Society (MDS) diagnostic criteria for Parkinson's (PD) (Postuma et al., 2015)

The first essential criterion is parkinsonism, which is defined as bradykinesia, in combination with at least 1 of rest tremor or rigidity. Examination of all car- dinal manifestations should be carried out as described in the MDS–Unified Parkinson Disease Rating Scale.[30] Once parkinsonism has been diagnosed:

Diagnosis of Clinically Established PD requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

Diagnosis of Clinically Probable PD requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria
   If 1 red flag is present, there must also be at least 1 supportive criterion If 2 red flags, at least 2 supportive criteria are needed
   No more than 2 red flags are allowed for this category

Supportive criteria

1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
   a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
   b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.
2. Presence of levodopa-induced dyskinesia
3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination) 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy Absolute exclusion criteria: The presence of any of these features rules out PD:
1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze evoked nystag- mus, macro square wave jerks, hypermetric saccades)
2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades
3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria[31] within the first 5 y of disease
4. Parkinsonian features restricted to the lower limbs for more than 3 y
5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism
6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease
7. Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system
9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient's symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is *more likely* than PD

Red flags

1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset
2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment
3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs
5. Severe autonomic failure in the first 5 y of disease. This can include:
   a) Orthostatic hypotension[32]—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or
   b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount stress incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction
6. Recurrent (>1/y) falls because of impaired balance within 3 y of onset
7. Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y
8. Absence of any of the common nonmotor features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insom- nia, excessive daytime somnolence, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, sympto- matic orthostasis), hyposmia, or psychiatric dysfunction (depression, anxiety, or hallucinations)
9. Otherwise-unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry and isolated extensor plantar response)
10. Bilateral symmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is

observed on objective examination

Criteria Application:

1. Does the patient have parkinsonism, as defined by the MDS criteria?
   If no, *neither* probable PD nor clinically established PD can be diagnosed. *If yes:*
2. Are any absolute exclusion criteria present?
   If "yes," *neither* probable PD nor clinically established PD can be diagnosed. *If no:*
3. Number of red flags present ____
4. Number of supportive criteria present ____
5. Are there at least 2 supportive criteria *and* no red flags?
   If yes, patient meets criteira for clinically established PD. *If no:*
6. Are there more than 2 red flags?
   If "yes," probable PD *cannot* be diagnosed. *If no:*
7. Is the number of red flags equal to, or less than, the number of supportive criteria?
   If yes, patient meets criteria for probable PD

Appendix 2. Search strategy applied in the systematic review.

String no.	Query
#1. (Gait terms)	(((step* OR stride*) NEAR/2 (speed OR velocit* OR time* OR length* OR width* OR frequenc* OR rate* OR rhythm* OR variabilit* OR symmetr* OR asymmetr* OR count* OR number* OR distance* OR cadence*)):ti,ab) OR (((swing* OR stance* OR 'single support' OR 'double support') NEAR/2 (time* OR duration* OR variabilit* OR symmetr* OR asymmetr*)):ti,ab) OR (((spatiotemporal OR 'spatiotemporal') NEAR/2 (parameter* OR feature* OR characteristic*)):ti,ab) OR (((gait OR walk* OR ambulat*) NEAR/2 (speed OR velocit* OR time* OR cadence* OR pace* OR rhythm* OR volume* OR bout* OR duration* OR distance* OR intensit* OR variabilit* OR asymmetr* OR symmetr* OR parameter* OR feature* OR characteristic* OR assess* OR examin* OR analys* OR batter* OR measure* OR test*)) home OR domestic OR ((free OR daily) NEAR/2 living) OR 'real -world' OR 'real world' OR 'community ambulat*' OR (((day* OR daily OR ambulat* OR physical OR walk* OR monitor*) NEAR/2 activit*)) OR (((day* OR daily OR count* OR time OR number*) NEAR/2 (walk* OR step*)) OR ((sensor* OR record* OR monitor*) NEAR/2 (continu* OR activit* OR 'long-term' OR 'long term')) OR (Body NEAR/2 sensor*) OR Pedometer* OR *phone* OR (mobile NEAR/2 device*) :ti,ab)
#2 (Disease area terms)	'Parkinson disease'/exp OR 'parkinsonism' (parkinson* OR 'paralysis agitans')
#3 (Final)	#1 AND #2 AND (1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018 :py OR 2019:py OR 2020:py OR 2021:py)

Appendix 3. Table of data extraction methods for the full-text review

	Associated questions
Publication details	
Authors and affiliations	Who conducted the research?
Type	In what type of literature was the study published (Journal, grey literature, conference abstract)
Year	When was the study published?
Country/region	In which geographic region(s) did the study take place?
General details	
Study design	What was the study's design?
Study aims	What were the study's aims?
Population	What population was studied? Were there any specific inclusion/exclusion criteria such as disease severity, subtype, or age?
Included DMOS	Which DMOs were measured? How and in what setting were the DMOs measured?
Method of assessment	Were DMOs assessed during scripted testing in a laboratory setting? Were DMOs assessed during continuous assessment in the real-world?
Ecological validity	
Study setting	Were DMO quantitatively assessed during both unsupervised, continuous real-world assessment and supervised, scripted assessment in a clinic/laboratory environment, in the same study?
Differences in DMOs	What differences in DMOs occurred (or did not occur) between assessment condition? Did these differences reach statistical significance?
Known groups differences	
Study design	Were patients and controls matched or are the groups comparable with respect to appropriate criteria (height, age, sex)? Was

	gait analysis controlled for gait speed? Did the study focus on a specific subgroup or population?
Differences in DMOs	What differences in DMOs occurred (or did not occur) between people with PD and healthy controls? Did these differences reach statistical significance?
Convergent validity/Stratified groups differences	
Analytical methods	How did the authors measure the relationship between clinically relevant measures and DMOs? What association measure was used?
Clinically relevant measures	What clinically relevant measures were studied?
Relationship strength	What was the strength of the reported relationship between the measure and the DMO? Was the association statistically significant?
Predictive capacity	
Model description	Does the study report a multivariate analysis, a prediction model, a model based on machine learning? Which covariates were included in the model? Which analytical methods were used?
Clinically relevant outcomes	What clinically relevant outcomes were studied to assess the DMO's prognostic value?
Prognostic value	Did the DMO provide prognostic value with respect to the studied outcome?
Model description	Does the study report a multivariate analysis, a prediction model, a model based on machine learning? Which covariates were included in the model? Which analytical methods were used?
Systematic Review	
Risk of bias (quality assessment)	What is risk of bias and quality of the included articles?

Assessment of heterogeneity	Were the studies heterogenous in number of outcomes such as: population, intervention, technology used, assessment method, length of assessment and others.
Summary effect size	Within each study what is the effect size relative to each RQ?
Publication Bias	What proportion of the studies reported statistically significant or clinically favourable results?
Subgroup analysis and meta regression	What is the effect size of CLINIC or HOME assessment upon DMOs with respect to the four RQs?

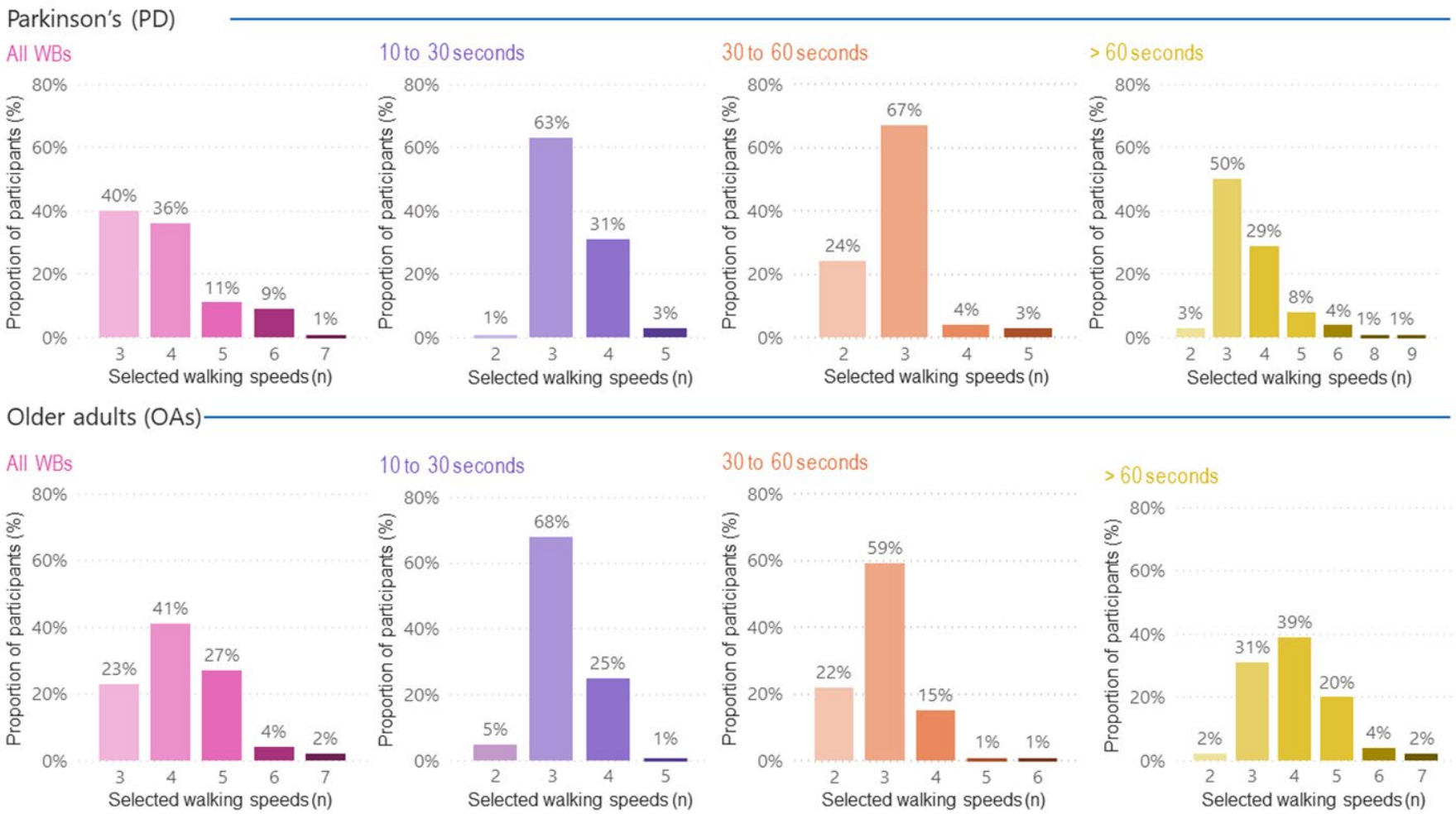
Appendix 4. Differences identified in the measurement methods of the supervised studies

Instrument	n (%)
Wearable device (other locations)	4 (57%)
Wearable device (Lower back)	2 (28%)
Instrumented walkway	1 (14%)
Measurement task	
Straight walk	5 (83%)
Straight and curvilinear walking	3 (50%)
Single or dual task?	
Single	5 (83%)
Single and dual task	1 (16%)
Walking speed	
Self-selected	4 (66%)
Self-selected and fast walking	1 (16%)
Did not specify	1 (16%)

Appendix 5. Demographic and clinical information of the PD participants that were excluded and included due to availability of indoor and outdoor data.

Group	PD excluded	PD included
n	7	12
Age (yrs)	**74 ± 6**	**66 ± 7**
Sex (Male / Female, n)	5/2	10/2
Height (metres)	1.72 ± 8.1	1.75 ± 055
Body Mass (kg)	78.68 ± 14.03	79.6 ± 14.52
BMI	26.57 ± 4.91	25.87 ± 3.96
Number of Walking bouts	1984 ± 216	5016 ± 948
Real-world walking speed (m/s)	**0.85 ± 0.09**	**1.08 ± 0.13**
MDS-UPDRS III	**27.57 ± 20**	**24.75 ± 10.32**
Hoehn and Yahr Stage		
I, n (%)	1 (14%)	3 (25%)
II, n (%)	4 (57%)	7 (58%)
III, n (%)	2 (28%)	2 (16%)
IV, n (%)	0	0

'-'describes an empty field, due to data availability. BMI = Body Mass Index. MDS-UPDRS III = Movement Disorder Society – Unified Parkinson's Disease Rating Scale – Part III. Bold indicates significance difference between included and excluded participants

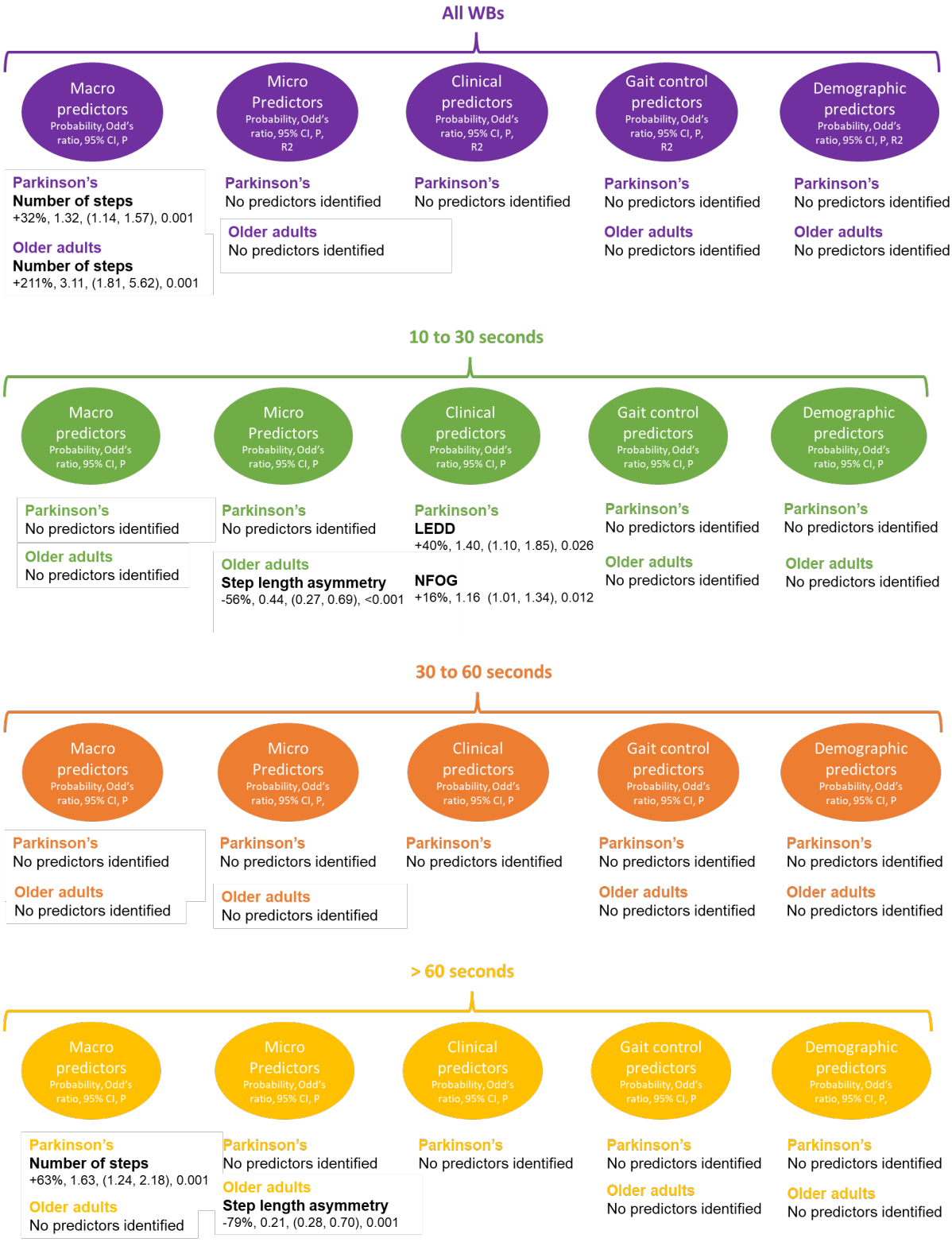


Appendix 6. The number and proportion of selected walking speeds estimated for Parkinson's and older adults participants, at each walking bout duration threshold.

Appendix 7. Real-world information for Parkinson's and older adults participants from the 36-month time point of ICICLE-GAIT

All WBs		
Variable	**PD**	**OA**
Number of walking bouts (n)	4426 ± 1504	4396 ± 1336
Number of walking bouts per day (n)	634 ± 24	635 ± 179
Step count (n)	83326 ± 36133	91465 ± 31878
Daily step count (n)	10806 ± 4764	11935 ± 4070
Number of selected speeds (n)	4 (3:7)	4 (3:7)
RWS (m/s)	0.78 ± 0.08	0.88 ± 0.09
Variability	0.18 ± 0.08	0.85 ± 0.11
Alpha	1.63 ± 0.04	1.58 ± 0.17
10 to 30 seconds		
Variable	**PD**	**OA**
Number of walking bouts (n)	1362 ± 485	1467 ± 451
Number of walking bouts per day (n)	195 ± 69	210 ± 64
Step count (n)	23340 ± 8393	24516 ± 7607
Daily step count (n)	3348 ± 1198	3515 ± 1091
Number of selected speeds (n)	3 (2:5)	3 (2:5)
RWS (m/s)	0.74 ± 0.06	0.79 ± 0.05
Variability	0.29 ± 0.10	0.29 ± 0.01
Alpha	3.54 ± 0.17	3.45 ± 0.13
30 to 60 seconds		
Variable	**PD**	**OA**
Number of walking bouts (n)	270 ± 141	316 ± 121
Number of walking bouts per day (n)	38 ± 20	45 ± 17
Step count (n)	12451 ± 6808	14312 ± 5632
Daily step count (n)	1787 ± 979	2053 ± 804
Number of selected speeds (n)	3 (2:5)	3 (2:6)
RWS (m/s)	0.79 ± 0.06	0.84 ± 0.06
Variability	0.18 ± 0.01	0.18 ± 0.01
Alpha	4.95 ± 0.39	4.86 ± 0.26
> 60 seconds		
Variable	**PD**	**OA**
Number of walking bouts (n)	151 ± 96	171 ± 78
Number of walking bouts per day (n)	21 ± 13	24 ± 11
Step count (n)	29449 ± 21024	35485 ± 18994
Daily step count (n)	4227 ± 3006	5088 ± 2721
Number of selected speeds (n)	3 (2:8)	4 (2:8)
RWS (m/s)	0.80 ± 0.08	0.94 ± 0.13
Variability	0.16 ± 0.03	0.57 ± 0.11
Alpha	2.68 ± 0.69	2.57 ± 0.33

RWS: Real-world Walking Speed; Number of walking bouts and step count reported as average across the week.



Appendix 8. Strongest independent predictors of the number of selected walking speeds, within each category of predictor across each WB duration for PD and OA participants

Appendix 9. The number of selected walking speeds estimated at each assessment time point and WB duration for Parkinson's and older adults participants.

WB duration	18 months		36 months		54 months		72 months	
(seconds)	PD	OA	PD	OA	PD	OA	PD	OA
All > 10	4 [2 , 7]	4 [3 , 9]	4 [3 , 7]	4 [3 , 7]	4 [3 , 9]	4 [3 , 6]	4 [3 , 7]	4 [3 , 6]
10 to 30	3 [2 , 5]	3 [2 , 4]	3 [2 , 5]	3 [2 , 5]	3 [2 , 5]	3 [2 , 4]	3 [2 , 5]	3 [2 , 6]
30 to 60	3 [2 , 4]	3 [2 , 4]	3 [2 , 5]	3 [2 , 6]	3 [2 , 4]	3 [2 , 4]	**4 [2 , 6]**	**3 [2 ,5]**
> 60	3 [2 , 6]	4 [2 , 9]	**3 [2 , 9]**	**4 [2 , 7]**	4 [2 , 9]	4 [3 , 7]	4 [2 , 5]	4 [3 , 9]

Data presented as median values and ranges. Highlighted in bold indicates statistically significant difference in selected walking speeds between OA and PD participants.

References

Adams, J.L., Dinesh, K., Snyder, C.W., Xiong, M., Tarolli, C.G., Sharma, S., Dorsey, E.R., Sharma, G., 2021. A real-world study of wearable sensors in Parkinson's disease. npj Parkinsons Dis. 7, 106.

Alcock, L., Galna, B., Lord, S., Rochester, L., 2016. Characterisation of foot clearance during gait in people with early Parkinson's disease: Deficits associated with a dual task. J Biomech 49, 2763–2769. https://doi.org/10.1016/j.jbiomech.2016.06.007

Alcock, L., Galna, B., Perkins, R., Lord, S., Rochester, L., 2018. Step length determines minimum toe clearance in older adults and people with Parkinson's disease. J Biomech 71, 30–36.

Ammar, A., Brach, M., Trabelsi, K., Chtourou, H., Boukhris, O., Masmoudi, L., Bouaziz, B., Bentlage, E., How, D., Ahmed, M., Müller, P., Müller, N., Aloui, A., Hammouda, O., Paineiras-Domingos, L.L., Braakman-Jansen, A., Wrede, C., Bastoni, S., Pernambuco, C.S., Mataruna, L., Taheri, M., Irandoust, K., Khacharem, A., Bragazzi, N.L., Chamari, K., Glenn, J.M., Bott, N.T., Gargouri, F., Chaari, L., Batatia, H., Ali, G.M., Abdelkarim, O., Jarraya, M., Abed, K.E., Souissi, N., Van Gemert-Pijnen, L., Riemann, B.L., Riemann, L., Moalla, W., Gómez-Raja, J., Epstein, M., Sanderman, R., Schulz, S.V., Jerg, A., Al-Horani, R., Mansi, T., Jmail, M., Barbosa, F., Ferreira-Santos, F., Šimunič, B., Pišot, R., Gaggioli, A., Bailey, S.J., Steinacker, J.M., Driss, T., Hoekelmann, A., 2020. Effects of COVID-19 Home Confinement on Eating Behaviour and Physical Activity: Results of the ECLB-COVID19 International Online Survey. Nutrients 12, E1583.

Aradi, S.D., Hauser, R.A., 2020. Medical Management and Prevention of Motor Complications in Parkinson's Disease. Neurotherapeutics 17, 1339–1365.

Ashburn, A., Stack, E., Ballinger, C., Fazakarley, L., Fitton, C., 2008. The circumstances of falls among people with Parkinson's disease and the use of Falls Diaries to facilitate reporting. Disability and Rehabilitation 30, 1205–1212.

Ashman, K.M., Bird, C.M., Zepf, S.E., 1994. Detecting Bimodality in Astronomical Datasets. The Astronomical Journal 108, 2348.

Atrsaei, A., Corra, M.F., Dadashi, F., Vila-Cha, N., Maia, L., Mariani, B., Maetzler, W., Aminian, K., 2021. Gait speed in clinical and daily living assessments in Parkinson's disease patients: performance versus capacity. NPJ PARKINSONS DISEASE 7.

Baroudi, L., Yan, X., Newman, M.W., Barton, K., Cain, S.M., Shorter, K.A., 2022. Contextualizing Walking Speed in the Real World. SSRN Journal.

Bates, D., 2020. Package "lme4."

Bayat, S., Naglie, G., Rapoport, M., Stasiulis, E., Chikhaoui, B., Mihailidis, A., 2020. Inferring Destinations and Activity Types of Older Adults From GPS Data: Algorithm Development and Validation. JMIR Aging 3, e18008. https://doi.org/10.2196/18008

Bicket, A.K., Mihailovic, A., E, J.-Y., Nguyen, A., Mukherjee, M.R., Friedman, D.S., Ramulu, P.Y., 2020. Gait in Elderly Glaucoma: Impact of Lighting Conditions, Changes in Lighting, and Fear of Falling. Transl Vis Sci Technol 9, 23.

Bloem, B.R., 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.

Bonci, T., Keogh, A., Del Din, S., Scott, K., Mazzà, C., on behalf of the Mobilise-D consortium, 2020. An Objective Methodology for the Selection of a Device for Continuous Mobility Assessment. Sensors 20, 6509.

Boripuntakul, S., Lord, S.R., Brodie, M.A.D., Smith, S.T., Methapatara, P., Wongpakaran, N., Sungkarat, S., 2014. Spatial variability during gait initiation while dual tasking is increased in individuals with mild cognitive impairment. J Nutr Health Aging 18, 307–312.

Braak, H., Braak, E., 2000. Pathoanatomy of Parkinson's disease. J Neurol 247, II3–II10.

Breasail, M.Ó., Biswas, B., Smith, M.D., Mazhar, M.K.A., Tenison, E., Cullen, A., Lithander, F.E., Roudaut, A., Henderson, E.J., 2021. Wearable GPS and Accelerometer Technologies for Monitoring Mobility and Physical Activity in Neurodegenerative Disorders: A Systematic Review. Sensors 21, 8261.

Brodie, M.A., Coppens, M.J., Ejupi, A., Gschwind, Y.J., Annegarn, J., Schoene, D., Wieching, R., Lord, S.R., Delbaere, K., 2017. Comparison between clinical gait and daily-life gait assessments of fall risk in older people. Geriatrics & Gerontology International 17, 2274–2282.

Bryant, M.S., Rintala, D.H., Hou, J.G., Charness, A.L., Fernandez, A.L., Collins, R.L., Baker, J., Lai, E.C., Protas, E.J., 2011. Gait variability in Parkinson's disease: Influence of walking speed and dopaminergic treatment. Neurological Research 33, 959–964.

Buckley, C., Alcock, L., McArdle, R., Rehman, R.Z.U., Del Din, S., Mazzà, C., Yarnall, A.J., Rochester, L., 2019. The Role of Movement Analysis in Diagnosing and Monitoring Neurodegenerative Conditions: Insights from Gait and Postural Control. Brain Sci 9, 34.

Buckley, C., Cavadino, A., Del Din, S., Lord, S., Taylor, L., Rochester, L., Kerse, N., 2020. Quantifying Reliable Walking Activity with a Wearable Device in Aged Residential Care: How Many Days Are Enough? Sensors (Basel) 20.

Campbell, W.I., Lewis, S., 1990. Visual analogue measurement of pain. Ulster Med J 59, 149–154.

Cavanaugh, J.T., Ellis, T.D., Earhart, G.M., Ford, M.P., Foreman, K.B., Dibble, L.E., 2012. Capturing ambulatory activity decline in Parkinson's disease. J Neurol Phys Ther 36, 51–57.

Chastin, S.F.M., Baker, K., Jones, D., Burn, D., Granat, M.H., Rochester, L., 2010. The pattern of habitual sedentary behavior is different in advanced Parkinson's disease. Mov Disord 25, 2114–2120.

Choi, B.C.K., Pak, A.W.P., Choi, J.C.L., Choi, E.C.L., 2007. Daily step goal of 10,000 steps: a literature review. Clin Invest Med 30, E146-151.

Chung, J., Boyle, J., Wheeler, D.C., 2022. Relationship between Life-Space Mobility and Health Characteristics in Older Adults Using Global Positioning System Watches. J Appl Gerontol 41, 1186–1195.

Ciravegna, F., Gao, J., Ireson, N., Copeland, R., Walsh, J., Lanfranchi, V., 2019. Active 10: Brisk Walking to Support Regular Physical Activity, in: Proceedings of the 13th EAI International Conference on Pervasive Computing Technologies for Healthcare. Presented at the PervasiveHealth'19: The 13th International Conference on Pervasive Computing Technologies for Healthcare, ACM, Trento Italy, pp. 11–20.

Coates, L., Shi, J., Rochester, L., Del Din, S., Pantall, A., 2020. Entropy of Real-World Gait in Parkinson's Disease Determined from Wearable Sensors as a Digital Marker of Altered Ambulatory Behavior. Sensors (Basel) 20, E2631.

Coronavirus: Strict new curbs on life in UK announced by PM, 2020. . BBC News.

Corrà, M.F., Atrsaei, A., Sardoreira, A., Hansen, C., Aminian, K., Correia, M., Vila-Chã, N., Maetzler, W., Maia, L., 2021. Comparison of Laboratory and Daily-Life Gait Speed Assessment during ON and OFF States in Parkinson's Disease. Sensors (Basel) 21, 3974.

Curtze, C., Nutt, J.G., Carlson-Kuhta, P., Mancini, M., Horak, F.B., 2015. Levodopa Is a Double-Edged Sword for Balance and Gait in People With Parkinson's Disease. Movement Disorders 30, 1361–1370.

Czech, M., Demanuele, C., Erb, M.K., Ramos, V., Zhang, H., Ho, B., Patel, S., 2020. The Impact of Reducing the Number of Wearable Devices on Measuring Gait in Parkinson Disease: Noninterventional Exploratory Study. JMIR Rehabil Assist Technol 7, e17986.

Dauer, W., Przedborski, S., 2003. Parkinson's Disease: Mechanisms and Models. Neuron 39, 889–909.

Deane, K.H.O., Flaherty, H., Daley, D.J., Pascoe, R., Penhale, B., Clarke, C.E., Sackley, C., Storey, S., 2014. Priority setting partnership to identify the top 10 research priorities for the management of Parkinson's disease. BMJ Open 4, e006434.

Debelle, H., Packer, E., Beales, E., Bailey, H., Mc Ardle, R., Brown, P., Hunter, H., Ciravegna, F., Ireson, N., Evers, J., Niessen, M., Shi, J., Yarnall, A., Rochester, L., Alcock, L., Din, S., 2023. Feasibility and usability of a digital health technology system to monitor mobility and assess medication adherence in mild-to-moderate Parkinson's disease. Frontiers in Neurology 14.

Del Din, S., Galna, B., Godfrey, A., Bekkers, E.M.J., Pelosin, E., Nieuwhof, F., Mirelman, A., Hausdorff, J.M., Rochester, L., 2019. Analysis of Free-Living Gait in Older Adults With and Without Parkinson's Disease and With and Without a History of Falls: Identifying Generic and Disease-Specific Characteristics. J Gerontol A Biol Sci Med Sci 74, 500–506.

Del Din, S., Galna, B., Lord, S., Nieuwboer, A., Bekkers, E.M.J., Pelosin, E., Avanzino, L., Bloem, B.R., Olde Rikkert, M.G.M., Nieuwhof, F., Cereatti, A., Della Croce, U., Mirelman, A., Hausdorff, J.M., Rochester, L., 2020. Falls Risk in Relation to Activity Exposure in High-Risk Older Adults. J Gerontol A Biol Sci Med Sci 75, 1198–1205.

Del Din, S., Godfrey, A., Galna, B., Lord, S., Rochester, L., 2016a. Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length. Journal of NeuroEngineering and Rehabilitation 13, 46–46.

Del Din, S., Godfrey, A., Rochester, L., 2016b. 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 Journal of Biomedical and Health Informatics 20, 838–847.

Del Din, S., Kirk, C., Yarnall, A.J., Rochester, L., Hausdorff, J.M., 2021. Body-Worn Sensors for Remote Monitoring of Parkinson's Disease Motor Symptoms: Vision, State of the Art, and Challenges Ahead. J Parkinsons Dis.

Delgado-Ortiz, L., Polhemus, A., Keogh, A., Sutton, N., Remmele, W., Hansen, C., Kluge, F., Sharrack, B., Becker, C., Troosters, T., Maetzler, W., Rochester, L., Frei, A., Puhan, M.A., Garcia-Aymerich, J., 2023. Listening to the patients' voice: a conceptual framework of the walking experience. Age Ageing 52, afac233.

Deuschl, G., Beghi, E., Fazekas, F., Varga, T., Christoforidi, K.A., Sipido, E., Bassetti, C.L., Vos, T., Feigin, V.L., 2020. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. The Lancet Public Health 5, e551–e567.

Diffey, B.L., 2011. An overview analysis of the time people spend outdoors. British Journal of Dermatology 164, 848–854.

Duncan, R.P., Leddy, A.L., Earhart, G.M., 2011. Five Times Sit to Stand Test Performance in Parkinson Disease. Arch Phys Med Rehabil 92, 1431–1436.

Duncan, S., Stewart, T.I., Oliver, M., Mavoa, S., MacRae, D., Badland, H.M., Duncan, M.J., 2013. Portable Global Positioning System Receivers: Static Validity and Environmental Conditions. American Journal of Preventive Medicine 44, e19–e29.

El-Gohary, M., Peterson, D., Gera, G., Horak, F.B., Huisinga, J.M., 2017. Validity of the instrumented push and release test to quantify postural responses in persons with multiple sclerosis. Arch Phys Med Rehabil 98, 1325–1331.

Ellmers, Toby J., Wilson, M.R., Kal, E.C., Young, W.R., 2022. Standing up to threats: Translating the two-system model of fear to balance control in older adults. Experimental Gerontology 158, 111647. https://doi.org/10.1016/j.exger.2021.111647
Ellmers, Toby J, Wilson, M.R., Norris, M., Young, W.R., 2022. Protective or harmful? A qualitative exploration of older people's perceptions of worries about falling. Age Ageing 51, afac067.

Emre, M., Aarsland, D., Brown, R., Burn, D.J., Duyckaerts, C., Mizuno, Y., Broe, G.A., Cummings, J., Dickson, D.W., Gauthier, S., Goldman, J., Goetz, C., Korczyn, A., Lees, A., Levy, R., Litvan, I., McKeith, I., Olanow, W., Poewe, W., Quinn, N., Sampaio, C., Tolosa, E., Dubois, B., 2007. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22, 1689–1707; quiz 1837.

European Parkinson's disease Association, E.P.D., 2020. What is Parkinson's?

Falla, M., Dodich, A., Papagno, C., Gober, A., Narduzzi, P., Pierotti, E., Falk, M., Zappini, F., Colosimo, C., Turella, L., 2021. Lockdown effects on Parkinson's disease during COVID-19 pandemic: a pilot study. Acta Neurol Belg 121, 1191–1198.

Foley, C.N., Mason, A.M., Kirk, P.D.W., Burgess, S., 2020. MR-Clust: clustering of genetic variants in Mendelian randomization with similar causal estimates. Bioinformatics 37, 531–541.

Friedman, J., Friedman, H., 1993. Fatigue in Parkinson's disease. Neurology 43, 2016–2018.

Fujikawa, J., Morigaki, R., Yamamoto, N., Oda, T., Nakanishi, H., Izumi, Y., Takagi, Y., 2022. Therapeutic Devices for Motor Symptoms in Parkinson's Disease: Current Progress and a Systematic Review of Recent Randomized Controlled Trials. Front Aging Neurosci 14, 807909.

Galna, B., Lord, S., Burn, D.J., Rochester, L., 2015. Progression of gait dysfunction in incident Parkinson's disease: impact of medication and phenotype. Mov Disord 30, 359–67.

Galperin, I., Hillel, I., Del Din, S., Bekkers, E.M.J., Nieuwboer, A., Abbruzzese, G., Avanzino, L., Nieuwhof, F., Bloem, B.R., Rochester, L., Della Croce, U., Cereatti, A., Giladi, N., Mirelman, A., Hausdorff, J.M., 2019. Associations between daily-living physical activity and laboratory-based assessments of motor severity in patients with falls and Parkinson's disease. Parkinsonism & Related Disorders 62, 85–90.

Garcia, T.P., Marder, K., 2017. Statistical Approaches to Longitudinal Data Analysis in Neurodegenerative Diseases: Huntington's Disease as a Model. Curr Neurol Neurosci Rep 17, 14. https://doi.org/10.1007/s11910-017-0723-4

Geerse, D.J., Roerdink, M., Marinus, J., van Hilten, J.J., 2019. Walking adaptability for targeted fall-risk assessments. Gait Posture 70, 203–210.

Gehlsen, G.M., Whaley, M.H., 1990. Falls in the elderly: Part II, Balance, strength, and flexibility. Arch Phys Med Rehabil 71, 739–741.

Giladi, N., Horak, F.B., Hausdorff, J.M., 2013. Classification of gait disturbances: distinguishing between continuous and episodic changes. Mov Disord 28, 10.1002/mds.25672.

Giladi, N., Shabtai, H., Rozenberg, E., Shabtai, E., 2001. Gait festination in Parkinson's disease. Parkinsonism & Related Disorders 7, 135–138.

Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M.B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A.E., Lees, A., Leurgans, S., LeWitt, P.A., Nyenhuis, D., Olanow, C.W., Rascol, O., Schrag, A., Teresi, J.A., van Hilten, J.J., LaPelle, N., Movement Disorder Society, U.R.T.F., 2008. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 23, 2129–70.

Goldsack, J.C., Coravos, A., Bakker, J.P., Bent, B., Dowling, A.V., Fitzer-Attas, C., Godfrey, A., Godino, J.G., Gujar, N., Izmailova, E., Manta, C., Peterson, B., Vandendriessche, B., Wood, W.A., Wang, K.W., Dunn, J., 2020. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). npj Digit. Med. 3, 1–15.

Goodier, J., 2007. The Cambridge Dictionary of Statistics (3rd edition). Reference Reviews 21, 49–49. https://doi.org/10.1108/09504120710728860

Hass, C.J., Bishop, M., Moscovich, M., Stegemöller, E.L., Skinner, J., Malaty, I.A., Wagle Shukla, A., McFarland, N., Okun, M.S., 2014. Defining the Clinically Meaningful Difference in Gait Speed in Persons With Parkinson Disease. Journal of Neurologic Physical Therapy 38, 233–238.

Hausdorff, J.M., 2009. Gait dynamics in Parkinson's disease: Common and distinct behavior among stride length, gait variability, and fractal-like scaling. Chaos 19, 026113.

Havlikova, E., Rosenberger, J., Nagyova, I., Middel, B., Dubayova, T., Gdovinova, Z., W Groothoff, J., P van Dijk, J., 2008. Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease. Parkinsonism Relat Disord 14, 187–192.

Herlofson, K., Larsen, J.P., 2003. The influence of fatigue on health-related quality of life in patients with Parkinson's disease. Acta Neurol Scand 107, 1–6.

Hickey, A., Din, S.D., Rochester, L., Godfrey, A., 2016. Detecting free-living steps and walking bouts: validating an algorithm for macro gait analysis. Physiol. Meas. 38, N1.

Hiden, H., Woodman, S., Watson, P., Cala, J., 2013. Developing cloud applications using the e-Science Central platform. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences 371, 20120085.

Hill, E.J., Mangleburg, C.G., Alfradique-Dunham, I., Ripperger, B., Stillwell, A., Saade, H., Rao, S., Fagbongbe, O., von Coelln, R., Tarakad, A., Hunter, C., Dawe, R.J., Jankovic, J., Shulman, L.M., Buchman, A.S., Shulman, J.M., 2021. Quantitative mobility measures complement the MDS-UPDRS for characterization of Parkinson's disease heterogeneity. Parkinsonism Relat Disord 84, 105–111.

Hillel, I., Gazit, E., Nieuwboer, A., Avanzino, L., Rochester, L., Cereatti, A., Croce, U.D., Rikkert, M.O., Bloem, B.R., Pelosin, E., Del Din, S., Ginis, P., Giladi, N., Mirelman, A., Hausdorff, J.M., 2019. Is every-day walking in older adults more analogous to dual-task walking or to usual walking? Elucidating the gaps between gait performance in the lab and during 24/7 monitoring. Eur Rev Aging Phys Act 16, 6.

Hirsch, J., Winters, M., Clarke, P., McKay, H., 2014. Generating GPS activity spaces that shed light upon the mobility habits of older adults: A descriptive analysis. International journal of health geographics 13, 51.

Hobert, M.A., Nussbaum, S., Heger, T., Berg, D., Maetzler, W., Heinzel, S., 2019. Progressive Gait Deficits in Parkinson's Disease: A Wearable-Based Biannual 5-Year Prospective Study. Front Aging Neurosci 11, 22.

Holden, S.K., Finseth, T., Sillau, S.H., Berman, B.D., 2018. Progression of MDS-UPDRS Scores Over Five Years in De Novo Parkinson Disease from the Parkinson's Progression Markers Initiative Cohort. Mov Disord Clin Pract 5, 47–53.

Hollman, J.H., McDade, E.M., Petersen, R.C., 2011. Normative spatiotemporal gait parameters in older adults. Gait Posture 34, 111–118.

Horak, F.B., Mancini, M., 2013. Objective Biomarkers of Balance and Gait for Parkinson's Disease using Body-worn Sensors. Mov Disord 28, 1544–1551.

Hughes, A., 1992. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of Neurology 55, 181–184.
Hughes, A.J., Daniel, S.E., Lees, A.J., 2001. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 57, 1497–1499.

Hulzinga, F., Nieuwboer, A., Dijkstra, B.W., Mancini, M., Strouwen, C., Bloem, B.R., Ginis, P., 2020. The New Freezing of Gait Questionnaire: Unsuitable as an Outcome in Clinical Trials? Mov Disord Clin Pract 7, 199–205.

Hyndman, D., Ashburn, A., Stack, E., 2002. Fall events among people with stroke living in the community: Circumstances of falls and characteristics of fallers. Archives of Physical Medicine and Rehabilitation 83, 165–170.

Iansek, R., Danoudis, M., Bradfield, N., 2013. Gait and cognition in Parkinson's disease: implications for rehabilitation. Rev Neurosci 24, 293–300.

J. Jankovic, M.M., 1990. Variable expression of Parkinson's disease: A base-line analysis of the DAT ATOP cohort. Neurology 40, 1529–1529.

Jaeger, S.U., Wohlrab, M., Schoene, D., Tremmel, R., Chambers, M., Leocani, L., Corriol-Rohou, S., Klenk, J., Sharrack, B., Garcia-Aymerich, J., Rochester, L., Maetzler, W., Puhan, M., Schwab, M., Becker, C., 2022. Mobility endpoints in marketing authorisation of drugs: what gets the European medicines agency moving? Age and Ageing 51, afab242.

Jankovic, J., 2008. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79, 368–76.

Jankovic, J., 2005. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. Mov Disord 20 Suppl 11, S11-16. https://doi.org/10.1002/mds.20458
Jankowska, M.M., Schipperijn, J., Kerr, J., 2015. A framework for using GPS data in physical activity and sedentary behavior studies. Exerc Sport Sci Rev 43, 48–56.

Jehu, D.A., Davis, J.C., Falck, R.S., Bennett, K.J., Tai, D., Souza, M.F., Cavalcante, B.R., Zhao, M., Liu-Ambrose, T., 2021. Risk factors for recurrent falls in older adults: A systematic review with meta-analysis. Maturitas 144, 23–28.

Jette, A.M., Haley, S.M., Coster, W.J., Kooyoomjian, J.T., Levenson, S., Heeren, T., Ashba, J., 2002. Late life function and disability instrument: I. Development and evaluation of the disability component. J Gerontol A Biol Sci Med Sci 57, M209-216.

Johansson, M.E., Cameron, I.G.M., Van der Kolk, N.M., de Vries, N.M., Klimars, E., Toni, I., Bloem, B.R., Helmich, R.C., 2022. Aerobic Exercise Alters Brain Function and Structure in Parkinson's Disease: A Randomized Controlled Trial. Ann Neurol 91, 203–216.

Kalia, L.V., Lang, A.E., 2015. Parkinson's disease. The Lancet 386, 896–912.

Kalilani, L., Asgharnejad, M., Palokangas, T., Durgin, T., 2016. Comparing the Incidence of Falls/Fractures in Parkinson's Disease Patients in the US Population. PLoS One 11, e0161689.

Kandola, A., Vancampfort, D., Herring, M., Rebar, A., Hallgren, M., Firth, J., Stubbs, B., 2018. Moving to Beat Anxiety: Epidemiology and Therapeutic Issues with Physical Activity for Anxiety. Curr Psychiatry Rep 20, 63.

Keogh, A., Alcock, L., Brown, P., Buckley, E., Brozgol, M., Gazit, E., Hansen, C., Scott, K., Schwickert, L., Becker, C., Hausdorff, J., Maetzler, W., Rochester, L., Sharrack, B., Vogiatzis, I., Yarnall, A., mazzà, C., Caulfield, B., 2023. Acceptability of wearable devices for measuring mobility remotely: Observations from the Mobilise-D technical validation study. DIGITAL HEALTH 9, 205520762211507.

Keogh, A., Taraldsen, K., Caulfield, B., Vereijken, B., 2021. It's not about the capture, it's about what we can learn": a qualitative study of experts' opinions and experiences regarding the use of wearable sensors to measure gait and physical activity. Journal of NeuroEngineering and Rehabilitation 18, 78.

Kerr, J., Duncan, S., Schipperijn, J., Schipperjin, J., 2011. Using Global Positioning Systems in Health Research A Practical Approach to Data Collection and Processing. American journal of preventive medicine 41, 532–40.

Kim, Y., Brown, R., 2022. Effect of meteorological conditions on leisure walking: a time series analysis and the application of outdoor thermal comfort indexes. Int J Biometeorol 66, 1109–1123.

Kirk, C., Rehman, R. zia ur, Galna, B., Alcock, L., Ranciati, S., Palmerini, L., Garcia-Aymerich, J., Hansen, C., Schaeffer, E., Berg, D., Maetzler, W., Rochester, L., Din, S., Yarnall, A., 2023a. Can Digital Mobility Assessment Enhance the Clinical Assessment of Disease Severity in Parkinson's Disease? Journal of Parkinson's Disease 1–11.
Kirk, C., Kuederle, A., Micó-Amigo, M.E., Bonci, T., Paraschiv-Ionescu, A., Ullrich, M., Soltani, A., Gazit, E., Salis, F., Alcock, L., Aminian, K., Becker, C., Bertuletti, S., Brown, P., Buckley, E., Cantu, A., Carsin, A.-E., Caruso, M., Caulfield, B., Din, S., 2023b. Estimating real-world walking speed from a single wearable device: analytical pipeline, results and lessons learnt from the Mobilise-D technical validation study.

Kluge, F., Din, S.D., Cereatti, A., Gaßner, H., Hansen, C., Helbostad, J.L., Klucken, J., Küderle, A., Müller, A., Rochester, L., Ullrich, M., Eskofier, B.M., Mazzà, C., Consortium, on behalf of the M.-D., 2021. Consensus based framework for digital mobility monitoring. PLOS ONE 16, e0256541.

Knapik, A., Szefler-Derela, J., Wasiuk-Zowada, D., Siuda, J., Krzystanek, E., Brzęk, A., 2021. Isolation Related to the COVID-19 Pandemic in People Suffering from Parkinson's Disease and Activity, Self-Assessment of Physical Fitness and the Level of Affective Disorders. Healthcare (Basel) 9, 1562.
Kowalsky, D.B., Rebula, J.R., Ojeda, L.V., Adamczyk, P.G., Kuo, A.D., 2021. Human walking in the real world: Interactions between terrain type, gait parameters, and energy expenditure. PLoS One 16, e0228682.

Kyrdalen, I.L., Thingstad, P., Sandvik, L., Ormstad, H., 2019. Associations between gait speed and well-known fall risk factors among community-dwelling older adults. Physiother Res Int 24, e1743.

Liddle, J., Ireland, D., McBride, S.J., Brauer, S.G., Hall, L.M., Ding, H., Karunanithi, M., Hodges, P.W., Theodoros, D., Silburn, P.A., Chenery, H.J., 2014. Measuring the Lifespace of People With Parkinson's Disease Using Smartphones: Proof of Principle. JMIR Mhealth Uhealth 2, e13.

Liu, Y., Zhang, G., Tarolli, C.G., Hristov, R., Jensen-Roberts, S., Waddell, E.M., Myers, T.L., Pawlik, M.E., Soto, J.M., Wilson, R.M., Yang, Y., Nordahl, T., Lizarraga, K.J., Adams, J.L., Schneider, R.B., Kieburtz, K., Ellis, T., Dorsey, E.R., Katabi, D., 2022. Monitoring gait at home with radio waves in Parkinson's disease: A marker of severity, progression, and medication response. Sci. Transl. Med. 14, eadc9669.

Lord, S., Baker, K., Nieuwboer, A., Burn, D., Rochester, L., 2011a. Gait variability in Parkinson's disease: an indicator of non-dopaminergic contributors to gait dysfunction? J Neurol 258, 566–572.

Lord, S., Chastin, S.F.M., McInnes, L., Little, L., Briggs, P., Rochester, L., 2011b. Exploring patterns of daily physical and sedentary behaviour in community-dwelling older adults. Age Ageing 40, 205–210. https://doi.org/10.1093/ageing/afq166

Lord, S., Galna, B., Rochester, L., 2013a. Moving forward on gait measurement: Toward a more refined approach. Movement Disorders 28, 1534–1543.

Lord, S., Galna, B., Verghese, J., Coleman, S., Burn, D., Rochester, L., 2013b. Independent domains of gait in older adults and associated motor and nonmotor attributes: validation of a factor analysis approach. J Gerontol A Biol Sci Med Sci 68, 820–7.

Lord, S., Godfrey, A., Galna, B., Mhiripiri, D., Burn, D., Rochester, L., 2013c. Ambulatory activity in incident Parkinson's: more than meets the eye? J Neurol 260, 2964–2972

Lu, L., Zhang, J., Xie, Y., Gao, F., Xu, S., Wu, X., Ye, Z., 2020. Wearable Health Devices in Health Care: Narrative Systematic Review. JMIR Mhealth Uhealth 8, e18907.

Luis-Martínez, R., Di Marco, R., Weis, L., Cianci, V., Pistonesi, F., Baba, A., Carecchio, M., Biundo, R., Tedesco, C., Masiero, S., Antonini, A., 2021. Impact of social and mobility restrictions in Parkinson's disease during COVID-19 lockdown. BMC Neurol 21, 332.

Mak, M.K.Y., Wong-Yu, I.S.K., 2019. Exercise for Parkinson's disease. Int Rev Neurobiol 147, 1–44.

Mancini, M., Horak, F.B., Zampieri, C., Carlson-Kuhta, P., Nutt, J.G., Chiari, L., 2011. Trunk accelerometry reveals postural instability in untreated Parkinson's disease. Parkinsonism Relat Disord 17, 557–562.

Mancini, M., Salarian, A., Carlson-Kuhta, P., Zampieri, C., King, L., Chiari, L., Horak, F.B., 2012. ISway: a sensitive, valid and reliable measure of postural control. Journal of NeuroEngineering and Rehabilitation 9, 59.

Mancini, M., Shah, V.V., Stuart, S., Curtze, C., Horak, F.B., Safarpour, D., Nutt, J.G., 2021. Measuring freezing of gait during daily-life: an open-source, wearable sensors approach. J Neuroeng Rehabil 18, 1

Mancini, M., Weiss, A., Herman, T., Hausdorff, J.M., 2018. Turn Around Freezing: Community-Living Turning Behavior in People with Parkinson's Disease. Front Neurol 9, 18.

Masala, C., Petretto, D.R., 2008. From disablement to enablement: Conceptual models of disability in the 20th century. Disability and Rehabilitation 30, 1233–1244.

Mazzà, C., Alcock, L., Aminian, K., Becker, C., Bertuletti, S., Bonci, T., Brown, P., Brozgol, M., Buckley, E., Carsin, A.-E., Caruso, M., Caulfield, B., Cereatti, A., Chiari, L., Chynkiamis, N., Ciravegna, F., Del Din, S., Eskofier, B., Evers, J., Garcia Aymerich, J., Gazit, E., Hansen, C., Hausdorff, J.M., Helbostad, J.L., Hiden, H., Hume, E., Paraschiv-Ionescu, A., Ireson, N., Keogh, A., Kirk, C., Kluge, F., Koch, S., Küderle, A., Lanfranchi, V., Maetzler, W., Micó-Amigo, M.E., Mueller, A., Neatrour, I., Niessen, M., Palmerini, L., Pluimgraaff, L., Reggi, L., Salis, F., Schwickert, L., Scott, K., Sharrack, B., Sillen, H., Singleton, D., Soltani, A., Taraldsen, K., Ullrich, M., Van Gelder, L., Vereijken, B., Vogiatzis, I., Warmerdam, E., Yarnall, A., Rochester, L., 2021. Technical validation of real-world monitoring of gait: a multicentric observational study. BMJ Open 11, e050785.

Mc Ardle, R., Del Din, S., Donaghy, P., Galna, B., Thomas, A.J., Rochester, L., 2021. The Impact of Environment on Gait Assessment: Considerations from Real-World Gait Analysis in Dementia Subtypes. Sensors (Basel) 21, 813.

Mc Ardle, R., Del Din, S., Morris, R., Alcock, L., Yarnall, A.J., Burn, D.J., Rochester, L., Lawson, R.A., On Behalf Of The Icicle-Pd Study Group, null, 2022. Factors Influencing Habitual Physical Activity in Parkinson's Disease: Considering the Psychosocial State and Wellbeing of People with Parkinson's and Their Carers. Sensors (Basel) 22, 871.

Merchant, R.A., Chen, M.Z., Wong, B.L.L., Ng, S.E., Shirooka, H., Lim, J.Y., Sandrasageran, S., Morley, J.E., 2020. Relationship Between Fear of Falling, Fear-Related Activity Restriction, Frailty, and Sarcopenia. J Am Geriatr Soc 68, 2602–2608.

Micó-Amigo, M.E., Bonci, T., Paraschiv-Ionescu, A., Ullrich, M., Kirk, C., Soltani, A., Küderle, A., Gazit, E., Salis, F., Alcock, L., Aminian, K., Becker, C., Bertuletti, S., Brown, P., Buckley, E., Cantu, A., Carsin, A.-E., Caruso, M., Caulfield, B., Cereatti, A., Chiari, L., D'Ascanio, I., Eskofier, B., Fernstad, S., Froehlich, M., Garcia-Aymerich, J., Hansen, C., Hausdorff, J.M., Hiden, H., Hume, E., Keogh, A., Kluge, F., Koch, S., Maetzler, W., Megaritis, D., Mueller, A., Niessen, M., Palmerini, L., Schwickert, L., Scott, K., Sharrack, B., Sillén, H., Singleton, D., Vereijken, B., Vogiatzis, I., Yarnall, A.J., Rochester, L., Mazzà, C., Del Din, S., for the Mobilise-D consortium, 2023. Assessing real-world gait with digital technology? Validation, insights and recommendations from the Mobilise-D consortium. Journal of NeuroEngineering and Rehabilitation 20, 78.

Middleton, A., Fritz, S.L., Lusardi, M., 2015. Walking speed: the functional vital sign. J Aging Phys Act 23, 314–22.

Mikolaizak, A.S., Rochester, L., Maetzler, W., Sharrack, B., Demeyer, H., Mazzà, C., Caulfield, B., Garcia-Aymerich, J., Vereijken, B., Arnera, V., Miller, R., Piraino, P., Ammour, N., Gordon, M.F., Troosters, T., Yarnall, A.J., Alcock, L., Gaßner, H., Winkler, J., Klucken, J., Schlenstedt, C., Watz, H., Kirsten, A.-M., Vogiatzis, I., Chynkiamis, N., Hume, E., Megaritis, D., Nieuwboer, A., Ginis, P., Buckley, E., Brittain, G., Comi, G., Leocani, L., Helbostad, J.L., Johnsen, L.G., Taraldsen, K., Blain, H., Driss, V., Frei, A., Puhan, M.A., Polhemus, A., Basea, M.B. de, Gimeno, E., Hopkinson, N.S., Buttery, S.C., Hausdorff, J.M., Mirelman, A., Evers, J., Neatrour, I., Singleton, D., Schwickert, L., Becker, C., Jansen, C.-P., Consortium, and members of the clinical validation study (WP4) on behalf of M.-D., 2022. Connecting real-world digital mobility assessment to clinical outcomes for regulatory and clinical endorsement–the Mobilise-D study protocol. PLOS ONE 17, e0269615.

Milanović, Z., Pantelić, S., Trajković, N., Sporiš, G., Kostić, R., James, N., 2013. Age-related decrease in physical activity and functional fitness among elderly men and women. Clin Interv Aging 8, 549–556.

Mirelman, A., Bonato, P., Camicioli, R., Ellis, T.D., Giladi, N., Hamilton, J.L., Hass, C.J., Hausdorff, J.M., Pelosin, E., Almeida, Q.J., 2019. Gait impairments in Parkinson's disease. Lancet Neurol 18, 697–708.

Mirelman, A., Rochester, L., Maidan, I., Del Din, S., Alcock, L., Nieuwhof, F., Rikkert, M.O., Bloem, B.R., Pelosin, E., Avanzino, L., Abbruzzese, G., Dockx, K., Bekkers, E., Giladi, N., Nieuwboer, A., Hausdorff, J.M., 2016. Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial. Lancet 388, 1170–1182.

Morris, M.E., Iansek, R., Matyas, T.A., Summers, J.J., 1996. Stride length regulation in Parkinson's disease. Normalization strategies and underlying mechanisms. Brain 119 (Pt 2), 551–568.

Morris, M.E., Iansek, R., Matyas, T.A., Summers, J.J., 1994. Ability to modulate walking cadence remains intact in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 57, 1532–1534.

Morris, R., Hickey, A., Del Din, S., Godfrey, A., Lord, S., Rochester, L., 2017a. A model of free-living gait: A factor analysis in Parkinson's disease. Gait & Posture 52, 68–71.

Morris, R., Lord, S., Bunce, J., Burn, D., Rochester, L., 2016. Gait and cognition: Mapping the global and discrete relationships in ageing and neurodegenerative disease. Neurosci Biobehav Rev 64, 326–345.

Morris, R., Lord, S., Lawson, R.A., Coleman, S., Galna, B., Duncan, G.W., Khoo, T.K., Yarnall, A.J., Burn, D.J., Rochester, L., 2017b. Gait Rather Than Cognition Predicts Decline in Specific Cognitive Domains in Early Parkinson's Disease. The Journals of Gerontology: Series A 72, 1656–1662.

Moustafa, A.A., Chakravarthy, S., Phillips, J.R., Gupta, A., Keri, S., Polner, B., Frank, M.J., Jahanshahi, M., 2016. Motor symptoms in Parkinson's disease: A unified framework. Neuroscience & Biobehavioral Reviews 68, 727–740.

Mukaka, M., 2012. A guide to appropriate use of Correlation coefficient in medical research. Malawi Med J 24, 69–71.

Mündermann, L., Corazza, S., Andriacchi, T.P., 2006. The evolution of methods for the capture of human movement leading to markerless motion capture for biomechanical applications. J Neuroengineering Rehabil 3, 6.

Nadif, R., Febrissy, M., Andrianjafimasy, M.V., Le Moual, N., Gormand, F., Just, J., Pin, I., Siroux, V., Matran, R., Dumas, O., Nadif, M., 2020. Endotypes identified by cluster analysis in asthmatics and non-asthmatics and their clinical characteristics at follow-up: the case-control EGEA study. BMJ Open Respir Res 7, e000632.

Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53, 695–699.

Nieuwboer, A., Giladi, N., 2013. Characterizing freezing of gait in Parkinson's disease: models of an episodic phenomenon. Mov Disord 28, 1509–1519.

Nieuwboer, A., Rochester, L., Herman, T., Vandenberghe, W., Emil, G.E., Thomaes, T., Giladi, N., 2009. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. Gait Posture 30, 459–463.

Noyce, A.J., Bestwick, J.P., Silveira-Moriyama, L., Hawkes, C.H., Giovannoni, G., Lees, A.J., Schrag, A., 2012. Meta-Analysis of Early Nonmotor Features and Risk Factors for Parkinson Disease. Ann Neurol 72, 893–901.

Osaba, M.Y., Martelli, D., Prado, A., Agrawal, S.K., Lalwani, A.K., 2020. Age-related differences in gait adaptations during overground walking with and without visual perturbations using a virtual reality headset. Sci Rep 10, 15376.

Pääsuke, M., Ereline, J., Gapeyeva, H., Joost, K., Mõttus, K., Taba, P., 2004. Leg-extension strength and chair-rise performance in elderly women with Parkinson's disease. J Aging Phys Act 12, 511–524.

Pacini Panebianco, G., Bisi, M.C., Stagni, R., Fantozzi, S., 2018. Analysis of the performance of 17 algorithms from a systematic review: Influence of sensor position, analysed variable and computational approach in gait timing estimation from IMU measurements. Gait & Posture 66, 76–82.

Pang, M.Y., 2021. Physiotherapy management of Parkinson's disease. Journal of Physiotherapy 67, 163–176.

Paraschiv-Ionescu, A., Newman, C.J., Carcreff, L., Gerber, C.N., Armand, S., Aminian, K., 2019. Locomotion and cadence detection using a single trunk-fixed accelerometer: validity for children with cerebral palsy in daily life-like conditions. Journal of NeuroEngineering and Rehabilitation 16, 24.

Paraschiv-Ionescu, A., Soltani, A., Aminian, K., 2020. Real-world speed estimation using single trunk IMU: methodological challenges for impaired gait patterns*, in: 2020 42nd Annual International Conference of the IEEE Engineering in Medicine Biology Society (EMBC). Presented at the 2020 42nd Annual International Conference of the IEEE Engineering in Medicine Biology Society (EMBC), pp. 4596–4599.

Park, J.-H., Stelmach, G.E., 2007. Force development during target-directed isometric force production in Parkinson's disease. Neurosci Lett 412, 173–178.

Parkinson’s UK, 2020. Parkinson’s UK. URL https://www.parkinsons.org.uk/about-us/reporting-parkinsons-information-journalists (accessed 5.25.22).

Pazzaglia, C., Imbimbo, I., Tranchita, E., Minganti, C., Ricciardi, D., Lo Monaco, R., Parisi, A., Padua, L., 2020. Comparison of virtual reality rehabilitation and conventional rehabilitation in Parkinson’s disease: a randomised controlled trial. Physiotherapy 106, 36–42.

Pelicioni, P.H.S., Menant, J.C., Latt, M.D., Lord, S.R., 2019. Falls in Parkinson’s Disease Subtypes: Risk Factors, Locations and Circumstances. Int J Environ Res Public Health 16, E2216.

Pelicioni, P.H.S., Pereira, M.P., Lahr, J., dos Santos, P.C.R., Gobbi, L.T.B., 2021. Assessment of Force Production in Parkinson’s Disease Subtypes. International Journal of Environmental Research and Public Health 18, 10044.

Peterson, D.S., Horak, F.B., 2016. Neural Control of Walking in People with Parkinsonism. Physiology (Bethesda) 31, 95–107.

Piazza, S.J., Cavanagh, P.R., 2000. Measurement of the screw-home motion of the knee is sensitive to errors in axis alignment. Journal of Biomechanics 33, 1029–1034.

Pinheiro, J., 2020. Package “nlme.”

Pirker, W., Katzenschlager, R., 2017. Gait disorders in adults and the elderly. Wien Klin Wochenschr 129, 81–95.

Pistacchi, M., Gioulis, M., Sanson, F., De Giovannini, E., Filippi, G., Rossetto, F., Marsala, S.Z., 2017. Gait analysis and clinical correlations in early Parkinson’s disease. Funct Neurol 32, 28–34.

Plotnik, M., Giladi, N., Hausdorff, J.M., 2008. Bilateral coordination of walking and freezing of gait in Parkinson’s disease. European Journal of Neuroscience 27, 1999–2006.

Poewe, W., 2008. Non-motor symptoms in Parkinson’s disease. Eur J Neurol 15 Suppl 1, 14–20.

Polhemus, A., Ortiz, L.D., Brittain, G., Chynkiamis, N., Salis, F., Gaßner, H., Gross, M., Kirk, C., Rossanigo, R., Taraldsen, K., Balta, D., Breuls, S., Buttery, S., Cardenas, G., Endress, C., Gugenhan, J., Keogh, A., Kluge, F., Koch, S., Micó-Amigo, M.E., Nerz, C., Sieber, C., Williams, P., Bergquist, R., de Basea, M.B., Buckley, E., Hansen, C., Mikolaizak, A.S., Schwickert, L., Scott, K., Stallforth, S., van Uem, J., Vereijken, B., Cereatti, A., Demeyer, H., Hopkinson, N., Maetzler, W., Troosters, T., Vogiatzis, I., Yarnall, A., Becker, C., Garcia-Aymerich, J., Leocani, L., Mazzà, C., Rochester, L., Sharrack, B., Frei, A., Puhan, M., 2021. Walking on common ground: a cross-disciplinary scoping review on the clinical utility of digital mobility outcomes. npj Digit. Med. 4, 1–14.

Port, R.J., Rumsby, M., Brown, G., Harrison, I.F., Amjad, A., Bale, C.J., 2021. People with Parkinson's Disease: What Symptoms Do They Most Want to Improve and How Does This Change with Disease Duration? J Parkinsons Dis 11, 715–724.

Postuma, R.B., Berg, D., Stern, M., Poewe, W., Olanow, C.W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A.E., Halliday, G., Goetz, C.G., Gasser, T., Dubois, B., Chan, P., Bloem, B.R., Adler, C.H., Deuschl, G., 2015. MDS clinical diagnostic criteria for Parkinson's disease. Movement Disorders 30, 1591–1601.

Powell, L.E., Myers, A.M., 1995. The Activities-specific Balance Confidence (ABC) Scale. J Gerontol A Biol Sci Med Sci 50A, M28-34.

Pradhan, S., Kelly, V.E., 2019. Quantifying physical activity in early Parkinson disease using a commercial activity monitor. Parkinsonism Relat Disord 66, 171–175.

Pringsheim, T., Jette, N., Frolkis, A., Steeves, T.D.L., 2014. The prevalence of Parkinson's disease: A systematic review and meta-analysis. Movement Disorders 29, 1583–1590.

Raccagni, C., Gassner, H., Eschlboeck, S., Boesch, S., Krismer, F., Seppi, K., Poewe, W., Eskofier, B.M., Winkler, J., Wenning, G., Klucken, J., 2018. Sensor-based gait analysis in atypical parkinsonian disorders. Brain Behav 8, e00977.

Raccagni, C., Nonnekes, J., Bloem, B.R., Peball, M., Boehme, C., Seppi, K., Wenning, G.K., 2020. Gait and postural disorders in parkinsonism: a clinical approach. J Neurol 267, 3169–3176.

Rainham, D., Krewski, D., McDowell, I., Sawada, M., Liekens, B., 2008. Development of a wearable global positioning system for place and health research. International Journal of Health Geographics 7, 59.

Rehman, R.Z.U., Buckley, C., Micó-Amigo, M.E., Kirk, C., Dunne-Willows, M., Mazzà, C., Shi, J.Q., Alcock, L., Rochester, L., Del Din, S., 2020. Accelerometry-Based Digital Gait Characteristics for Classification of Parkinson's Disease: What Counts? IEEE Open Journal of Engineering in Medicine and Biology 1, 65–73.

Rehman, R.Z.U., Guan, Y., Shi, J.Q., Alcock, L., Yarnall, A.J., Rochester, L., Del Din, S., 2022. Investigating the Impact of Environment and Data Aggregation by Walking Bout Duration on Parkinson's Disease Classification Using Machine Learning. Frontiers in Aging Neuroscience 14.

Reynolds, D., 2009. Gaussian Mixture Models, in: Li, S.Z., Jain, A. (Eds.), Encyclopedia of Biometrics. Springer US, Boston, MA, pp. 659–663.

Richards, J., Levine, D., Whittle, M.W., 2022. Whittle's Gait Analysis - E-Book: Whittle's Gait Analysis - E-Book. Elsevier Health Sciences.

Ripley, B., Venables, B., Bates, D.M., ca 1998), K.H. (partial port, ca 1998), A.G. (partial port, Firth, D., 2022. MASS: Support Functions and Datasets for Venables and Ripley's MASS.

Rochester, L., Baker, K., Nieuwboer, A., Burn, D., 2011. Targeting dopa-sensitive and dopa-resistant gait dysfunction in Parkinson's disease: Selective responses to internal and external cues. Movement Disorders 26, 430–435.

Rochester, L., Chastin, S.F.M., Lord, S., Baker, K., Burn, D.J., 2012. Understanding the impact of deep brain stimulation on ambulatory activity in advanced Parkinson's disease. J Neurol 259, 1081–1086.

Rochester, L., Galna, B., Lord, S., Burn, D., 2014. The nature of dual-task interference during gait in incident Parkinson's disease. Neuroscience 265, 83–94.

Rochester, L., Jones, D., Hetherington, V., Nieuwboer, A., Willems, A.-M., Kwakkel, G., Wegen, E.V., 2006. Gait and gait-related activities and fatigue in Parkinson's disease: What is the relationship? Disability and Rehabilitation 28, 1365–1371.

Rochester, L., Mazza, C., Mueller, A., Caulfield, B., McCarthy, M., Becker, C., Miller, R., Piraino, P., Viceconti, M., Dartee, W.P., Garcia-Aymerich, J., Aydemir, A.A., Vereijken, B., Arnera, V., Ammour, N., Jackson, M., Hache, T., Roubenoff, R., 2020. A Roadmap to Inform Development, Validation and Approval of Digital Mobility Outcomes: The Mobilise-D Approach. Digit Biomark 4, 13–27.

Rogers, G., Davies, D., Pink, J., Cooper, P., 2017. Parkinson's disease: summary of updated NICE guidance. BMJ 358, j1951.

Schipperijn, J., Kerr, J., Duncan, S., Madsen, T., Klinker, C.D., Troelsen, J., 2014. Dynamic Accuracy of GPS Receivers for Use in Health Research: A Novel Method to Assess GPS Accuracy in Real-World Settings. Frontiers in public health 2, 21.

Schlachetzki, J.C.M., Barth, J., Marxreiter, F., Gossler, J., Kohl, Z., Reinfelder, S., Gassner, H., Aminian, K., Eskofier, B.M., Winkler, J., Klucken, J., 2017. Wearable sensors objectively measure gait parameters in Parkinson's disease. PLoS One 12, e0183989.

Scott, K., Bonci, T., Salis, F., Alcock, L., Buckley, E., Gazit, E., Hansen, C., Schwickert, L., Aminian, K., Bertuletti, S., Caruso, M., Chiari, L., Sharrack, B., Maetzler, W., Becker, C., Hausdorff, J.M., Vogiatzis, I., Brown, P., Del Din, S., Eskofier, B., Paraschiv-Ionescu, A., Keogh, A., Kirk, C., Kluge, F., Micó-Amigo, E.M., Mueller, A., Neatrour, I., Niessen, M., Palmerini, L., Sillen, H., Singleton, D., Ullrich, M., Vereijken, B., Froehlich, M., Brittain, G., Caulfield, B., Koch, S., Carsin, A.-E., Garcia-Aymerich, J., Kuederle, A., Yarnall, A., Rochester, L., Cereatti, A., Mazzà, C., for the Mobilise-D consortium, 2022. Design and validation of a multi-task, multi-context protocol for real-world gait simulation. Journal of NeuroEngineering and Rehabilitation 19, 141.

Scrucca, L., Fop, M., Murphy, T.B., Raftery, A.E., 2016. mclust 5: Clustering, Classification and Density Estimation Using Gaussian Finite Mixture Models. R J 8, 289–317.

Sedgwick, P., Greenwood, N., 2015. Understanding the Hawthorne effect. BMJ 351, h4672.

Shah, V.V., McNames, J., Harker, G., Mancini, M., Carlson-Kuhta, P., Nutt, J.G., El-Gohary, M., Curtze, C., Horak, F.B., 2020a. Effect of Bout Length on Gait Measures in People with and without Parkinson's Disease during Daily Life. Sensors (Basel) 20.

Shah, V.V., McNames, J., Mancini, M., Carlson-Kuhta, P., Nutt, J., El-Gohary, M., Lapidus, J., Horak, F., Curtze, C., 2020b. Digital Biomarkers of Mobility in Parkinson's Disease During Daily Living. J Parkinsons Dis 10, 1099–1111.

Shah, V.V., McNames, J., Mancini, M., Carlson-Kuhta, P., Spain, R., Nutt, J., El-Gohary, M., Curtze, C., Horak, F., 2020c. Laboratory versus daily life gait characteristics in patients with multiple sclerosis, Parkinson's disease, and matched controls. Journal of NeuroEngineering and Rehabilitation 17, 159.

Shah, V.V., McNames, J., Mancini, M., Carlson-Kuhta, P., Spain, R., Nutt, J., El-Gohary, M., Curtze, C., Horak, F., 2020d. Quantity and quality of gait and turning in people with multiple sclerosis, Parkinson's disease and matched controls during daily living. JOURNAL OF NEUROLOGY 267, 1188–1196.

Sheikh, J.I., Yesavage, J.A., 1986. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clinical Gerontologist: The Journal of Aging and Mental Health 5, 165–173.

Shulman, L., 2010. The Clinically Important Difference on the Unified Parkinson's Disease Rating Scale. JAMA Neurology 67, 64–70.

Sigurdsson, H.P., Raw, R., Hunter, H., Baker, M.R., Taylor, J.-P., Rochester, L., Yarnall, A.J., 2021. Noninvasive vagus nerve stimulation in Parkinson's disease: current status and future prospects. Expert Review of Medical Devices 18, 971–984.

Silva-Batista, C., Corcos, D.M., Kanegusuku, H., Piemonte, M.E.P., Gobbi, L.T.B., de Lima-Pardini, A.C., de Mello, M.T., Forjaz, C.L.M., Ugrinowitsch, C., 2018. Balance and fear of falling in subjects with Parkinson's disease is improved after exercises with motor complexity. Gait Posture 61, 90–97.

Smets, E.M., Garssen, B., Bonke, B., De Haes, J.C., 1995. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 39, 315–325.

Smulders, K., Dale, M.L., Carlson-Kuhta, P., Nutt, J.G., Horak, F.B., 2016. Pharmacological treatment in Parkinson's disease: Effects on gait. Parkinsonism & Related Disorders 31, 3–13.

Soltani, A., Aminian, K., Mazza, C., Cereatti, A., Palmerini, L., Bonci, T., Paraschiv-Ionescu, A., 2021. Algorithms for walking speed estimation using a lower-back-worn inertial sensor: A cross-validation on speed ranges. IEEE Trans Neural Syst Rehabil Eng PP.

Stalvey, B.T., Owsley, C., Sloane, M.E., Ball, K., 1999. The Life Space Questionnaire: A Measure of the Extent of Mobility of Older Adults. J Appl Gerontol 18, 460–478.

Stone, E., Skubic, M., Rantz, M., Abbott, C., Miller, S., 2015. Average in-home gait speed: Investigation of a new metric for mobility and fall risk assessment of elders. Gait & Posture 41, 57–62.

Suri, A., VanSwearingen, J., Baillargeon, E.M., Crane, B.M., Moored, K.D., Carlson, M.C., Dunlap, P.M., Donahue, P.T., Redfern, M.S., Brach, J.S., Sejdić, E., Rosso, A.L., 2023. Association Of Gait Quality with Daily-Life Mobility: An Actigraphy and Global Positioning System Based Analysis in Older Adults. IEEE Transactions on Biomedical Engineering 1–10.

Talbot, L.A., Musiol, R.J., Witham, E.K., Metter, E.J., 2005. Falls in young, middle-aged and older community dwelling adults: perceived cause, environmental factors and injury. BMC Public Health 5, 86.

Tanaka, K., Wada-Isoe, K., Yamamoto, M., Tagashira, S., Tajiri, Y., Nakashita, S., Nakashima, K., 2014. Clinical evaluation of fatigue in Japanese patients with Parkinson's disease. Brain Behav 4, 643–649.

Taoum, A., Chaudru, S., de Müllenheim, P.-Y., Congnard, F., Emily, M., Noury-Desvaux, B., Bickert, S., Carrault, G., Mahé, G., Le Faucheur, A., 2021. Comparison of Activity Monitors Accuracy in Assessing Intermittent Outdoor Walking. Medicine and Science in Sports and Exercise 53, 1303–1314.

Terashi, H., Taguchi, T., Ueta, Y., Okubo, Y., Mitoma, H., Aizawa, H., 2020. Analysis of non-invasive gait recording under free-living conditions in patients with Parkinson's disease: relationship with global cognitive function and motor abnormalities. BMC Neurology 20, 161.

Terashi, H., Utsumi, H., Ishimura, Y., Mitoma, H., 2013. Independent regulation of the cycle and acceleration in parkinsonian gait analyzed by a long-term daily monitoring system. Eur Neurol 69, 134–141.

Toda, H., Maruyama, T., Tada, M., 2020. Indoor vs. Outdoor Walking: Does It Make Any Difference in Joint Angle Depending on Road Surface? Front Sports Act Living 2, 119.

Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E., 2010. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25, 2649–2653.

Toosizadeh, N., Mohler, J., Lei, H., Parvaneh, S., Sherman, S., Najafi, B., 2015. Motor Performance Assessment in Parkinson's Disease: Association between Objective In-Clinic, Objective In-Home, and Subjective/Semi-Objective Measures. PLoS One 10, e0124763.

Tsukita, K., Sakamaki-Tsukita, H., Takahashi, R., 2022. Long-term Effect of Regular Physical Activity and Exercise Habits in Patients With Early Parkinson Disease. Neurology 98, e859–e871.

Uhrbrand, A., Stenager, E., Pedersen, M.S., Dalgas, U., 2015. Parkinson's disease and intensive exercise therapy--a systematic review and meta-analysis of randomized controlled trials. J Neurol Sci 353, 9–19.

Ullrich, M., Küderle, A., Reggi, L., Cereatti, A., Eskofier, B.M., Kluge, F., 2021. Machine learning-based distinction of left and right foot contacts in lower back inertial sensor gait data, in: 2021 43rd Annual International Conference of the IEEE Engineering in Medicine Biology Society (EMBC). Presented at the 2021 43rd Annual International Conference of the IEEE Engineering in Medicine Biology Society (EMBC), pp. 5958–5961.

Van Ancum, J.M., van Schooten, K.S., Jonkman, N.H., Huijben, B., van Lummel, R.C., Meskers, C.G.M., Maier, A.B., Pijnappels, M., 2019. Gait speed assessed by a 4-m walk test is not representative of daily-life gait speed in community-dwelling adults. Maturitas 121, 28–34.

Verschuur, C.V.M., Suwijn, S.R., Boel, J.A., Post, B., Bloem, B.R., van Hilten, J.J., van Laar, T., Tissingh, G., Munts, A.G., Deuschl, G., Lang, A.E., Dijkgraaf, M.G.W., de Haan, R.J., de Bie, R.M.A., 2019. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. New England Journal of Medicine 380, 315–324.

Viceconti, M., Penna, S.H., Dartee, W., Mazzà, C., Caulfield, B., Becker, C., Maetzler, W., Garcia-Aymerich, J., Davico, G., Rochester, L., 2020. Toward a regulatory qualification of real-world mobility performance biomarkers in parkinson's patients using digital mobility outcomes. Sensors 20, 1–13.

Viceconti, M., Tome, M., Dartee, W., Knezevic, I., Hernandez Penna, S., Mazzà, C., Caulfield, B., Garcia-Aymerich, J., Becker, C., Maetzler, W., Troosters, T., Sharrack, B., Davico, G., Corriol-Rohou, S., Rochester, L., the Mobilise-D Consortium, 2022. On the use of wearable sensors as mobility biomarkers in the marketing authorization of new drugs: A regulatory perspective. Frontiers in Medicine 9.

Villafaña, J.A., Hernandez, S., Alvarado, A., Shimada, K., Pimiento, C., Rivadeneira, M.M., Kriwet, J., 2020. First evidence of a palaeo-nursery area of the great white shark. Sci Rep 10, 8502.

Warmerdam, E., Hausdorff, J.M., Atrsaei, A., Zhou, Y., Maetzler, W., 2020. Long-term unsupervised mobility assessment in movement disorders. The Lancet Neurology.

Webber, S.C., Porter, M.M., 2009. Monitoring Mobility in Older Adults Using Global Positioning System (GPS) Watches and Accelerometers: A Feasibility Study. Journal of Aging and Physical Activity 17, 455–467.

Weiss, A., Herman, T., Giladi, N., Hausdorff, J.M., 2015. New evidence for gait abnormalities among Parkinson's disease patients who suffer from freezing of gait: insights using a body-fixed sensor worn for 3 days. J Neural Transm (Vienna) 122, 403–410.

Weiss, A., Herman, T., Giladi, N., Hausdorff, J.M., 2014. Objective Assessment of Fall Risk in Parkinson's Disease Using a Body-Fixed Sensor Worn for 3 Days. PLoS One 9, e96675.

Wettstein, M., Wahl, H.-W., Diehl, M.K., 2013. A multidimensional view of out-of-home behaviors in cognitively unimpaired older adults: examining differential effects of socio-demographic, cognitive, and health-related predictors. Eur J Ageing 11, 141–153.

Wettstein, M., Wahl, H.-W., Shoval, N., Oswald, F., Voss, E., Seidl, U., Frölich, L., Auslander, G., Heinik, J., Landau, R., 2015. Out-of-Home Behavior and Cognitive Impairment in Older Adults: Findings of the SenTra Project. J Appl Gerontol 34, 3–25.

Wilson, J., Alcock, L., Yarnall, A.J., Lord, S., Lawson, R.A., Morris, R., Taylor, J.-P., Burn, D.J., Rochester, L., Galna, B., 2020. Gait Progression Over 6 Years in Parkinson's Disease: Effects of Age, Medication, and Pathology. FRONTIERS IN AGING NEUROSCIENCE 12.

Yang, C.-C., Hsu, Y.-L., 2010. A Review of Accelerometry-Based Wearable Motion Detectors for Physical Activity Monitoring. Sensors (Basel) 10, 7772–7788.

Yarnall, A.J., Breen, D.P., Duncan, G.W., Khoo, T.K., Coleman, S.Y., Firbank, M.J., Nombela, C., Winder-Rhodes, S., Evans, J.R., Rowe, J.B., Mollenhauer, B., Kruse, N., Hudson, G., Chinnery, P.F., O'Brien, J.T., Robbins, T.W., Wesnes, K., Brooks, D.J., Barker, R.A., Burn, D.J., ICICLE-PD Study Group, 2014. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. Neurology 82, 308–316.

Zahoor, I., Shafi, A., Haq, E., 2018. Pharmacological Treatment of Parkinson's Disease, in: Stoker, T.B., Greenland, J.C. (Eds.), Parkinson's Disease: Pathogenesis and Clinical Aspects. Codon Publications, Brisbane (AU).

Zanardi, A.P.J., da Silva, E.S., Costa, R.R., Passos-Monteiro, E., Dos Santos, I.O., Kruel, L.F.M., Peyre-Tartaruga, L.A., 2021. Gait parameters of Parkinson's disease compared with healthy controls: a systematic review and meta-analysis. Sci Rep 11, 752.

Zeng, X.-T., Zhang, Y., Kwong, J., Zhang, C., Li, S., Sun, F., Niu, Y.-M., Du, L., 2015. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. Journal of evidence-based medicine 8.

Zhang, L., Yan, Y., Liu, G., Han, B., Fei, J., Zhang, Y., 2022. Effect of fatigue on kinematics, kinetics and muscle activities of lower limbs during gait. Proc Inst Mech Eng H 236, 1365–1374.

Zhang, W.-S., Gao, C., Tan, Y.-Y., Chen, S.-D., 2021. Prevalence of freezing of gait in Parkinson's disease: a systematic review and meta-analysis. J Neurol 268, 4138–4150.

Zijlstra, W., Hof, A.L., 2003. Assessment of spatio-temporal gait parameters from trunk accelerations during human walking. Gait Posture 18, 1–10.

Zimmermann, M., Chong, A.K., Vechiu, C., Papa, A., 2020. Modifiable risk and protective factors for anxiety disorders among adults: A systematic review. Psychiatry Research 285, 112705.