THE EFFICACY OF A TRUNK STRENGTHENING PROGRAM FOR IMPROVING POSTURAL STABILITY IN PEOPLE WITH PARKINSON'S DISEASE: A RANDOMISED CONTROLLED TRIAL

A DISSERTATION SUBMITTED TO THE GRADUATE SCHOOL

FOR THE DEGREE

DOCTOR OF PHILOSOPHY

BY

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FEBRUARY 2017

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I Abstract

Introduction - Parkinson's disease (PD) is a neurodegenerative disorder characterized by a series of motor and non-motor symptoms that collectively impact the independence and quality of life of this population. Symptoms of postural instability are amongst the most disabling and appear to be significantly influenced by a reduced capacity to control the trunk segment due to impaired trunk muscle function, muscle weakness and reduced inter-segmental mobility. Considering the trunk comprises approximately 60% of the body's weight and that standard pharmacological therapies are known to be largely ineffective for the management of symptoms affecting this segment (i.e. axial symptoms), it is clear that alternative therapies are required to ensure postural stability during dynamic tasks. Exercise has been shown to be successful for improving various measures of clinical balance and motor function in people with PD, but the evidence for its capacity to improve dynamic postural stability and reduce falls in this population is less conclusive. The inconsistent findings presented in previous studies may be explained, at least in part, by the tendency for such research to rely upon clinical tests of mobility and balance that incorporate Likert scales that lack the capacity to detect subtle changes in function. With recent advances in the usability of wearable sensor technologies, it is now possible to incorporate these highly sensitive devices to improve the objectivity of postural stability assessments. Despite the potential of these systems, there is a need for clearer guidelines regarding the best placements and outcome measures to use to help guide their use in clinical settings. To address the apparent shortcomings of the existing literature, the four studies presented in this dissertation sought to determine whether wearable sensors could be used to improve clinical assessments of postural stability in people with PD and to examine whether a 12-week trunk-specific exercise intervention was capable of improving measures of static and dynamic postural stability in this population.

Methods – To determine the extent to which wearable sensors might be suitable for assessing postural stability in people with PD, a systematic search of three scientific databases was performed to identify papers that had previously used these devices to assess standing and walking stability in this population. Of the 340 articles identified through the search, 26 were considered suitable for inclusion in the review and were subsequently appraised for methodological quality and synthesized. For Study 2, patients with idiopathic PD were invited to participate in a cross-sectional experiment aimed at examining the relationship between clinical tests and movement symmetry. Of the participants involved in Study 2, those who reported experiencing one or more falls or two or more near misses in the past year were also invited to participate in a randomized controlled trial seeking to investigate the effects of a trunk-specific exercise program on static (Study 3) and dynamic (Study 4) postural stability. At baseline, participants completed clinical tests of disease severity, mobility, balance, balance confidence and quality of life and laboratory assessments of walking stability and trunk muscle function. Following baseline, participants involved in Studies 3 and 4 were randomised to either a 12-week supervised trunk-specific exercise program or a 12-week falls prevention education program. Following the completion of the 12-week intervention, participants were reassessed using the same test battery completed at baseline and following a further 12-week retention period (i.e. 24 weeks following baseline). To determine whether the 12-week exercise-based intervention was successful at improving clinical and objective measures of static and dynamic postural stability, linear mixed model analyses were conducted with the level of significance set at $p<0.05$. For the assessments of static postural stability, daily levodopa equivalent dose and age were entered as covariates, while daily levodopa equivalent dose and walking speed were included as covariates in the models examining dynamic postural stability.

Results – The results of the systematic review (Study 1) indicated that accelerometers placed on the head and trunk were the most commonly used wearable sensor for assessing postural stability in people with PD. The most successful measure used was identified differences in postural stability was the harmonic ratio; a measurement of movement symmetry. For the cross-sectional study (Study 2), patients were stratified based on disease stage into either a Mild (Hoehn & Yahr Stage 1) or Moderate (Hoehn & Yahr Stages 2 to 3) PD group. The results highlighted that the Moderate PD group had poorer quality of life ($p=0.001$), reduced balance confidence ($p<0.001$) and increased gait and falls difficulty ($p=0.040$). Furthermore, for these patients, gait disability and the number of previous falls were both negatively correlated with multiple components of all head ($\rho=-0.537$ to -0.693, $p\leq0.05$) and most trunk ($\rho=-0.595$ to -0.766, $p\leq0.015$) movement symmetry. For the Mild PD group, six-meter walk time was positively correlated with medial-lateral head symmetry ($\rho=0.573$, $p=0.041$) and linear regression highlighted a significant predictive relationship ($p=0.036$) between these outcomes. For Mild and Moderate PD, balance confidence predicted anterior-posterior trunk ($p=0.012$) and vertical head ($p=0.047$) movement symmetry, respectively.

For those participants involved in the 12-week phase II randomised controlled trial (Studies 3 and 4), the results indicated that neither therapy (exercise or education) led to a significant change in clinical measures of symptom severity, mobility, balance, balance confidence, gait and falls difficulty, and quality of life. However, the statistical analyses revealed that, without vision on a foam surface, patients in the Exercise group had reduced sway area and sway variability at both the 12- ($p=0.003$-0.01; medial-lateral variability only) and 24-week ($p=0.001$-0.04; medial-lateral and anterior-posterior variability) time points compared with baseline. In contrast, the education group demonstrated increased postural sway area at 24-weeks ($p=0.04$) compared with baseline.

With respect to the measures of head and trunk symmetry, medial-lateral trunk symmetry ($p=0.002$) had declined in the Education group at 12 weeks relative to the baseline measures. These declines were complemented by clinical reductions in peak and baseline activation of the upper (peak: $p=0.02$; baseline: $p<0.001$) and lower (peak: $p<0.001$; baseline: $p<0.001$) erector spinae at 24-weeks. In contrast, the Exercise group demonstrated improved anterior-posterior head symmetry ($p=0.04$) at 24-weeks and improved anterior-posterior trunk symmetry at the 12- ($p<0.001$) and 24-week ($p=0.01$) time points compared with baseline. In regards to movement amplitude, pairwise comparisons revealed greater vertical head ($p<0.001$) and anterior-posterior ($p<0.001$), medial-lateral ($p<0.001$) and vertical ($p=0.003$) trunk movement amplitudes for the Education group at 12-weeks relative to baseline. While vertical head ($p<0.001$) movement amplitude had decreased by the 24-week assessment, anterior-posterior ($p=0.01$), medial-lateral ($p=0.01$) and vertical ($p<0.001$) trunk movement amplitudes all remained elevated at 24-weeks relative to baseline. Similar changes were highlighted in movement amplitude for the Exercise group, with vertical head ($p<0.001$) movement amplitude increasing at 24-weeks relative to baseline and medial-lateral trunk movement amplitude increased at 24-weeks relative to the baseline ($p<0.001$) and 12-week ($p<0.001$) assessments.

Conclusions - This thesis presents evidence to suggest that more objective measures can provide greater insight into small, yet meaningful changes in symptom severity for people with PD. Clinical variables of disease severity, mobility, balance, and balance confidence were not influenced by the exercise intervention, however, objective and continuous measures of movement symmetry, movement amplitude, postural sway, and muscle function did. As an end result, this thesis has demonstrated that a low-intensity trunk specific exercise program can be useful for improving functioning in PD, and that accelerometers can be an alternative method for improving the assessment of postural stability in clinical settings. Furthermore, the

presented findings provide evidence on specific ways to improve the treatment and assessment of postural instability in PD, which should assist with promoting an improved independence and overall quality of life of these individuals.

II List of Tables

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IV List of Abbreviations

ABC	=	Activities-specific Balance Confidence Scale
ACE	=	Addenbrooke's Cognitive Examination
AP	=	Anterior-Posterior
EC	=	Eyes Closed
EMG	=	Electromyography
EO	=	Eyes Open
ES	=	Erector Spinae
H&Y	=	Hoehn & Yahr Stage Score
HR	=	Harmonic Ratio
ML	=	Medial-Lateral
MVC	=	Maximal Voluntary Contraction
PD	=	Parkinson's Disease
PDQ-39	=	39-item Parkinson's Disease Questionnaire
RMS	=	Root Mean Square
ROC	=	Receiver Operating Characteristics
UPDRS	=	Unified Parkinson's Disease Rating Scale
UPDRS I	=	UPDRS sub-scale I: Mentation, Behaviour and Mood
UPDRS II	=	UPDRS sub-scale II: Activities of Daily Living
UPDRS III	=	UPDRS sub-scale III: Motor Examination
UPDRS IV	=	UPDRS sub-scale IV: Complications of Therapy
VT	=	Vertical

V Declaration

I hereby declare that this thesis presents work carried out by myself and does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any University.

To the best of my knowledge, it does not contain any materials previously published or written by another person except where due reference has been made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.

Signature of Candidate

Date

January 25, 2017

VI Acknowledgements

I would like to thank Professor Peter Silburn and the team at Neurosciences Queensland for their support and assistance with participant recruitment for this research.

To the participants, without your devotion and kindness, this research would not have been possible. I thank you for your support and it has been a pleasure serving you.

To Dr Tim Blackmore and Eamon Conway, I want to thank you for your support and the time that you each spent writing the Matlab code used to process my data.

I want to thank my co-supervisor Professor Geraldine Naughton for her expert advice and support throughout my PhD.

I want to thank my parents for supporting me throughout this process. It has been a journey of a lifetime and your support has helped me get through it.

Finally, to Dr Michael Cole, my primary supervisor, who has helped guide me along this journey every step of the way I thank him for his unwavering support and for his help in making this dream of mine a reality.

1.0 Introduction

Parkinson's disease (PD) is an age-related neurodegenerative condition resulting from the loss of the dopaminergic innervation within the basal ganglia that are involved in regulation of many functions, including movement. The depletion of dopamine results in an overall increase in the inhibition of movement, leading to slower and sometimes completely arrested performance [248]. Currently, the triggers for these degenerative changes remain unclear and although multiple risk factors have been identified, age and gender are the only risk factors supported by moderate evidence for the development of PD [120]. Males are approximately 1.5 times more likely to develop PD than females [231], and the prevalence increases incrementally across the lifespan. As such, approximately 1 in 300 people aged between 55 and 64 years are likely to develop the condition, compared with approximately 9 in 300 people aged 85 years and older [189]. With the loss of the dopaminergic cells and the development of PD, a number of deficits in motor control may emerge and these may include slowness of movement (bradykinesia), resting tremor, and muscle rigidity [154].

With progression of the disease, symptoms affecting postural stability and gait can also develop and may include a stooped or flexed trunk posture, slower walking speed and reduced arm swing while ambulating; all of which can increase the risk of falls. Traditionally, both clinical and biomechanical methods have been employed to assess standing and walking balance in people with PD. Accelerometers are amongst the most commonly used biomechanical devices for the collection of the continuous data used to identify differences in gait [232] and head stability [25] across a range of age groups and pathologies. Furthermore, recent research has tested the ability of different acceleration-based measures to predict the risk of falls in older individuals [58, 249], but the suitability of accelerometers to assess postural stability in people with PD is currently less clear.

While motor symptoms are more often examined in research, people with PD may also experience non-motor symptoms that significantly impair their health and quality of life. Common non-motor symptoms experienced by people with PD include: depression, anxiety, cognitive impairment, insomnia, loss of smell (anosmia), and altered digestive function [154]. The severity of symptoms may be dependent on the rate of disease progression and the fact that each patient can experience vastly different symptoms adds to the complexity of comprehensively and effectively managing this condition.

While PD presents a number of significant challenges to the physiological and psychological health and wellbeing of individuals and their loved ones, it also poses a significant financial burden to these people and the public health system. In 2011, a report prepared for Parkinson's Australia identified that the costs associated with PD totalled an estimated $8.3 billion per annum for the Australian population [189]. In other populations, the annual estimated costs of PD are reported to be $23 billion USD (≈$29.3 billion AUD) [107] and £600 million (≈$1.2 billion AUD) [68] for the United States of America and the United Kingdom, respectively. In each case, these estimates represented the direct costs associated with the condition and, hence include the costs incurred by individuals and those attributable to the medical treatment and health care provided by the governments. However, if one considers that 19% of those diagnosed with PD are of working age (15-64) [189], it is clear that the economic impact of the condition is further influenced by a number of significant indirect costs, including income lost due to reduced productivity within the workforce. Given that the number of Australians living with PD (64,000 in 2011) is expected to double by 2031 [189], it is likely that the economic and social costs associated with the disease will also increase at a similar rate.

Impairments of balance are among the most debilitating consequences of the ageing process for otherwise healthy individuals. Such age-related changes are known to contribute to

the increased number of falls experienced by people aged 65 years and older, with research consistently reporting that one in three older adults fall at least once each year [125, 134]. Forty percent of the falls experienced by individuals aged 65 years and over result in injuries requiring hospital treatment [125] and, hence, influence an individual's mortality, morbidity and quality of life. Unfortunately, the incidence of falling is increased for high-risk populations, such as people with PD, with up to 68% of these individuals reported to fall at least once each year [43, 259]. While a number of disease-specific characteristics have been implicated as contributors to this increased risk, the motor symptoms experienced by patients are believed to be the most significant contributors to postural instability in this cohort.

In bipedal stance and locomotion, it is the role of the postural control system to maintain the centre of gravity within the body's base of support, such that balance and postural stability can be controlled and falls are prevented. However, even relatively healthy older adults demonstrate an age-related decline in postural stability during tasks that require dynamic postural control (such as walking, turning), which can put ageing individuals at an increased risk of falling [39]. From a mechanical perspective, the trunk is believed to play a significant role in dynamic postural control by attenuating movement-related forces and stabilising the head [116]. Head stability has a well-recognised role in the maintenance of equilibrium, as it houses the vestibular and visual systems, which contribute to the inertial guidance required for stable locomotion [199]. People with PD have impaired head and trunk control [43], which contributes to the postulation that decreased trunk control and balance are potentially related to the higher rate of falls in people with PD [43, 83, 86]. While it is currently unclear whether these deficits stem from insufficient or inappropriate muscle recruitment patterns or excessive segmental stiffness, these findings suggest that it is important to improve postural control for people with PD.

To date, extensive research has been focused on determining the efficacy of various interventions for improving balance and reducing falls risk in people with PD [2, 6, 63]. On the basis of such research, it has become widely recognised that exercise is an effective means of improving and/or maintaining cardiovascular health, physical endurance, and muscular strength; all of which enhance systemic functioning and independence. Exercise has also been shown to be effective in improving postural stability and reducing falls [10, 216], while also improving symptoms of anxiety and depression [73] in otherwise healthy older adults. In a population of people with PD, exercise was shown to be an effective means of improving motor symptoms on the Unified Parkinson's Disease Rating Scale (UPDRS) motor score [139] and decreasing the overall falls risk score derived from knee extensor strength, the coordinated stability test and the Freezing of Gait questionnaire [2]. Furthermore, exercise may improve measures of postural sway performed during the Sensory Organisation Test in people with PD [99, 238]. However, currently few studies have investigated whether exercise can improve head and trunk control during dynamic activities, such as walking. Given that 45-48% of falls occur during walking and other forms of locomotion [7, 17], there is clear need for research to determine whether targeted exercise interventions can improve dynamic postural stability in people with PD.

Given the apparent gaps in the existing literature, this program of research sought to establish the utility of wearable sensors for the assessment of stability under static and dynamic conditions in people with PD and determine whether the outcomes derived from these devices offer additional diagnostic information over common clinical assessments. Furthermore, this research aimed to determine whether a 12-week exercise-based intervention was effective at improving measures of static and/or dynamic postural stability in people with PD. It was hypothesised that the use of wearable sensors for the assessment of static and dynamic stability would offer additional insight into the balance and gait problems experienced by people with

PD. Furthermore, given that previous research has consistently highlighted the benefits of regular exercise for a range of populations, it was hypothesized that a trunk-specific exercise program would contribute to improvements in the stability of people with PD under both static and dynamic conditions.

2.0 Literature Review

2.1 Parkinson's disease and basal ganglia dysfunction

Parkinson's disease is a neurodegenerative hypokinetic disorder that results in complex collection of motor and non-motor symptoms and is characterised by movements that are reduced in speed and amplitude. The symptoms of the condition are caused by a reduction in the amount of dopamine produced within the basal ganglia. From a structural perspective, the basal ganglia are comprised of a collection of nuclei that include the caudate nucleus, putamen, globus pallidus (pallidum), subthalamic nucleus and substantia nigra [109]. However, a number of these structures are often sub-divided in practice due to differences in their cytoarchitecture and/or function. Specifically, the caudate nucleus and the putamen are collectively referred to as the striatum, as these structures act as a relay centre receiving dopaminergic signals from the substantia nigra, as well as sensory and motor signals from other regions of the central nervous system. It is postulated that this information is sent to the basal ganglia to assist with the scaling and modulation of movement. The substantia nigra are located within the midbrain and are considered to have both a compact (pars compacta) and reticular (pars reticulata) component, while the globus pallidus is considered to comprise both an internal (globus pallidus internus) and external (globus pallidus externus) part. The cell bodies of the dopamine-producing neurons in the basal ganglia are located in the substantia nigra pars compacta and, from here, their axons project to the nuclei of the striatum [109].

For the most part, structures forming the basal ganglia are comprised of neurons that are inhibitory in nature and, hence, activation of these structures serves to inhibit or prevent the action of the cells with which they synapse. The only exceptions to this rule are the neurons within the subthalamic nuclei, which are excitatory and, hence, facilitate the action of the cells with which they synapse. To date, two primary neural pathways with complementary functions have an accepted involvement in motor control. These pathways are intuitively referred to as

direct and indirect pathways. Action potentials passed through the basal ganglia via the direct pathway serve to disinhibit the motor thalamus and, hence promote movement, while neural commands passing along the indirect pathway inhibit the motor thalamus and reduce movement. As stated earlier, most neurons in the basal ganglia are inhibitory in nature, however, dopaminergic input from the substantia nigra pars compacta excites the striatum in the direct pathway while inhibiting the striatum in the indirect pathway.

To completely appreciate how the motor thalamus is influenced differently by these two independent pathways, it is necessary to consider each in detail. In the direct pathway, dopaminergic input from the substantia nigra pars compacta and excitatory signals from the motor cortices activate the inhibitory striatal neurons that project to the globus pallidus internus. The excitation of the inhibitory striatal neurons results in the output of the globus pallidus internus and/or substantia nigra pars reticulata being heavily inhibited and leads to reduced inhibition of the motor thalamus and the promotion of movement (Figure 1A). In the indirect pathway, dopaminergic input from the substantia nigra pars compacta inhibits striatal neurons while the cerebral cortices excite striatal neurons that project to the globus pallidus externus. The combination of these two signals results, overall, in the inhibition of the nuclei in the globus pallidus externus. As the neurons that project from the globus pallidus externus to the subthalamic nucleus are inhibitory in nature, inhibition of these structures reduces their capacity to inhibit the excitatory neurons of the subthalamic nucleus. As such, activation of the excitatory neurons projecting from the subthalamic nucleus to the globus pallidus internus and/or substantia nigra pars reticulata is increased; ultimately increasing their capacity to inhibit the motor thalamus and movement (Figure 1B). Given this understanding, it is evident that the direct and indirect pathways work synergistically together to scale and control movement based on the input from the motor cortices that is dictated by the specific demands of a task.

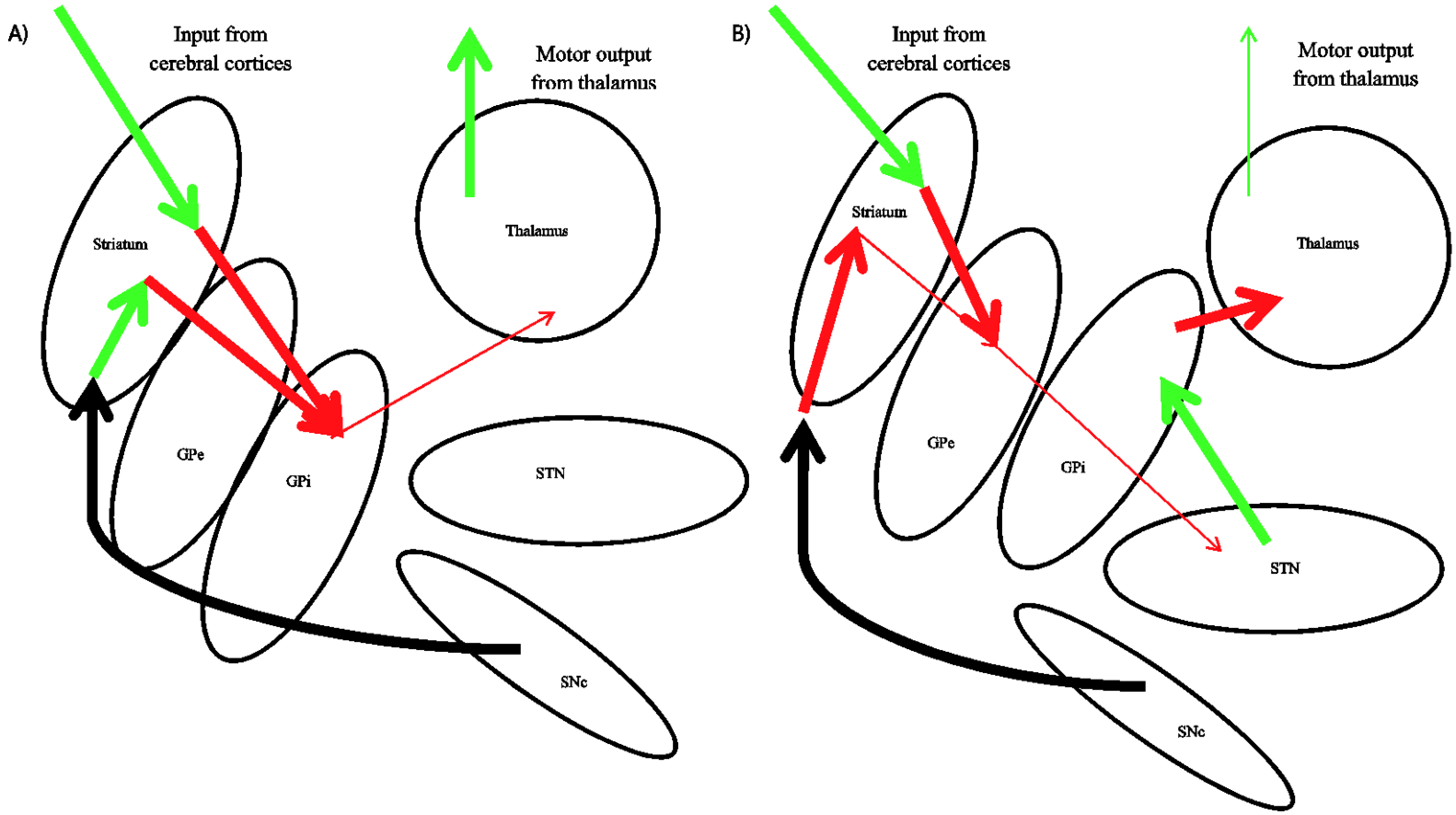

Figure 1: Visual representation of the A) direct; and B) indirect pathways in a healthy adult.

Black lines represent dopamine input, green lines represent glutaminergic input (excitatory) and red lines represent GABAergic input (inhibitory). The weight of the line represents the strength of the output from one structure to the next, such that a heavier red line represents greater inhibition of the target structure.

In the direct pathway, death of dopaminergic cells within the substantia nigra pars compacta results in reduced excitation of the striatum via the substantia nigra pars compacta results in an overall reduction in the inhibition of the globus pallidus internus. In turn, the inhibitory output of the globus pallidus internus is increased, which ultimately leads to greater inhibition of the motor thalamus and reduced movement (Figure 2A). In contrast, reduced dopamine in the indirect pathway reduces the inhibition of the striatum allowing it to further inhibit the globus pallidus externus. The increased inhibition of the globus pallidus externus further reduces its capacity to inhibit the excitatory nuclei of the subthalamic nucleus, allowing them to further activate the inhibitory nuclei of the globus pallidus internus and/or substantia nigra pars reticulata. As an end result, the globus pallidus internus and/or substantia nigra pars reticulata inhibit the motor thalamus to a greater extent and ultimately impair movement (Figure 2B) [109]. In summary, the loss of dopaminergic innervations within the substantia nigra pars compacta leads to reduced facilitation of movement via the direct pathway and increased inhibition of movement via the indirect pathway and, hence, helps us to understand the hypokinetic symptoms that characterise the condition.

The concomitant activity of the direct and indirect pathways is believed to influence movement in much the same way that a brake pedal in a car can influence its motion. In a perfect scenario, the body's movements are neither over nor under regulated, hence they are smooth and controlled. However, if activity along the indirect pathway is inadequate, the motor thalamus is insufficiently inhibited (i.e. the brake pedal is released) and movements become uncontrolled (hyperkinetic). In contrast, insufficient activity along the direct pathway and/or excessive activity along the indirect pathway will result in insufficient excitation of the motor thalamus (i.e. too much pressure on the brake pedal) and result in slow or completely arrested movements (hypokinetic). By modulating the activity between the direct and indirect pathways (regulated by dopamine), the basal ganglia can assist with scaling movements to meet the demands of the task. Dysfunction of the pathways within the basal ganglia can lead to impairment of normal neurological function

between the basal ganglia, thalamus, and numerous motor and perceptual areas of the cerebral cortex. Eventually, these impairments lead to the development of the complex collections of motor and non-motor symptoms that are not easily managed [192].

Despite the universal acceptance that the motor and non-motor symptoms of PD arise due to the degeneration of dopaminergic innervation within the basal ganglia [248], the specific 'trigger' or pathophysiology that leads to these changes still remains largely unknown. Nevertheless, there is moderate to strong evidence of a number of risk factors that are believed to be associated, to some extent, with the development of PD. The factor with the strongest link to the development of PD is age and it is typically considered quite rare for individuals under the age of 40 years to develop the condition [51]. Approximately 1 to 2% of people aged over 60 years have PD, but the incidence of developing the condition rises sharply during later life, with 3 to 4% in individuals aged over 80 years [46] and 4 to 5% over 85 years [248]. In addition to age, advances in genetic science have also provided evidence to suggest that first-degree relatives of people with PD (e.g. parents, siblings) face a 2.7 to 4.4 times greater risk of developing PD than those without familial links to the condition [233]. The increased risk associated with having a family link to PD is believed to be the result of specific genetic mutations. One such mutation that has been widely researched is the Leucine-Rich Repeat Kinase 2 gene mutation, which has been linked with the development of PD in some patient groups [79, 178]. Although these factors are supported by a growing body of research, the evidence supporting other reported risk factors including environmental exposures to pesticides, herbicides and heavy metals remains relatively weak [51]. Several studies have shown that people who smoke and/or regularly consume caffeinated products (e.g. coffee) have a reduced risk of developing PD, but the protective mechanisms are unclear [51]. Also, these habits may increase the individual's risk of other health-related conditions and, in the absence of stronger scientific evidence [51], would not be promoted.

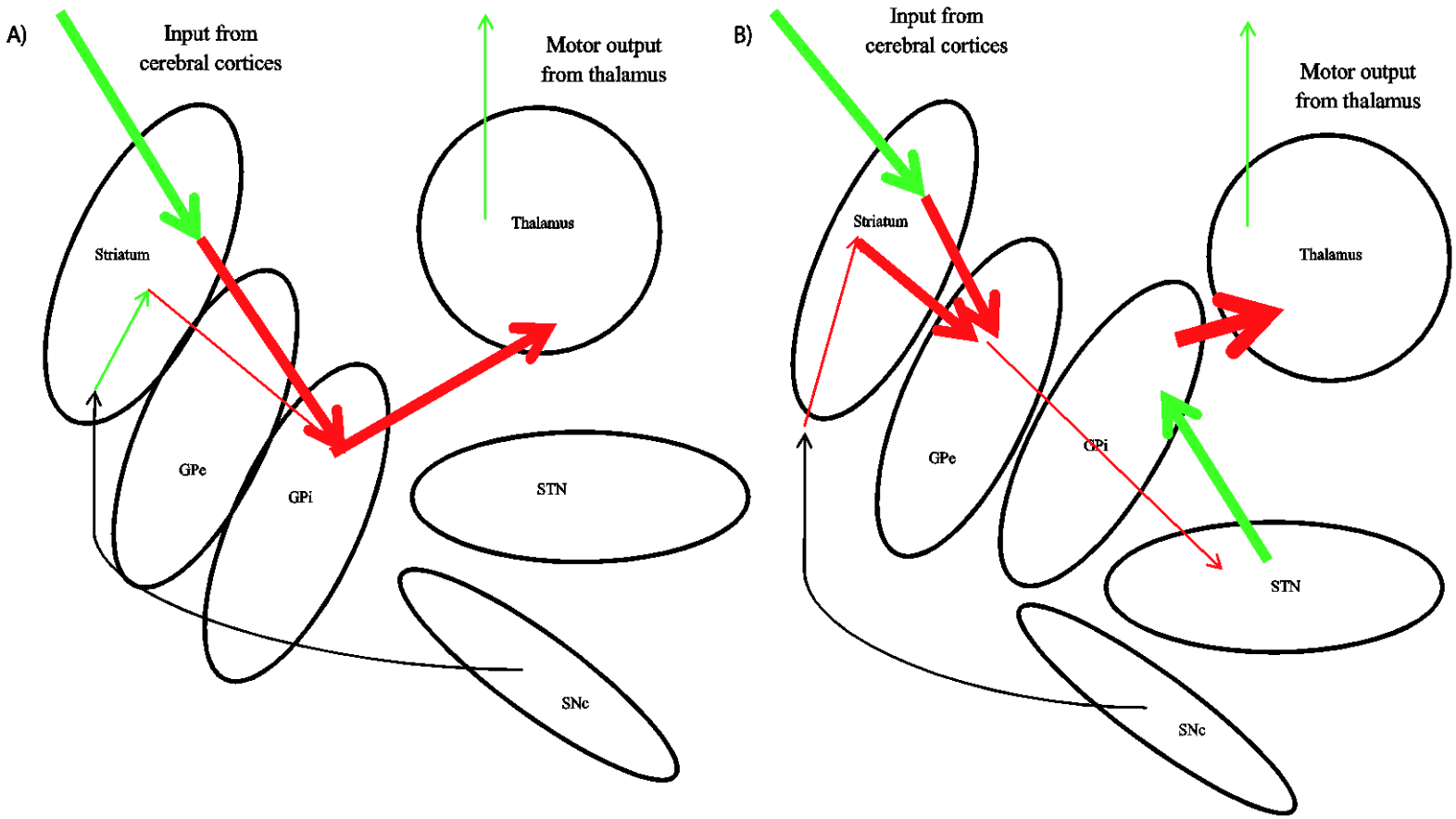

Figure 2: Visual representation of the A) direct; and B) indirect pathways in a person with PD.

Black lines represent dopamine input, green lines represent glutaminergic input (excitatory) and red lines represent GABAergic input (inhibitory). The weight of the line represents the strength of the output from one structure to the next, such that a heavier red line represents increased inhibition of the target structure.

2.2 Symptoms of Parkinson's disease

While each individual with PD will likely experience a different collection of symptoms, the most common motor symptoms associated with the condition include resting tremor, reduced amplitude or speed of movement (bradykinesia), rigidity, and postural instability [248]. Bradykinesia is often considered one of the most disabling characteristics of the disease because approximately 80 to 90% of people with PD are affected by this symptom. In patients with greater symptom severity [143], bradykinesia can progress to an inability to initiate or continue movement (akinesia) and can present clinically as an inability to perform smooth and rapid alternating finger movements, speech problems, or difficulties with the initiation of gait and/or turning while walking [182]. The inability to initiate and/or continue walking is known as freezing of gait and is considered to be one of the main risk factors for falls in people with PD [37].

Like bradykinesia, resting tremor also occurs in 80 to 90% of PD cases and presents as rhythmic involuntary movements that typically affect the hands, legs, jaw or tongue and are only present when the patient is at rest. While resting tremor is usually the first and most visible symptom of the disease, it is rarely the cause of major disability for individuals [248]. This is likely due to the fact that patients often experience relief (or at least a significant diminution) from this symptom when the extremity affected is voluntarily moved [54] .

Joint stiffness or muscle rigidity occurs in more than 90% of individuals with PD [248] and is characterised by involuntary and concomitant activation of limb flexors and extensors, which increase the joint's resistance to passive movement. Such symptoms are most common in the extremities (e.g. wrists, ankles), but can also affect the axial skeleton (e.g. neck), particularly during the latter stages of the disease. Clinically, the joint stiffness observed in people with PD is often described as either an intermittent (cogwheel rigidity) or constant (lead-pipe rigidity) resistance to passive movement [248].

Changes in postural stability and gait often lead to significant disability for people with PD and while they are typically exacerbated in more advanced cases of the disease, they can also pose a significant burden to patients during the earlier stages of the condition. These symptoms have the potential to significantly impact a patient's ability to safely navigate their home and community environments [248]; ultimately impacting their confidence, independence and overall quality of life. While the nature of these gait changes can vary considerably from patient to patient, previous research has identified a number of common differences in the walking patterns of people with PD. Specifically, Parkinson's disease gait is often characterized by slower walking velocities [43, 131, 171, 222], shorter steps [30, 43, 131, 171, 222], greater stride length variability [131], and less arm swing [154] than healthy aged-matched controls. Other reported changes in walking patterns include decreased ankle joint range of motion [131, 172, 222], reduced joint power for the ankle at push off and decreased hip power generation and absorption [222]. Although many of the spatial characteristics of gait are known to be affected by PD (e.g. step length), multiple studies have shown that temporal characteristics, such as stride frequency (or cadence), are similar between individuals with PD and age-matched controls [30, 43, 222, 228].

More recently, it has been shown that the disease-related changes in walking patterns are more pronounced in people with PD who fall [8, 42, 43, 128], suggesting that declines in mobility may contribute to the increased risk of falling in this population. Specifically, individuals with PD who fall demonstrate increased variability in the time taken to complete each stride [42, 210] and exhibit reduced toe clearances compared with age-matched controls when walking on compliant surfaces [42]. The increased stride time variability and decreased toe clearance observed in PD fallers on compliant surfaces were not evident for PD non-fallers and, hence, could highlight an increased risk of falling for these individuals when transferring from different surfaces or encountering obstacles. This is supported by research showing that

two of the most common causes of falling in people with PD are tripping and walking on less predictable surfaces [7, 17]. In addition to these changes in gait characteristics, research also highlights changes in trunk function for people with PD [23], which may have impaired the capacity of these individuals to maintain postural stability.

Unlike other symptoms, such as resting tremor, rigidity and bradykinesia, postural instability and gait difficulties typically do not respond well to common pharmacological therapies [19]. As such, even for optimally-medicated patients, the impaired motor function associated with these symptoms has the potential to significantly increase their risk of experiencing falls and fall-related injuries.

2.3 The incidence and risk factors for falls

The term 'fall' has been assigned multiple definitions within the literature, but researchers have typically considered a fall to be "an unintentional coming to the ground or some lower level not as a result of a major intrinsic event (e.g. stroke or syncope) or overwhelming hazard" [235]. While falls can be potentially harmful for any person, they pose a significantly greater problem for older adults who face an increased risk of injury due to age-related changes in postural responses, muscular strength, and bone density [157, 220, 246]. According to prospective research, approximately one third of community-dwelling older adults aged over 65 years will fall at least once each year [125, 134], compared with 40% of adults aged 80 years over [125]. While these figures demonstrate the significant problem that falls can pose to an otherwise healthy population, it is important to consider that the risk of falling is often much higher for people with PD. Prospective research shows that between 65 and 68% of people with PD fall a least once in a given a year, with 43 to 50% of these individuals experiencing recurrent falls [43, 259]. Furthermore, it was estimated that falls and fall-related injuries in people with PD cost the Australian Health Care System $27.5 million

AUD in 2010 [189], highlighting the significant economic burden that these incidents pose. Given that the incidence of PD is expected to almost double in Australia to 115,300 by 2031 [189], a better understanding of the mechanism(s) that contribute to falls in these individuals will help in the treatment of the condition.

According to previous prospective research that has sought to gain an improved understanding of the circumstances surrounding falls in community-dwelling older adults [7, 17], falls most commonly occurred during ambulation (45 to 48%); often due to trips (29 to 34%) or while carrying an object (6 to 9%). In contrast, examination of the circumstances surrounding the falls reported by people with PD indicate that while a similar proportion of falls are reported to occur during ambulation (45%), a further 32% and 21% are reported to occur while the patient is standing or transferring, respectively [7]. These statistics appear to highlight the importance of developing improved methods for managing symptoms of postural instability and gait disability, as the circumstance surrounding falls in people with PD are largely attributable to difficulties with postural control during static and dynamic activities.

In addition to studies investigating the circumstances leading to falls, the efficacy of both clinical and experimental tests for identifying participants at an increased risk of falling has also been evaluated. Identifying factors to accurately predict patients with an increased risk of future falls is salient, as an improved understanding of these factors can lead to better treatment options for 'at risk' patients. A previous meta-analysis of six studies examining falls in people with PD demonstrated that a history of recurrent falls was the strongest independent predictor of future falls in people with PD; achieving a sensitivity and specificity of 68% and 81%, respectively [196]. However, the use of previous falls as a predictor of future falls ignores the need to identify the underlying mechanism of the incident to limit the risk of future events. Interestingly, however, the addition of clinical measures of symptom severity (i.e. the UPDRS) and disease stage (i.e. the Hoehn and Yahr stage score (H&Y)) to the predictive model did not

improve the researchers' capacity to predict future falls [196]. In contrast to these findings, two separate studies [41, 147] have provided evidence to suggest that reduced balance confidence is a significant independent predictor of future recurrent falls in people with PD.

A common clinical test used by researchers to assess older adults [22, 29, 38] and people with PD [6, 20, 72, 119, 147] is the Timed Up and Go test. It consists of an individual being timed with a stopwatch while completing a single task of rising from a chair, walking 3 meters, turning around, and returning to be seated. Longer performance times on the Timed Up and Go test have been associated with increased falls risk in individuals with PD [147]. In contrast to the Timed Up and Go test, the Berg Balance Scale includes multiple tasks that are individually scored on a Likert-based scale; allowing an overall composite score for balance to be derived. Lower scores (poorer performance) on the Berg Balance Scale are associated with an increased fall risk in older adults [38, 125]. However, despite the established relationships between falls risk and individual clinical scores, such as falls history, fear of falling, Timed Up and Go performance times and Berg Balance Scale total score, larger prospective research suggests that such clinical assessments have a poor capacity to predict future falls in people with PD [119]. Given the limited capacity for individual assessments to predict falls in PD populations, more recent research has sought to develop multivariate falls prediction models to improve the ability to identify patients who are at an increased risk of future falls. One such multivariate model included the UPDRS total score, the freezing of gait score, the occurrence of orthostatic hypotension, the total score for the Tinetti Balance and Gait test and the extent of anterior-posterior postural sway. The combination of these variables in a binary logistic regression model produced a multivariate model that was able to predict prospective falls in people with PD with a 78% sensitivity and 84% specificity [119]. Nevertheless, despite the promising outcomes of this multivariate model, it is worth noting that 42 of the 101 participants included in this cohort had a history of prior falls. Application of the multivariate model to the

59 patients who reported no history of prior falls yielded a similar sensitivity (77%), but a lower specificity (72%). A possible short-coming of the existing multivariate falls prediction models is that they have traditionally relied more heavily on patient self-report data and/or subjective clinical scales that are based on Likert scales. Given that a high percentage of the falls experienced by people with PD occur during dynamic activities and that the adequate control of the trunk and head segments is considered critical to postural stability, it may now be possible to improve these models by incorporating outcomes that better capture the dysfunction of the axial system in these patients.

2.4 The role of the trunk in maintaining postural stability

Given the trunk and head comprise 60% of the overall mass of the body [257], biomechanists have considered trunk control to be critical in maintaining postural stability, particularly during dynamic tasks. In a previous study examining segmental stability for different upper body regions in a healthy population, it was shown that trunk movements were smaller than those of the head and neck during walking [48]. However, separate research involving healthy individuals has demonstrated that trunk acceleration patterns are less regular than head accelerations during gait [116]. The authors argued that while the movements of the trunk may be smaller than the head and neck, the irregular trunk accelerations provide evidence that the segment acts as a low-pass filter to attenuate forces and ensure more regular and smooth movements of the head.

As previously stated, head stability is believed to be salient for maintaining balance, as both the visual and vestibular systems are located in this region; systems fundamental for feedback during postural control. For example, an exaggerated forward tilt of the head during walking serves to lock the position of the head relative to the trunk, which improves head stabilisation [199]. However, if an individual was unable to adequately control the trunk

segment during dynamic tasks, then the exaggerated movements of the trunk would have a direct impact on head stability and overall balance.

Multiple differences in trunk control have been observed in people with PD compared with other populations. For example, increased trunk stiffness (quantified as a reduced capacity to rotate the trunk) has been observed during sit-to-stand [179], gait [240] and turning [101] in people with PD compared with healthy age-matched controls. The mechanism for increased trunk stiffness in this population appears to be related to an underlying dysfunction of the trunk muscles, as research shows that patients have increased co-activation and background activity of the erector spinae and abdominal muscles during multidirectional translations [56]. Similarly, recent results have shown that people with PD who prospectively reported falling demonstrated significantly greater peak erector spinae activity during walking than age-matched controls [40]. Furthermore, these patients had significantly greater levels of baseline activity (activity between muscle bursts) for the erector spinae compared with the controls. Interestingly, these differences in baseline activity were shown to be significant predictors of the medial-lateral pelvis, trunk and head displacement [40] that has been linked with future falls in previous research [42, 43]. The authors argued that the increased activation of the erector spinae may have been indicative of an underlying dysfunction of the deeper and more fatigue-resistant muscles involved in postural control (i.e. multifidus, transverse abdominus). If this were the case, the larger and more superficial muscles may have been required to compensate for this deficit and more actively contribute to trunk stability. However, given these superficial muscles of the trunk are considered prime movers, they are typically more easily fatigued than their deeper counterparts. As such, an increased reliance on these muscles may have potential implications for the overall stability of these individuals. Importantly, the PD patients who did not fall during the 12-month follow-up period exhibited erector spinae activations that were not dissimilar to the control groups, which the authors argued may imply

that such deficits in trunk muscle function may be unique to a sub-population of patients. Unfortunately, separate evidence suggests that these deficits in neuromuscular function and the associated increase in trunk stiffness (i.e. reduced mobility) are further compounded by disease-related declines in trunk muscle strength, which are reportedly evident even in patients who have very mild symptom severity [23]. By specifically targeting the improved function of the trunk extensors (erector spinae, multifidus), flexors (rectus abdominus) and rotators (obliques), it may be possible to improve the strength of these muscles and improve the overall mobility and stability of the trunk [24].

While there is currently a paucity of research that has specifically sought to explain how differences in trunk muscle activation may contribute to falls in people with PD, an understanding of the erector spinae's role in trunk control during healthy gait may provide some insight into this relationship. In healthy individuals, the erector spinae muscles show a phasic increase in activation just after heel-contact to counter forward trunk flexion during walking [256]. This activation may stabilize the spine and attenuate the impact forces that travel vertically during walking. In general terms, the muscles turn on during heel contact and then become relatively inactive during the leg's swing phase. If this pattern of activity becomes compromised, as described recently for people with PD who fall, trunk stiffness may potentially be increased (excessive activity) or decreased (reduced activity) and ultimately influence postural stability. For example, an increase in the activation of the erector spinae and abdominal muscles would serve to stiffen the trunk and potentially influence its capacity to attenuate the movement-related forces that project upwards from the feet. Without appropriate attenuation, these forces would likely impair the quality of the visual and/or vestibular information used in balance control and potentially increase the individual's risk of falling. Given the established importance of the trunk for maintaining postural stability during dynamic tasks and the apparent deficits in trunk muscle activation reported for patients who fall, it would

seem reasonable to suggest that interventions that specifically target improving the mobility, strength and/or endurance of this region may be beneficial for patients who are unstable during walking.

2.5 Exercise for improving postural stability

The use of structured and progressive home-based exercise programs has demonstrated effectiveness for improving balance and reducing falls rates in older people prone to falls [10, 216]. Furthermore, research shows that regular and structured exercise regimes contribute to a reduction in the severity of symptoms for individuals with PD [2, 112, 139] and lead to improvements in strength [47, 85] balance [47], and postural stability [55] for these individuals. Despite these benefits, the quality of evidence regarding the efficacy of exercise in reducing the rate of falls in people with PD requires strengthening [85]. Previously, it was demonstrated that an 8-week exercise program completed twice per week either at home or under the guidance of a physiotherapist produced significant improvements in the severity of motor symptoms for a group of 19 PD patients (based on Part III of the UPDRS) [139]. However, these interventions did not improve scores for a number of clinical measures of balance and mobility, including the Berg Balance Scale, Activities-specific Balance Confidence (ABC) scale, or the Timed Up and Go test. It was concluded that since improvements were only seen in the UPDRS motor subscale, there was a need for more sensitive and objective assessments to evaluate improvements in mobility and postural stability for individuals with mild to moderate PD. In a more recent study, researchers sought to reduce the rate of falls in a groups of 142 recurrent PD fallers by implementing a similar six-week home-based physiotherapy program aimed at improving lower-leg strength, joint range of motion (ankle, pelvic tilt, trunk and head), balance (static, dynamic and functional) and walking (inside and outside) [6]. The results of this study demonstrated that the six-week period of physiotherapy did not lead to any

significant improvements in the patients' performances on clinical tests including, the Functional Reach test, the Berg Balance Scale, the Self-Assessment Parkinson's Disease Disability Scale or the Quality of Life Thermometer test. Furthermore, in spite of their relatively large sample size, the authors were only able to report a trend towards a reduction in falls rates following the intervention; a finding that the authors attributed to insufficient statistical power [6]. Additional studies have implemented similar physiotherapy-based programs that were administered three times per week over a ten-week [84] or six-month period [2] aimed at improving lower leg strength and balance in people with PD. Based on the collection of prospective falls diaries, the results of these studies showed no significant changes in falls rates [84] and no significant improvement in falls risk score [2], Berg Balance Scale or the Timed Up and Go test [2, 84]. A possible limitation of these studies was that they have primarily used clinical tests of mobility and physiological function to evaluate postural stability, rather than using more quantitative tools that are known to be sensitive to small, yet meaningful changes in postural control. For example, an improvement in Timed Up and Go test time following an exercise intervention would mean that an individual has improved their mobility, but it would not necessarily mean that this individual was more stable while performing the task. As such, it may be important to incorporate independent outcome measures of mobility and stability when evaluating the efficacy of an exercise-based intervention to ensure that improvements in mobility do not inadvertently exacerbate a patient's risk of falling. A second potential short coming of these studies is that they have primarily focussed exclusively on improving balance and the strength of the lower limb muscles in people with PD. However, given the significant role that the trunk segment plays in maintaining head stability and postural control during dynamic tasks [116], it seems reasonable to suggest that a more specific exercise program that focuses on improving trunk strength, endurance and/or mobility could help to improve postural stability.

Given its considerable size and mass, the trunk relies upon the precisely timed and scaled contraction of many muscles to maintain its stability and facilitate movement. While each of these muscles perform important functional roles, research suggests that the erector spinae and multifidus, which extend bilaterally and vertically along the length of the spine, are two of the most important for stabilising the trunk during human locomotion. As a superficial posterior trunk muscle, the erector spinae is considered to be a prime mover and is primarily responsible for extending, rotating and laterally flexing the spine. In contrast, the multifidus muscles are situated deeper to the erector spinae and due to their reduced capacity to generate large forces (due to reduced moment arms) are considered to be major contributors to stabilizing the lumbar and thoracic spine [74]. During normal walking, the erector spinae [256] and multifidus muscles demonstrate a phasic pattern of activation that presents as prominent bursts that each coincide with heel strike. These precisely timed activations are reportedly responsible for resisting the forward flexion moment of the trunk that occurs during the braking phase of the gait cycle [5, 57] and ultimately serves to maintain the relatively vertical position of the spine. Given the involvement in maintaining trunk alignment during walking, it is perhaps not surprising that deterioration of these muscles has been shown to contribute to lumbar instability in people with lower back pain [74]. Given that those with PD have been shown to have reduced trunk muscle strength [23] and abnormal trunk muscle activations during gait [40] compared with controls, it seems reasonable to suggest that specific training of these muscles may be beneficial for regaining the function of these muscles and restoring dynamic stability.

However, there is currently a paucity of research examining the effects of targeted exercises aimed at improving the strength and endurance of the trunk on functional improvements in individuals with PD. Given the deficits in trunk muscle strength and the increased trunk stiffness that is often evident in this patient group, exercises that target improvements in trunk

muscle strength and mobility could be vital to improving measures of balance. Support for this notion was provided in an earlier study that reported improvements in peak trunk torque and isometric trunk strength in people with PD following a 12-week exercise program completed twice per week [24]. However, as this study only reported changes in trunk muscle function under static conditions (i.e. isometrically), it remains unclear whether these improvements would translate to better stability for people with PD under static and/or dynamic conditions. Nonetheless, exercises aimed at improving core muscle function have been shown to improve postural stability in otherwise healthy older adults. For example, in older adults identified as being at a higher risk of falling, a year-long once-a-week group exercise program utilizing exercises designed to improve balance, coordination, aerobic capacity and muscle strength was associated with a reduced rate of falls during a prospective one-year follow-up when compared with an education group [10]. In addition to reducing falls rates, the exercise group also demonstrated improvements in three measures of balance 1) postural sway on a firm surface with eyes open; 2) postural sway on a firm surface with eyes closed; and 3) the coordinated stability test [10]. More recently, a six-week exercise program specifically targeting the muscles of the lower abdomen and posterior trunk significantly improved performances on the Berg Balance Scale in a group of elderly women [96]. Furthermore, aquatic balance training and core stability training were effective at significantly improving single leg balance in a group of 30 males when compared with age-matched controls [209]. However, the test of dynamic stability involved the participants balancing on their dominant leg while extending their non-dominant leg as far as possible in three different directions (Y-balance test). While this test may be a good measurement of maintaining single leg balance while manoeuvring the other leg, it would be interesting to see how such training translates to tasks like walking, where the body experiences forces that are sufficient to destabilise the trunk.

Studies that have sought to improve trunk mobility with the implementation of a trunk-specific intervention are also limited, but Bartolo and Serrao [11] used a multi-faceted program incorporating stretching, gait training, muscle conditioning, and balance to improve trunk mobility in a group of PD patients with and without lateral trunk flexion. Their results suggested that the exercise program was effective at improving lateral trunk flexion range of motion for those patients presenting with lateral trunk flexion. A separate study contrasting the efficacy of usual physical therapy with kayaking-type exercises for improving trunk mobility reported that both interventions were effective for improving trunk rotation in people with PD [217]. Unfortunately, despite these promising findings [11, 217], neither study provided a comprehensive description of the exercises performed by the participants, which substantially limits the reproducibility of these interventions.

In summary, there is a growing body of evidence indicating that structured exercise programs have the potential to improve muscle strength and symptom severity in people with PD. However, the existing literature has presented mixed findings concerning the efficacy of such therapies for improving postural stability, mobility and falls risk in this population. A possible reason for the inconsistent findings within the literature may be related to the fact that many of these studies have used clinical tests to evaluate these attributes and, given their design, may be incapable of detecting small, yet meaningful changes in function. With the improved portability of laboratory-grade equipment, it may now be possible to implement more objective measures of static and dynamic postural stability into these studies. The successful integration of sensitive instruments into such research would make it possible to determine how useful trunk-specific exercises can be for improving symptoms of postural instability and gait disability in people with PD.

2.6 Objective Assessments of Postural Stability

Over the decades, multiple methods have been developed and implemented for the assessment of postural stability in both clinical and laboratory settings. Tests that have traditionally been used in clinical settings are designed to be time-efficient, cost-effective and to have relatively little need for specialised equipment. Some common tests that have been used to assess balance in people with PD include the Berg Balance Scale [3, 62, 65, 76, 96, 238], the Tinetti Balance and Gait assessment [76, 115, 203] and the Timed Up and Go test [119]. The Berg Balance Scale and Tinetti Balance and Gait assessment are both comprise numerous items that are each subjectively rated by the clinician or another trained assessor on a Likert scale. In contrast, the Timed Up and Go test is a clinical test of mobility that involves the assessor recording the time taken for the patient to stand from a seated position, walk 3-meters, turn 180° and return to the seat to sit down. While such assessments are convenient to use to assess balance and mobility in the clinical setting, they are generally limited by floor and ceiling effects and, hence, may not be sensitive to subtle changes in a patient's performance. Given this limitation, it is possible that quantitative biomechanical methods, which provide more continuous datasets, may be more useful for monitoring gradual changes in symptoms and allowing "at-risk" patients to be more easily identified.

Of the many different methods used to objectively examine balance and mobility in people with PD, the most common techniques include videography/motion analysis, posturography and wearable sensors. While they are often not suited to smaller clinical environments, two-dimensional videography and three-dimensional motion analysis have been shown to provide valid assessments of balance during clinical tests (e.g. push and release, single leg stance, sit to stand) for healthy adults and people with and PD [191]. Nevertheless, such systems require regular calibration, participant preparation and additional time and expertise to accommodate setup and analysis of the data. In addition to being time-consuming, these systems can also be quite expensive making them impractical for small clinical practices operating on a limited budget.

A more cost-effective and portable technique that is commonly used to objectively evaluate standing balance is posturography, which uses centre of pressure data derived from a force platform to provide insight into the weight-shift patterns of the patient. Traditionally, force platforms were heavy and bulky pieces of equipment that were required to be secured to sturdy mounting brackets embedded within the floor of a laboratory. However, with the miniaturization of technology, these devices are now more portable and, hence, much easier to integrate into real-world settings. The Neurocom SMART Balance Master incorporates built in moveable force plates to provide an analysis of balance through increased difficulty based on the manipulation of the three sensory systems: vision, vestibular function, and somatosensation. The sensory organization test is a common test conducted using this specialized equipment to assess postural stability in people with PD [113, 126, 127, 176, 262]. Importantly, measures of postural sway have been shown to be sensitive to differences in postural sway between elderly adult fallers and non-fallers [125, 159, 245] and have also been shown to predict future falls in people with PD [119]. Nevertheless, despite their many benefits, force platforms are limited to the assessment of postural stability during quiet stance and, hence are not particularly suited to the evaluating walking stability.

Due to the shortcomings of posturography, wearable sensors (e.g. accelerometers, inertial sensors, gyroscopes) have become increasingly more popular in recent years, as they are relatively inexpensive, easy to use, and require minimal setup time. One such wearable sensor is an accelerometer, which intuitively assesses acceleration in one (uni-axial), two (bi-axial) or three (tri-axial) dimensions. Descriptions of the method used within accelerometers to assess movement often refer to a mass-spring system [118]. In this model, movement compresses or stretches the spring in the mass-spring system, causing the spring to generate a force proportional to the amount that it is compressed or stretched [118]. Given the stiffness of the spring and the mass are both known quantities, the resultant acceleration can be determined from the amount by which the spring is displaced in response to the movement [118]. While numerous accelerometer types exist, one of

the most common forms is the microelectromechanical system capacitive accelerometer. Microelectromechanical system accelerometers are comprised of pairs of capacitors surrounding a silicon mass and as the mass is displaced by the patient's movement and/or gravity, an electrical signal that is proportional to the magnitude of the displacement is generated from an imbalance between the opposing capacitors [118]. In PD, accelerometers have been shown to be a valid and reliable method for measuring postural sway during static tasks [152] and can also measure postural stability during dynamic tasks such as walking either in the laboratory [129, 138] or in real-world settings [251, 253]. If appropriately implemented, accelerometers have the potential to significantly improve the ways in which clinicians assess neurological populations both in the clinic and their real-world environments.

2.7 Summary

With an ageing demographic, age-related neurodegenerative conditions such as PD are likely to become increasingly prevalent in our society. While medical science has led to the development of many useful clinical assessments of physiological and psychological function, there is an apparent need to develop improved methods of objectively assessing postural stability in people with PD. Wearable sensors, such as accelerometers, are gaining improved popularity in the field, but there is currently no consensus regarding the best ways to implement these devices for the assessment of this population. Research is needed to address this, as improved assessments of movement have the potential to assist health care professionals with the treatment and management of PD symptoms. Furthermore, alternative therapy options are required to help manage symptoms of postural instability and gait disability in people with PD, as these symptoms are largely unresponsive to levodopa therapy and commonly lead to falls [19].

3.0 Statement of the Problem

Falls are a significant problem for community-dwelling older people, but pose an even greater threat to high-risk populations such as PD. Deficits in postural stability are a key factor in many of these falls, and could result from an impaired capacity to coordinate and/or control larger segments of the body, such as the trunk. Given that the trunk and head comprise 60% of the overall mass of the body [257], it seems reasonable to suggest that there is a need for the trunk to be well-controlled in order to maintain postural stability. However, the neurodegenerative changes associated with PD contribute to a number of significant alterations in trunk posture and function, including deficits in trunk muscle strength [23] and increased trunk muscle co-activation [56]. These changes ultimately contribute to an increase in trunk rigidity [101, 179, 240] and greater lateral [11] and/or forward [11, 43] flexion of the trunk, which presents in the stooped posture associated with this condition. Considering that these deficits influence postural stability, an important goal of managing patients with PD should be to improve the symptoms that affect the axial skeleton to minimise their effect on a patient's overall postural stability. However, existing research indicates that current pharmacological and surgical therapies for the symptoms of PD are largely ineffective with respect to the management of motor symptoms affecting the axial system. This evidence highlights the clear need to identify and evaluate alternate therapies that may be effective for the management of these symptoms. Given that targeted strength and endurance exercises [24] and mobility training [11, 217] have been shown to be effective for improving the mobility and dynamic function of the trunk in people with PD, it seems reasonable to assess whether such interventions are also effective for improving objective measures of postural stability in this population. To date, a small number of studies have evaluated the efficacy of exercise-based interventions for improving clinical measures of balance and mobility in people with PD [6, 84]. Furthermore, these studies have sought to determine whether regular exercise was

beneficial, with respect to reducing the rate and number of falls in this population. Despite these efforts, the evidence concerning the benefits of exercise for the management of these complex symptoms has been mixed, suggesting that further research is required to determine the potential benefits of this therapy. Given the established link between deficits in postural stability and falls in people with PD, many of these studies also evaluated the efficacy of their intervention using established clinical assessments of balance and mobility. However, these assessments generally rely upon patient self-report or Likert scales, which potentially limit their sensitivity to detecting small, yet meaningful changes in patient function. This limitation may assist with explaining why some interventions have reported no significant improvement in clinical measures of balance following an exercise intervention [6, 14, 61, 63, 88, 115], while others have reported significant improvements in these outcomes [14, 35, 76, 88, 115, 161, 166, 229, 238, 258, 264].

On the basis of these collective outcomes, one might argue that although traditional tests are easily administered in clinical settings where time may be limited, these assessments may lack the sensitivity to describe subtle changes in patient function. With the use of more sensitive measures of postural stability it is postulated that clinically-important improvements in postural stability may have been observed in these patient cohorts. However, more objective methods for assessing mobility and postural stability (e.g. three-dimensional motion analysis) have traditionally been too expensive and impractical to integrate into most clinical settings. With the introduction of light-weight and inexpensive wearable sensors (e.g. accelerometers), it may now be possible to provide a more cost-effective and clinically-feasible alternative to improve the sensitivity of clinical assessments of balance and mobility. For example, research shows that an accelerometer positioned on the head and/or trunk can provide continuous and objective data that allows changes in standing and walking stability to be easily assessed for patient populations [25, 232]. Nevertheless, despite the potential that this technology offers,

there is currently a lack of consensus within the existing literature regarding the most appropriate site(s) for affixing such devices to people with PD (e.g. head, trunk and/or pelvis) and the most appropriate outcomes for assessing meaningful changes in static and dynamic postural stability in this population. With an improved understanding of the suitability of wearable sensors for assessing standing and walking stability, the specific deficits that increase a patient's risk of falling can be identified and targeted interventions can be developed to improve trunk muscle function and overall postural stability.

4.0 Research Aims and Hypotheses

The program of research outlined in this thesis ultimately sought to address four aims that would bridge a number of gaps in our understanding of the suitability of exercise-based interventions for improving postural stability in people with PD and the possible benefits of wearable sensors for assessing postural stability in this patient cohort. Four inter-related studies were developed (Figure 3) to specifically address the following aims:

Aim 1: To systematically review the existing literature to determine the suitability of wearable sensors for assessing static and dynamic postural stability in people with Parkinson's disease.

To address this aim, Study 1 systematically reviewed the available literature that reported using wearable sensors to assess static or dynamic postural stability in people with PD. Specifically, this review had three primary goals, which included determining:

i. The type(s) of wearable sensor most commonly used to assess postural stability in people with PD.
ii. The anatomical landmark(s) most commonly reported for the placement of wearable sensors during the assessment of postural stability in people with PD.
iii. The specific measures of postural stability most commonly shown to highlight postural stability deficits in people with PD.

The results of this systematic review were used to inform the methods used in three subsequent experimental studies presented in this thesis.

Aim 2: To determine whether common clinical assessments of balance and mobility were capable of providing insight into a patient's postural stability during walking

As outlined previously, many clinical tests have been developed to assess various aspects of balance and mobility. Due to their widespread use in hospital settings, these tools

have traditionally been used to assess the efficacy of exercise-based interventions. However, the tendency for these instruments to rely upon Likert scales and/or qualitative assessments of function is likely to have implications for their sensitivity to detect subtle changes in balance and/or mobility. To determine to what extent clinical tests of balance, balance confidence, gait difficulty and/or mobility were capable of providing insight into postural stability while walking, Study 2 used a cross-sectional design to correlate the outcomes of these clinical tests with the measure(s) found to be most commonly used to assess dynamic postural stability in Study 1 (i.e. the systematic review). It was hypothesised that clinical measures of mobility, gait difficulty, postural stability and balance confidence would not be related to objective measures of dynamic postural stability and, therefore, would offer limited insight into a patient's balance during dynamic tasks, such as walking.

Aim 3: To determine whether a 12-week trunk-specific exercise program was more effective than education at improving postural sway and clinical measures of symptom severity, balance, balance confidence and gait difficulty in people with PD.

To address this aim, Study 3 was designed to be a blind phase II randomised controlled trial in which patients were allocated to either a 12-week exercise program aimed at improving trunk mobility and endurance or a 12-week education program aimed at reducing falls risk. Patients were assessed at three time points; i) prior to the intervention (baseline); ii) immediately following the intervention (12-weeks); and iii) 12-weeks following the completion of the intervention (24-weeks). It was hypothesized that the exercise group would demonstrate reduced postural sway and improved symptom severity, balance confidence and gait difficulty immediately following the 12-week intervention and that these improvements would be maintained up to 12-weeks following the completion of the program.

Aim 4: To determine whether a 12-week exercise program that focused on improving the trunk mobility and endurance was more effective than a fall-prevention education program for improving accelerometer-based measures of gait symmetry in people with PD.

The aim of Study 4 was addressed using the same blind phase II randomised controlled trial approach adopted for Study 3. Head and trunk accelerations were assessed during unconstrained walking at Baseline, 12-weeks and 24-weeks using tri-axial accelerometers, while the activation patterns of the thoracic and lumbar erector spinae were evaluated using surface electromyography. It was hypothesised that the patients receiving the 12-week exercise program would demonstrate greater improvements in accelerometer-based measures of gait symmetry than patients in the education group and that these improvements would be retained up to 12-weeks after the completion of the program. Furthermore, it was hypothesised that involvement in the exercise program would influence the activation patterns of the thoracic and lumbar erector spinae.

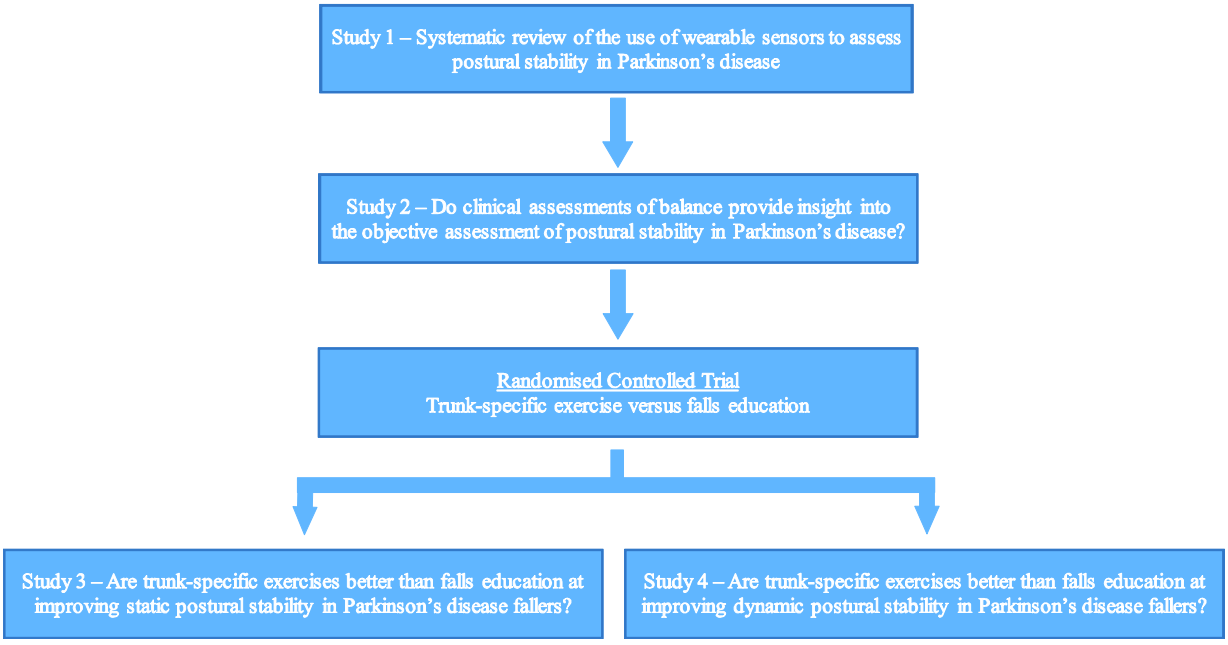

Figure 3: Summary of the four inter-related studies comprising this program of research

5.0 Study 1: Wearable sensor use for assessing standing balance and walking stability in people with Parkinson's disease: A systematic review

With the introduction of more affordable and sensitive measuring devices, such as wearable sensors, it is now becoming feasible for clinicians to conduct more objective assessments of postural stability within the clinical environment. However, to date, there has been little consensus amongst researchers regarding the most effective methods to adopt and the most sensitive outcomes to consider to improve the chances of correctly identifying 'at risk' patients. As such, the following chapter presents a systematic review of the literature concerning the use of wearable sensors for the assessment of postural stability under both static (standing balance) and dynamic (walking) conditions for people with PD.

NOTE: The following chapter presents the findings of the following peer-reviewed manuscript, which has been reformatted for the purposes of this dissertation:

Hubble, R. P., Naughton, G. A., Silburn, P. A., & Cole, M. H. (2015). Wearable sensor use for assessing standing balance and walking stability in people with Parkinson's disease: A systematic review. *PLoS One, 10(*4), e0123705

5.1 Abstract

Background: Postural instability and gait disability threaten the independence and well-being of people with Parkinson's disease and increase the risk of falls and fall-related injuries. Prospective research has shown that commonly-used clinical assessments of balance and walking lack the sensitivity to accurately and consistently identify those people with Parkinson's disease (PD) who are at a higher risk of falling. Wearable sensors provide a portable and affordable alternative for researchers and clinicians who are seeking to objectively assess movements and falls risk in the clinical setting. However, there is currently no consensus regarding the optimal placements for sensors and the best outcome measures to use for assessing standing balance and walking stability in PD patients. Hence, this systematic review aimed to examine the available literature to establish the best sensor types, locations and outcomes to assess standing balance and walking stability in this population.

Methods: Papers listed in three electronic databases were searched by title and abstract to identify articles measuring standing balance or walking stability with any kind of wearable sensor among adults diagnosed with PD. To be eligible for inclusion, papers were required to be full-text articles published in English between January 1994 and December 2014 that assessed measures of standing balance or walking stability with wearable sensors in people with PD. Articles were excluded if they; i) did not use any form of wearable sensor to measure variables associated with standing balance or walking stability; ii) did not include a control group or control condition; iii) were an abstract and/or included in the proceedings of a conference; or iv) were a review article or case study. The targeted search of the three electronic databases identified 340 articles that were potentially eligible for inclusion, but following title, abstract and full-text review only 26 articles were deemed to meet the inclusion criteria.

Included articles were assessed for methodological quality and relevant data from the papers were extracted and synthesized.

Results: Quality assessment of these included articles indicated that 31% were of low methodological quality, while 58% were of moderate methodological quality and 11% were of high methodological quality. All studies adopted a cross-sectional design and used a variety of sensor types and outcome measures to assess standing balance or walking stability in people with PD. Despite the typically low to moderate methodological quality, 81% of the studies reported differences in sensor-based measures of standing balance or walking stability between different groups of PD patients and/or healthy controls.

Conclusion: These data support the use of wearable sensors for detecting differences in standing balance and walking stability between people with PD and controls. Further high-quality research is needed to better understand the utility of wearable sensors for the early identification of PD symptoms and for assessing falls risk in this population.

PROSPERO Registration: CRD42014010838

5.2 Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disorder that results from the loss of neurons within the basal ganglia that produce dopamine, an important neurotransmitter involved in the regulation of movement. As medical advances have extended the life expectancy of the average person, clinical and experimental methods need to progress as well in order to improve the management of the symptoms associated with the disease. It is well understood that deficits in balance and gait are common and disabling features of PD that significantly increase an individual's risk of falling [218], hence many clinical assessments have been developed to evaluate these symptoms in this population. The most common assessments include the Berg Balance Scale [119, 127], the Tinetti Gait and Balance assessment [119], the Timed up and Go test [119, 147] and the postural instability and gait disability score derived from the Unified Parkinson's Disease Rating Scale (UPDRS) [119, 139]. These assessments are suited to clinical settings because they require little equipment to conduct and provide almost immediate outcomes that can be reported to the patient. However, prospective research shows these tests have poor sensitivity and specificity for identifying prospective fallers in the PD population [119] and may not be sufficiently sensitive to detect changes in balance and walking in individuals with mild to moderate disease severity [2, 6, 84, 134].

Given the inherent short-comings of the aforementioned clinical tests, previous research has sought to improve the objectivity of these measures to enhance their ability to track symptom progression and evaluate patient risk. Camera-based three-dimensional motion analysis systems have been commonly used in laboratory settings to examine the walking patterns of people with PD [42, 43, 255]. However, the methods associated with these assessments are often time-consuming and require specific expertise and expensive motion capture systems that are not suited to smaller clinical spaces. Wearable sensors, such as

accelerometers or inertial measurement units, offer a more portable, flexible and moderately-priced alternative to camera-based motion analysis systems. Moreover, they do not require excessive space for normal operation and outcome measures can be output almost immediately without the need for significant post-processing procedures. Given these strengths, research has recently sought to improve the sensitivity of clinical assessments, such as the Timed Up and Go test, by incorporating accelerometers or inertial measurement units to provide continuous measures of walking [95, 152, 187, 207, 252]. The results of this research demonstrated that by instrumenting the Timed Up and Go test with a wearable sensor, it was possible to detect differences in the performances of people with PD compared with controls [95, 152, 187, 207, 252].

Wearable sensors have recently been shown to have good test-retest reliability for assessing individuals with PD, particularly for acceleration-based measures calculated in the time domain (e.g. Jerk; the first time derivative of acceleration) [152]. Furthermore, there is a growing body of literature supporting the use of wearable sensors to assess standing balance or walking for; i) people with PD and controls [12, 67, 138, 150-152, 187, 208, 213, 214, 240, 253, 261, 263]; ii) PD fallers and non-fallers [129, 251]; iii) people with different PD sub-types [75, 95, 205, 215, 250]; iv) carriers and non-carriers of the Leucine-Rich Repeat Kinase 2 gene [163]; and v) people at high risk of developing PD (HRPD) [93, 144]. Results from these studies demonstrated that outcomes derived from wearable sensors were capable of detecting differences in standing balance between HRPD patients, people with PD and controls [144] and could discriminate HRPD patients from controls when combined with the functional reach test in a logistic regression model [93]. In addition to these findings, three-dimensional accelerometers positioned on the head, trunk or pelvis, have highlighted less rhythmic walking patterns for people with PD who retrospectively reported falling compared with patients who did not fall [129, 251]. Collectively, these results suggest that wearable sensors may not only

be useful for evaluating changes in a patient's balance or gait patterns, but may also offer a means of screening individuals for various risk factors associated with PD or falls. Nevertheless, it is clear that scientifically-rigorous prospective research is needed before clear recommendations can be provided regarding the use of these devices as predictive instruments for clinical populations.

Despite the expanding body of evidence to support the use of wearable sensors for assessing function in people with PD, it is important to recognise that this area of science is still developing. Furthermore, the adoption of such varying methodological approaches in the existing literature makes it difficult to determine which sensor types are the best to use and which placements and outcome measures are optimal to maximise the utility of these devices. As such, it was the purpose of this systematic review to examine the available literature that utilised wearable sensors to measure standing and walking balance in people with PD and provide a summary of the best sensor types, locations and outcomes based on a consensus of the literature.

5.3 Methods

This review was registered with the International Prospective Register of Systematic Reviews on September 3, 2014 (PROSPERO Registration: CRD42014010838). The search strategy and research protocol are included in Appendix A and outline the specific search terms and the systematic procedures adhered to for this study.

5.3.1 Search Strategy

An electronic database search of titles and abstracts was performed in January 2015 using PubMed, EMBASE and the Cochrane Library to identify articles measuring standing balance and walking stability with any kind of wearable sensor among adults diagnosed with

PD. The following terms were used for the literature search: ‘Parkinson’, ‘Parkinson’s’, ‘walk’, ‘gait’, ‘balance’, ‘stability’, ‘sensor’, ‘gyroscope’, ‘inertial’, ‘acceleration’ and ‘accelerometer’. Specifically, papers that were included in this review were required to have the term ‘Parkinson or Parkinson’s’ AND (‘walk’ OR ‘gait’ OR ‘balance’ OR ‘stability’) AND (‘sensor’ OR ‘gyroscope’ OR ‘inertial’ OR ‘accelerometer’ OR ‘acceleration’) located within the title and/or abstract. In addition to the systematic electronic database search, a targeted search of the bibliographies of relevant articles was also performed to identify any additional studies for inclusion.

5.3.2 Selection Criteria

Only original, full-text articles published in English between January 1994 and December 2014 that assessed standing balance or walking stability with wearable sensors in people with PD were included in this review. Articles were excluded if they; i) did not use any form of wearable sensor to measure variables associated with standing balance or walking stability; ii) did not include a control group or control condition; iii) were an abstract and/or included in the proceedings of a conference; or iv) were a review article or case study. All studies that met the inclusion criteria were considered for review, irrespective of their research design (cross-sectional, randomised controlled trial, etc). After the initial literature search was completed, two assessors (RPH, MHC) independently screened each of the papers based on their title and abstract and made a decision on the suitability of the paper for inclusion in the review. Once both reviewers had completed this process, any and all discrepancies between the two assessments were discussed until a consensus was reached regarding each paper. Full-text articles were retrieved for all of the papers selected for inclusion based on the title and abstract review process and the full-text of these articles was reviewed for suitability by one assessor

(RPH). A flow diagram illustrating the study selection and exclusion process is provided in Figure 4.

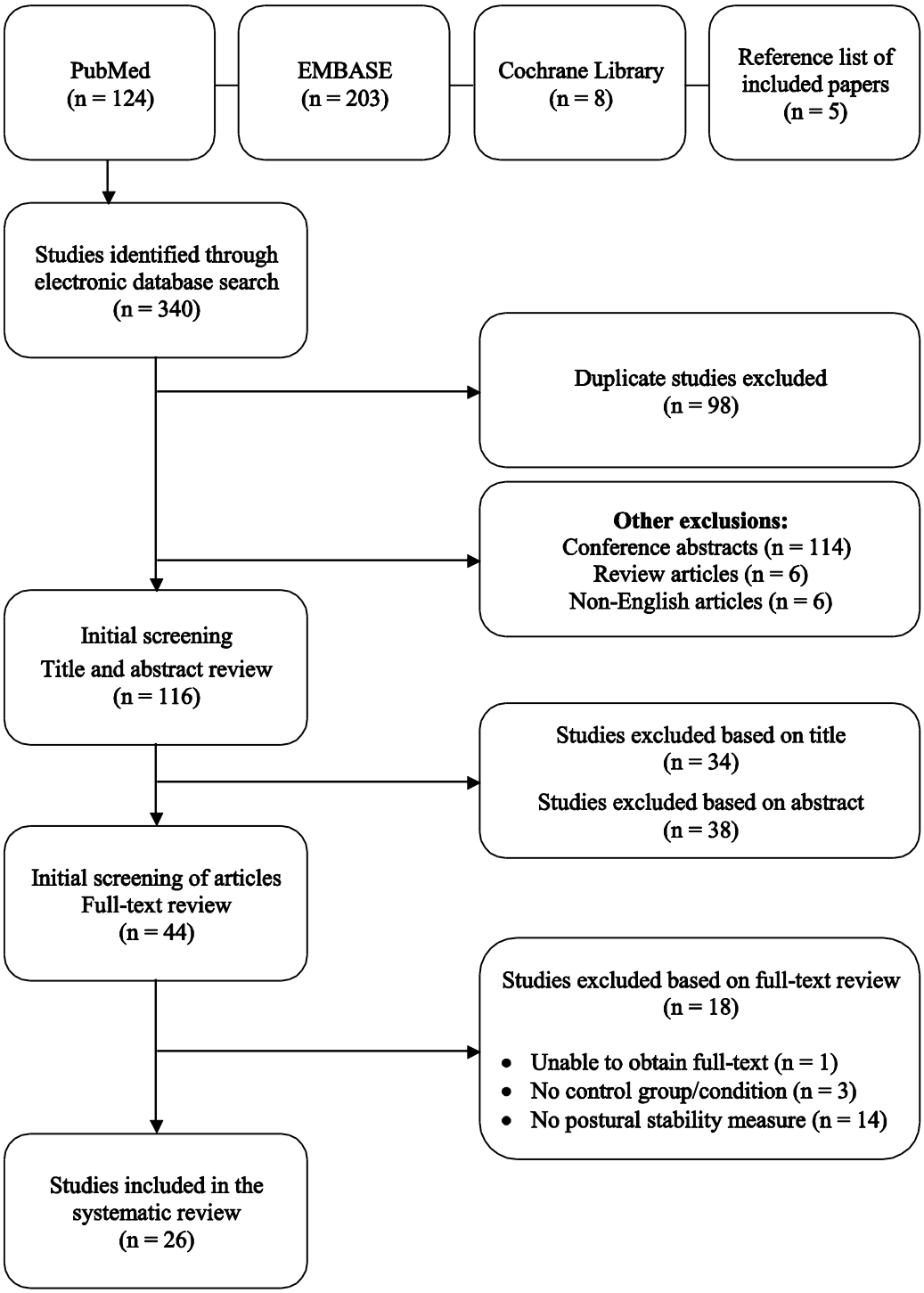

Figure 4: Flow diagram illustrating the systematic review process

5.3.3 Data Extraction and Quality Assessment

Upon selection of the articles for inclusion, one assessor (RPH) extracted and collated information concerning the type and number of participants, their mean age, disease duration and symptom severity, as well as the type and location of the wearable sensor(s) used and the major findings of each study (Table 1). The included studies presented a range of outcomes that sought to gain a better insight into the deficits of standing balance and walking stability evident in people with PD and these included; i) the root mean square (RMS) of segmental accelerations; ii) the harmonic ratio; iii) Jerk (the first derivative of acceleration); iv) step or stride variability; v) step or stride regularity/symmetry; and vi) other less commonly-used measures of stability.

In addition to extracting and compiling these data, a quality assessment was performed by one assessor (RPH) using a modified version of a previously-developed 27-item quality checklist, designed to accommodate both randomised and non-randomised studies [14]. To evaluate the overall methodological quality of each paper, 25 of the criteria on the quality assessment tool were assigned a score of one point if the criterion was met or a zero if the criterion was not met (Appendix B). If it was not possible or unreasonably difficult for the assessor to determine whether the information required for a particular criterion had been provided by the authors, a score of zero was given for that criterion. Of the remaining two questions on the quality checklist, one question evaluating whether potentially confounding variables had been reported by the authors was assessed on a 2-point scale, where the study was given 2 points if confounders were clearly described, 1 point if they were partially described or 0 points if they were not described. The final methodological aspect of the studies that was evaluated was statistical power, which was more heavily weighted than the other criteria and assessed on a 5-point scale. Studies that achieved a statistical power of $\leq$70% for the standing balance or walking stability measures were given a score of zero, while those that

achieved powers of 80, 85, 90, 95 or 99% were assigned scores of 1 to 5, respectively. Where an appropriate statistical power calculation was not provided by the authors, it was necessary to evaluate the statistical power of each study based on the data presented by the authors. If a statistical power calculation was not reported and the raw data were not presented, the paper was given a score of zero for this criterion. After each paper was assessed against these criteria, the scores were summed and divided by the maximum total points to yield a final score that represented the percentage of total possible points earned. This percentage score was used to evaluate the overall quality of the study using quartiles to classify the methodological quality of the article as either very low (≤25%), low (>25%, but ≤50%), moderate (>50%, but ≤75%) or high (>75%).

5.4 Results

The initial database search identified 335 articles that were potentially eligible for inclusion in this review. Of the 335 studies identified, 98 were excluded as duplicates, 114 were conference abstracts, 6 were review articles and 6 were written in a language other than English. The remaining 115 papers were screened by title and abstract, which resulted in 34 being excluded, based on title and 38 being excluded based on abstract. A manual search was conducted of the bibliographies of those papers that were considered appropriate for full-text review, which identified 5 additional papers for consideration. Following full-text review of the remaining 44 studies, a further 18 studies were excluded, including 1 that was unattainable, 3 that had no control group or condition and 14 that had no sensor-based measure of standing balance or walking stability. The remaining 26 articles were selected for inclusion in this systematic review.

5.4.1 Study Design and Methodological Quality

All 26 studies included within this review had a cross-sectional research design with a broad aim of using different types of wearable sensors to observe or identify differences in standing balance or walking stability for Parkinson's disease compared with controls or a control condition (e.g. on medication vs. off medication, PD subtypes). Given their cross-sectional nature, ten items were excluded from the methodological quality checklist, as they specifically targeted qualities that are unique to intervention studies. The decision to exclude these criteria was made to ensure that the overall quality of the studies included in this review was not unfairly biased by these items that were not relevant to their chosen design.

Based on the appraisal of methodology quality, 8 papers were identified as being of low methodological quality (range = 31.8% to 50.0%), 15 papers were of moderate methodological quality (range = 54.5% to 72.7%) and three papers were of high methodological quality (range = 77.3% to 90.9%). In general, the reviewed papers performed poorly on those criteria that addressed external validity (e.g. representativeness of the sample), internal validity (e.g. identification of and adjustment for potential confounders) and statistical power (e.g. no power calculation and insufficient details to make an informed appraisal). A full scoring of the methodological quality of each study included within this review can be seen in Table 1.

Table 1: Methodological quality assessment of articles included in systematic review

Quality Assessment Criterion																													
Article	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**2**	**2**	**26**	**27**	**Total**	**%**
Baston 2014 [12]	1	1	1		0	0	1			0	0	0	0			1		1		1	1	0			0		0	9	40.9
Fazio 2013 [67]	1	1	1		0	1	1			0	0	0	0			1		1		1	0	0			0		5	13	59.1
Gago 2014 [75]	1	1	1		2	1	1			1	0	0	0			1		1		1	1	0			1		0	13	59.1
Hasmann 2014 [93]	1	0	1		1	1	1			1	0	0	0			1		1		1	0	1			0		3	13	59.1
Herman 2014 [95]	1	1	1		1	1	1			1	0	0	0			1		1		1	0	0			1		5	16	72.7
Latt 2009 [129]	1	1	1		2	1	1			0	0	0	0			1		1		1	1	0			1		5	17	77.3
Lowry 2010 [137]	1	1	1		1	1	1			1	0	0	0			0		1		1	0	0			1		0	10	45.5
Lowry 2009 [138]	1	1	1		2	1	1			1	0	0	0			1		1		1	0	0			1		3	15	68.2
Maetzler 2012 [144]	1	1	1		2	1	1			1	0	0	0			1		1		1	0	0			1		0	12	54.5
Mancini 2011 [151]	1	1	1		1	1	1			1	0	0	0			1		1		1	0	0			1		5	16	72.7
Mancini 2012 [152]	1	1	1		0	1	1			1	0	0	0			1		1		1	0	0			0		3	12	54.5
Mancini 2012 [150]	1	1	1		0	1	1			1	0	0	0			0		1		1	0	0			0		3	11	50.0
Mirelman 2013 [163]	1	1	1		2	1	1			1	1	0	1			1		1		1	1	0			1		5	20	90.9
Palmerini 2011 [188]	1	1	0		2	0	1			0	0	0	0			1		1		1	0	0			1		0	9	40.9
Palmerini 2013 [187]	1	1	1		1	1	1			1	0	0	0			1		1		1	0	0			0		5	15	68.2
Rocchi 2014 [205]	1	1	1		0	0	1			0	0	0	0			1		1		1	0	0			0		0	7	31.8
Sant'Anna 2011 [208]	1	1	1		2	1	1			1	0	0	0			1		1		1	0	0			1		3	15	68.2
Sejdic 2014 [213]	1	1	0		0	1	1			0	0	0	0			1		1		1	0	0			0		3	10	45.5
Sekine 2004 [215]	1	1	0		1	1	1			0	0	0	0			1		1		1	0	0			0		5	13	59.1
Sekine 2004 [214]	1	1	0		2	1	1			0	0	0	0			1		1		1	0	0			0		3	12	54.5
Van Emmerik 1999	1	1	1		2	0	1			1	0	0	0			1		1		1	0	0			1		0	11	50.0
Weiss 2011 [253]	1	1	1		1	1	1			1	0	0	0			1		1		1	1	0			1		5	17	77.3
Weiss 2014 [250]	1	1	1		1	1	1			1	0	0	0			1		1		1	0	0			1		5	16	72.7
Weiss 2014 [251]	1	1	1		1	1	1			1	0	0	0			1		1		1	0	0			1		5	16	72.7
Yang 2011 [261]	1	1	0		0	0	1			1	0	0	0			1		0		1	0	0			0		3	9	40.9
Zampieri 2009 [263]	1	1	1		2	1	1			1	0	0	0			1		1		1	0	0			1		0	12	54.5

5.4.2 Sensor Type and Placement

Multiple wearable sensor types were used within the included articles to assess measures of standing balance and walking stability. Of these studies, 69% reported using three-dimensional accelerometers [67, 75, 93, 95, 129, 137, 138, 163, 187, 188, 205, 213-215, 250, 251, 253, 261], 27% used inertial sensors [12, 144, 150-152, 208, 263], and 4% used other types of sensors [240, 263]. Similarly, there were multiple protocols described with respect to the placement of the wearable sensors on the human body. Of the 26 included studies, 85% reported placing a wearable sensor on either the lumbar or sacral region of the trunk [12, 67, 75, 93, 95, 137, 138, 144, 150-152, 163, 187, 188, 205, 208, 213-215, 250, 251, 253] and 15% reported placing devices on other body landmarks (e.g. head, shank, wrist) [129, 240, 261, 263]. Details regarding the studies included in this review that reported using each specific type and placement of sensors are summarised in Table 2.

Table 2: Details of studies included within the systematic review

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Baston 2014 [12]	PD = 5 (62.0±6.0) PSP = 7 (68.0±5.0) Control = 7 (68.0±7.0)	***UPDRS III*** PD = 34.0±14.0	Not Reported	Inertial Sensor Freq: 128 Hz - L5 - Shank	RMS acceleration - Anterior-posterior (AP)	Dynamic Posturography	No significant difference between PD and controls for AP acceleration during all conditions of the Sensory Organisation Test (SOT). PD had reduced AP accelerations for conditions 4 and 5 of the SOT compared with the PSP group.
Fazio 2012 [67]	PD = 17 (60-85) Ataxia = 24 (20-85) Control = 24 (20-85)	***UPDRS III*** PD = 22.5±3.6	Not Reported	3D Accelerometer Freq: 20 Hz - Sternum - Front pelvis - Back pelvis	RMS acceleration - For sum of sternum accelerations - For sum of front pelvis accelerations - For sum of back pelvis accelerations RMS Jerk - For sum of sternum accelerations	Gait	PD patients had lower Jerk scores compared with controls, but were not significantly different to ataxic patients. PD had significantly lower RMS accelerations for the sternum and two pelvis locations compared with the ataxic and control participants.

Gago 2014 [75]	IPD = 10 (73 [61-79]) VPD = 5 (77 [63-84])	***MDS-UPDRS III*** IPD = 30 [15-53] VPD = 44 [33-57]	IPD 6.0 [5.0-10.0] VPD 5.0 [3.0-9.0]	3D Accelerometer Freq: 113 Hz - Lower back	Length of sway Maximum sway distance Mean sway distance Maximum linear velocity	Quiet Stance	Idiopathic PD (IPD) patients had significantly increased length and maximum distance of sway during normal stance while on medication. Sway length and maximum distance was also greater for the IPD group when eyes were closed compared with open during the Romberg test off medication. Compared with the IPD patients, vascular PD patients had increased mean distance of sway during normal stance and greater maximal distance of sway compared with the IDP patients during the Romberg test with eyes closed off medication.
Hasmann 2014 [93]	PD = 13 (65.0±9.4) HRPD = 31 (62.6±5.0) Control = 13 (63.9±7.3)	***UPDRS III*** PD = 26.8±11.0 HRPD = 3.0±3.0 Control = 0.2±0.6	PD 4.5±2.8	3D Accelerometer Freq: Not reported - Lower back	Mean acceleration - Anterior-posterior (AP) - Medial-lateral (ML) Jerk - Anterior-posterior (AP)	Functional Reach	Compared with controls, PD had increased mean acceleration in the AP and ML directions, but the groups did not differ significantly with respect to AP or ML Jerk scores.
Herman 2014 [95]	PD PIGD = 31 (65.0±7.7) PD TD = 32 (64.6±11.6)	***UPDRS III - OFF*** PIGD = 38.7±10.5 TD = 39.5±12.5 ***UPDRS III – ON*** PIGD = 33.3±10.0 TD = 33.4±11.6	PIGD 5.7±3.7 TD 5.4±3.2	3D Accelerometer Freq: 100 Hz - Lower back	Harmonic ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Stride regularity Stride timing variability	Gait	For usual walking, PIGD patients had reduced stride regularity and reduced vertical HRs compared with the TD group while off medication. Accelerometer-derived measures from a 3-day period of in-home activity monitoring revealed that the PIGD group had reduced stride regularity and lower harmonic ratios in both the AP and VT directions compared with the TD group.

Latt 2009 [129]	***PD Fallers vs. Non-Fallers:*** Non-Faller = 33 (63.0±4.0) Faller = 33 (67.0±2.0) Control = 33 (67.0±4.0)	***Hoehn & Yahr*** Non-faller = 1 (1-1) Faller = 3 (3-4) ***UPDRS III*** Non-faller = 12.0±3.0 Faller = 21.0±3.0	PD NF 7.0±2.0 PD F 9.0±2.0	3D Accelerometer Freq: 200 Hz - Head - Sacrum	Harmonic Ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) RMS Acceleration - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Step timing variability	Gait	Compared with controls and PD non-fallers, fallers had increased step timing variability. With the exception of AP head accelerations, PD fallers had significantly reduced head and pelvis accelerations compared with non-fallers and controls. Controls had higher AP head accelerations compared with PD fallers, and PD non-fallers had lower ML accelerations for the pelvis than controls. PD fallers had lower AP and VT HRs for the head and lower AP, ML and VT HRs for the pelvis compared with non-fallers and controls. PD non-fallers had lower VT HRs for the head and pelvis and lower AP HRs for the head compared with controls. Non-fallers also had greater ML HRs for the head compared with fallers.
Lowry 2010 [137]	PD = 7 (70.3±8.5)	***Hoehn & Yahr*** PD = 2.4±0.5	PD 6.2±4.7	3D Accelerometer Freq: 200 Hz - L3	Harmonic Ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT)	Gait	Cognitive cueing (thinking "big step" during the swing phase) and verbal cueing (assessor saying "big step" during the swing phase) both improved AP HR compared with preferred gait (without cues).
Lowry 2009 [138]	PD = 11 (68.0±7.7) Control = 11 (69.0±8.8)	***Hoehn & Yahr*** PD = 1.9±0.8	PD 5.2±4.0	3D Accelerometer Freq: 200 Hz L2	Harmonic Ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Stride timing variability Stride length variability	Gait	PD and controls did not differ significantly with respect to stride length variability, stride timing variability or AP, ML and VT HRs. After normalising these data to walking speed, PD patients had lower AP and ML HRs compared with controls.

Maetzler 2012 [144]	PD = 12 (61.5±2.2) HRPD = 20 (61.9±1.5) Control = 14 (63.9±1.9)		***Hoehn & Yahr*** PD = 2.0±0.0 ***UPDRS III - OFF*** PD = 26.5±10.9 HRPD = 3.3±2.4 Control = 1.1±1.7	PD 4.3±2.6	Inertial Sensor Freq: 100 Hz L3/L4	RMS acceleration - Anterior-posterior (AP) - Medial-lateral (ML) Jerk - Anterior-posterior (AP) - Medial-lateral (ML) Frequency with 95% of signal (F95) - Anterior-posterior (AP) - Medial-lateral (ML) Mean sway velocity	Quiet Stance	The PD and control groups did not differ significantly for AP or ML RMS accelerations or Jerk scores, even when vision was occluded and/or somatosensory feedback was reduced. However, the high risk of PD (HRPD) group had greater AP and ML RMS accelerations than PD patients and controls while standing on a foam surface with eyes closed and greater scores than PD when standing on a firm surface with eyes closed. The HRPD group also had greater AP and ML Jerk scores than the PD and controls group during the foam eyes closed task. Groups did not differ with respect to F95 or mean sway velocity.
Mancini 2011 [151]	PD = 13 (60.4±8.5) Control = 12 (60.2±8.2)		***Hoehn & Yahr*** PD = 1.8±0.6 ***UPDRS III*** PD = 28.2±11.2	PD 14.3±6.9	Inertial Sensor Freq: 50 Hz L5	RMS Acceleration - Resultant of AP and ML Jerk - Resultant of AP and ML Frequency with 95% of signal (F95) - Resultant of AP and ML Mean sway velocity	Quiet Stance	Compared with controls, the PD group had significantly greater RMS accelerations, Jerk scores and mean sway velocity measures while standing on a firm surface with eyes open, but not with eyes closed. Groups did not differ with respect to the F95 measure.

Mancini 2012 [152]	***Study 1*** PD = 13 (60.4±8.5) Control = 12 (60.2±8.2) ***Study 2*** PD = 17 (67.1±7.3) Control = 17 (67.9±6.1)		***Study 1*** ***UPDRS III*** PD = 28.1±11.2 ***Study 2*** ***UPDRS III*** PD = 28.3±10.4	Not Reported	Inertial Sensor Freq: 50 Hz L5	RMS Acceleration - Resultant of AP and ML Jerk - Resultant of AP and ML Frequency with 95% of signal (F95) - Resultant of AP and ML Mean sway velocity Length of sway Mean sway distance Sway area	Quiet Stance	Compared with controls, the PD group had significantly higher RMS accelerations, Jerk scores, sway distances and sway areas, but the groups did not differ with respect to the F95 measure, mean sway velocities or length of sway.
Mancini 2012 [150]	PD = 13 (60.4±8.5) Control = 12 (60.2±8.2)		***Hoehn & Yahr*** PD = 1.8±0.2 ***UPDRS III*** PD = 26.6±3.5	Not Reported	Inertial Sensor Freq: 50 Hz L5	RMS acceleration - Anterior-posterior (AP) - Medial-lateral (ML) Jerk - Anterior-posterior (AP) - Medial-lateral (ML) Frequency with 95% of signal (F95) - Anterior-posterior (AP) - Medial-lateral (ML) Mean sway velocity - Anterior-posterior (AP) Medial-lateral (ML)	Quiet Stance	For RMS accelerations, a significant main effect for group showed that PD participants had greater ML accelerations than controls, while the AP axis fell marginally short of statistical significance. PD participants also had higher AP and ML Jerk scores at baseline, but ML Jerk was also larger for the PD patients at the 3-6 and 12-month follow-up time points. There were also significant main effects for group for ML F95 values and mean sway velocity along the ML axis, indicating that the PD group had larger values for both of these measures compared with control.

Mirelman 2013 [163]	***PD LRRK2 Gene:*** Carrier = 50 (62.6±9.6) Non-Carrier = 50 (60.2±11.3)	***Hoehn & Yahr*** Carrier = 2-3 Non-Carrier = 2-3 ***UPDRS Total*** Carrier = 27.9±14.2 Non-Carrier = 26.9±13.3	Carrier 4.4±3.3 Non-Carrier 6.1±6.1	3D Accelerometer Freq: Not reported Lower back	***Preferred vs. Fast speed vs. Dual-task:*** Stride timing variability Step regularity (step-to-step consistency) Width of dominant frequency Anterior-posterior (AP)	Gait	Carriers of the LRRK2 gene had greater stride timing variability and less step regularity than non-carriers during preferred speed, fast speed and dual-task (serially subtracting 3s) walking. Carriers also had a greater gait variability during preferred and fast walking, as evidenced by the greater width of the dominant frequency. Significant group by condition interactions suggested that the carriers had a greater increase in stride timing variability and a greater width of the dominant frequency with increased task complexity (i.e. dual tasking) compared with non-carriers.
Palmerini 2013 [187]	PD = 20 (62.0±7.0) Control = 20 (64.0±6.0)	***Hoehn & Yahr*** PD = 2.4±0.2	PD 5.2±4.1	3D Accelerometer Freq: 100 Hz L5	RMS acceleration - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Normalised Jerk - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Harmonic ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Phase coordination index	Timed Up and Go	During the gait and turning portions of the Timed Up and Go test, PD patients had significantly lower AP and ML normalised Jerk scores than control participants. Similarly, during the gait component of the test, PD participants also had lower AP and VT HRs compared with controls. The two groups did not differ significantly for any of the other accelerometer-based measures.

Palmerini, 2011 [188]	PD Control	= 20 (62.0±7.0) = 20 (64.0±6.0)	***Hoehn & Yahr*** PD = ≤2.5 ***UPDRS-III*** PD = 26.6±7.1	Not Reported	3D Accelerometer Freq: 100 Hz - L5	High Frequency Power - Anterior-posterior (AP) - Medial-lateral (ML) Frequency Dispersion - Anterior-posterior (AP) - Medial-lateral (ML) Sway Range - Anterior-posterior (AP) Medial-lateral (ML)	Quiet Stance	Compared with controls, the PD group had significantly higher high frequency power in the ML direction during the dual task condition and significantly lower AP frequency dispersion scores while standing on a foam surface. AP sway range was not significantly different between groups. A wrapper feature selection approach determined that ML high frequency power on a firm surface with eyes open, AP frequency dispersion on a foam surface with eyes open and AP sway range on foam surface with eyes closed represented the best candidate subset to distinguish PD from controls.

Rocchi, 2014 [205]	PD PIGD = 40 (64.5±6.9) PD TD = 26 (67.6±9.9) Control = 15 (78.2±3.9)	***UPDRS III*** PD PIGD = 38.3±10.9 PD TD = 43.3±13.4	PD PIGD 5.1±3.6 PD TD 5.7±2.8	3D Accelerometer Freq: 100 Hz Lower back	***Feet together vs. Semi-tandem:*** Centroidal frequency (CF) - Anterior-posterior (AP) Length of sway - Anterior-posterior (AP) - Medial-lateral (ML) - 2-dimensional (2D) Mean sway velocity - Anterior-posterior (AP) Medial-lateral (ML)	Quiet Stance	The TD group had significantly lower CF values than controls for all experimental tasks and the PIGD group also had lower CF values than controls for all conditions except semi-tandem stance with eyes closed. The TD and PIGD groups did not differ with respect to CF during any of the experimental tasks. CF values were influenced by foot position for the two PD groups (PIGD and TD) with greater values recorded during semi-tandem stance. Results were similar for sway velocity and length of sway, with all groups typically showing higher values with eyes closed compared with eyes open. The groups did not differ for sway velocity or length of sway for the feet together or semi-tandem stance trials with eyes open, but the PIGD and TD groups had lower values compared with controls during the EC conditions.

Sant'Anna 2011 [208]	PD = 11 (60.0±8.6) Control = 11 (61.0±7.8)	***Hoehn & Yahr*** PD = 1.6±0.6 ***UPDRS-PIGD*** PD = 0.7±1.1	PD 1.1±1.1	1D Gyroscopes Freq: 200 Hz - Anterior shank 2D Gyroscopes Freq: 200 Hz Wrist	Symbolic symmetry index (SI_{symb}) Symmetry index (SI_{index}) Gait asymmetry (SI_{GA}) Symmetry angle (SI_{angle}) Maximum angular velocity ratio (SI_{ratio}) Trend symmetry (SI_{trend}) LCEA symmetry magnitude (SI_{LCEA})	Gait	Of the symmetry measures derived from the gyroscopes placed on the shanks and wrists, only the SI_{index}, SI_{GA}, SI_{ratio} and SI_{symb} values for the wrist sensors were significantly higher for PD participants. Evaluation of the area under the Receiver Operating Characteristic (ROC) curves for these four outcomes showed that only SI_{ratio} and SI_{symb} were able to differentiate PD from controls, but the higher Intra-class Correlation Coefficients for SI_{symb} indicated that this outcome was more robust for differentiating between the two cohorts.
Sejdić 2014 [213]	PD = 10 (≥65 years) Neuropathy = 11 (≥65 years) Control = 14 (≥65 years)	***Hoehn & Yahr*** PD = 2-3	Not Reported	3D Accelerometer Freq: 100 Hz L3	Lyapunov exponent (LE) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Harmonic ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Entropy rate - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Cross entropy rate - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT)	Gait	There were no significant differences between the groups for AP, ML or VT Lyapunov exponents, but PD patients had less gait rhythmicity in the vertical direction (decreased VT HRs) compared with healthy controls. With respect to the entropy measure, the PD and peripheral neuropathy groups both had significantly greater ML values than controls, but there were no group differences for cross entropy rate.

Sekine 2004 [215]	PD Control	= 11 (66±9.6) = 10 (66.3±5.3)	***Hoehn & Yahr*** PD = 1-2	Not Reported	3D Accelerometer Freq: 1024 Hz L5/S1 region	Fractal Brownian Motion - Anterior-posterior (AP) - Medial-lateral (ML) Vertical (VT)	Gait	The fractal values for the AP, ML and VT directions were significantly higher for the individuals with PD compared with controls. Also, the AP, ML and VT fractal dimensions were all significantly negatively correlated with walking speed for the PD group, but not controls.
Sekine 2004 [214]	Mild PD Severe PD Control	= 11 (66.0±9.6) = 5 (57.4±19.1) = 10 (66.3±5.3)	***Hoehn & Yahr*** Mild PD = 1-2 Severe PD = 3-4	Not Reported	3D Accelerometer Freq: 1024 Hz L5/S1 region	Vertical patterns - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Circular patterns - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Horizontal patterns - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT)	Gait	Controls did not differ significantly from the mild or severe PD groups for AP, ML or VT vertical patterns. Circular patterns were different between the groups, with both mild and severe PD participants having larger values than controls in the AP and VT directions, while severe PD patients also had higher AP circular patterns than mild PD patients. Severe PD patients had greater short horizontal patterns than controls in all three directions and lower long horizontal patterns in the AP and VT than controls. Severe PD patients also had greater short horizontal patterns in the AP, ML, VT than mild PD patients and mild PD patients had lower values than controls for long horizontal patterns in the AP and VT directions.

van Emmerik 1999 [240]	PD Control	= 27 (53.7±10.6) = 11 (*not reported*)	***Hoehn & Yahr*** PD = 1.5 ±0.6 ***UPDRS III*** PD = 16.7±6.2	PD 2.3±1.4	1D Accelerometer Freq: 104 Hz Shank	Stride timing variability Relative phase analysis	Gait	Stride timing variability was not significantly different between PD and controls, but variability significantly decreased for both groups as walking velocity increased. Continuous relative phase was also larger for controls compared with PD patients between walking speeds of 0.2 and 1.4 m/s.
Weiss 2011 [253]	PD Control	= 22 (65.9±5.9) = 17 (69.9±8.8)	***Hoehn & Yahr*** PD = 2.5±0.4 ***UPDRS III*** PD = 23.6±9.4	PD 4.8±3.8	3D Accelerometer Freq: 256 Hz Lower back	Stride timing variability Width of the dominant harmonic	Gait	Stride timing variability was significantly higher for PD patients compared with healthy controls. Similarly, the width of the dominant harmonic of the power spectral density of the locomotor band of the acceleration signal was significantly greater for PD patients, both on and off medication, compared with controls. Furthermore, the width of the dominant harmonic was greater for patients when off medication compared with on medication.

Weiss 2014 [250]	***PD Freezer vs. Non-Freezer:*** Non-Freezer = 44 (66.5±8.8) Freezer = 28 (64.4±8.7)	***Hoehn & Yahr*** Non-Freezer = 2.4±0.5 Freezer = 3.2±0.8 ***UPDRS III - OFF*** Non-Freezer = 42.3±12.9 Freezer = 46.2±12.2 ***UPDRS III - ON*** Non-Freezer = 35.6±12.8 Freezer = 36.3±11.7	Non-Freezer 6.7±2.2 Freezer 7.5±4.5	3D Accelerometer Freq: Not reported Lower back	Harmonic ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Stride regularity - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Width of dominant frequency - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT)	Gait	Freezers had decreased AP, ML and VT harmonic ratios and stride regularity compared with non-freezers. PD freezers also had a significantly greater width of the dominant frequency in the VT and AP directions. Harmonic ratios and stride regularity were significantly correlated with the new freezing of gait questionnaire and the width of the dominant frequency in the VT and AP direction were also significantly correlated with this clinical test.
Weiss 2014 [251]	***PD Fallers vs. Non-Fallers:*** Non-Faller = 67 (64.0±9.8) Faller = 40 (66.5±8.2)	***Hoehn & Yahr*** Non-Faller = 2.4±0.5 Faller = 2.9±0.8	Non-Faller 5.2±3.1 Faller 6.1±4.0	3D Accelerometer Freq: 100 Hz Lower back	Harmonic ratio (HR) - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Stride regularity - Anterior-posterior (AP) - Medial-lateral (ML) - Vertical (VT) Width of dominant frequency - Anterior-posterior (AP) - Medial-lateral (ML) Vertical (VT)	Gait	During a 3-day assessment of gait and mobility, fallers exhibited reduced HRs in both the AP and VT directions. PD fallers also had less VT stride regularity than non-fallers and a greater width of the dominant frequency for the AP and VT directions.

Yang 2011 [261]	PD = 5 (78.0±9.8) Control = 5 (26.0±3.1)	***Hoehn & Yahr*** PD = 2-3	Not Reported	3D Accelerometer Freq: 50 Hz Lateral pelvis 1D Gyroscopes Freq: 200 Hz - Anterior shank	Step regularity Stride regularity Step symmetry	Gait	There were no significant differences observed in step regularity, stride regularity or step symmetry between PD patients and controls.
Zampieri 2009 [263]	PD = 12 (60.4±8.5) Control = 12 (60.2±8.2)	***Hoehn & Yahr*** PD = 1.6±0.5 ***UPDRS III*** PD = 20.0±9.4	PD 1.1±1.1	2D Gyroscopes Freq: 200 Hz - Wrist Inertial Sensor Freq: 200 Hz - Sternum	Stride length variability Stride timing variability	Timed Up and Go	PD and control groups did not differ with respect to stride length variability or stride time variability.

PD: Parkinson's disease; **PSP:** Progressive supranuclear palsy; **IPD:** Idiopathic Parkinson's disease; **VPD:** Vascular Parkinson's disease; **HRPD:** People at high-risk of Parkinson's disease; **UPDRS:** Unified Parkinson's Disease Rating Scale; **MDS-UPDRS:** Movement Disorders Society's revision of the Unified Parkinson's Disease Rating Scale; **Freq:** Sampling frequency of wearable sensor; **LRRK2:** Leucine-Rich Repeated Kinase 2; **PIGD:** Postural Instability and Gait Disability

5.4.3 Assessment of standing balance and walking stability

Of the 26 included studies, 65% used wearable sensors to assess walking during clinical tests, such as the Timed up and Go Test [187, 263] or during assessments of straight-line walking at a self-selected speed [67, 95, 129, 137, 138, 163, 208, 213-215, 240, 250, 251, 253, 261]. A wide range of sampling frequencies were used to assess walking stability in the reviewed studies, with authors reporting sampling frequencies that ranged from 20 to 1024 Hz. The remaining 9 studies (35%) assessed standing balance using an instrumented functional reach test [93], dynamic posturography [12] or one of many pre-existing clinical tests conducted during quiet stance (i.e. the Romberg test, tandem stance, semi-tandem stance, standing with eyes open and eyes closed) [75, 144, 150-152, 188, 205]. Understandably, the wearable sensors used in these studies were generally set to collect data at a slower rate to those used for assessing the dynamic tasks, with reported sampling frequencies ranging from 50 to 128 Hz.

The included studies reported multiple outcomes of standing balance and walking stability, which were calculated from the signals provided by the wearable sensors (e.g. accelerations). Of these outcomes, the most commonly-reported measures of standing balance included postural sway velocity (23% of studies) [75, 144, 150-152, 205], RMS accelerations (19% of studies) [12, 144, 150-152] and Jerk (19% of studies) [93, 144, 150-152]. The most commonly-reported measures of walking stability included, the harmonic ratio (31% of studies) [95, 129, 137, 138, 187, 213, 250, 253] and stride timing variability (27% of studies) [95, 129, 138, 163, 240, 253, 263]. A definition of each of the outcome measures of standing balance and walking stability that were used in the studies is provided in Table 3.

Table 3: Definition of the sensor-based measures of standing and walking stability.

Outcome Measure	Definition of Measure	
Standing Balance or Walking Stability		**Articles**
Mean acceleration	The average of the Anterior-posterior (AP), Medial-lateral (ML) or vertical (VT) accelerations during a specific phase of the movement. Provides an indication of the rate of change in the velocity of the body during this phase. Under static conditions, larger values would represent poorer control.	[93]
Root mean square (RMS) acceleration	Taking the RMS of the accelerations makes all values of the time series positive, to yield an average positive amplitude for AP, ML or VT accelerations. Like mean accelerations, RMS accelerations provides an indication of the rate of change in velocity, but is more robust for data that has both positive and negative values.	[12, 67, 129, 144, 150-152, 187]
Jerk	Time series of the first derivative of acceleration (third derivative of displacement), representing the rate of change of acceleration. It is calculated from the raw AP, ML or VT accelerations. During steady movements, the body should be neither accelerating nor decelerating rapidly, hence Jerk scores should be smaller for more stable people.	[93, 144, 150-152]

Root mean square (RMS) Jerk	Similar to RMS accelerations, RMS Jerk mathematically converts all values to a positive number and provides an average value for the AP, ML and VT Jerk time series. In lay terms, the RMS Jerk provides a single value that describes the jerkiness of the movement.	[67]
Normalised Jerk	RMS Jerk score divided by overall movement time. Provides similar information to RMS Jerk, but takes into account differences in task duration for different populations.	[187]
Standing Balance		
Maximum sway distance	The resultant of AP and ML displacement is calculated for an inertial measurement unit placed at the height of the centre of mass (COM; 55% of height). Maximum sway distance is the single largest value recorded throughout the trial. Provides insight into the extremes of postural sway.	[75]
Mean sway distance	The resultant of AP and ML displacement is calculated for an inertial measurement unit placed at the height of the COM (55% of height). Mean sway distance is the average of all resultant values recorded throughout the trial. Larger values represent poorer postural control.	[75, 152]
Sway Range	The overall range of displacement of the centre of mass (COM; estimated from an inertial measurement unit positioned on the trunk) in the Anterior-posterior (AP) and Medial-lateral (ML) directions. Larger values represent an increased amount of postural sway.	[188]

Length of sway	The total distance travelled by the COM on the transverse plane. Increased length of sway indicates more sway per unit of time and, hence, reduced postural control.	[75, 152, 205]
Mean sway velocity	The first integral of the AP, ML or VT acceleration signals. Higher sway velocities represent more erratic postural adjustments and, hence, poorer postural control.	[144, 150-152, 205]
Sway area	The elliptical area that encapsulates the sway path derived from the AP and ML accelerations. Larger sway areas represent an increased volume of sway, which may suggest poorer balance.	[152]
F95	The frequency below which 95% of the acceleration signals power is present. Higher frequencies would represent a larger number of postural adjustments to maintain balance during the trial.	[144, 150-152]
Centroidal frequency	The frequency at which the power of the signal above and below is exactly balanced (i.e. the centre point). The centroidal frequency can be calculated for the AP, ML and VT axes separately. Lower frequencies represent poorer postural control.	[205]
High frequency power	Percentage of the acceleration signal that is present between 4 and 7 Hz. A greater proportion of data in this high frequency band represents increased postural adjustment and postural sway.	[188]

Frequency dispersion	A unitless frequency-based measure of variability. Values closer to zero would represent more regular patterns of sway, while values closer 1 represent a greater degree of variability.	[188]
Walking Stability		
Harmonic Ratio	A measure of the stability of gait-related accelerations by evaluating the stride-to-stride regularity of the harmonics within the acceleration signal. Walking patterns that produce higher ratios have more regular acceleration profiles over successive gait cycles (i.e. less stride-to-stride variability); hence, the gait pattern is deemed to be more stable.	[95, 129, 137, 138, 187, 213, 250, 251]
Step and stride regularity	The regularity of the AP, ML or VT acceleration profiles from step-to-step or stride-to-stride. Higher regularity scores represent a more rhythmic and consistent walking pattern and is often said to reflect a more stable gait pattern.	[95, 163, 250, 251, 261]
Step symmetry	Ratio of step regularity to stride regularity. A ratio closer to 1 represents greater symmetry between the left and right steps, while values closer to 0 indicate poorer symmetry.	[261]

Step and stride timing variability	The standard deviation (SD) or the coefficient of variation ((SD/mean)*100) of all step or stride times collected during a trial. Greater variability represents a less rhythmic walking pattern that is often said o reflect a less stable gait pattern.	[95, 129, 138, 163, 240, 253, 263]
Stride length variability	The standard deviation (SD) or the coefficient of variation ((SD/mean)*100) of all stride lengths collected for the left and right leg collected throughout a trial. Greater variability represents a less predictable and, hence, less stable walking pattern.	[138]
Lyapunov exponent	A non-linear measure that assesses the sensitivity of the system to perturbations in the AP, ML or VT directions. The Lyapunov exponent provides an indication of the local dynamic stability of the gait pattern, with lower values representing increased local stability during gait.	[213]
Entropy rate	Assesses the regularity of the AP, ML and VT accelerations. Values range from 0, which represents no regularity (maximum randomness) to 1, which represents maximum regularity.	[213]
Cross entropy rate	Non-linear measure of asynchrony between two related time series. Used to assess how well the pattern of AP acceleration (for example) can predict ML accelerations. Higher values indicate more synchronisation between the acceleration patterns and, hence, a more stable gait pattern.	[213]

Width of the dominant frequency	The width of the dominant harmonic of the power spectral density of the acceleration signal. Greater widths, represent greater dispersion and greater variability of the gait pattern.	[163, 250, 251, 253]
Relative phase analysis	A graphic-based analysis that plots the angular position of a segment against the angular velocity of the same segment. Relative phase analysis provides a measure of the coordination between two adjoining segments (e.g. pelvic and trunk) and the overall stability of this pattern.	[240]
Phase coordination index (PCI)	Stable walking has step times that are approximately half the length of the gait cycle (i.e. 180° of a 360° cycle). Deviation from this expectation is considered an inaccuracy. The PCI is a summary measure that combines this value representing the accuracy with the coefficient of variation, representing consistency; hence the PCI is considered a measure of gait coordination.	[187]
Symmetry index (SI_{index})	The SI_{index} compares movements from one side (e.g. injured) to the other side (e.g. uninjured). Perfect symmetry is represented by zero and larger numbers represent more asymmetry.	[208]
Gait asymmetry (SI_{GA})	Mean swing time is calculated for both left and right legs. Gait asymmetry is the natural log (ln) of the swing time of the leg with the shortest swing time divided by the swing time of the leg with the longer swing time. Values closer to zero represent a symmetrical movement pattern.	[208]

Symmetry angle (SI_{angle})	Measures the relationship between discrete values obtained from the left and right side and is derived when the right-side value is plotted against the left-side value to create a line that forms an angle with the x-axis. Angles that deviate from 45° represent some degree of asymmetry.	[208]
Maximum angular velocity ratio (SI_{ratio})	Ratio of the maximum angular velocity of the left leg (averaged over all gait cycles) to maximum angular velocity of the right leg (averaged over all gait cycles). Values that are closer to zero represent better symmetry between the left and right sides of the body.	[208]
Trend symmetry (SI_{trend})	Translated data from the left and right sides of the body are used to derive eigenvectors. Trend symmetry assesses the ratio of the variability *about* the eigenvector (y-axis) to the variability *along* the eigenvector (x-axis). A value of zero represents perfect symmetry.	[208]
LCEA symmetry magnitude (SI_{LCEA})	Applies a latency corrected ensemble average (LCEA) to assess the correlation between the magnitudes of the signals collected from the left and right sides of the body using a cross-correlation approach. Larger values represent a greater degree of symmetry.	[208]

Fractal Brownian Motion	Fractal measures provide an indication of the complexity of the AP, ML, VT accelerations during walking. Higher values represent more complex walking patterns, hence walking patterns that are more difficult to coordinate and control effectively.	[214]
Vertical Patterns	A time-frequency pattern of the energy of the acceleration signal for AP, ML and VT directions. Vertical patterns represent impulse type activities during the walking cycle.	[215]
Circular Patterns	A time-frequency pattern of the energy of the acceleration signal for AP, ML and VT directions. Circular patterns characterise irregular burst like patterns during the walking cycle.	[215]
Horizontal Patterns	A time-frequency pattern of the energy of the acceleration signal for AP, ML and VT directions. Horizontal patterns represent long-term smooth and regular activities.	[215]

AP = anterior-posterior; **ML** = medial-lateral; **VT** = Vertical; **RMS** = root mean square; **COM** = centre of mass; **SD** = standard deviation; **LCEA** = latency corrected ensemble average

5.5 Discussion

The purpose of this systematic review was to examine the existing literature to determine the best types of wearable sensors and the most appropriate anatomical placements and outcome measures to assess deficits in balance and gait between people with PD and controls. Using the methodological quality assessment tool adapted from Downs and Black [60], it was determined that the overall quality of scientific reporting in this area is largely of low to moderate quality. In general, the reviewed papers were lacking details concerning the representativeness of the study population (external validity), the approaches adopted to identify and account for confounding variables (internal validity) and an appropriate justification for the chosen sample size. Interestingly, 62% of the included studies received a score of zero for all of the criteria related to at least two of these three areas, while one study (4%) received a score of zero for all three of these areas. The heavier weighting attributed to the sample size criterion is indicative of the importance of ensuring that a study has sufficient statistical power to identify a difference where one exists and, hence, minimise the likelihood of incorrectly accepting the null hypothesis (i.e. Type II error) [177]. Of the 26 studies included in this review, not one reported the results of a sample size calculation, but 13 (50%) had fewer than 15 participants in each of their groups [12, 75, 137, 138, 150-152, 208, 213-215, 261, 263] and 3 others (12%) had at least one group with fewer than this number [93, 144, 240]. While it is important to emphasise that a large sample size is not always required to address a specific research question, reporting the outcome of an appropriate a-priori statistical power calculation is beneficial for determining the overall rigor of the reported findings.

Of the other methodological aspects that were poorly reported, the lack of appropriate detail regarding the influence of confounding variables is quite significant, as failure to account for these factors may result in a study observing a significant change that is simply the manifestation of another variable that has not been adequately controlled for [219]. For

example, it is widely recognised that gait and balance variables are influenced by walking speed [1, 64, 94, 98, 130] and age [80, 90, 226], hence if groups differ for either or both of these variables, appropriate adjustments should be made to account for this. Of the reviewed studies, 15 (58%) described the principal confounder(s) of their research and reported having made adjustments to their outcomes to account for these variable(s) [75, 95, 129, 137, 138, 144, 151, 163, 188, 208, 240, 250, 251, 253, 263]. Of the remaining studies, 4 (15%) provided a description of the potential confounders, but did not clearly describe how they were accounted for in their analyses [93, 187, 214, 215], while 7 (27%) neither reported nor accounted for their potential confounders [12, 67, 150, 152, 205, 213, 261]. In the study by Fazio et al [67], it was reported that people with PD had significantly lower accelerations and Jerk scores than ataxic patients and healthy controls. However, the age of the patients in the PD group (n=17) ranged from 60-85 years, while the ataxic patients (n=24) and controls (n=24) were aged between 20 and 85 years, with more than 60% of these participants aged less than 60 years. Furthermore, the authors reported that the PD and ataxic patients walked significantly slower than the control participants. Given the differences in age and walking speed between the cohorts, it is difficult to determine whether the reported differences in acceleration profiles were indicative of disease-related changes or whether they were simply representative of age-related and/or speed-related factors. Identifying all potential confounders in this type of research and reporting how they have been accounted for in the analyses is critical to ensuring that any changes in outcome can be confidently attributed to the treatment or disease of interest. Collectively, the results of the methodological quality assessment identified that issues related to internal and external validity and statistical power are typically poorly reported in the literature. However, it should be emphasised that this does not suggest that the authors did not consider some or all of these factors, but rather suggests that these areas should be given more attention in the reporting of future research. To improve the overall methodological quality of

research in this area, it is recommended that scientists use existing research reporting guidelines (e.g. CONSORT, STROBE) when designing their studies.

Despite the outlined shortcomings in the reporting of the methods, 81% of the studies described differences between different PD groups and/or a healthy control group for one or more of their sensor-based measures of standing balance or walking stability [67, 75, 93, 95, 129, 137, 138, 150-152, 163, 187, 188, 205, 208, 213-215, 240, 250, 251, 253]. However, contradictory findings reported in separate studies suggest that some of the reported outcomes may be more robust than others. For example, 2 studies that compared PD patients with controls using a standing balance assessment reported no significant differences between the groups for Jerk scores [93, 144], while 3 others reported significantly greater Jerk scores for PD patients [150-152]. Similarly, 2 studies reported no differences between people with PD and controls for RMS accelerations [12, 144], while 3 studies reported significantly greater RMS accelerations for PD patients [150-152]. Sway velocity was another common measure used to evaluate standing balance, but similarly only 3 studies [150, 151, 205] reported differences between people with PD and controls, while the remaining 3 did not [75, 144, 152]. It is interesting to note, however, that contradictory findings were presented by the 3 studies that did report differences between patients and controls for sway velocity, as one study reporting reduced values for PD patients while standing with eyes closed [205], while the others reported greater values for people with PD while standing with eyes open [150, 151], but not eyes closed [151]. While each of the studies that assessed standing balance derived their outcomes from a wearable sensor positioned on the trunk [12, 75, 93, 144, 150-152, 205], there were some methodological differences that may explain the discrepancies observed between the studies' reported outcomes. The studies that reported no significant differences in Jerk scores, RMS accelerations and sway velocities assessed standing balance using a semi-tandem stance test [144], the Sensory Organisation Test [12], the Romberg test [75] or an instrumented version of

the functional reach test [93]. In contrast, the studies that reported significant differences for Jerk, RMS accelerations and sway velocities assessed participants during quiet standing with the heels separated by 10 cm [150-152] or while they stood with their feet together or in a semi-tandem stance with their eyes open and closed [205]. Given the available evidence, it seems that the best recommendation for clinicians seeking to assess standing balance using wearable sensors would be to calculate RMS accelerations or Jerk scores from trunk accelerations collected while patients are standing with their eyes open and their heels 10 cm apart. However, a degree of caution may be required when considering this recommendation, as three of the four studies that reported differences in standing balance for people with PD appear to have used the same patient cohort, as the reported demographics are the same for each study [150-152]. As such, it is possible that the overall interpretation of the existing literature in this area may be biased and the transferability of the findings may be more limited than they appear.

In addition to the 9 studies that used wearable sensors to assess standing balance, the remaining 65% used these devices to assess walking stability. These studies reported numerous outcome measures derived from the acceleration signals, but the Harmonic Ratio (HR) was the most commonly-reported measure and was calculated for the head [129] and lumbosacral region [95, 129, 137, 138, 187, 213, 250, 251]. The HR seems to be a sensitive and versatile measure of walking stability, as the reviewed literature reports differences between people with PD and controls [129, 138, 187, 213], PD freezers and non-freezers [250], PD fallers and non-fallers [129, 251], PD patients with different dominant symptoms [95] and different methods of cueing for people with PD [137]. Stride timing variability was the second most common outcome measure for the studies that assessed walking stability, but careful review of the included studies suggested that it may not be a dependable measure for discriminating between different populations. Of the 7 studies that reported this outcome, 3 studies described differences in stride timing variability between PD fallers and non-fallers [129], PD patients

and controls [129, 253] or carriers and non-carriers of the Leucine-Rich Repeat Kinase 2 gene mutation [163]. In contrast, 4 studies reported no differences between PD patients and controls [138, 240, 263] or patients with different sub-types of PD [95]. A common characteristic of those studies that did report differences for the HR and stride timing variability was that they each assessed walking stability during straight line walking. As such, it is recommended that clinicians who wish to assess walking stability using wearable sensors calculate the HR from trunk accelerations collected while patients are walking in a straight line at a self-selected speed. While there is some evidence to support the use of stride timing variability to assess walking stability, it would be recommended as a secondary measure due to the inconsistencies evident within the current literature.

While it was not the primary focus of this review to evaluate the effects of anti-parkinsonian medications, such as levodopa, on measures of standing balance and walking stability, it is an important factor that warrants consideration. It is widely recognised that levodopa improves symptoms of PD (based on the UPDRS) [75, 95], spatiotemporal gait characteristics (e.g. stride length) [185, 210] and performance on clinical tests of balance, such as the Berg Balance scale [184]. Of the studies included in this review, 5 (19%) reported assessing standing balance or walking stability while patients were not medicated [12, 144, 187, 188, 205], 9 (35%) assessed patients on-medication [67, 129, 137, 138, 163, 213, 214, 250, 251] and 3 (12%) assessed patients in both on and off states [75, 95, 253]. Of the remaining studies, 6 (22%) assessed patients who were not yet being medicated for PD [150-152, 208, 240, 263], while 3 (12%) did not report whether their participants were on or off medication at the time of testing [93, 215, 261]. Interestingly, of those studies that did not report differences in standing balance or walking stability between different groups of PD patients and/or healthy controls, 2 assessed patients while they were off medication [12, 144], while the other did not report whether patients were assessed on or off medication [261]. Of the three studies that

assessed patients on and off medication, only two statistically compared their presented outcomes for the two conditions [75, 253]. For a group of idiopathic PD patients, it was reported that the length and maximal distance of postural sway was significantly increased during normal stance when patients were assessed on medication [75], which would typically be interpreted as a greater amount of sway during the medicated state. During walking, Weiss et al. [253] reported a significant reduction in the width of the dominant harmonic in the acceleration signal when patients were tested on medication, which represented less variability in the gait patterns of medicated patients. While there is a clear need for further research in this area, the presented findings suggest that wearable sensors can be effectively used to evaluate changes in standing balance and walking stability for different patients who are assessed with or without anti-parkinsonian medication.

Considering that 66% of individuals with PD fall at least once in a given year [43, 259] and that nearly 50% of these falls occur during locomotion [7, 17], assessing walking stability and falls risk is critical to ensure that high-risk patients can be easily identified by clinicians. However, to date, there is a paucity of research evaluating the capacity for wearable sensors to identify people with PD who are at a higher risk of prospectively falling. Two of the studies included in this review compared people with PD who retrospectively reported having no falls (non-fallers) to those who reported falling at least once (fallers) in the previous 12 months [129, 251]. Both of these studies reported that PD fallers had less symmetrical movements for the pelvis or lower trunk (as assessed using the HR) in both the anterior-posterior (forward-backward) and vertical directions compared with PD non-fallers [129, 251] and controls [129]. While their retrospective nature makes it difficult to determine whether these deficits were contributory to the patients falling or whether they are perhaps a consequence of an increased fear of future falls, the results of these studies provide some support for the use of wearable sensors for screening patients for falls risk. Nevertheless, further prospective research is needed

to confirm whether sensor-based measures of standing balance or walking stability are suitable for the assessing falls risk and predicting future falls in this population.

As with any review of this nature, there are a number of limitations that should be considered when reviewing this research. Firstly, the results of the methodological quality assessment included in this systematic review are based on the assessor's (RPH) interpretation of each of the studies. The results reflect the quality of the reporting of the research and, hence, should not be seen as a critique of the significance of the research and its outcomes. Secondly, given the relatively small number of studies that have been published in this area and the wide variety of research questions addressed using wearable sensors, it is difficult to make strong recommendations regarding the most appropriate equipment, placements and outcomes for assessing standing balance and walking stability in people with PD. For example, there may be other anatomical sites for sensor placement that offer superior sensitivity to those identified in this review. Furthermore, other more complex measures of stability, such as the Lyapunov exponent, may be more appropriate for assessing stability than those outcomes that have traditionally been used in Parkinson's disease research. While the maximum Lyapunov exponent has not been used to assess walking stability in people with PD, it has been used to examine healthy younger and older adults and is known to have excellent construct validity [27]. In light of these limitations, the results presented in this systematic review should be considered preliminary and additional work will be required as this field of science continues to evolve

In conclusion, wearable sensors provide a light-weight, portable and affordable alternative to more expensive three-dimensional motion analysis systems and are effective for detecting changes in standing balance and walking stability in people with PD. However, it appears that some outcome measures may be more useful than others for discriminating patient cohorts from controls. Specifically, measures of Jerk and RMS acceleration for the trunk seem

to be the best sensor-based measures of standing balance, even under less challenging conditions (i.e. feet apart on a firm surface with eyes open). For assessments of walking stability, a trunk-mounted wearable sensor can be used to assess the symmetry of dynamic gait patterns using the HR calculated for the three axes of motion. While some studies have provided support for other more complex frequency-based measures of postural stability, additional research is essential to objectively assess the utility of these measures for the PD population. Future research should give careful consideration to the internal and external validity of their methods and provide an appropriate sample size calculation to support their study, as these aspects have typically been poorly reported in the existing literature.

6.0 General Methods for the Experimental Studies

The results of the systematic review (Study 1) answered a number of questions that were considered pertinent to the design of the subsequent experimental studies (i.e. Studies 2 to 4). Specifically, it was established that accelerometers placed on the axial skeleton, specifically the head and/or trunk, have been the most commonly used wearable sensor for assessing aspects of static and dynamic postural stability in people with PD. Furthermore, measures of Jerk and RMS acceleration derived from trunk-based accelerometers seem to be the best sensor-based measures of standing balance, while the rhythmicity (or symmetry) of head and/or trunk accelerations are best suited to the assessment of dynamic tasks. The following section, which outlines the general methods of the experimental studies, was developed with the outcomes of the systematic review in mind. It should be noted that this chapter only presents the methods that were common across all of the experimental studies, while additional detail concerning the specific methods employed for each investigation is included in the following chapters.

NOTE: The protocol for the randomised controlled trial portion of this research was published in the following peer-reviewed manuscript:

Hubble, R. P., Naughton, G. A., Silburn, P. A., & Cole, M. H. (2014). Trunk muscle exercises as a means of improving postural stability in people with Parkinson's disease: a protocol for a randomised controlled trial. *BMJ open*, *4*(12), e006095.

6.1 Participant Recruitment

For the purposes of this research, 683 individuals diagnosed with idiopathic PD, based on the UK Brain Bank Criteria [106] were invited to participate via; i) neurology clinics; ii) community support groups; and iii) a pre-existing database of individuals who had expressed an interest in participating in research. Prospective participants were sent an information letter outlining the details of the research and inviting them to contact a member of the research team if they were interested in volunteering for the research (Appendix C). Of these patients, 571 did not respond to the invitation and 19 declined to participate, and initial phone screening revealed another 63 patients who did not meet the inclusion criteria. Participants were excluded if they: i) were unable to stand and walk independently without the use of a walking aid, ii) had uncontrolled hypertension, iii) were taking psychotropic medications, iv) had any significant limitations due to osteoporosis, v) had any orthopaedic surgery within the previous year, vi) had any serious neck, shoulder or back injuries; including spinal fusions, or vii) had received deep brain stimulation surgery to manage their symptoms.

Following the phone screening process, 30 patients were scheduled for baseline assessments at the university. At the baseline assessment, clinical tests used as screening tools were performed before laboratory tests were performed. Participants were excluded if they had any significant visual (Bailey-Lovie high contrast visual acuity > 0.30 logMAR [9]) or cognitive impairment (Addenbrooke's Cognition Examination Revised (ACE-R) [162] total score <82). One additional participant was excluded with an ACE-R score < 82, leaving 29 individuals eligible for Study 2.

Following the completion of the baseline assessments (see Section 6.2), participants who had reported experiencing at least 1 fall or 2 or more near misses in the previous 12 months (n=24) were invited to participate in a 12-week randomised controlled trial, which formed the basis of Studies 3 and 4. Of the 24 patients invited to participate in the randomised controlled

trial, 22 accepted the invitation and were randomised to one of the two intervention groups. For the purpose of this research, a fall was defined as "any coming to the ground or lower level not as the result of a major intrinsic event or overwhelming hazard" and a near-miss was defined as "an event during which an individual felt that he/she was going to fall but did not actually do so" [6].

The recruitment and assessment of all participants was completed between February 2014 and November 2015 and all data collection was conducted at the Brisbane campus of the Australian Catholic University. Prior to their involvement in this research, all volunteers were asked to provide written informed consent in accordance with the Declaration of Helsinki (Appendix D). The experimental procedures for this research were approved by the Australian Catholic University Human Research Ethics Committee (Appendix E; approval number 2013-223Q). The processes of recruitment and data collection are summarised in Figure 5.

6.2 Data Collection

6.2.1 Cognition and Visual Function Screening

Those individuals who were deemed eligible to participate based on telephone screening and who provided written informed consent were asked to attend a Baseline testing session at the Australian Catholic University (Brisbane). During this session, participants were screened for any significant deficits in cognitive function and/or visual acuity using the ACE-R and Bailey-Lovie high contrast visual acuity assessments, respectively. The ACE-R is a clinical test that assesses five aspects of cognitive function, including attention and orientation, memory, fluency, language and visuospatial ability. The assessment has been shown to have excellent reliability [156, 162] and has established validity for assessing and classifying dementia [156, 202]. The ACE-R is scored out of a maximum of 100 points, with higher scores representing better overall performance and it has been used previously used to assess various

aspects of cognition in people with PD [201, 202]. Furthermore, research shows that a cut-off score of 82 out of 100 yields a high sensitivity (82%) and specificity (100%) for detecting dementia in ageing populations [162].

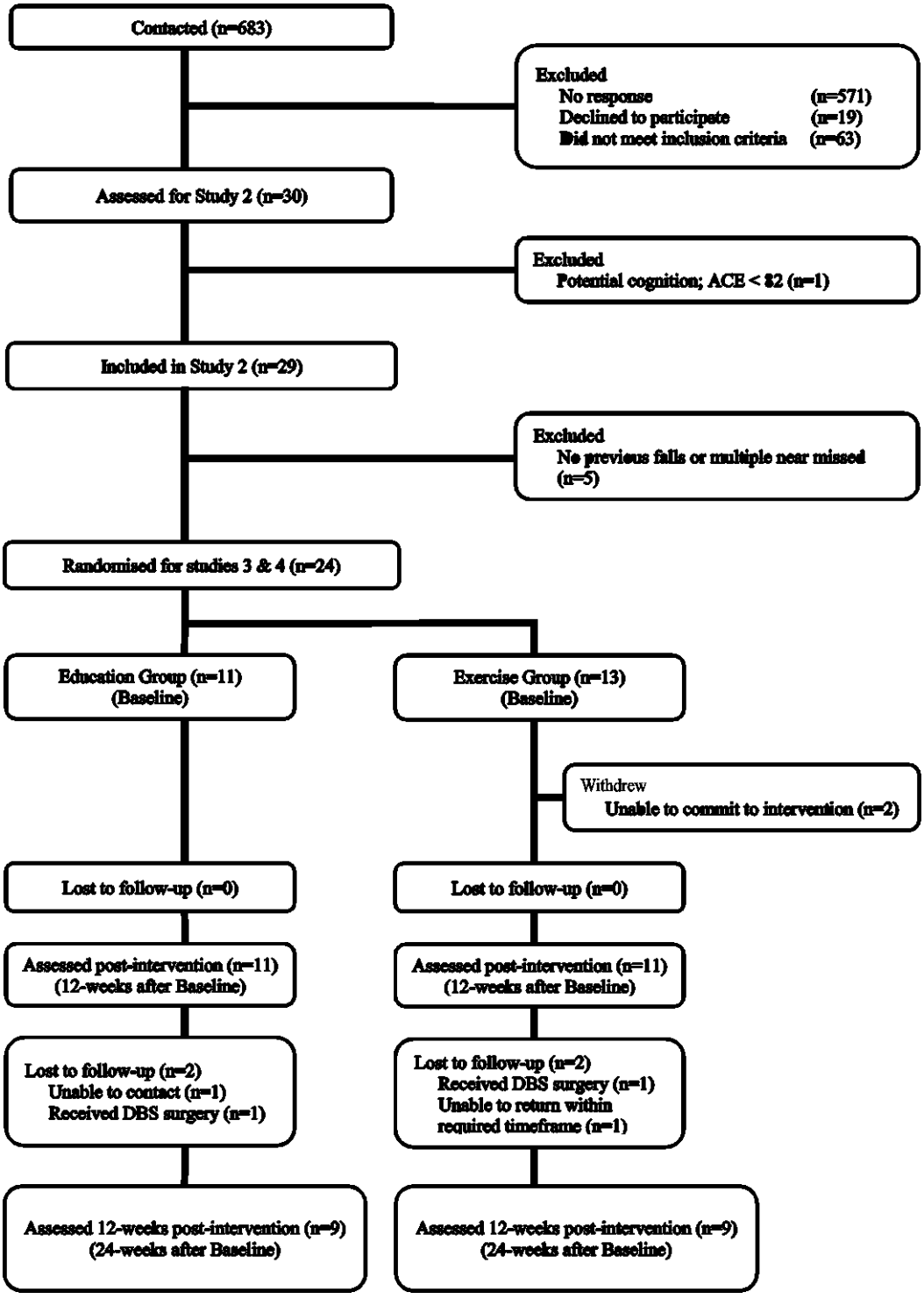

Figure 5: Summarises the recruitment, screening and data collection processes of this research.

The standardized Bailey-Lovie high contrast visual acuity chart is a common assessment of visual function that presents 11 lines, each comprising 5 letters. As the individual being assessed progresses downward after reading each line of the chart, the size of letters on each line progressively gets smaller and, hence, become more difficult to read [9]. For the purposes of this study, participants were positioned 3.0 meters away from the chart wearing any lenses that they may have been prescribed to wear for distance vision. Starting on the top line (representing 6/30 vision), the participants were asked to read each letter aloud before progressing to the next line. This process was repeated until the participant was unable to determine the letter presented on the chart. The Bailey-Lovie high contrast visual acuity chart has been deemed a reliable and valid tool for assessing visual acuity [136] and similar charts are routinely used in standard optometry clinics. Participants with significant visual (Bailey-Lovie high contrast visual acuity >0.30 logMAR) and/or cognitive (ACE score <82) impairment were excluded prior to completing any further baseline testing (Table 4).

6.2.2 Clinical Assessments

Following the assessments of cognitive and visual function, eligible participants were asked to provide details of any prescription medications that they routinely consumed to manage their parkinsonian symptoms and/or any other medical conditions. Each participant then completed a battery of tests that included clinical assessments of; i) symptom severity (the UPDRS [71]); ii) disease stage (the modified H&Y stage score [100]; the Schwab & England Activities of Daily Living Scale [212]); iii) gait impairment (the PD Gait and Falls Questionnaire [77]); iv) balance confidence (the ABC scale [198]); v) mobility (Timed Up and Go [197] test); and vi) quality of life (39-item Parkinson's Disease Questionnaire (PDQ-39) [195]). The UPDRS is the most widely used clinical tool for assessing symptom severity in people with PD [71] and comprises four distinct parts; each addressing a different aspect of the disease. The first part

assesses changes in mentation, behaviour and mood, while the second evaluates the patient's perceived difficulties with completing common activities of daily living. The third section of the UPDRS assesses the severity of the patient's motor symptoms, while the fourth sub-scale evaluates the nature and impact of any complications that are commonly related to the therapeutic management of the condition [66]. Given this research was concerned with assessing static and dynamic postural stability in people with PD, only the motor sub-section of the UPDRS (UPDRS III) was completed for each participant. The motor subscale has been shown to have excellent internal reliability [223, 224, 241], good test-retest [225] and is capable of strong inter-rater [225] reliability and moderate to excellent construct validity based on correlations with multiple clinical assessments [28, 77, 183, 223, 224].

The Hoehn and Yahr scale is a five point assessment scale used to rate the severity or stage of Parkinson's disease based on the severity and distribution of a patient's symptoms [100]. Although developed over 30 years ago, it has not been formally assessed for reliability, however, it is the second most widely used tool (after the UPDRS) to assess disease severity in people with PD [82]. Nevertheless, the Hoehn and Yahr scale is considered to be a reliable tool as it is moderately correlated with other valid and reliable tests of disease and symptom severity for PD [77, 153, 223, 224].

Functional independence in daily living is important to individuals with PD. The Schwab and England Activities of Daily living scale is used to evaluate a patient's ability to independently and efficiently perform daily tasks. This assessment rates the individual's overall independence on a scale of 0 to 100%, with a score of 100% representing complete independence when performing common activities of daily living [212]. Once again, clinometric data are limited for this measure; however, it has moderate test-retest reliability [49], adequate inter and intra-rater reliability [158] and has is known to be well correlated with other well established and trialled assessments of disease severity of PD [153, 223] (Table 4).

The PD Gait and Falls Questionnaire comprises 16 questions that assess the severity of common symptoms of PD and other Parkinsonian syndromes that affect walking ability and promote falls [77]. Each item on this questionnaire is scored on a Likert scale of 0-4, with higher scores reflecting a greater perceived impairment due to the described symptoms. The scores of six questions included in this questionnaire are summed to provide the Freezing of Gait score, which assesses symptoms specifically associated with the inability to initiate and/or continue walking (i.e. freezing of gait). The PD Gait and Falls Questionnaire lacks inter and intra rater reliability due to the subjective nature of this self-reported measure, However, it has high internal consistency and reliability, good test-retest reliability, and is deemed valid as it has been correlated with a number of other similar measures of symptom severity (Table 4). It also has low to moderate concurrent and predictive validity with a number of clinical tests.

6.2.3 Fear of Falling

The Activities-specific Balance Confidence scale is a 16-item questionnaire that asks participants to rate how confident they are that they will not overbalance or become unsteady while performing a number of normal everyday tasks. Balance confidence is self-reported on a scale from 0 to 100%, with lower scores representing less confidence and, hence, a greater fear of falling while performing the activity. As another self-reported and subjective score, it lacks an inter-rater reliability, but internal and test-retest reliability are acceptable (Table 4). More recently it has been able to independently predict future recurrent fallers in PD [41].

6.2.4 Mobility

A frequently used, inexpensive and convenient assessment of basic movement ability is the Timed Up and Go test. It measures the time taken for an individual to rise from a standard armchair, walk three meters until both feet cross a line, turn around, and then walk back to the

chair and sit back down (Figure 6). For this study, participants were seated in a 42 cm high chair with their feet flat on the floor, their back flat against the backrest and their arms resting on the armrests, which were situated 20 cm above the seat. Upon the word 'GO,' participants were required to stand from the chair and walk at a brisk, but comfortable pace to a line on the floor three meters away, turn around and return to the chair to sit down. The time taken to complete the test was recorded by the assessor using a stopwatch. For all of the experimental studies included in this thesis, participants completed five barefoot trials of the Timed Up and Go test, which has been shown to have moderate to strong test-retest, intra-rater and inter-rater reliability (Table 4).

6.2.5 Quality of Life

Although there are a number of quality of life inventories, few address the specific issues that affect the quality of life for patients with PD. The PDQ-39 is a short PD-specific assessment of quality of life comprising 39 questions scored on a 5 point Likert scale. The survey includes questions relating to difficulties experienced with mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. It has high internal consistency, moderate to high test-retest reliability, and moderate to strong correlations with clinical tests of disease severity (Table 4).

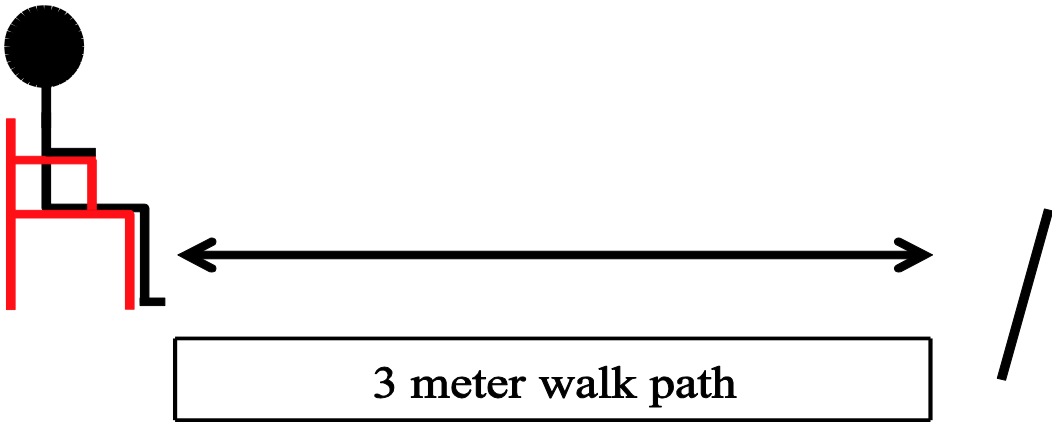

Figure 6: Diagrammatical representation of the Timed Up and Go test.

Table 4: Reliability and validity of the clinometric instruments used for patient evaluation.

Test	Reliability			Validity		
	Internal consistency median[range]	**Test-Retest** median[range]	**Inter/Intra-rater** median[range]	**Internal**	**Construct (Convergent/Discriminant)**	**Criterion (Predictive/Concurrent)**
Balance Confidence						
Activity-specific Balance Confidence Scale [198]	α = 0.95 [0.91-0.96] [135, 167, 193, 225]	ICC = 0.79 [0.77-0.94] [49, 121, 225]	***Inter-rater*** Self-Reported, not applicable Self-Reported, not applicable ***Intra-rater*** Not Available	Not Available	***General Construct*** FES-I r = -0.68 [167] mSAFEE r = -0.68 [167] CoF r = -0.56 [167] Gait Speed r_s = 0.56 [175] Posturography r_s = 0.37-0.61 [175] ***Convergent*** Not Available ***Discriminant*** Differences in FOF in PD vs. Controls 58% sensitivity, 96% specificity [193] Differences in FOF in HLGDs vs controls 96% sensitivity, 96% specificity [193] Differences in FOF in PD vs HLGDs 97% sensitivity, 32% specificity [193] Reduced falls risk in PD for ABC score > 80 OR = 0.06 [147]	***General Criterion*** Not Available ***Predictive*** Future falls ROC = 0.82 69 (93% sensitivity, 67% specificity [149] ***Concurrent*** ABC-6 r = 0.96-0.97 [135] ABC-5 r = 0.95 [135] Berg Balance Scale r_s = 0.50 [135] FR r = 0.184 [135] 1-Leg Stance r = 0.26 [135] Tandem Stance r = 0.357 [135] Timed Up and Go Test r = -0.372 [135] 6MW r = 0.458 [135] PIGD r_s = -0.38 [135] UPDRS Motor r_s = -0.22 [135] Knee muscle strength r_s = 0.301 [148]

					No Reduced falls risk in PD with moderate ABC score OR = 0.10 [147]	UPDRS-PG r_s = -0.661 [148]
Cognition Revised Addenbrooke's Cognitive Examination [162]	α = 0.79 [0.78-0.80] [156, 162]	Not Available	***Inter-rater*** Not Available ***Intra-rater*** Not Available	Not Available	***General Construct*** DSM-IV k = 0.59-0.62 [156] ***Convergent*** CDR r_s = -0.321 [162] ***Discriminant*** Not Available	***General Criterion*** Not Available ***Predictive*** Not Available ***Concurrent*** CDR r_s = -0.321 [162] DSIM-IV ROC = 0.91 [156]
Visual Function Bailey-Lovie high contrast visual acuity [9]	Reliable [136]	Not Available	***Inter-rater*** Not Available ***Intra-rater*** Not Available	Valid [136]	***General Construct*** Not Available ***Convergent*** Not Available ***Discriminant*** Not Available	***General Criterion*** Not Available ***Predictive*** Not Available ***Concurrent*** Not Available
Quality of Life Parkinson's disease questionnaire 39 [195]	Total scale α = 0.85 [0.84-0.96] [26, 50, 111, 140, 141] Sub-scales: Mobility α = 0.94 [0.69-0.96] [26, 33, 50, 69, 89, 124, 140-142, 168, 195] Activities of Daily Living (ADL)	Total Scale ICC = 0.82 [0.79-0.86] [121, 140] Sub-scales: Mobility ICC =0. 85 [0.74-0.95] [33, 89, 140-142, 195] Activities of Daily Living (ADL) ICC = 0.87 [0.71-0.96] [33, 89, 140-142, 195]	***Inter-Rater*** Total Scale ICC = 0.55 [70] Sub-scales: Mobility ICC = 0.66 [70] Activities of Daily Living ICC = 0.67 [70] Emotional Well-Being ICC = 0.47 [70] Stigma ICC = 0.35 [70] Social Support ICC = 0.40 [70]	r_s = 0.09-0.70 [153]	***General Construct*** Age at diagnosis r = -0.27 [168] Disease duration r = 0.27 [168] ***Convergent*** PDQ-39 Mobility to SF-36 Physical Functioning r = -0.88 [33] PDQ-39 ADL to SF-36 Role limitations due to physical problems r = -0.59 [33]	***General Criterion*** Not Available ***Predictive*** Not Available ***Concurrent*** Not Available

α = 0.89[0.85-0.90] [26, 33, 50, 69, 89, 124, 140-142, 168, 195]

Emotional Well-Being
α = 0.87 [0.79-0.90] [26, 33, 50, 69, 89, 124, 140-142, 168, 195]

Stigma
α = 0.86 [0.78-0.88] [26, 33, 50, 69, 89, 124, 140-142, 168, 195]

Social Support
α = 0.69 [0.51-0.87] [26, 33, 50, 69, 89, 124, 140-142, 168, 195]

Cognition
α = 0.70 [0.63-087] [26, 33, 50, 69, 89, 124, 140-142, 168, 195]

Communication
α = 0.80 [0.74-0.87] [26, 33, 50, 69, 89, 124, 140-142, 168, 195]

Bodily Discomfort
α = 0.72[0.59-0.87][26, 33, 50, 69,

Emotional Well-Being
ICC = 0.87 [0.62-0.95] [33, 89, 140-142, 195]

Stigma
ICC = 0.86 [0.67-0.90] [33, 89, 140-142, 195]

Social Support
ICC = 0.75 [0.56-0.95] [33, 89, 140-142, 195]

Cognition
ICC = 0.83 [0.71-0.93] [33, 89, 140-142, 195]

Communication
ICC = 0.81 [0.70-0.86] [33, 89, 140-142, 195]

Bodily Discomfort
ICC = 0.81 [0.68-0.88] [33, 89, 140-142, 195]

Cognition
ICC = 0.38 [70]
Communication
ICC = 0.38 [70]
Bodily Discomfort
ICC = 0.56 [70]

Intra-Rater
Not Available

PDQ-39 Emotional Well-Being to SF-36 mental health
r = -0.78 [33]
PDQ-39 Bodily Discomfort to SF-36 Bodily pain
r = -0.73 [33]
PDQ-39 Social Support to SF-36 Social Functioning
r = -0.22 [33]
H&Y
r_s = 0.58 [153]
SES
r_s = -0.60 [153]
UPDRS I-III
r_s = 0.49-0.69 [153]
PDQL
r_s = -0.91 [153]

Discriminant
PDQ-39 Subscales:
Mobility to Tremor
r = 0.21 [33]
Mobility to Stiffness
r = 0.54
Mobility to Slowness
r = 0.74 [33]
Mobility to Freezing
r = 0.64 [33]
Mobility to Jerking
r = 0.41 [33]

	89, 124, 140-142, 168, 195]					
Symptom Severity and Disease Stage						
Unified Parkinson's Disease Rating Scale Part III - Motor Sub-scale [66]	α = 0.90 [0.88-0.95] [223, 224, 241]	ICC = 0.89 [225]	*Inter-rater* *ICC = 0.82 [204]* *Intra-rater* *Not Available*	Not Available	*General Construct* *H&Y* *Eta = 0.58[0.55-0.61][223, 224]* *Freezing of Gait Questionnaire* *r = 0.40 [77]* *PDQ-39* *rs = 0.49-0.69 [153]* *SES* *Eta = 0.65 [223]* *Webster Scale* *rs = 0.94 [183]* *Convergent* *Not Available* *Discriminant* *Not Available*	*General Criterion* *Not Available* *Predictive* *Not Available* *Concurrent* *H&Y* *rs = 0.75 [241]* *Berg Balance Scale* *rs = -0.69 [28]* *Timed Up and Go Test* *rs = 0.58 [28]*
Modified Hoehn & Yahr Scale [110]	Single score, not applicable	Not Available	***Inter-rater*** Not Available ***Intra-rater*** Not Available	Not Available	***General Construct*** UPDRS III Eta = 0.61 [223] Eta = 0.55 [224] PDQ-39 r_s = 0.58 [153] ***Convergent*** *Freezing of Gait Questionnaire* r = 0.66 [77] ***Discriminant*** Not Available	***General Criterion*** Not Available ***Predictive*** Not Available ***Concurrent*** UPDRS III r_s = 0.75 [241]

Schwab & England Activities of Daily Living Scale [212]	Not Applicable	ICC = 0.70 CI 0.43-0.86 [49]	***Inter-rater*** ICC = 0.60 [158] ***Intra-rater*** ICC = 0.65 [158]	Not Available	***General construct*** UPDRS III Eta = 0.65 [223] PDQ-39 r_s = -0.60 [153] ***Convergent*** Not Available ***Discriminant*** Not Available	***General Criterion*** Not Available ***Predictive*** Not Available ***Concurrent*** Not Available
PD Gait and Falls Questionnaire [77]	α = 0.90 [0.89-0.96] [77, 78]	ICC = 0.83 [0.83-0.84] [78]	***Inter-rater*** Self-Reported not applicable ***Intra-rater*** Not Available		***General Construct*** Not Available ***Convergent*** UPDRS I r = 0.20 [78] UPDRS II ON-Phase r = 0.40 [78] OFF-Phase r = 0.34 [78] UPDRS III ON-Phase r = 0.34 [0.28-0.40] [77, 78] OFF-Phase r = 0.49 [78] UPDRS Item: Freezing when Walking ON-Phase r = 0.43 [78] OFF-Phase r = 0.74 [78] UPDRS Item: Walking ON-Phase r = 0.23 [78] OFF-Phase r = 0.34 [78] UPDRS Item: Depression	***General Criterion*** Not Available ***Predictive*** Predict PDQ-39 score R^2 change = 0.23 [65] ***Concurrent*** UPDRS Total: r = 0.48 [77] UPDRS I r = 0.08 [77] r_s = 0.41 [0.35-0.48] [180, 230] UPDRS II r = 0.43 [77] r_s = 0.66 [180] UPDRS III r = 0.40 [77] r_s = 0.59 [180] UPDRS Part IV r_s = 0.62 [180] H&Y ON-Phase r = 0.66 [77] r_s = 0.46 [180] OFF-Phase r_s = 0.65 [180]

r = 0.16 [78]
UPDRS Item: Intellectual Impairment
r = 0.11 [78]
UPDRS Item: Tremor ON-Phase
r = 0.07 [78]
PDQ-39 Subscale Mobility
r = 0.55 [78]
Activities of Daily Living
r = 0.33 [78]
Emotional Well-being
r = 0.30 [78]
Bodily Discomfort
r = 0.28 [78]
Communication
r = 0.23 [78]
Social support
r = 0.17 [78]
Stigma
r = 0.14 [78]
Cognition
r = 0.12 [78]
H&Y
r = 0.66 [77]

Discriminant
Not Available

Phonological verbal fluency
r_s = -0.464 [4]
Frontal assessment battery
r_s = 0.501 [4]
Timed Up and Go Test
r_s = 0.40 [180]
PD Duration
r_s = 0.42 [180]
Fall-Efficacy Scale
r_s = -0.59 [180]
Age
r_s = 0.05 [180]
Physical Functioning scale of 36-item short-form health survey
r_s = -0.48 [180]
Comfortable/Fast gait speed
r_s = -0.32 [180]
UPDRS Item 13: Falling unrelated to freezing
r_s = 0.55 [180]
UPDRS Item 15: Walking
r_s = 0.56 [180]
UPDRS Item 29: Gait
r_s = 0.54 [180]
SES
r_s = -0.048 [230]
PDQ-39
r = 0.57 [65]

Clinical Mobility Timed Up and Go [197]	Not Available	ICC = 0.83 [0.69-0.99] [28, 49, 102, 173, 225]	***Inter-rater*** ICC = 0.99 [0.83-0.99] [16, 133, 173, 197, 243] ***Intra-rater*** ICC = 0.98 [0.93-0.99] [16, 133, 197, 243]	***General Construct*** Not Available ***Convergent*** Not Available ***Discriminant*** Not Available	***General Criterion*** Not available ***Predictive*** Not available ***Concurrent*** UPDRS III r_s = 0.58 [28] ABC r = -0.37 [135] PD Gait and Falls r_s = 0.40 [180]

α = Cronbach's alpha , **CDR** = Clinical Dementia Rating , **CGS** = Comfortable gait speed, **CI** = Confidence Interval, **CoF** = Consequences of Falling scale, **DSIM-IV** = Diagnostic and statistical manual of mental disorders, fourth edition, **Eta** = Eta correlation coefficient, **FES-I** = Fall-efficacy Scale International, **H&Y** = Hoehn and Yahr, **ICC** = Intraclass correlation coefficient, **k** = kappa score, **OR** = Odds ratio, **PDQ-39** = 39-item Parkinson's Disease Questionnaire, **PDQL** = Parkinson's Disease Quality of Life Questionnaire, **PIGD** = Postural Instability and Gait Disability, **r** = Pearson's correlation coefficient, $\mathbf{r_s}$ = Spearman's Rank Correlation Coefficient, **ROC** = receiver operating characteristics, **SES** = Schwab and England Scale, **T** = time, **UPDRS** = Unified Parkinson's Disease Rating Scale, **UPDRS I** = UPDRS sub-scale I: Mentation, Behaviour and Mood, **UPDRS II** = UPDRS sub-scale II: Activities of Daily Living, **UPDRS III** = UPDRS sub-scale III: Motor Examination, **UPDRS IV** = UPDRS sub-scale IV: Complications of Therapy

Of the participants included in this research, 27 out of 29 (93%) were prescribed anti-parkinsonian medications as a means of managing their symptoms. To ensure that the data collected were representative of the real-world setting, all participants were assessed on medication, as research has shown that anti-parkinsonian medications, such as Levodopa, can improve motor symptoms severity based on the UPDRS motor sub-scale [87, 184, 210] and the Hoehn and Yahr stage score [87, 184, 185, 210]. In addition to symptom severity, Levodopa has also been shown to improve mobility, by increasing walking speed and step length in people with PD [30, 185].

6.3 Statistical Analysis

To assess for any significant differences between groups for Studies 2, 3, and 4, continuous demographic variables (e.g. age, height, mass) were contrasted using a one-way analysis of variance (ANOVA), while the Chi-square tests were used to identify any differences in the frequency of categorical data (e.g. gender, Hoehn and Yahr stage score). If the assumptions of normal distribution (Shapiro-Wilks test) and/or homogeneity of variance (Levene's test) were violated, the equivalent non-parametric Kruskal-Wallis test was used for the continuous measures [244]. The specific statistical analyses used to examine the relationship(s) between outcomes and/or changes in the primary outcomes following the intervention are described in the subsequent chapters of this thesis.

7.0 Study 2: Assessing stability in mild and moderate Parkinson's disease: Can clinical measures provide insight?

Traditionally, the efficacy of exercise-based interventions seeking to improve postural stability and/or reduce falls has been evaluated using a collection of widely-accepted clinical assessments. However, research shows that these types of assessments are not well-suited to identifying patients at risk of falling [119], which seems to suggest that the somewhat subjective nature of these assessments may render them inadequate for objectively appraising changes in postural stability following an intervention. As outlined in Study 1, accelerometers are becoming widely adopted by clinicians and researchers for the assessment of postural stability in people with PD. Accelerometers were primarily placed on the head and trunk and the harmonic ratio was the most common measure for detect differences in gait symmetry between people with PD and other populations. Using these findings as guidance, Study 2 was designed to determine whether accelerometer-based measures of postural stability were related to clinical measures of mobility, balance, balance confidence and/or gait difficulty in a cohort of PD patients.

NOTE: this chapter presents the findings of the following peer-reviewed manuscript, which has been reformatted for the purposes of this dissertation:

Hubble, R. P., Naughton, G. A., Silburn, P. A., & Cole, M. H. (2016). Assessing stability in mild and moderate Parkinson's disease: Can clinical measures provide insight? *Gait & Posture, 49(*1), 7-13.

7.1 Abstract

Background: In the clinic, the mobility of people with Parkinson's disease (PD) is often assessed using timed tests, such as the 6-meter walk and Timed up and Go tests. Given their wide-spread acceptance, these tests have also been used to assess the efficacy of exercise-based falls prevention interventions for this population. However, it is currently unclear whether these mobility assessments provide insight into changes in walking; hence research is needed to determine their suitability for assessing postural control in PD patients. This cross-sectional study aimed to investigate the relationship between accelerometer-derived measures of movement rhythmicity and clinical measures of mobility, balance confidence and gait difficulty in people with Parkinson's disease (PD).

Methods: Twenty-nine independently-living PD patients (Hoehn & Yahr stages 1-3) with no history of significant injury or orthopaedic/deep brain stimulation surgery were recruited from a database of patients who had expressed an interest to participate in research. Participants completed clinical assessments of mobility, postural stability, balance confidence and symptom severity, while head and trunk symmetry was evaluated during gait using accelerometers. Following data collection, patients were stratified based on disease stage into either a Mild (Hoehn & Yahr Stage 1) or Moderate (Hoehn & Yahr Stages 2 to 3) PD group.

Results: The results highlighted that the Moderate PD group had poorer quality of life, reduced balance confidence and increased gait and falls difficulty. Furthermore, for these patients, gait disability and the number of previous falls were both negatively correlated with multiple components of head and trunk rhythmicity. For the Mild PD group, six-meter walk time was positively correlated with ML head rhythmicity and linear regression highlighted a significant predictive relationship between these outcomes. For the Mild and Moderate PD groups, balance

confidence respectively predicted anterior-posterior trunk rhythmicity and vertical head rhythmicity.

Conclusion: While these findings demonstrate that falls history and the Gait and Falls questionnaire provide moderate insight into head and trunk symmetry in Moderate PD patients, objective and clinically-feasible measures of postural instability would assist with the management of these symptoms.

7.2 Introduction

Postural instability is one of the most disabling symptoms of Parkinson's disease (PD) and significantly increases the risk of falling [248]. The costs of falls and falls-related injuries are not well established for many countries [247], but Australian estimates indicate that approximately AUD$27.5 million was spent on injuries associated with falls and falls-related injuries in 2010 [189]. Given the significant physical and financial burden associated with falls in PD, a clear need exists to develop an improved capacity to assess symptoms of postural instability to assist with early identification and treatment. For people with PD, symptoms of postural instability are often accompanied by a decline in the patient's mobility [225]. Traditionally, clinical tests like the Timed up and Go [249] and 10-meter [225] (or 6-meter [21]) walk tests have been used to assess changes in mobility for a range of healthy [21] and pathological [225] populations. Given the ease with which the clinical tests can be administered and their widespread use in hospitals and other clinical settings, it is not surprising that such tests are often used to assess the efficacy of exercise interventions aimed at improving mobility and/or preventing falls in people with PD [61]. Despite their widespread use for the assessment of people with PD [264], research suggests that some of these clinical tests are not always able to identify differences in mobility between people with PD and age-matched controls [207, 252]. Therefore, while the Timed Up and Go and 6-meter walk tests are widely acceptable as clinical tests of mobility, a need exists for further investigations to determine whether such clinical tests have the capacity to identify changes in postural stability in people with PD.

The improved availability and affordability of wearable sensors have now made it feasible to develop and/or enhance clinical assessments to incorporate more objective measures of walking stability. For example, the objectivity of the assessment can be significantly improved by placing a wearable sensor on a patient's body during the performance of the Timed Up and Go test [252]. Specifically, research using this adaptation of the Timed Up and

Go test has reported differences in the amplitude, symmetry, and smoothness of segmental motion (as measured using RMS accelerations, harmonic ratios and jerk, respectively) for people with PD compared with age-matched controls [187]. Of the numerous accelerometer-based outcomes reported in the literature, the harmonic ratio (HR) is the most commonly reported for people with PD [104] and provides a measure of gait symmetry by assessing the ratio of in-phase accelerations to out-of-phase accelerations within a given gait cycle [164]. Additionally, the HR has the capacity to discriminate PD patients with a history of falling from patients who have not previously fallen [129]. Despite its frequent use in the research setting, more traditional tests of mobility continue to be used in daily clinical practices. As such, this study aimed to determine whether the results of common clinical tests of mobility, balance confidence and gait difficulty correlate with laboratory-based measures of postural stability to determine whether these assessments offer insight into deficits in postural stability for people with PD. It was hypothesised that clinical measures of mobility, gait difficulty, postural stability, and balance confidence would not be related to movement symmetry and, therefore, offer limited insight into dynamic postural stability.

7.3 Methods

7.3.1 Participants

Thirty participants diagnosed with idiopathic PD, based on the UK Brain Bank Criteria were recruited and screened for eligibility via the methods outlined in Section 6.1. Following the assessment of cognitive function, it was determined that one of the participants achieved a score of 68 out of 100 on the revised Addenbrooke's Cognitive Examination. Given that scores of less than 82 are predictive of cognitive impairment [162], this participant was not required to complete the remaining assessments and was excluded from the experiment. Of the remaining 29 patients (Table 5), 5 reported no history of falls or near misses within the previous

12 months, while 24 reported experiencing at least one falls and/or two or more near misses in past year. For the purposes of this study, a fall was defined as "any coming to the ground or other lower level not as the result of a major intrinsic event or overwhelming hazard" [6]. Similarly, a near miss was defined as "an event on which an individual felt that they were going to fall but did not actually do so" [6]. Experimental procedures were approved by the University's Human Research Ethics Committee and all volunteers provided written informed consent to participate (Appendix D). An a-priori sample size calculation based on a p-value of 0.05, a power of 80% and a large effect size (ρ=0.6) indicated that at least 13 participants were required per group to examine the relationships between the clinical tests and harmonic ratios.

7.3.2 Clinical Assessments

Individuals attending a single testing session during which they completed the battery of clinical tests outlined in Section 6.2, which included assessments of vision, cognition, disease stage and symptom severity (UPDRS III, H&Y stage score, Schwab and England Activities of Daily Living Scale; PD Gait and Falls Questionnaire); balance confidence (the ABC scale); and quality of life (PDQ-39). Using the data collected during the assessment of motor symptoms, a clinical measure of postural instability and gait disability was calculated for each participant by summing the scores for items 27 to 30 from the UPDRS III [181]. In addition to these clinical questionnaires, participants were also asked to perform 5 trials of the Timed Up and Go test while being timed by the experimenter. The preparation and procedures implemented for the Timed Up and Go test are outlined in Section 6.2.4 and illustrated diagrammatically in Figure 6.

Table 5: Demographics and results for the assessments of mobility, balance confidence, quality of life and symptom severity for the Mild and Moderate PD groups.

	All PD (n = 29)	Mild PD (n = 13)	Moderate PD (n = 16)	Test	p-value
Demographics					
Male	21 (72.4%)	8 (61.5%)	13 (81.3%)	3	0.238
Age (years)	64.7 ± 6.4	62.8 ± 7.1	66.3 ± 5.4	1	0.147
Height (cm)	171.7 ± 8.0	170.6 ± 8.9	172.6 ± 7.3	1	0.504
Mass (kg)	80.4 ± 20.1	78.8 ± 20.2	81.7 ± 20.7	1	0.709
Body Mass Index (kg/m^2)	27.0 ± 5.3	26.8 ± 5.1	27.2 ± 5.6	1	0.853
Cognition and Vision					
Addenbrooke's Cognitive Exam	91.7 ± 6.1	92.5 ± 5.2	91.1 ± 6.8	1	0.527
High Contrast Visual Acuity (LogMAR)	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	2	0.475
Balance Confidence and Quality of Life					
Previous Fallers	23 (79.3%)	11 (84.6%)	12 (75.0%)	3	0.525
Previous Falls	1.4 ± 2.0	1.2 ± 1.5	1.6 ± 2.4	2	0.846
Activities-specific Balance Confidence (%)	77.8 ± 24.8	93.2 ± 6.6	65.4 ± 27.4	2	**<0.001**
39-Item Parkinson's Disease Questionnaire	23.5 ± 15.3	14.9 ± 6.9	30.4 ± 16.9	2	**0.001**
Mobility					
Timed Up and Go Total Time (s)	9.4 ± 1.5	9.0 ± 1.2	9.8 ± 1.7	1	0.202
6-Meter Walk Test (s)	4.7 ± 0.6	4.8 ± 0.5	4.7 ± 0.7	1	0.647
Neurological Examination					
Disease Duration (years)	6.7 ± 5.3	4.9 ± 1.1	8.1 ± 6.8	2	0.288
Unified Parkinson's Disease Rating Scale (Part III)	14.4 ± 11.5	9.1 ± 2.3	18.8 ± 14.1	2	**0.004**
Hoehn & Yahr Stage Score	1.7 ± 0.7	1.0 ± 0.0	2.2 ± 0.4	2	**<0.001**
Schwab & England Activities of Daily Living Scale	86.6 ± 7.5	90.0 ± 4.1	83.8 ± 8.5	2	0.056
Freezing of Gait Score	4.9 ± 5.2	2.7 ± 2.9	6.7 ± 6.0	2	**0.040**
Postural Instability and Gait Disorder Score	1.9 ± 1.6	0.8 ± 1.0	2.7 ± 1.6	2	**0.002**
Retropulsion Test	0.5 ± 0.7	0.2 ± 0.4	0.8 ± 0.9	2	0.083
Levodopa (mg/day)	618.3 ± 432.1	545.2 ± 350.7	677.8 ± 491.7	1	0.421
Dopamine Agonists	6 (20.7%)	2 (15.4%)	4 (25.0%)	3	0.468
Catechol-O-Methyl Transferase Inhibitors	9 (31.0%)	4 (30.8%)	5 (31.3%)	3	0.885
Monoamine Oxidase Inhibitors	10 (34.5%)	3 (23.1%)	7 (43.8%)	3	0.194
Benzodiazepine	1 (3.4%)	1 (7.7%)	0 (0.0%)	3	0.274

Note: Test 1 = One-way analysis of variance; Test 2 = Mann-Whitney U test; Test 3 = Chi-square test

7.3.3 Objective Gait Assessment

Following the completion of the clinical assessments, the 29 participants completed four gait trials along a 10-meter walkway at a comfortable and self-selected pace. Participants were given a minimum of 30 seconds rest between trials to minimise the risk of fatigue. During this task, gait speed was measured with the Speedlight timing system (SWIFT Performance Equipment, Alstonville, Australia), which comprised two pairs of gates that were positioned 6 meters apart (Figure 7). Gait speed has been shown to influence accelerometer-based measures, like the harmonic ratio [130], therefore, gait speed was collected to facilitate adjustments for

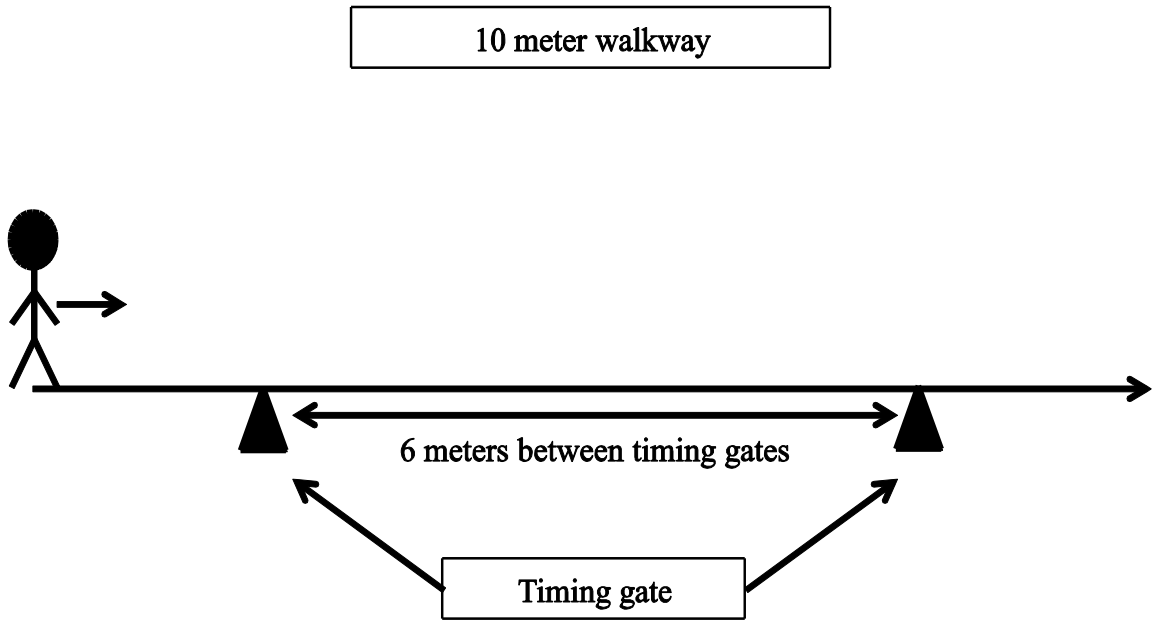

Figure 7: Set-up of walkway for assessment of gait

gait speed. Two microelectromechanical three-dimensional accelerometers sampling as a rate of 500 Hz (Noraxon Inc., Scottsdale, AZ) were used to assess gait symmetry. Prior to commencing data collection the two accelerometers were statically calibrated using methods that have been described previously [165]. Specifically, the calibration procedure involved aligning each sensing axis of the accelerometers perpendicular to a horizontal surface to determine a conversion factor describing the magnitude of gravitational acceleration (1 gravitational unit or 1g). Accelerometers have been shown to have moderate to excellent

concurrent [34, 44, 92, 260] and construct validity [53] and moderate to excellent test-retest reliability [34, 81, 123] when placed on the trunk to assess gait in younger [44, 81, 260] and older adults [34, 44, 53, 81, 92], as well as people with knee osteoarthritis [123] and Parkinson's disease [53].

Following static calibration, an accelerometer was firmly attached over the occipital protuberance of the skull via a sport headband, while another was attached directly to the skin over the spinous process of the 10th thoracic vertebra (T10) using double-sided tape and Micropore (Figure 8). It is well understood that movement of the soft-tissue beneath an accelerometer can contribute to the introduction of accelerations that are not specifically related to the movement of interest [155]. As both the occipital protuberance and the spinous processes are typically not masked by thick layers of soft tissue, these sites were considered optimal for minimising the risk of introducing this error. Furthermore, the results of Study 1 provided support for these placements for accelerometer-based assessments of postural stability [104].

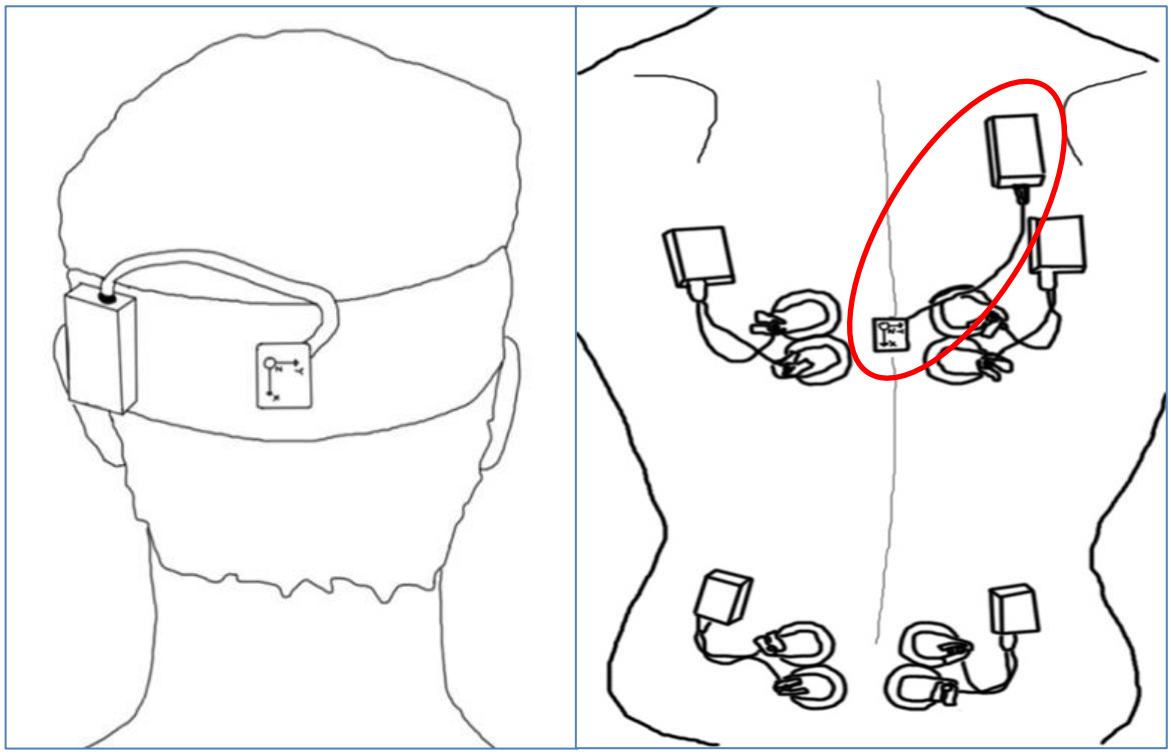

Figure 8: Positioning of the head and trunk accelerometers

7.3.4 Data Analysis

Following data collection, raw accelerations were transformed to a horizontal-vertical orthogonal coordinate system [164]. Transformation of the data was necessary because accelerometers measurements occur relative to a local rather than global coordinate system. The sensor may deviate from the horizontal plane due to inaccurate placement or curvature of the spine or the bony landmark to which it is attached. This tilt in the sensor not only detects the dynamic movement acceleration, but also registers the effects of gravity, which must be corrected for in acquiring a true estimate of the movement accelerations [164]. After transforming the data to a horizontal-vertical orthogonal coordinate system (Figure 9A), accelerations were low-pass filtered using a bi-directional fourth order Butterworth filter, with a cut-off frequency of 30 Hz as used in previous research [116, 117]. Given that 99% of accelerations during walking occur below 15 Hz [155], a cut-off frequency of 30 Hz was considered adequate to capture walking related activity and limit higher frequencies not related to movement. Filtered and transformed accelerations for the anterior-posterior, medial-lateral, and vertical axes were then used to derive the accelerometer-based outcomes for the head and trunk segments, separately. Specifically, the accelerometer-based measures included: i) the harmonic ratio and ii) root mean square (RMS) accelerations, both of which were shown to be suitable for assessing postural stability during dynamic tasks in Study 1 [104].

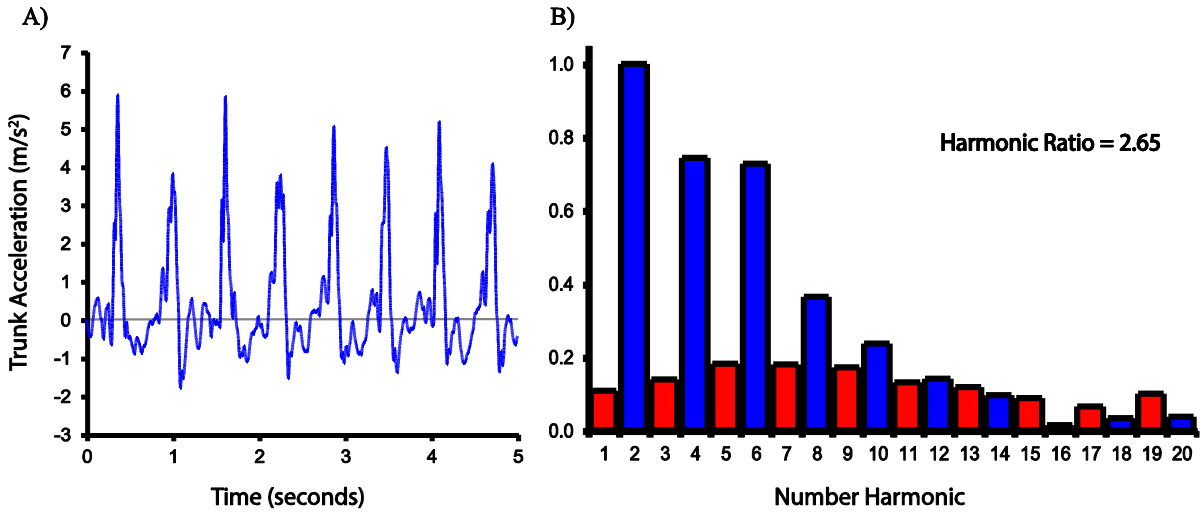

Figure 9: Example of the A) vertical trunk acceleration; and B) first 20 harmonics of the signal.

In order to calculate the harmonic ratio, the time-series data were divided into individual gait cycles by identifying the positive peaks in the vertical trunk accelerations, which coincided with heel contact [129, 137, 138, 160]. Using a custom Matlab program (version R2015), anterior-posterior, medial-lateral and vertical harmonic ratios were calculated for four consecutive gait cycles identified within the central portion of each walking trial. To facilitate this, the transformed anterior-posterior, medial-lateral and vertical accelerations were converted from the time domain to the frequency domain using a Finite Fourier Transformation. Following this transformation, the harmonics of the fundamental frequencies of the signals are plotted to show the in-phase (or even) harmonics and the out-of-phase (or odd) harmonics (Figure 9B).

As the harmonic ratio is calculated over the course of a gait cycle, two subsequent heel strikes with the same foot (e.g. right foot) are separated by an inter-mediate step with the alternate foot (e.g. left foot). Given each gait cycle includes two steps, the harmonics of the anterior-posterior and vertical accelerations occur in multiples of two, which would normally contribute to much higher values for the even harmonics in healthy gait. Given this point, calculation of the anterior-posterior and vertical harmonic ratios involves dividing the sum of the first 10 even harmonics by the sum of the first 10 odd harmonics [160]. This yields a ratio of the in-phase to out-of-phase harmonics and provides insight into the degree of symmetry within the three-dimensional head and trunk acceleration profiles. Given the nature of this calculation, larger numbers are representative of more symmetrical movements, while lower numbers indicate less symmetrical movements [13]. In contrast to anterior-posterior and vertical accelerations, medial-lateral accelerations during a gait cycle are characterised by a change in direction approximately mid-stride, as the body's weight is shifted from the left to right foot (or vice versa). As such, the odd harmonics represent the in-phase accelerations and are generally of higher amplitude than the even harmonics for the medial-lateral accelerations of healthy walking. To derive the ML

harmonic ratio, it was necessary to divide the sum of the first 10 odd harmonics by the sum of the first 10 even harmonics within the chosen stride [160].

$$RMS\ Acceleration_j = \sqrt{\frac{\sum_{i=j-w}^{j+w} acceleration_{index(i)}^2}{2w+1}}$$

Where: j = the output index

w = the window size

index(i) = i if first_index ≤ i ≤ last_index

index(i) = first_index if i < first_index

index(i) = last_index if i > first_index

Equation 1

In addition to the harmonic ratio, root mean square (RMS) accelerations were also calculated as a secondary outcome measure for the head and the trunk (Equation 1). The results of Study 1 indicated that there was a need for further research to determine the utility of RMS accelerations for the assessment of postural stability in people with PD [104].

7.3.5 Statistical Analysis

Data were sub-divided based on each patient's H&Y stage score. Patients with mild symptoms affecting one side of the body only (H&Y Stage 1) were combined to form a Mild PD group, while data for patients presenting with Mild (H&Y Stage 2) to Moderate (H&Y Stage 3) bilateral symptoms were combined to form a Moderate PD group. The outcome measures for each group were assessed for normality and homogeneity of variance and the groups were statistically contrasted using the procedures outlined in Section 6.3.

Bivariate correlations were used to establish the degree of association between the clinical tests of mobility and stability and the laboratory-based measures of gait symmetry. To

determine the appropriateness of the parametric Pearson's correlation coefficient, the normality of the continuous measures was assessed using the Shapiro-Wilk test and where a p-value of less than 0.05 was returned, the non-parametric Spearman's Rho test was used. Linear regression analyses examined whether clinical measures of mobility, postural stability, balance confidence and gait difficulty were capable of explaining a significant proportion of the variance in head and trunk rhythmicity during walking. Statistical analyses were performed in Statistical Package for the Social Sciences (SPSS v.22, New York, USA) and the level of statistical significance was set at $p<0.05$.

7.4 Results

In accordance with the strict inclusion and exclusion criteria adhered to throughout the participant recruitment phase, all participants were free of any significant medical conditions (other than PD) that may have influence their balance and/or gait and presented with no significant physical, psychological or visual disabilities at the time of testing. Based on the neurological assessment, the 29 patients included in this study had mild to moderate symptoms of PD, were independently living and most (90%) were taking anti-parkinsonian medication. Patients comprising the Moderate PD group were shown to have more severe motor symptoms ($p=0.004$) and reported poorer balance confidence ($p<0.001$), poorer quality of life ($p<0.001$), a greater incidence of freezing of gait ($p=0.040$) and increased postural instability and gait difficulty ($p=0.002$) compared with the Mild PD group (Table 5).

7.4.1 Correlation Analyses

Tests of normality indicated a number of the continuous outcome measures were not normally distributed; hence the non-parametric Spearman's Rho test was used to assess the relationships between the clinical tests and the accelerometer-based measures of gait symmetry

(Table 6). For the whole PD sample, previous falls were positively correlated with the gait and falls questionnaire (ρ=0.508, p=0.005) and negatively correlated with the 6-meter walk time (ρ=-0.466, p=0.011), as well as all harmonic ratios for the head (ρ=-0.448 to -0.513, p≤0.02) and trunk (ρ=-0.437 to -0.623, p≤0.02). The sub-group analyses indicated these relationships were further strengthened for the Moderate PD patients, when patients with milder symptoms were considered separately. Specifically, the bivariate correlations revealed that previous falls were moderately and positively correlated with gait and falls difficulty (ρ=0.600, p=0.014) and moderately and negatively correlated with 6-meter walk time (ρ=-0.531, p=0.034) in addition to all head (ρ=-0.537 to -0.693, p≤0.05) and most trunk (ρ=-0.595 to -0.766, p≤0.015) harmonic ratios. In contrast, the number of previous falls was moderately and positively correlated with balance confidence (ρ=0.555, p=0.049) and moderately and negatively correlated with AP trunk rhythmicity (ρ=-0.611, p=0.027) for the Mild PD patients.

Analysis of the two mobility assessments demonstrated that the 6-meter walk time was negatively correlated with gait speed (ρ=-1.000, p<0.001) and positively correlated with the Timed Up and Go total time (ρ=0.519, p=0.004) and medial-lateral head HR (ρ=0.416, p=0.025). The sub-group analyses showed that the 6-meter walk time was moderately and positively correlated with Timed Up and Go total time (ρ=0.624, p=0.010) for the Moderate PD group, while ML head rhythmicity was moderately and positively correlated with the 6-meter walk time (ρ=0.573, p=0.041) for the Mild PD group. For the whole PD cohort, the Timed Up and Go total time was negatively correlated with gait speed (ρ=-0.519, p=0.004) and balance confidence (ρ=-0.565, p=0.001), but the sub-group analyses revealed that these relationships only remained significant for the Moderate PD group (gait speed: ρ=-0.624, p=0.010; ABC: ρ=-0.708, p=0.002).

Similar to clinical tests of mobility, the retropulsion test was negatively correlated with balance confidence (ρ=-0.595, p=0.001) and positively associated with the Gait and Falls

questionnaire (ρ=0.434, p=0.019). Additionally, the Gait and Falls questionnaire was moderately and negatively correlated with balance confidence (ρ=-0.555, p=0.002) and AP trunk movement symmetry (ρ=-0.425, p=0.022). The sub-group analyses indicated that the retropulsion test was moderately and negatively correlated with balance confidence (ρ=-0.652, p=0.006) and AP head movement symmetry (ρ=-0.499, p=0.049) for the Moderate PD group. Furthermore, for the Moderate PD group, the gait and falls questionnaire was moderately and negatively correlated with balance confidence (ρ=-0.521, p=0.038) and most head (ρ=-0.526 to -0.538, $p<0.05$) and all trunk (ρ=-0.510 to -0.642, $p<0.05$) HRs. No other relationships were observed between the questionnaires and the objective measures of walking stability (Table 6).

Table 6: Correlation between the harmonic ratios and clinical assessments of balance and mobility for the entire PD cohort and the Mild and Moderate sub-groups

			All PD		Mild PD		Moderate PD	
			Spearman's Rho	**p-value**	**Spearman's Rho**	**p-value**	**Spearman's Rho**	**p-value**
Retrospective Falls	6-Meter Walk Time		**-0.466**	**0.011***	-0.344	0.250	**-0.531**	**0.034***
	Timed Up and Go Total Time		-0.169	0.381	-0.194	0.526	-0.193	0.474
	Retropulsion Test		0.008	0.965	0.077	0.802	0.055	0.839
	Gait & Falls Questionnaire		**0.508**	**0.005***	0.274	0.365	**0.600**	**0.014***
	Activities-Specific Balance Confidence Scale		0.039	0.839	**0.555**	**0.049***	0.038	0.889
	Harmonic Ratio (Head)	AP	**-0.465**	**0.011***	-0.521	0.068	**-0.537**	**0.032***
		ML	**-0.448**	**0.015***	-0.320	0.286	**-0.579**	**0.019***
		VT	**-0.513**	**0.004***	-0.436	0.137	**-0.693**	**0.003***
	Harmonic Ratio (Trunk)	AP	**-0.524**	**0.004***	**-0.611**	**0.027***	-0.430	0.097
		ML	**-0.437**	**0.018***	-0.272	0.369	**-0.595**	**0.015***
		VT	**-0.623**	**<0.001***	-0.436	0.137	**-0.766**	**0.001***
6-Meter Walk Time	Gait Speed		**-1.000**	**<0.001***	**-1.000**	**<0.001**	**-1.000**	**<0.001***
	Timed up and Go Total Time		**0.519**	**0.004***	0.287	0.343	**0.624**	**0.010***
	Retropulsion Test		0.082	0.672	-0.286	0.344	0.268	0.315
	Gait & Falls Questionnaire		-0.134	0.487	-0.034	0.913	-0.158	0.560
	Activities-Specific Balance Confidence Scale		-0.197	0.307	-0.228	0.453	-0.474	0.064
	Harmonic Ratio (Head)	AP	0.163	0.397	0.571	0.571	0.174	0.520
		ML	**0.416**	**0.025***	**0.573**	**0.041***	0.365	0.165
		VT	0.035	0.857	0.174	0.571	-0.026	0.922
	Harmonic Ratio (Trunk)	AP	0.020	0.918	0.025	0.936	0.038	0.888
		ML	0.313	0.099	0.446	0.126	0.194	0.471
		VT	0.003	0.988	0.209	0.492	-0.091	0.737

Timed Up and Go Total	Gait Speed		**-0.519**	**0.004***	-0.287	0.343	**-0.624**	**0.010***
	Retropulsion Test		0.320	0.091	-0.171	0.577	0.413	0.112
	Gait & Falls Questionnaire		0.352	0.061	0.539	0.058	0.257	0.336
	Activities-Specific Balance Confidence Scale		**-0.565**	**0.001***	-0.472	0.104	**-0.708**	**0.002***
		AP	0.358	0.057	0.440	0.133	0.035	0.897
	Harmonic Ratio (Head)	ML	0.326	0.084	0.225	0.459	0.169	0.531
		VT	0.297	0.118	0.324	0.280	0.107	0.692
		AP	0.053	0.783	0.280	0.354	-0.187	0.488
	Harmonic Ratio (Trunk)	ML	0.278	0.145	0.473	0.103	-0.075	0.782
		VT	0.110	0.570	0.110	0.721	-0.097	0.720
Retropulsion Test	Gait Speed		-0.082	0.672	0.286	0.344	-0.268	0.315
	Gait & Falls Questionnaire		**0.434**	**0.019***	0.087	0.777	0.349	0.185
	Activities-Specific Balance Confidence Scale		**-0.595**	**0.001***	-0.143	0.641	**-0.652**	**0.006***
		AP	-0.297	0.118	-0.285	0.345	**-0.499**	**0.049***
	Harmonic Ratio (Head)	ML	-0.143	0.458	-0.513	0.073	-0.422	0.104
		VT	0.119	0.540	-0.057	0.853	-0.051	0.851
		AP	-0.102	0.597	0.342	0.253	-0.275	0.303
	Harmonic Ratio (Trunk)	ML	0.089	0.645	0.228	0.454	-0.173	0.523
		VT	0.116	0.550	0.114	0.711	-0.064	0.814
Gait & Falls	Gait Speed		0.134	0.487	0.034	0.913	0.158	0.560
	Activities-Specific Balance Confidence Scale		**-0.555**	**0.002***	0.007	0.982	**-0.521**	**0.038***
		AP	-0.176	0.360	0.067	0.827	**-0.526**	**0.036***
	Harmonic Ratio (Head)	ML	-0.107	0.579	0.079	0.799	**-0.538**	**0.032***
		VT	-0.042	0.828	0.163	0.595	-0.496	0.051
		AP	**-0.425**	**0.022***	-0.115	0.708	**-0.642**	**0.007***
	Harmonic Ratio (Trunk)	ML	-0.201	0.296	0.129	0.674	**-0.510**	**0.044***
		VT	-0.267	0.162	0.022	0.942	**-0.638**	**0.008***

Activities-Specific	Gait Speed		0.197	0.307	0.228	0.453	0.474	0.064
Confidence Scale		AP	-0.119	0.540	0.025	0.936	-0.032	0.905
	Harmonic Ratio (Head)	ML	-0.256	0.181	0.014	0.964	0.159	0.557
		VT	-0.322	0.088	0.061	0.844	-0.291	0.274
		AP	-0.014	0.944	-0.505	0.078	0.126	0.641
	Harmonic Ratio (Trunk)	ML	-0.209	0.277	-0.356	0.233	-0.153	0.572
		VT	-0.158	0.414	0.168	0.583	-0.112	0.680

AP = Anterior-posterior, ML = Medial-lateral, VT = Vertical, * = Significant correlation

7.4.2 Regression Analysis

The linear regression analyses performed for the entire PD cohort indicated that, of all of the clinical assessments conducted, the 6MWT and ABC scale were the only tests able to predict any component of head or trunk movement symmetry. Specifically, the 6MWT predicted medial-lateral head HRs ($p=0.041$) and the ABC scale predicted vertical head HRs ($p=0.032$). Similar results were found for the regression analyses that was conducted for the two sub-groups; with the 6MWT predicting medial-lateral head HRs ($p=0.036$) for the Mild PD group and the Activities-specific Balance Confidence scale predicted anterior-posterior trunk HRs ($p=0.012$) and vertical head HRs ($p=0.047$) for the Mild and Moderate PD groups, respectively (Table 7).

Table 7: Linear regressions for the harmonic ratios and clinical assessments of balance and mobility for the entire PD cohort and the Mild and Moderate sub-groups

		All PD			Mild PD			Moderate PD		
		Unstandardized beta (B)	**Standardised Beta (β)**	**p-value**	**Unstandardized beta (B)**	**Standardised Beta (β)**	**p-value**	**Unstandardized beta (B)**	**Standardised Beta (β)**	**p-value**
Retrospective Falls										
	AP	-0.499	-0.179	0.354	-0.668	-0.316	0.293	-0.491	-0.153	0.572
Harmonic Ratio (Head)	ML	-0.478	-0.164	0.395	-0.301	-0.125	0.683	-0.787	-0.236	0.379
	VT	-0.671	-0.271	0.155	-0.469	-0.287	0.342	-1.074	-0.331	0.211
	AP	-0.755	-0.238	0.214	-0.868	-0.352	0.239	-0.671	-0.191	0.479
Harmonic Ratio (Trunk)	ML	-0.437	-0.135	0.486	-0.218	-0.100	0.746	-0.729	-0.181	0.502
	VT	-0.683	-0.321	0.089	-0.506	-0.319	0.288	-0.934	-0.374	0.154
6-Meter Walk Time										
	AP	0.121	0.154	0.424	0.148	0.222	0.465	0.142	0.160	0.553
Harmonic Ratio (Head)	ML	**0.348**	**0.382**	**0.041***	**0.500**	**0.585**	**0.036***	0.423	0.398	0.127
	VT	0.064	0.086	0.657	0.160	0.299	0.322	-0.003	-0.003	0.993
	AP	0.036	0.183	0.846	0.030	0.040	0.897	0.040	0.037	0.892
Harmonic Ratio (Trunk)	ML	0.237	0.238	0.214	0.296	0.404	0.171	0.224	0.180	0.504
	VT	0.005	0.008	0.966	0.177	0.330	0.270	-0.076	-0.110	0.684
Timed Up and Go Total										
	AP	0.663	0.363	0.053	0.676	0.459	0.115	0.535	0.265	0.321
Harmonic Ratio (Head)	ML	0.577	0.272	0.153	0.263	0.139	0.651	0.547	0.226	0.400
	VT	0.516	0.301	0.113	0.255	0.215	0.482	0.664	0.291	0.274
	AP	0.036	0.016	0.933	0.413	0.246	0.418	-0.256	-0.104	0.701
Harmonic Ratio (Trunk)	ML	0.713	0.309	0.103	0.817	0.503	0.080	0.423	0.149	0.581
	VT	0.302	0.214	0.265	0.138	0.116	0.705	0.273	0.174	0.519

Retropulsion Test										
	AP	-0.243	-0.271	0.155	-0.128	-0.267	0.378	-0.491	-0.483	0.058
Harmonic Ratio (Head)	ML	-0.124	-0.199	0.538	-0.259	-0.419	0.154	-0.402	-0.330	0.212
	VT	0.085	0.101	0.603	0.028	-0.072	0.815	-0.007	-0.006	0.982
	AP	-0.107	-0.098	0.612	0.153	0.280	0.354	-0.308	-0.249	0.352
Harmonic Ratio (Trunk)	ML	0.059	0.052	0.790	0.044	0.084	0.785	-0.109	-0.077	0.778
	VT	0.051	0.074	0.703	0.020	0.053	0.864	-0.069	-0.087	0.748
Gait & Falls Questionnaire										
	AP	-3.309	-0.207	0.282	0.238	0.052	0.866	-8.161	-0.449	0.081
Harmonic Ratio (Head)	ML	-2.575	-0.154	0.425	0.765	0.147	0.631	-8.745	-0.465	0.070
	VT	-0.774	-0.055	0.779	0.557	0.158	0.607	-5.408	-0.295	0.268
	AP	-6.204	-0.341	0.071	-0.096	-0.018	0.954	-9.312	-0.469	0.067
Harmonic Ratio (Trunk)	ML	-3.315	-0.178	0.355	0.180	0.038	0.902	-8.699	-0.383	0.143
	VT	-2.140	-0.175	0.363	-0.402	-0.117	0.703	-5.602	-0.397	0.127
Activities-Specific Balance Confidence Scale										
	AP	-6.767	-0.199	0.300	-3.088	-0.329	0.272	-3.881	-0.108	0.691
Harmonic Ratio (Head)	ML	-9.947	-0.281	0.140	-4.230	-0.397	0.180	-4.687	-0.126	0.642
	VT	**-12.013**	**-0.399**	**0.032***	-0.922	-0.127	0.679	**-18.297**	**-0.504**	**0.047**
	AP	-6.616	-0.171	0.374	**-7.332**	**-0.669**	**0.012***	-7.555	-0.192	0.475
Harmonic Ratio (Trunk)	ML	-6.457	-0.164	0.395	-4.123	-0.424	0.149	-4.191	-0.093	0.731
	VT	-8.144	-0.315	0.096	-0.745	-0.106	0.731	-8.898	-0.319	0.229

AP = Anterior-posterior, ML = Medial-lateral, VT = Vertical, * = Significant linear predictor

7.5 Discussion

The purpose of this study was to examine whether common clinical tests of mobility, postural stability, balance confidence and gait difficulty were capable of providing insight into walking stability in people with PD. Overall, the results indicated that individuals with moderate disease severity reported experiencing poorer balance confidence, greater postural instability and gait difficulty and poorer quality of life than patients with milder symptoms. However, the Moderate and Mild PD groups showed similar results from ANOVA tests for between-group differences for the clinically-administered assessments, including the retropulsion test, Timed Up and Go and 6MWT. Similar findings were evident for the correlation analyses, which indicated that the outcomes of the clinically-administered tests were not correlated with the measures of head and trunk movement symmetry. However, patients in the Moderate PD group who reported a greater number of previous falls and/or greater difficulties with gait and falls did record poorer head and trunk movement symmetry than patients with milder symptoms. These findings were similar to previous research showing PD fallers with moderate symptoms had poorer head and pelvis rhythmicity during gait than patients with milder symptoms who had not previously fallen [129].

Collectively, these findings suggest that clinical measures of balance, mobility, gait difficulty and balance confidence may not provide the most thorough insight into the walking rhythmicity of individuals with milder symptoms. However, for patients with more advanced symptoms, assessments relying more on a patient's self-reported difficulties may offer better insight into the gait rhythmicity of these patients. These findings appear to have important clinical implications and suggest that objectively evaluating patients' mobility without considering their perceived difficulties may inadvertently result in important information regarding falls risk being overlooked. Nevertheless, it is widely recognised that self-report assessments can be limited by the potential bias associated with patients over- or under-

reporting their difficulties. Hence more objective tests would greatly benefit the clinical assessment of postural stability in people with mild symptom severity of PD.

The retropulsion test is among the most commonly used clinical assessment of postural stability for people with PD and is incorporated into the motor sub-section of the UPDRS [71]. Despite widespread use and an apparent capacity to assess a patient's stability under static conditions, a major limitation lies in the inability to discriminate PD fallers from non-fallers [251] or single fallers from recurrent fallers in cohorts with and without PD [20]. While the findings largely agreed with these studies, it is important to highlight that the retropulsion test was significantly correlated with anterior-posterior head rhythmicity in individuals with moderate symptom severity. Given the retropulsion test examines a patient's postural response to a firm backward pull on their shoulders, it is perhaps not surprising that individuals scoring more poorly on the retropulsion test also demonstrated poorer anterior-posterior head control during gait (i.e. lower anterior-posterior head HRs).

The poor relationship between the retropulsion test and the continuous measures of head and trunk symmetry may be explained, at least in part, by a number of factors. First, the retropulsion test is somewhat limited by its use of a Likert scale that ranges from zero (normal response) to four (unable to stand without assistance). Specifically, for a patient's score to change from a zero to a one for the retropulsion test, he/she must demonstrate a retropulsive gait pattern and recover without assistance. Given the marked heterogeneity of PD symptoms, it is very likely that some patients will develop difficulties that affect their gait and balance, but do not manifest in the form of a retropulsive gait pattern during this test. A second factor potentially influencing the applicability of the retropulsion test to dynamic situations could be that quiet stance rather than under dynamic conditions is used assesses postural stability. Given that only 32% of falls occur during standing [7], it is possible that the retropulsion test may be

limited in its capacity to explain the factors contributing to the 66% of falls that occur during ambulation and transfer events [7].

Another major finding of this study was that the number of previous falls experienced by patients in the Mild PD group was significantly and positively correlated with balance confidence; suggesting that individuals who fell more had greater balance confidence. This finding is in contrast with a growing body of literature that supports the use of the Activities-specific Balance Confidence scale for assessing balance confidence in people with PD and for identifying patients at an increased risk of future recurrent falls [147, 149]. While the uncharacteristically high balance confidence reported for individuals in the Mild PD group may have been influenced by their higher level of motor functioning (i.e. lower UPDRS III scores) and the improved quality of life reported for these patients, it remains unclear what attributes of the disease most influence individuals' perceived risk of falling. As such, a future need exists to examine how self-reported balance confidence changes with disease progression and to establish what symptoms are most likely to influence a fear of falling.

As with any study, our results should be considered in the context of a number of limitations. First, our sample size, particularly once stratified based on disease severity, may be considered quite small from a statistical perspective. While the two groups were at least the size of the minimum group size determined in our a-priori sample size calculation, further research involving larger cohorts would be warranted. Second, the patients involved in this study were typically of mild to moderate disease severity (Hoehn & Yahr stages 1 to 3), hence the transferability of our findings may be limited to similar patient cohorts. The potential biases in self-reported recall is also acknowledged but were justified within the need to more closely examine typical clinical assessments. Longitudinal or cohort studies of changing risks and symptoms would better improve the information available from the tests used in this study using a cross-sectional design. Third, this study presents the results of a relatively large number

of correlations and linear regressions, which may increase the risk of identifying a statistically significant relationship where one does not truly exist (i.e. Type 1 error). Nevertheless, all p-values have been reported within the tables and these should be considered when interpreting the clinical meaningfulness of the reported outcomes. Finally, it should be acknowledged that there are a number of other stability measures that can be derived from accelerometer data, which have not been examined as part of this research. As these alternate measures would not be expected to share the same relationships with the clinical measures presented in this study, the reported findings should be considered specific to the harmonic ratio.

Nevertheless, the findings of this study suggest that existing clinical tests of mobility, postural stability, balance confidence and gait difficulty typically provide little insight into movement symmetry in individuals with mild symptom severity. In contrast, the Gait and Falls questionnaire and knowledge of the patient's falls history may provide additional insight into head and trunk symmetry in individuals with moderate symptom severity. However, given that these measures rely on accurate patient recall, the development and implementation of objective and clinically-feasible measures of postural instability and gait disability would help to improve the monitoring and management of postural instability and gait disability in people with PD.

8.0 Study 3: Exercise improves postural sway in Parkinson disease: A blind phase II randomised-controlled trial

As hypothesized, the results of Study 2 suggested that a large number of common clinical assessments of balance, mobility, balance confidence and gait disability may not be capable of providing significant insight into changes in postural stability during dynamic tasks. Building on these findings, Study 3 adopted a randomised controlled trial design to investigate whether a 12-week exercise-based intervention that targeted enhanced mobility and endurance of the trunk was effective at improving a patient's postural stability during static tasks. Given the outcomes of Study 2, this study was designed to incorporate both clinical assessments of postural stability and more continuous measures of postural control to ensure that any small, yet clinically-relevant changes in a patient's function could be identified.

8.1 Abstract

Background: The trunk is important in maintaining postural stability during static and dynamic situations. People with Parkinson's disease (PD) have reported deficits in trunk control that may contribute to poor postural stability in this population. Furthermore, symptoms of postural instability are relatively unresponsive to anti-parkinsonian medication and neurological surgery. Considering the deficits in control trunk control and its importance in maintaining stability, the objective of this study was to investigate the effects of a 12-week trunk-specific exercise program on postural sway in people with PD.

Methods: Twenty-four PD patients with a history of falls completed baseline assessments of symptom severity, fear of falling, mobility and quality of life. Postural sway was analysed with a portable force platform. Following baseline testing, participants were randomised to receive either 12-weeks of exercise or education. Baseline tests were repeated 12 and 24-weeks following baseline. This trial is listed with the Australian New Zealand Clinical Trials Registry (ACTRN12613001175763).

Results: Linear mixed model analyses showed no significant changes in clinical variables. The Exercise group reduced postural sway on a foam surface without vision at the 12 and 24-week time points ($p \leq 0.003$) compared with baseline values. The education group saw a significant increase in postural sway on the foam surface without vision ($p=0.02$) and a decrease in sway length with vision ($p=0.03$) at the 12-week follow-up compared with baseline values. The exercise group reduced the standard deviation of medial-lateral ($p=0.006$) and anterior-posterior ($p=0.04$) centre of pressure postural sway variability 12-weeks following baseline, and the standard deviation of medial-lateral sway variability 24-weeks ($p=0.005$) post baseline,

and the exercise group maintained improvements in the standard deviation of anterior-posterior postural sway variability at the 24-week follow-up (p=0.04).

Conclusion: Scores on clinical assessment of symptom severity, balance, mobility and balance confidence did not significantly change following the 12-week exercise-based intervention, suggesting that they may lack the sensitivity to detect small, but clinically meaningful changes in function. In contrast, standard posturography assessment demonstrated that those patients who received the 12-week trunk-specific exercise program had significantly less postural sway following the intervention when conditions were most challenging (i.e. when vision and proprioception were impaired).

8.2 Introduction

While the maintenance of postural stability relies on the effective regulation and coordination of all body segments, the combined mass of the head and trunk (approximately 60% of the body's mass [257]) highlights the importance of these segments to the maintenance of equilibrium. While 33% of adults aged 60 years or over experience a fall in a calendar year [1, 125, 134], up to 68% of people with Parkinson's disease (PD) report as least one fall a year, with 50% of fallers reporting recurrent falls [43, 259]. Approximately 66% of falls occur during ambulation or transfers, while 32% of falls occur during standing [7]. While there is a growing body of research seeking to better understand the mechanism(s) surrounding the falls that occur during ambulation and transfer events, the 32% of falls that occur during static or standing situations are also a common focus of research in this area.

Levodopa replacement therapy and stereotactic neurosurgery are two of the most common medical treatments for the management of motor symptoms in PD, but symptoms of postural instability are known to be largely unresponsive to these treatments [19]. Due to the shortcomings of traditional therapies, researchers have sought to determine whether exercise or physical therapy may offer benefits to patients who experience these symptoms. In recent years, exercise has been shown to have a series of short-term benefits for people with PD, including improvements in clinical measures of mobility [2, 128, 139, 236, 237], balance [2, 128, 139, 236, 237], quality of life [186], cognitive function [174, 186] and symptom severity [236, 237]. There have also been a small number of studies that have investigated the efficacy of different non-invasive methods for improving balance and reducing falls risk in this high-risk population [2, 6, 63, 169, 170].

Despite their significant contribution to this area of research, the majority of these studies have relied upon clinical rating scales to assess the efficacy of their interventions, rather than more quantitative and continuous measures. Many of these clinical scales adopt Likert

scales to assess different aspects of physiological function and, hence, may be limited in their capacity to identify small, yet meaningful improvements in a patient's condition. The possible shortcomings of such assessments has been highlighted in prospective falls research, which demonstrated that many common clinical assessments are not capable of independently predicting future fallers in a PD population. Posturography is a technique that measures changes in the centre of pressure to provide insight into an individual's postural sway. Furthermore, research suggests that the outcomes derived from a posturographic analysis may be useful for predicting falls in people with PD [119]. Due to the apparent limitation of using only clinical assessments to evaluate changes in patient function following an intervention, this randomised-controlled trial sought to determine whether outcome measures derived via posturography could provide greater insight into the potential benefits of an exercise-based intervention. Specifically, it was the aim of this phase II randomised-controlled trial to establish whether a 12-week trunk-specific exercise program was more effective than education at improving objective measures of postural sway and clinical measures of symptom severity, balance, gait difficulty and balance confidence in people with PD. It was hypothesized that the patients who received the 12-weeks of exercise would show greater improvements in postural sway than the education group immediately following the 12-week intervention.

8.3 Methods

8.3.1 Participants

This study protocol was developed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [211]. Of the 29 participants involved in Study 2, the 24 who had a history of at least 1 fall in the previous 12 months or 2 or more near misses were invited to participate in this randomised controlled trial (Table 8). For the purposes of this study, a fall was defined as "any coming to the ground or other lower level not as the result of a major intrinsic event or overwhelming hazard" [6]. Similarly, a near miss was defined as "an event on which an individual felt that they were going to fall but did not actually do so" [6]. The processes involved with the recruitment and screening of the participants and the specific inclusion and exclusion criteria involved in this research are outlined in Section 6.1.

On the basis of an a-priori power calculation completed using the maximum excursion of the sway path presented in a previous study comparing PD fallers and PD non-fallers [206], it was determined that a minimum of 11 participants per group would be required to confidently report any significant changes in postural stability during challenging tasks (Cohen's d = 1.10, Power = 80%, p = 0.05). Given the primary outcome measures of this study were based on an assessment of the patients' postural sway patterns via posturography and that the study population was comprised of PD fallers, the study was deemed appropriate to determine an estimate of sample size. The experimental procedures for this study were approved by the Australian Catholic University Human Research Ethics Committee and all volunteers provided written informed consent in accordance with the Declaration of Helsinki to participate in the study.

Table 8: Demographics and scores for the clinical baseline assessments completed by the entire PD cohort and the Exercise and Education sub-groups.

	All (n = 22)	Education (n = 11)	Exercise (n = 11)		
	Mean ± SD / N (%)	**Mean ± SD / N (%)**	**Mean ± SD / N (%)**	**Test**	**Sig. (p)**
Demographics					
Gender (Male)	15 (68.2%)	8 (72.7%)	7 (63.6%)	3	0.65
Age (years)	65.4 ± 5.7	67.5 ± 5.8	63.3 ± 4.9	2	0.08
Height (cm)	170.6 ± 7.7	171.6 ± 7.7	169.7 ± 8.0	1	0.58
Mass (kg)	80.0 ± 20.3	78.6 ± 23.9	81.4 ± 17.0	1	0.76
Body Mass Index (kg/m^2)	27.2 ± 5.5	26.3 ± 5.9	28.2 ± 5.1	1	0.42
Cognition & Vision					
Addenbrooke's Cognitive Exam	91.5 ± 6.8	92.3 ± 5.4	90.6 ± 8.1	1	0.58
High Contrast Visual Acuity (LogMAR)	0.01 ± 0.1	0.04 ± 0.1	-0.02 ± 0.1	1	0.09
Mobility, Balance Confidence & Quality of Life					
Timed Up and Go (s)	9.3 ± 1.6	9.87 ± 1.7	8.85 ± 1.9	1	0.31
Activities-specific Balance Confidence (%)	80.8 ± 20.4	78.4 ± 26.0	83.3 ± 13.8	1	0.77
39-Item Parkinson's Disease Questionnaire	22.7 ± 11.6	24.1 ± 11.2	21.3 ± 12.2	1	0.49
Neurological Examination					
Disease Duration (years)	6.7 ± 5.0	7.0 ± 5.0	6.5 ± 5.2	2	0.84
Unified Parkinson's Disease Rating Scale (Part III)	19.4 ± 13.0	21.5 ± 11.7	17.3 ± 14.4	2	0.31
Hoehn & Yahr Stage Score	1.9 ± 0.6	2.0 ± 0.7	1.8 ± 0.6	3	0.50
Schwab & England Activities of Daily Living Scale	82.5 ± 8.8	81.0 ± 10.0	84.1 ± 7.7	2	0.34
Gait and Falls Questionnaire	10.7 ± 11.6	12.8 ± 13.5	8.6 ± 9.4	1	0.60
Freezing of Gait Score	5.3 ± 5.5	6.0 ± 5.9	4.6 ± 5.2	1	0.78
Retropulsion Test	0.4 ± 0.7	0.6 ± 0.7	0.6 ± 0.7	1	0.27
Levodopa Daily Equivalent Dose (mg)	716.5 ± 427.7	868.2 ± 475.7	564.8 ± 327.6	1	0.10
Dopamine Agonists	5 (22.7%)	3 (27.3%)	2 (18.2%)	3	0.61
Catechol-O-Methyl Transferase Inhibitors	8 (36.4%)	3 (27.3%)	5 (45.5%)	3	0.38
Monoamine Oxidase Inhibitors	8 (36.4%)	6 (54.5%)	2 (18.2%)	3	0.08
Benzodiazepines	1 (4.5%)	1 (9.1%)	0 (0.0%)	3	0.31

Note: Test 1 = One-way analysis of variance; Test 2 = Mann-Whitney U test; Test 3 = Chi-square test

8.3.2 Clinical Measures

Individuals who were considered to be eligible following the telephone screening process and who provided consent to participate in this study were invited to attend a testing session at the University to facilitate the collection of baseline data. Baseline data collection included the battery of clinical assessments described Section 6.2 and all participants were assessed approximately 1-2 hours following a scheduled dose of their anti-parkinsonian medication to ensure that the results were representative of how they might perform similar tasks in the real world.

8.3.3 Static Postural Sway

In addition to the clinical assessments, postural sway was also assessed for each participant using standard posturography techniques. Specifically, participants were required to complete two 30-second trials that involved standing as still as possible for each of the following conditions: i) on a firm surface with eyes open, ii) on a firm surface with eyes closed, iii) on a foam surface with eyes open and iv) on a foam surface with eyes closed. The manipulation of surface from a firm platform to a foam platform was guided by previous research, which has shown that balance may become more difficult for some participants when somatosensory feedback is reduced or deprived [119, 145, 146, 190, 194, 201]. The use of foam surfaces has been used previously to detect differences in postural stability between people with PD and healthy controls [239] as well as detecting differences in balance when different textured insoles were used [201]. Similarly, it is well understood that visual feedback plays a significant role in one's ability to orientate themselves relative to their environment, hence the eyes closed conditions were included to place a higher load on the other sensory systems involved in postural control. During each of the standing balance trials, postural sway was measured on a portable AccuGait force plate at an effective rate of 200 Hz (Advanced Mechanical Technology Inc.,

USA). While performing the balance task participants stood with their arms resting at their sides and their feet 10 cm apart looking at a cross that was placed at eye level 0.4 meters in front of them in front of them. These requirements were implemented as previous research has shown that standing balance can be improved when a near visual target is provided [227] and to ensure that assessments were standardised for each testing session.

Ground reaction forces and moments were measured by the force platform in all three axes of motion (vertical, anterior-posterior, and medial-lateral) via multiple sensors embedded within its upper surface. While attempting to stand still, the participant's centre of mass will oscillate, causing the fluctuations in the three-dimensional ground reaction forces and moments. These forces and moments are subsequently used to derive centre of pressure, which, in a relatively rigid system, reflects the movement patterns of the centre of mass (COM). To facilitate this process, the collected ground reaction forces and moments were passed to a laptop computer that was running the NetForce software (Advanced Mechanical Technology, Watertown MA, USA), where it was used to calculate the centre of pressure.

Using the centre of pressure data, outcome measures that included the 95% elliptical sway area, sway velocity and the variability of anterior-posterior and medial-lateral sway patterns (as determined using the standard deviation) were calculated using the BioAnalysis software (Advanced Mechanical Technology, Watertown MA, USA). The selection of these outcomes was guided by previous research which has reported differences in these measures for people with PD relative to controls [18, 108, 201] and for PD fallers compared with non-fallers [119].

8.3.4 Randomisation and Blinding

This study was designed to be a parallel group phase II randomised controlled trial. After baseline assessment, participants were assigned to a 12-week education or exercise intervention (Figure 10) using a random allocation sequence (block size=2; 1:1 ratio). This

random allocation sequence was generated by a member of the research team who was not involved in participant recruitment, assessment or group allocation (GAN), who was not involved in participant allocation or assessment. Originally, a secondary aim of this thesis was to examine the dose response of exercise with a third intervention group exercising an additional two days a week at home. However, a slow rate of participant recruitment resulted in a relatively small number of patients (from a statistical perspective) coming into the program and the third arm of the intervention had to be abandoned. To minimise the possibility of biasing the clinical assessments, an experienced movement disorders scientist who was blinded to the assigned group of participants (MHC) conducted each of these assessments.

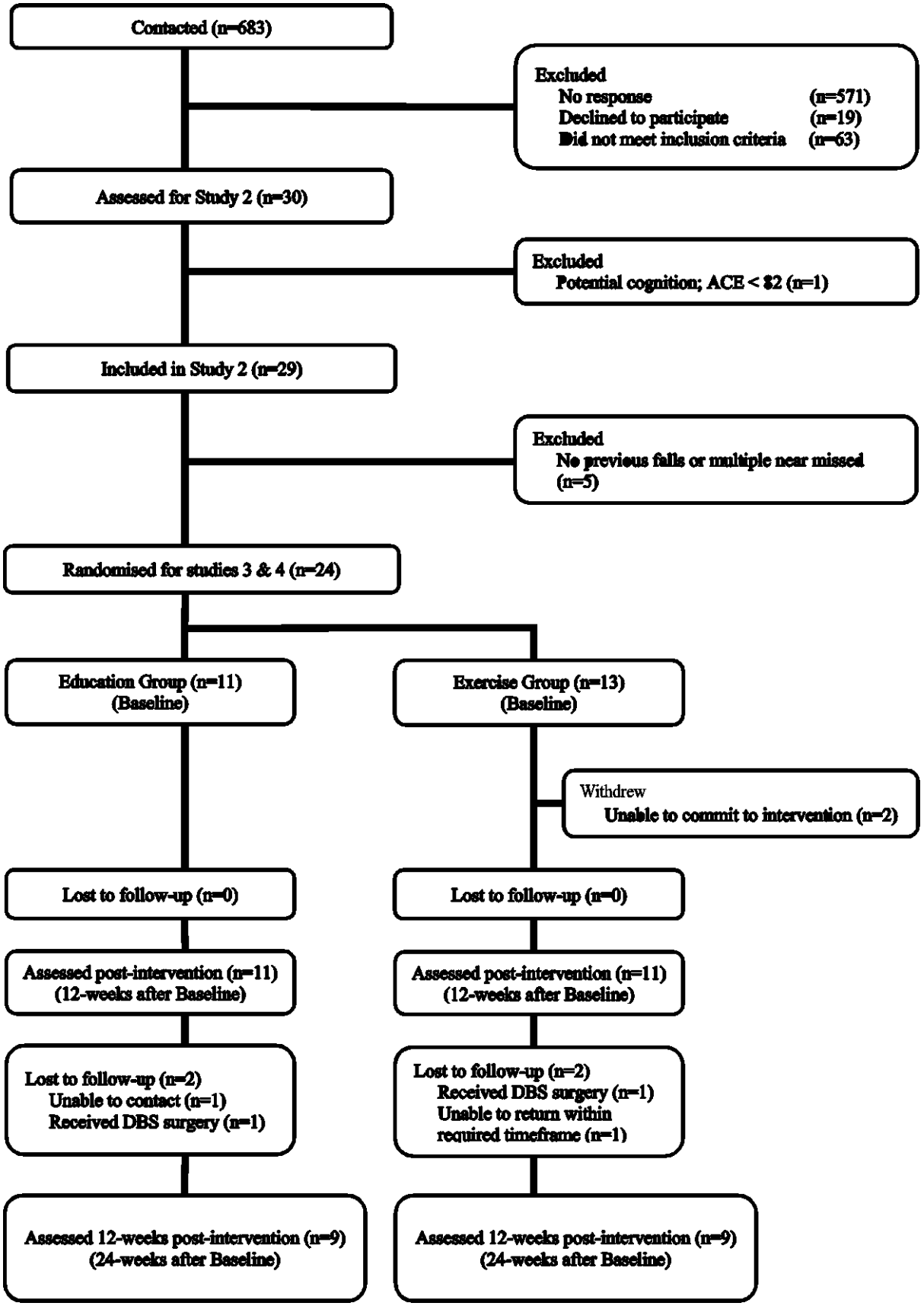

Figure 10: Flow diagram illustrating the recruitment and randomisation processes.

8.3.5 Intervention

Participants randomised to the education group were encouraged to continue their day-to-day lives, but received a weekly multi-disciplinary education pack that included health tips explaining how lifestyle (e.g. exercise) and/or condition-related issues (e.g. poor sleep quality) can influence their risk of falling and overall quality of life. The education brochures that were provided to the participants were created using scientific evidence drawn from pre-existing research and from freely-available information sheets produced by government and not-for-profit organisations.

Participants assigned to the exercise groups completed a low-level supervised, 12-week exercise program aimed at improving trunk mobility and endurance. The exercise group experienced one supervised session each week with a trained Exercise Scientist at the University. While it is possible that an exercise program completed on a more regular basis may offer greater benefits to less frequent programs, the once weekly face-to-face session was considered adequate based on similar programs leading to reduced falls risk in older adults [10]. The exercise program consisted primarily of exercises used previously in two different exercise-based interventions involving older adults [96] and people with PD [24]. The exercises focused on improving trunk muscle strength and endurance. Importantly, the program was designed to conform to the current recommendations for best clinical practice for the implementation of exercise-based interventions targeting improved postural stability [132, 216, 221]. Specifically, the program included components that sought to improve trunk mobility, trunk muscle strength and endurance, balance under challenging situations (i.e. on an unstable surface) and ambulation over different real-world terrains. As described earlier (Section 2.5), the appropriate activation of the superficial and deep muscles of the trunk is critical to the overall control of this segment during locomotion and is known to be impaired in people with PD [40]. By specifically targeting the function of these muscles, it was anticipated that such

impairments could be reversed and that this improved function may translate to improved static and dynamic stability. While the exercises incorporated into this program largely targeted the muscles of the trunk, it should be acknowledged that the muscles surrounding the shoulder, pelvis and neck were also likely to have been indirectly targeted, as they were required to stabilise their respective joints against gravity during the performance of the exercises. The program progressed in complexity to accommodate individuals with different physical capabilities (Table 9).

Table 9: Summarises the structure of the progressive trunk-specific exercise program

Task	Movement	Repetitions/Progression
Trunk Mobility Warm-up	Lateral bends	10 to the left 10 to the right
	Torso rotations	10 to the left 10 to the right
	Small arm circles	10 forward 10 backward
	Large arm circles	10 forward 10 backward
	Torso rotations with high and low reaching	10 reaching up to left, down to right 10 reaching up to right, down to left
Trunk Endurance	Abdominal hollowing Side bridging Front bridging Bird dog	Adjust difficulty of exercise by: • Increasing hold times • Increasing movement complexity • Introducing an unstable support surface
Mobility	Circuit involving stair ascent / descent and walking over surfaces of varying incline / decline and density	8-10 minutes of walking on an outdoor walking path
Active Cool Down	Hamstring stretch	2 sets of 20 second holds
	Quadriceps stretch	2 sets of 20 second holds
	Gastrocnemius / soleus stretch	2 sets of 20 second holds
	Triceps stretch	2 sets of 20 second holds
	Pectoral stretch	2 sets of 20 second holds

Each of the endurance exercises were repeated 10 times (i.e. 10 repetitions) and participants were asked to hold each static position for a duration of 5 (easy) to 20 (difficult)

seconds, with the hold time manipulated to adjust the difficulty of each exercise (Table 10). In addition to lengthening the static hold times, the difficult of the exercises was also manipulated by incorporating a round and flat air filled disc to create an unstable surface that challenged the participants' balance during the performance of the static holds. The walking portion of the program was completed on an outdoor walking path that specifically incorporated varying degrees of incline and decline, stairs and multiple surface types to simulate walking during activities of daily living. The various challenges offered by this walking course served to improve participants' capacity to safely and effectively ambulate in both predictable and unstable real world environments. Immediately following the completion of the 12-week intervention, all participants were re-assessed using the same tests completed at baseline. In addition, a follow-up assessment occurred 12 weeks after the completion of the intervention to examine whether any changes were retained longer term. Compliance to the intervention protocol and any adverse events was also monitored and reported by the researchers.

Table 10: Summarises the progressions and hold times for each of the trunk exercises

Trunk Exercise	Progression	Exercise Details	Hold time (seconds)
Abdominal Hollowing	1	Supine	5
	2	Seated	7
	3	Hands and knees	10
	4	Pelvic bridge	13
	5	Pelvic bridge and single leg extension	15
	6	Pelvic bridge and single leg extension (stability disc under foot)	17
Front Bridge	1	On a wall	20
	2	Forearms and knees	
	3	Forearms and feet	
	4	Forearms and feet (stability disc under feet)	
Side Bridging	1	On a wall	
	2	Forearms and knees	
	3	Forearms and feet	
	4	Forearms and feet (stability disc under feet)	
Bird Dog	1	Single arm raise	
	2	Single leg raise	
	3	Contralateral arm and leg raise	
	4	Contralateral arm and leg raise (stability disc under knee)	

8.3.6 Statistical Analysis

As there were a small number of participants who withdrew from the study prior to its completion, intention to treat analysis was not possible. Therefore, analyses of the clinical and biomechanical outcomes post-intervention were based on per protocol analysis. To assess for changes between groups at 12 and 24 weeks compared with baseline, linear mixed model analyses were used (Baseline vs. 12 weeks, Baseline vs. 24-weeks, 12 weeks vs. 24-weeks). These models included multiple repeated factors (Day, 3 levels; Vision, 2 levels; Surface, 2 levels), one fixed factor (Group; 2 levels) and 2 covariates (daily levodopa equivalent dose and age). Levodopa daily equivalent dose was included as a covariate, as previous research has shown that levodopa improves motor symptoms [184], while age was included due to the knowledge that postural sway is influenced by age [80]. If a significant difference was found, the Tukey's Least Significant Difference test was used to perform post-hoc comparisons between groups. Tukey's honestly significant difference determined the minimum mean raw score difference that had be obtained to declare two groups significantly different. The test also controls for the overall significant level when performing pairwise comparisons to reduce the chance of obtaining a Type 1 error [244]. Lastly, to highlight the clinical importance of the presented outcomes, the minimal detectable change (MDC) value for each outcome measure was derived. All data analyses were conducted using SPSS v.22 (New York, USA) with significance set at $p<0.05$.

8.4 Results

8.4.1 Study Population

Of the 24 participants who completed baseline assessments, 13 were assigned to the Exercise group and 11 were assigned to the Education group. Of the 13 allocated to the Exercise group, two withdrew from the study before completing the 12-week program citing their

inability to commit the time required for the exercise program. As such, these participants were not re-assessed at the 12- (post-intervention) or 24-week (retention) time points and their data were not included in the subsequent analyses. Statistical comparisons of the group indicated that, at baseline, the groups did not differ significantly with respect to demographics or their performance on the clinical assessments of cognition, vision, mobility, balance confidence, quality of life (Table 8). Among the 11 individuals completing the 12-week exercise-based intervention, compliance to the exercise program was 90%, on average, with the individual rates of compliance ranging from 67% to 100%. All participants included in this study were free of any significant medical conditions (other than PD) that may have influence their balance and/or gait and presented with no significant physical, psychological or visual disabilities at the time of testing.

Over the 12-week intervention period, each participant in the exercise group demonstrated improvements in trunk muscle strength and endurance, as evidenced by their progression from simple to more complex exercises and their longer front bridge hold times at the 12-week time-point relative to their week 1 assessment (Table 11). As the front bridge test was only conducted for the exercise group, it has not been included in subsequent statistical analysis, but it is interesting to note that, on average, participants recorded 141.66 ± 124.90% improvement in their static hold times following the program.

Table 11: Summary of each participant's progression through the exercise intervention

Participant		Exercise Progression # / Hold time (s)		Front Bridge Test Maximum Hold Time (s)		
	Trunk Exercise	Week 1	Week 12	Week 1	Week 12	Change
01	Abdominal Hollowing	2 (10)	6 (20)	34	62	+82%
	Front Bridging	1 (5)	4 (20)			
	Side Bridging	1 (7)	4 (20)			
	Bird Dog	1 (5)	4 (20)			
02	Abdominal Hollowing	2 (5)	4 (15)	10	15	+50%
	Front Bridging	1 (5)	2 (10)			
	Side Bridging	1 (5)	2 (10)			
	Bird Dog	1 (5)	2 (15)			
03	Abdominal Hollowing	2 (5)	6 (10)	38	42	+11%
	Front Bridging	1 (5)	3 (10)			
	Side Bridging	2 (5)	3 (10)			
	Bird Dog	1 (5)	3 (20)			
04	Abdominal Hollowing	2 (5)	6 (10)	17	67	+294%
	Front Bridging	1 (5)	4 (10)			
	Side Bridging	1 (5)	3 (10)			
	Bird Dog	1 (5)	4 (10)			
05	Abdominal Hollowing	2 (5)	6 (20)	42	72	+71%
	Front Bridging	1 (10)	4 (15)			
	Side Bridging	1 (10)	4 (15)			
	Bird Dog	1 (10)	4 (15)			
06	Abdominal Hollowing	2 (7)	6 (15)	15	69	+360%
	Front Bridging	2 (7)	3 (15)			
	Side Bridging	2 (7)	3 (15)			
	Bird Dog	2 (7)	4 (15)			
07	Abdominal Hollowing	2 (7)	6 (15)	12	40	+233%
	Front Bridging	2 (7)	3 (10)			
	Side Bridging	2 (7)	3 (10)			
	Bird Dog	2 (7)	4 (15)			
08	Abdominal Hollowing	2 (7)	5 (15)	5	19	+282%
	Front Bridging	1 (7)	3 (15)			
	Side Bridging	1 (7)	2 (15)			
	Bird Dog	2 (7)	3 (15)			
09	Abdominal Hollowing	4 (10)	6 (20)	41	59	+44%
	Front Bridging	3 (10)	4 (20)			
	Side Bridging	3 (10)	4 (20)			
	Bird Dog	3 (10)	4 (20)			
10	Abdominal Hollowing	4 (10)	6 (20)	134	213	+59%
	Front Bridging	3 (10)	4 (20)			
	Side Bridging	3 (10)	4 (20)			
	Bird Dog	3 (10)	4 (20)			
11	Abdominal Hollowing	2 (10)	6 (15)	61	98	+61%
	Front Bridging	3 (7)	4 (15)			
	Side Bridging	2 (7)	4 (15)			
	Bird Dog	3 (7)	4 (15)			

Between the 12- and 24-week assessments, an additional four participants were lost (two from the Exercise group and two from the Education group); two underwent deep brain stimulation surgery for their symptoms, one was unable to be contacted and one was unable to complete the 24-week assessment until 32-weeks after the baseline assessment. As such, the data presented for the 24-week follow-up assessment were derived from the 18 participants who completed all of the assessments at this time point.

8.4.2 Clinical Assessments

The results from the linear mixed model analyses for the clinical tests of mobility, balance confidence, quality of life and symptom severity revealed a number of significant group effects. Specifically, these highlighted that, in general, patients in the Education group reported poorer quality of life (PDQ-39, p=0.030), a greater severity of motor symptoms (UPDRS III, p=0.02) and larger daily doses of levodopa (p=0.02) than the Education group. Despite these findings, the statistical model identified no significant main effects for testing day or any significant Group*Day interactions for these clinical measures (Table 12).

Table 12: Means (± SD) scores for the clinical assessments of symptom severity, disease stage, mobility, balance confidence and quality of life

	Education			Exercise			Main Effects		Interaction
	Baseline	12-Week	24-Week	Baseline	12-Week	24-Week	Group	Day	Group*Day
Mobility and Balance Confidence									
Timed Up and Go (s)	9.87 ± 1.66	9.96 ± 2.02	8.85 ± 1.90	8.78 ± 1.29	9.26 ± 1.80	8.72 ± 0.90	ns	ns	ns
Activities-specific Balance Confidence (%)	78.35 ± 25.96	78.70 ± 23.09	89.06 ± 5.34	83.30 ± 13.78	74.15 ± 30.82	76.39 ± 31.21	ns	ns	ns
Quality of Life									
39-Item Parkinson's Disease Questionnaire	24.13 ± 11.24	22.84 ± 10.77	17.95 ± 7.78	21.33 ± 12.32	21.27 ± 14.38	16.60 ± 9.30	‡	ns	ns
Neurological Examination									
Unified Parkinson Disease Rating Scale III	21.45 ± 11.73	24.55 ± 10.15	19.50 ± 7.97	17.27 ± 14.40	16.45 ± 11.94	15.11 ± 5.80	‡	ns	ns
Hoehn & Yahr Stage Score	1.95 ± 0.69	2.14 ± 0.67	1.67 ± 0.41	1.77 ± 0.56	1.55 ± 0.69	1.56 ± 0.68	ns	ns	ns
Schwab & England Activities of Daily Living	80.91 ± 9.95	80.00 ± 7.07	85.00 ± 6.32	84.09 ± 7.69	84.55 ± 7.57	86.67 ± 8.29	ns	ns	ns
Gait and Falls Questionnaire	12.82 ± 13.50	10.36 ± 10.08	5.83 ± 4.88	8.64 ± 9.45	9.27 ± 12.19	5.44 ± 9.04	ns	ns	ns
Freezing of Gait	6.00 ± 5.92	5.27 ± 5.24	3.17 ± 2.64	4.64 ± 5.20	5.00 ± 6.00	2.89 ± 4.62	ns	ns	ns
Retropulsion Test	0.55 ± 0.69	0.55 ± 0.82	0.33 ± 0.52	0.27 ± 0.65	0.27 ± 0.65	0.11 ± 0.33	ns	ns	ns
Levodopa Daily Equivalents (mg)	868.23 ± 475.71	783.59 ± 530.36	794.00 ± 521.95	564.81 ± 327.58	569.55 ± 343.83	484.11 ± 338.37	‡	ns	ns

ns = no significant differences; **‡ =** Significant Group effect; **¥** = Significant Day effect; i = Significant difference between Baseline and 12-week; ii = Significant difference between Baseline and 24-week; iii = Significant difference between 12-week and 24-week; **Ŧ** = Significant Group*Day interaction; **a** = Significant difference between Baseline and 12-week for Education; **b** = Significant difference between Baseline and 24-week for Education; **c** = Significant difference between 12-week and 24-week for Education; **d** = Significant difference between Baseline and 12-week for Exercise; **e** = Significant difference between Baseline and 24-week for Exercise; **f** = Significant difference between 12-week and 24-week for Exercise

8.4.3 Static Postural Stability

Linear mixed model analyses reported no significant main effects for group or day for any of the outcome measures derived from the force platform ($p>0.05$). However, a significant main effect for surface was observed for all of the postural sway measures, with each outcome being greater during the trials completed on the foam surface ($p<0.001$). Similarly, significant main effects for vision were observed with each of the outcomes derived from the force platform, with the measures of postural sway being significantly greater during the eyes closed conditions ($p<0.001$).

In addition to the significant main effects, significant Group*Day*Surface*Vision interactions were observed for 95% elliptical sway area (Figure 11), sway velocity (Figure 12) and sway variability in both the AP (Figure 13) and ML (Figure 14) directions ($p<0.001$). Pairwise comparisons revealed that, while standing on the foam surface without vision, participants in the Exercise group had a reduced 95% elliptical sway area at both the 12- ($p=0.003$) and 24-week ($p=0.001$) time points compared with the baseline values. Furthermore, under these conditions, the Exercise group had less variable medial-lateral postural sway patterns at the 12- ($p=0.01$) and 24-week ($p=0.01$) time points compared with baseline values. Interestingly, following the 12-week intervention, sway velocity was significantly reduced for the Education group during the standing balance tasks completed on the foam surface with eyes open. However, despite these statistically significant reductions in sway area, sway velocity and sway variability, the reported MDC values suggest that these changes were insufficient to be considered clinically meaningful (Table 13).

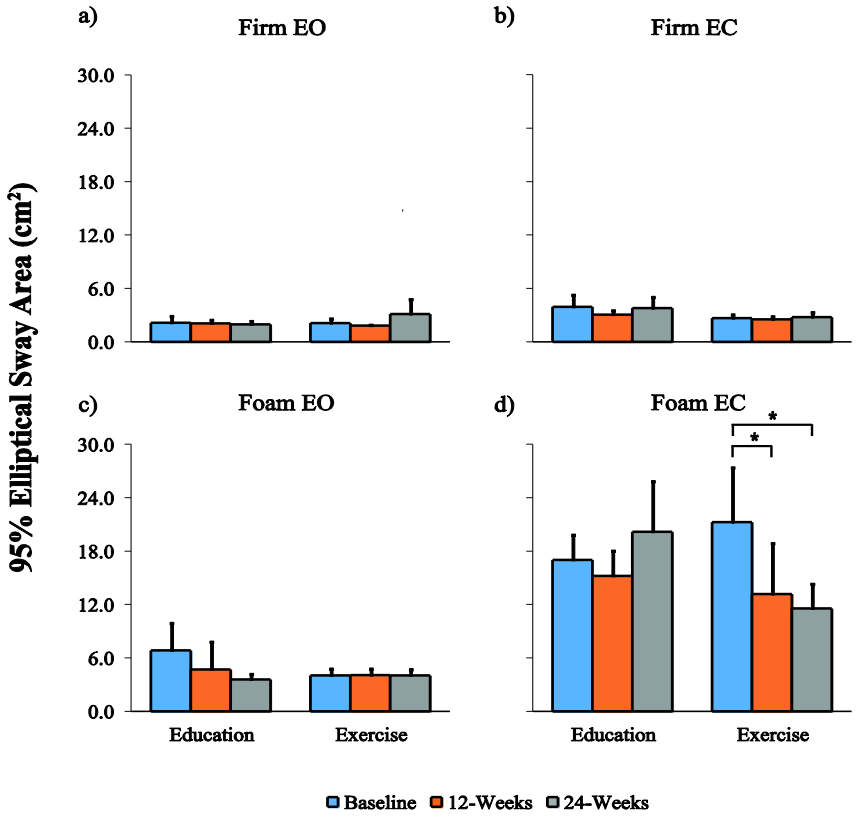

Figure 11: Mean (+1 SEM) 95% elliptical sway area for the Exercise and Education groups.

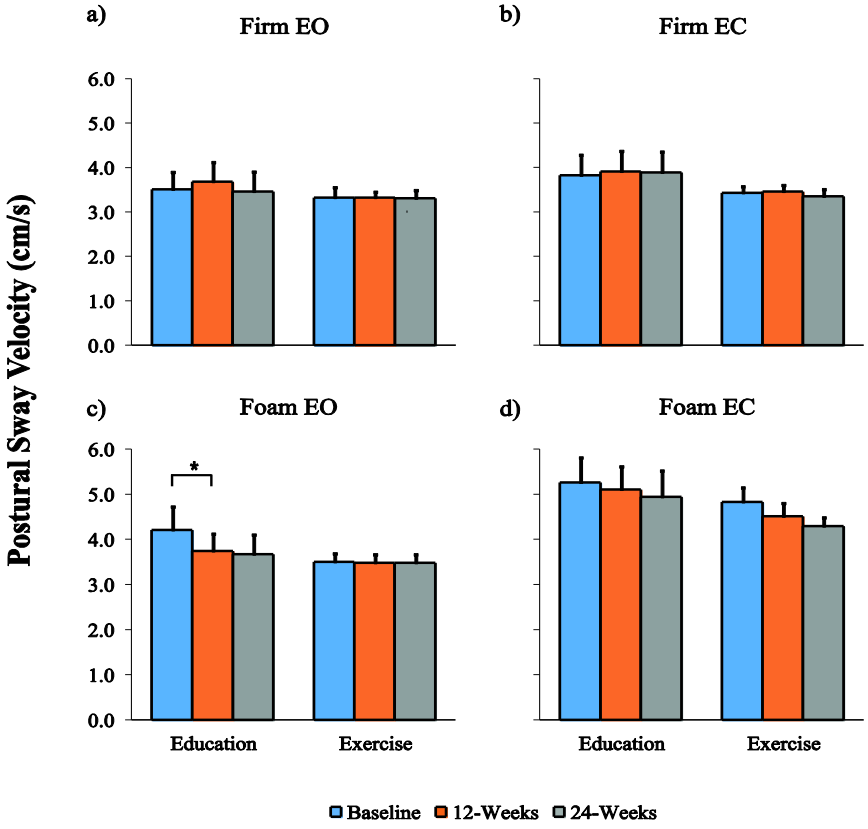

Figure 12: Mean (+1 SEM) sway velocity for the Exercise and Education groups.

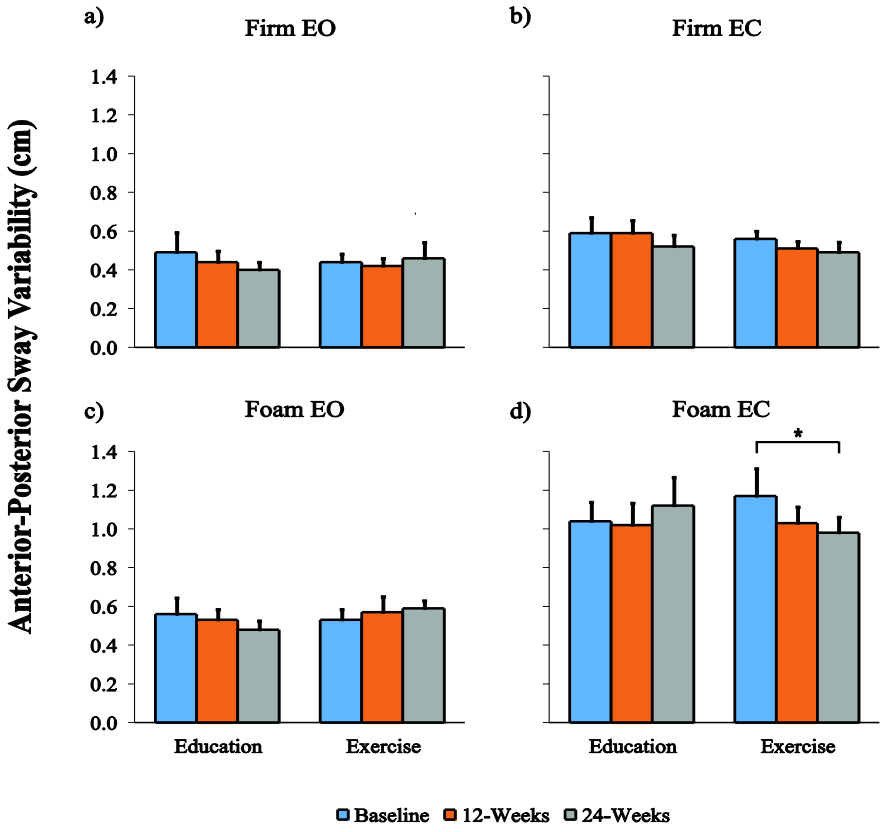

Figure 13: Mean (+1 SEM) AP sway variability for the Exercise and Education groups.

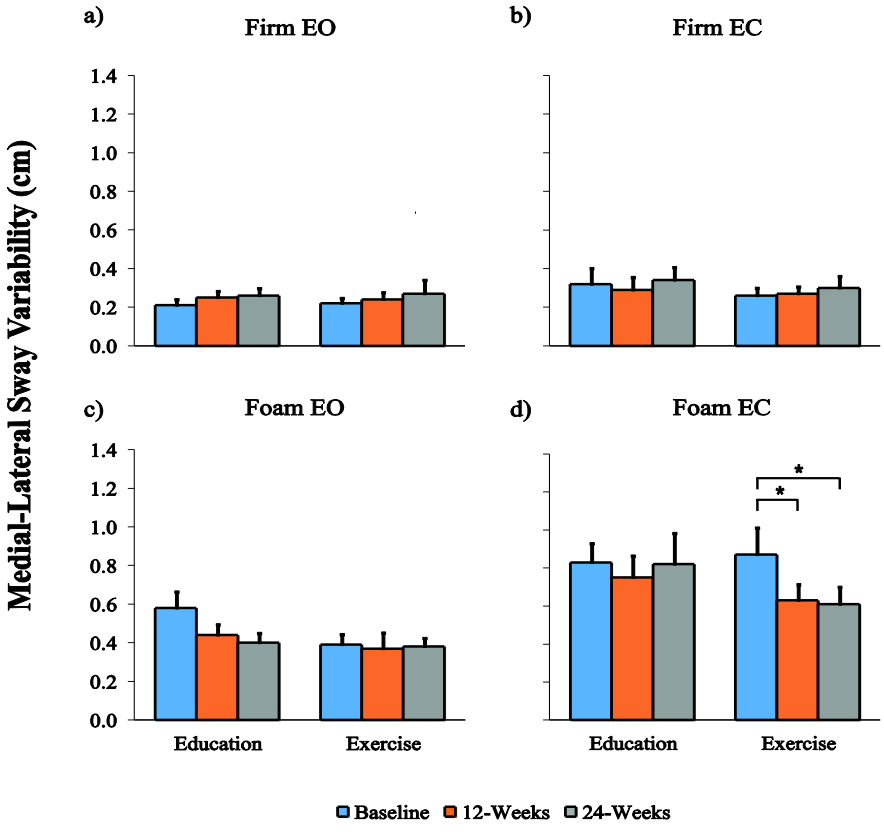

Figure 14: Mean (+1 SEM) ML sway variability for the Exercise and Education groups.

Table 13: Mean (and standard deviation) outcomes for the posturography assessments conducted at Baseline, 12-weeks and 24-weeks.

		Exercise			Education			Main Effects					Interactions
		Baseline	12-Week	24-Week	Baseline	12-Week	24-Week	Group	Day	MDC	Surface	Vision	Group*Day* Surface*Vision
95% Elliptical Area (cm^2)													
Firm	EO	2.09 ± 1.92	1.80 ± 1.21	3.11 ± 5.17	2.15 ± 2.57	2.06 ± 1.76	1.95 ± 1.26	ns	ns	1.81	‡	¥	ns
	EC	2.66 ± 1.48	2.52 ± 1.34	2.77 ± 1.80	3.94 ± 4.63	3.06 ± 1.66	3.80 ± 3.82	ns	ns	2.51			ns
Foam	EO	4.04 ± 2.63	4.05 ± 3.58	4.04 ± 2.13	6.84 ± 10.43	4.71 ± 3.44	3.58 ± 2.03	ns	ns	5.37			ns
	EC	21.26 ± 20.45	13.18 ± 8.42	11.57 ± 8.41	17.02 ± 9.56	15.21 ± 9.59	20.15 ± 17.29	ns	ns	11.86			**Ŧ, c, d, e**
Sway Velocity (cm/s)													
Firm	EO	3.32 ± 0.82	3.23 ± 0.49	3.31 ± 0.58	3.51 ± 1.34	3.68 ± 1.51	3.46 ± 1.38	ns	ns	0.88	‡	¥	ns
	EC	3.43 ± 0.46	3.46 ± 0.51	3.35 ± 0.53	3.82 ± 1.24	3.91 ± 1.58	3.89 ± 1.43	ns	ns	0.69			ns
Foam	EO	3.50 ± 0.66	3.48 ± 0.65	3.39 ± 0.59	4.21 ± 1.75	3.74 ± 1.31	3.67 ± 1.34	ns	ns	0.98			**Ŧ, a**
	EC	4.83 ± 1.11	4.51 ± 1.01	4.29 ± 0.63	5.26 ± 1.86	5.10 ± 1.75	4.94 ± 1.79	ns	ns	1.20			ns
AP Sway SD (cm)													
Firm	EO	0.44 ± 0.15	0.42 ± 0.14	0.46 ± 0.28	0.49 ± 0.35	0.44 ± 0.20	0.40 ± 0.14	ns	ns	0.21	‡	¥	ns
	EC	0.56 ± 0.14	0.51 ± 0.13	0.49 ± 0.19	0.59 ± 0.28	0.59 ± 0.23	0.52 ± 0.21	ns	ns	0.17			ns
Foam	EO	0.53 ± 0.19	0.57 ± 0.28	0.59 ± 0.14	0.56 ± 0.29	0.53 ± 0.19	0.48 ± 0.16	ns	ns	0.19			ns
	EC	1.17 ± 0.48	1.03 ± 0.29	0.98 ± 0.28	1.04 ± 0.34	1.02 ± 0.39	1.12 ± 0.50	ns	ns	0.33			**Ŧ, e**
ML Sway SD (cm)													
Firm	EO	0.22 ± 0.10	0.24 ± 0.13	0.27 ± 0.22	0.21 ± 0.11	0.25 ± 0.12	0.26 ± 0.12	ns	ns	0.08	‡	¥	ns
	EC	0.26 ± 0.11	0.27 ± 0.10	0.30 ± 0.12	0.32 ± 0.21	0.29 ± 0.05	0.34 ± 0.21	ns	ns	0.13			ns
Foam	EO	0.39 ± 0.13	0.37 ± 0.14	0.38 ± 0.15	0.58 ± 0.63	0.44 ± 0.16	0.40 ± 0.16	ns	ns	0.31			ns
	EC	0.87 ± 0.53	0.63 ± 0.22	0.61 ± 0.25	0.83 ± 0.31	0.75 ± 0.29	0.82 ± 0.38	ns	ns	0.33			**Ŧ, d, e**

MDC = minimal detectable change**, EO** = Eyes open; **EC** = Eyes closed; **SD =** standard deviation; **ML** = medial-lateral; **AP** = anterior-posterior; **ns** = no significant differences; ‡ = Significant Surface effect; **¥** = Significant Vision effect; **Ŧ** = Significant Group*Day*Surface*Vision interaction; **a** = Significant difference between Baseline and 12-week for Education; **b** = Significant difference between Baseline and 24-week for Education; **c** = Significant difference between 12-week and 24-week for Education; **d** = Significant difference between Baseline and 12-week for Exercise; **e** = Significant difference between Baseline and 24-week for Exercise; **f** = Significant difference between 12-week and 24-week for Exercise. **NOTE:** An asterisk (*) after a symbol indicates that the statistically-significant difference can also be considered clinically important.

8.5 Discussion

The purpose of this phase II randomised controlled trial was to evaluate whether a 12-week trunk-specific exercise program could improve clinical measures of symptom severity and mobility and/or objective measures of static postural stability. The exercise intervention did not lead to significant improvements in typical clinical measures of mobility, symptom severity or balance confidence. These findings are commensurate with previous exercise-based interventions that have previously fallen short of demonstrating significant improvements in clinical measures of balance and mobility after an 8-week [6, 139] 10-week [84] or 6-month [2] exercise program. Additionally exercise intervention has also previously failed to reduce falls risk [2] and falls rates [6, 84] in PD. Collectively, these findings suggest that clinical assessments, used widely to assess and monitor changes in patient health, balance and/or mobility in people with PD, may lack the necessary specificity and/or sensitivity to detect change following intervention. Clinical rating scales may be limited by the experience of the individual administering the assessment, poor reliability [205] and/or their dependence on Likert scales that may be insensitive to subtle changes in function. This notion seems to be supported by previous research which reported only moderate sensitivities (65-69%), specificities (62-69%) and accuracies (53-68%) for the Tinetti Balance and Gait tests, Berg Balance Scale, Timed Up and Go test, Functional Reach test and Physiological Profile Assessment of Falls Risk with respect to the prediction of prospective falls in people with PD [119]. Furthermore, the results of Study 2 highlighted weak relationships between objective measures of gait symmetry and clinical measures of balance and mobility for patients with mild to moderate PD [105].

In contrast to the clinical assessments, the objective assessment of postural stability during quiet stance revealed that the 12-week trunk-specific exercise program led to significant improvements in postural sway. Specifically, those who received the exercise intervention

demonstrated reductions in the 95% elliptical sway area and sway variability in the anterior-posterior and medial-lateral directions when completing the most challenging condition (i.e. on a foam surface without vision). These findings appear to be in contrast to previous studies, which reported no significant improvement in sway area [45] or sway range on firm [2, 121] or compliant [2] surfaces. However, a possible explanation for this disparity is that these earlier studies only assessed balance while patients stood on a firm surface with their eyes open. The significant main effects for vision and surface that were reported in the current study indicated that, irrespective of group, all measures of postural sway increased when somatosensory and/or visual feedback were impaired. Similar findings have been reported in previous research, which has shown improvements in balance following exercise intervention during conditions five [262] and six [14, 262] on the Sensory Organisation Test, which involve the manipulation or absence of proprioceptive and/or visual feedback. On the basis of these findings, it seems apparent that subtle changes in postural stability may not be easily detected during assessments conducted under less-challenging conditions.

In spite of the statistically significant changes observed in the Exercise group following the 12-week intervention, it is important to note that the minimal detectable change scores indicated that these improvements were not large enough to be considered clinically important. A possible means of enhancing such improvements in postural sway would be to increase the frequency of the exercise sessions and/or lengthen the duration of the overall program. Support for the potential benefits of increased exercise frequency may be provided by previous studies that have reported improvements in postural sway following a treadmill training intervention completed 3 to 4 times per week [14, 76]. As such, future research should seek to determine whether an increased frequency of trunk-specific exercises can yield both statistically significant and clinically important improvements in postural sway for people with PD.

The results of this study should be considered in light of a number of limitations. First, as a phase II randomised controlled trial, the sample size was relatively small, which may mean that the reporting of the secondary outcomes may be confounded by insufficient statistical power. Nevertheless, the a-priori sample size calculation indicated that data collected for the 11 participants at baseline and immediately following the 12-week intervention was adequate to achieve a level of 80% statistical power for the comparisons made for the sway measures between these two time points. When considering the results presented for the 24-week time point, it is important to recognise that four participants did not return for their final follow-up visit, hence the results represent response from only the remaining 9 individuals in each group. As such, while the comparisons reported between the baseline and 12-week assessments are supported by the a-priori power calculation, the loss of 2 participants from each of the groups during the latter stages of the study, would likely mean that the comparisons that involved the 24-week time point may be slightly underpowered. Second, given the longitudinal nature of this project, the potential impact of any changes in a patient's anti-parkinsonian medication needs to be considered. It is well recognised that anti-parkinsonian medications, such as levodopa, can significantly improve a patient's symptoms [184]; hence any changes to the frequency, dose and/or type of medication was carefully monitored. On the basis of this process, it was noted that during the 24-week period that followed the baseline assessment, 25% of those in the Education group and 36% of those in the Exercise group reported at least one change to their prescription medications. Nevertheless, statistical comparison of the patients' levodopa daily equivalents at the three time points indicated no significant increase or decrease in the effective amount of levodopa being taken by groups.

In conclusion, the findings of this study collectively provide evidence to suggest that regular trunk-specific exercises may lead to improvements in static postural stability under more challenging balancing conditions. However, these improvements do not appear to be

easily measured with existing clinical assessments and higher volumes of training may be necessary to achieve clinically meaningful improvements in postural control. Additional research is needed to determine whether a similar exercise-based intervention that is performed more frequently can be used to improve static postural stability in a larger cohort of PD patients and to ascertain whether similar improvements can be achieved during dynamic tasks.

9.0 Study 4 Exercise improves gait symmetry in Parkinson disease: A blind phase II randomised-controlled trial

Study 3 of this thesis revealed that the trunk specific exercise intervention was more effective than the education program at improving postural sway under challenging conditions, with some improvements in postural sway under challenging conditions being maintained after the 12-week retention period. However, it remains unknown whether these improvements in static postural stability extend to dynamic situations, such as walking. To address this issue, Study 4 was designed to examine whether the trunk-specific exercise intervention described in Study 3 was capable of improving gait symmetry and muscle function in people with PD.

NOTE: The following chapter presents the findings of the following peer-reviewed manuscript, which has been reformatted for the purposes of this dissertation.

Hubble, R. P., Naughton, G. A., Silburn, P. A., & Cole, M. H. (under review). Trunk exercises improve gait symmetry in Parkinson disease: A blind phase II randomised-controlled trial. *Movement Disorders*.

9.1 Abstract

Background: Deficits in head and trunk symmetry are linked to gait-related falls in Parkinson's disease (PD) and are often poorly managed with medications, emphasising the need for alternate therapies for symptom management. This blind phase II randomised-controlled trial sought to establish whether trunk-specific exercises could improve gait symmetry in PD.

Methods: Twenty-four PD patients with a history of falls, completed baseline assessments of symptom severity, fear of falling, mobility and quality of life. Head and trunk movement symmetry and erector spinae muscle activity were assessed during gait using three-dimensional accelerometers and surface electromyography, respectively. Following baseline testing, participants were randomly prescribed either 12-weeks of trunk-specific exercises or falls prevention education. Baseline tests were repeated post-intervention (12-weeks) and following a 12-week retention period (24-weeks). This trial is listed with the Australian New Zealand Clinical Trials Registry (ACTRN12613001175763).

Results: At 12-weeks, medial-lateral trunk ($p=0.002$) symmetry declined in the Education group relative to the baseline measures. These declines were complemented by clinical reductions in peak and baseline activation of the upper (peak: $p=0.02$; baseline: $p<0.001$) and lower (peak: $p<0.001$; baseline: $p<0.001$) erector spinae at 24-weeks. In contrast, the Exercise group demonstrated improved anterior-posterior ($p=0.04$) head symmetry at 24-weeks and improved anterior-posterior trunk symmetry at the 12- ($p<0.001$) and 24-week ($p=0.01$) time points compared with baseline.

Conclusions: These data suggest that trunk-specific exercises improved or, at least maintained, head and trunk symmetry during walking, which has implications for improving the independence and quality of life of people with PD. The decreased markers of trunk symmetry in the Education group over the relatively short period of time warrant further investigation.

9.2 Introduction

Postural instability is one of the most disabling symptoms of Parkinson's disease (PD) and contributes to falls in this population. Unfortunately, these symptoms are poorly managed by current pharmacological and surgical interventions [19], which emphasises the need for more effective alternative therapies for improving overall management of these patients. Exercise-based interventions are an inexpensive and easily-implemented form of therapy that has been shown to improve motor symptoms and clinical measures of balance, mobility and falls risk in PD [2, 6, 19, 63, 169, 170].

Despite these improvements, the rate and number of falls experienced by older adults [36, 203, 234] and people with PD [6, 36, 200, 203, 234] have not been significantly reduced. Previous research often cites insufficient power as the cause of non-significant findings [6], as the accuracy of falls data depends upon the honesty and diligence of the reporting participant. Objective measures of postural stability are suggested to provide greater insight into changes in postural stability in people with PD [105]; suggesting that these measures may be more appropriate for assessing subtle, yet meaningful, changes in a patient's function.

During locomotion, the maintenance of equilibrium relies upon one's ability to produce smooth and rhythmic movements of the head and trunk, which collectively comprise almost 60% of the body's mass [257]. Given the importance of these segments to dynamic postural control, researchers have commenced using lightweight body-mounted accelerometers to measure medial-lateral (side to side), anterior-posterior (front to back) and vertical (up and down) movement symmetry, as a proxy for gait stability [129, 138, 160, 257]. The harmonic ratio (HR) is one such measure [13, 130, 160, 237] that, in the context of walking, provides a measure of the symmetry of segmental accelerations during a single gait cycle [13]. Higher HRs describe improved gait symmetry and, hence are indicative of a more stable gait pattern. The harmonic ratio has previously been used to discriminate elderly adult fallers from non-

fallers [129] and is the most commonly used measure to assess movement symmetry in people with PD [104]. Specifically, the HR has identified differences in movement symmetry between PD patients and controls [104, 129, 138, 187, 213], PD freezers and non-freezers [250], PD patients with different dominant symptoms [95] and can even discriminate PD fallers from non-fallers [128, 129, 251].

While, one study involving people with cognitive deficits has examined the efficacy of exercise for improving gait symmetry in people with cognitive deficits [59], it is currently unknown whether targeted exercise can improve movement symmetry in people with PD. Given PD fallers demonstrate larger medial-lateral head [40, 42, 43] and trunk [40] movements during gait and that these movements are less symmetrical than non-fallers and age-matched controls [129], it is possible that exercises that target the mobility and endurance of these segments may assist with improving dynamic postural control in this population. As such, it was the purpose of this phase II randomised controlled trial to determine whether a 12-week exercise program that focused on improving the mobility and endurance of the trunk was more effective than a fall-prevention education program for improving gait symmetry in PD. It was hypothesised that patients would have improved gait symmetry following the exercise intervention.

9.3 Methods

9.3.1 Participants

This phase II randomised-controlled trial was developed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines [211]. To address the aim of this study, the same 22 participants described in Study 3 were invited to complete an additional gait assessment during the scheduled Baseline, 12-week and 24-week assessments (Table 14). The methods of participant recruitment and processes involved with assessing the

patients' eligibility to participate are outlined in Section 6.1.Prior to their involvement in this study, all volunteers provided written informed consent in accordance with the Declaration of Helsinki and the study's protocol (ACTRN12613001175763) [103] was approved by the University's Human Research Ethics Committee (Appendix E). The recruitment and assessment of all participants was completed between February 2014 and December 2015.

On the basis of an a-priori sample size calculation using medial-lateral trunk harmonic ratios recorded for people with PD during walking [138], a minimum of 11 participants was required per group to confidently report any significant changes in this gait symmetry (diff = 0.05, SD = 0.04, Cohen's d = 1.25, Power = 80%, p = 0.05). Given the longitudinal nature of the research, the target of recruiting 15 individuals per group allowed for a 25% attrition rate. The referenced study found that those with PD had significantly poorer anterior-posterior and medial-lateral gait symmetry (harmonic ratios) than healthy individuals while walking.

Table 14: Demographics and scores for the clinical baseline assessments completed by the entire PD cohort and the Exercise and Education sub-groups.

	All (n = 22) Mean ± SD / N (%)	Education (n = 11) Mean ± SD / N (%)	Exercise (n = 11) Mean ± SD / N (%)	Test	Sig. (p)
Demographics					
Gender (Male)	15 (68.2%)	8 (72.7%)	7 (63.6%)	3	0.65
Age (years)	65.4 ± 5.7	67.5 ± 5.8	63.3 ± 4.9	2	0.08
Height (cm)	170.6 ± 7.7	171.6 ± 7.7	169.7 ± 8.0	1	0.58
Mass (kg)	80.0 ± 20.3	78.6 ± 23.9	81.4 ± 17.0	1	0.76
Body Mass Index (kg/m^2)	27.2 ± 5.5	26.3 ± 5.9	28.2 ± 5.1	1	0.42
Cognition & Vision					
Addenbrooke's Cognitive Exam	91.5 ± 6.8	92.3 ± 5.4	90.6 ± 8.1	1	0.58
High Contrast Visual Acuity (LogMAR)	0.01 ± 0.1	0.04 ± 0.1	-0.02 ± 0.1	1	0.09
Mobility, Balance Confidence & Quality of Life					
Timed Up and Go (s)	9.3 ± 1.6	9.87 ± 1.7	8.85 ± 1.9	1	0.31
Activities-specific Balance Confidence (%)	80.8 ± 20.4	78.4 ± 26.0	83.3 ± 13.8	1	0.77
39-Item Parkinson's Disease Questionnaire	22.7 ± 11.6	24.1 ± 11.2	21.3 ± 12.2	1	0.49
Neurological Examination					
Disease Duration (years)	6.7 ± 5.0	7.0 ± 5.0	6.5 ± 5.2	2	0.84
Unified Parkinson's Disease Rating Scale (Part III)	19.4 ± 13.0	21.5 ± 11.7	17.3 ± 14.4	2	0.31
Hoehn & Yahr Stage Score	1.9 ± 0.6	2.0 ± 0.7	1.8 ± 0.6	3	0.50
Schwab & England Activities of Daily Living Scale	82.5 ± 8.8	81.0 ± 10.0	84.1 ± 7.7	2	0.34
Gait and Falls Questionnaire	10.7 ± 11.6	12.8 ± 13.5	8.6 ± 9.4	1	0.60
Freezing of Gait Score	5.3 ± 5.5	6.0 ± 5.9	4.6 ± 5.2	1	0.78
Retropulsion Test	0.4 ± 0.7	0.6 ± 0.7	0.6 ± 0.7	1	0.27
Levodopa Daily Equivalent Dose (mg)	716.5 ± 427.7	868.2 ± 475.7	564.8 ± 327.6	1	0.10
Dopamine Agonists	5 (22.7%)	3 (27.3%)	2 (18.2%)	3	0.61
Catechol-O-Methyl Transferase Inhibitors	8 (36.4%)	3 (27.3%)	5 (45.5%)	3	0.38
Monoamine Oxidase Inhibitors	8 (36.4%)	6 (54.5%)	2 (18.2%)	3	0.08
Benzodiazepines	1 (4.5%)	1 (9.1%)	0 (0.0%)	3	0.31

Note: Test 1 = One-way analysis of variance; Test 2 = Mann-Whitney U test; Test 3 = Chi-square test

9.3.2 Clinical Measures

Prior to randomisation, each participant completed a baseline assessment, which included a battery of clinical assessments that have been described in Section 6.2. All of the baseline assessments were conducted approximately 1-2 hours following one of the patient's scheduled doses of anti-parkinsonian medication to ensure that the results were representative of similar tasks performed in the real world. Participants with significant visual (Bailey-Lovie high contrast visual acuity >0.30 logMAR) and/or cognitive (ACE-R score <82) impairment were excluded prior to baseline testing.

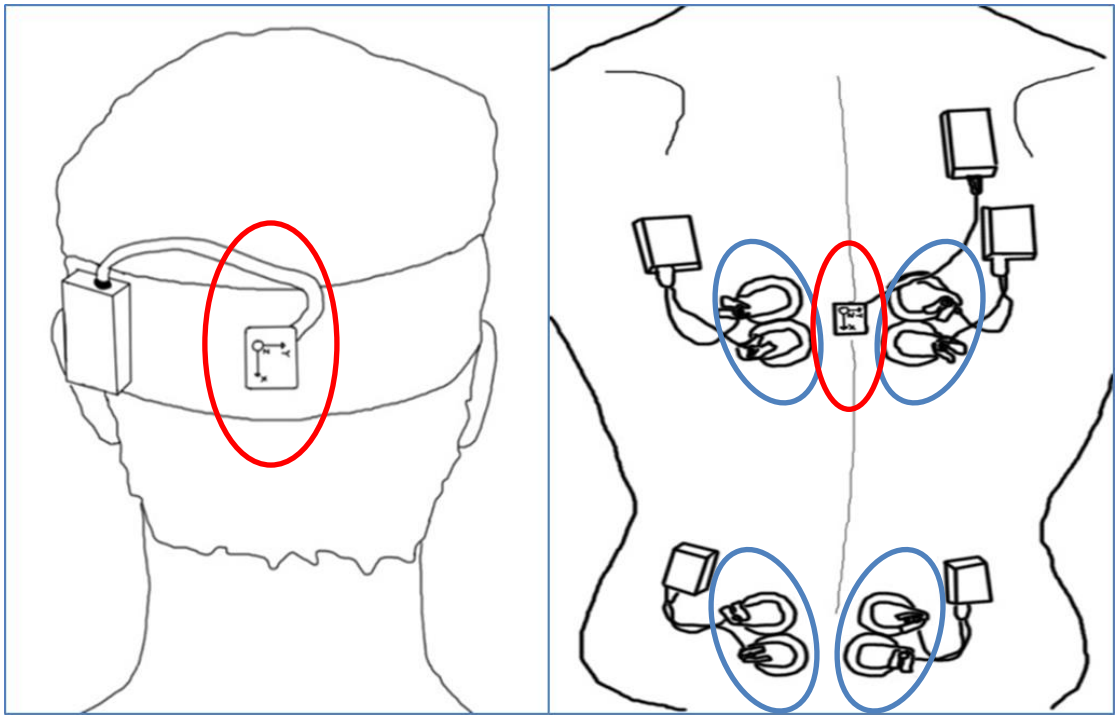

Figure 15: Placement of the head and trunk accelerometers (red) and surface electrodes (blue)

9.3.3 Gait Analysis

Following completion of the clinical assessments, participants were asked to perform four walking trials at a self-selected and comfortable speed along a 10-meter long walkway. While performing these trials, the three-dimensional acceleration patterns of the head and trunk (Figure 15) were assessed via two tri-axial accelerometers (500 Hz), while the activation patterns of the erector spinae muscles was evaluated using surface electromyography (1500

Hz). Prior to placing the accelerometers over the occipital protuberance and the 10th thoracic vertebra, each accelerometer was statically calibrating via the methods outlined in Section 7.3.3. This process served to establish a reference measure of the precise value recorded by each sensing axis for 1 gravitational unit.

To evaluate the muscle activation patterns of the upper and lower erector spinae during the walking trials, raw electromyograms were collected for the thoracic and lumbar erector spinae. Prior to applying the surface electrodes to these regions, the skin overlying the muscles of interest was prepared with an abrasive gel (NuPrep; Weaver & Company, Aurora, CO), and then cleaned thoroughly with an isopropyl alcohol wipe to minimise impedance at the electrode-skin interface and improve clarity of the myoelectric signal [97]. For individuals with excessive body hair, these areas were shaved prior to the application of NuPrep in order to maximise the fidelity of the myoelectric signal and ensure the best possible adherence to the skin. After skin preparation, four pairs of silver/silver chloride (Ag/AgCl) pre-gelled surface electrodes (AMBU Blue Sensor, Ballerup, DK; 34 mm diameter, 10 mm^2 sensing area) were placed with a centre-to-centre inter-electrode distance of 34 mm. Specifically, these electrode pairs were placed bilaterally 5 cm lateral to the spinous process of the T10 vertebral body and 2 cm lateral to the spinous process of the 3rd lumbar (L3) vertebral body (Figure 15) [242]. The erector spinae muscles were chosen for evaluation because individuals with PD are known to have more decreased trunk muscle performance than age-matched controls [23], which may influence their capacity to control trunk motion during walking. To facilitate synchronisation of head and trunk accelerations with trunk muscle activations, both datasets were wirelessly telemetered to a Telemyo DTS belt receiver and to a laptop running the MyoResearch XP software (Noraxon Inc., Scottsdale, AZ).

To allow for group and day comparisons, it was important for the muscle activation patterns to be normalised to a reference measure to allow for slightly different electrode placements from

day to day and/or anthropometric differences between the participants. While different methods of normalization have been reported in the literature (e.g. submaximal voluntary contractions, isokinetic maximal voluntary contraction), an isometric maximum voluntary isometric contraction was selected as it was considered to provide more reliable results [31] and had the ability to provide more information on the degree of muscle activation during walking than isokinetic methods [32]. Furthermore, submaximal tests do not produce reference values regarding the maximal capacity of the muscle, which may make it difficult to make comparisons between participants [91]. To facilitate the normalisation process, the activation patterns of the upper and lower erector spinae were expressed as a percentage of the peak activation recorded for these muscle during three maximum voluntary isometric contractions [91]. As people with PD are known to have more variable activation patterns [114] and take longer to achieve peak activity [254], participants were required to perform a minimum of three practice trials separated by a minimum of 30 seconds rest. This protocol ensured familiarisation with the movement and provided a warm up for the muscles before the maximal efforts. Participants were required to lie prone/prostrate on a padded table with their hips flexed and their feet on the floor with a Velcro strap placed over the lower torso to secure them to the table for safety. Each maximal effort involved simultaneously extending both hips to raise the legs to a horizontal position (i.e. 180°) at which point their movements were actively resisted by the researcher. This method was chosen in preference to the traditional Biering-Sorensen test to limit the potential difficulties that older participants may have with this more complex movement pattern [242]. The researchers verbally encouraged participants and visually-inspected each trial to ensure that muscle activation peaked before relaxation. The maximum value recorded for each muscle during the three trials was used for normalisation of walking data.

9.3.4 Data Processing – Gait symmetry

The primary outcome measure for this study was the harmonic ratio, which is derived from the head and trunk acceleration patterns and provides a measure of gait symmetry. A detailed description of the procedures involved in calculating the harmonic ratio has been provided in Study 2, but has been briefly summarised here for convenience. Raw head and trunk accelerations were transformed to a horizontal-vertical orthogonal coordinate system [164] to remove the effect of gravity from the anterior-posterior and medial-lateral axes of the sensors [164]. After transformation, accelerations were low-pass filtered using a bi-directional fourth order Butterworth filter, with a cut-off frequency of 30 Hz [117]. The time series of the filtered anterior-posterior, medial-lateral and vertical head and trunk accelerations were then divided into individual gait cycles by identifying the peaks in vertical trunk accelerations, which coincide with heel contact [129, 137, 138, 160]. The anterior-posterior, medial-lateral and vertical harmonic ratios were then calculated for successive gait cycles within each walking trial by dividing the sum of in-phase accelerations by the sum of out-of-phase accelerations [160].

9.3.5 Data Processing – Movement Amplitude and Muscle Function

In addition to the harmonic ratio, the amplitude of head and trunk accelerations was also assessed by processing the transformed and filtered anterior-posterior, medial-lateral and vertical accelerations using the root mean square (RMS) method outlined in Section 7.3.4.

For the assessment of muscle function, the three gait cycles completed for each leg produced eight peaks of muscle activity (i.e. 4 left and 4 right footfalls, yield 3 left and 3 right gait cycles; 1 peak per footfall) and the normalised amplitude of these peaks was then averaged to represent peak muscle activation. To evaluate the extent to which these superficial trunk muscles 'switched off' between strides, the minimum EMG amplitude between successive heel

contacts (i.e. within the seven troughs between the eight activation peaks) was determined and averaged to represent the baseline level of activation. Processing of the raw electromyograms was completed in the MyoResearch MR 3.6.20. As electromyography data from the trunk muscles are often contaminated by the electrical activity of cardiac muscle, an adaptive filter was initially applied to raw data to attenuate any electrocardiogram artefact. Data were then full-wave rectified and low-pass filtered using a 4^{th} order Butterworth filter that had a cut-off frequency of 20 Hz [52]. The peak amplitude of the EMG signal throughout the gait cycle was evaluated by calculating the root mean square value of the signal over consecutive 50 ms windows (i.e. 75 samples) with a 74 sample overlap. To facilitate normalisation of the EMG data, the data collected during the maximum voluntary isometric contraction trials were processed using the same procedures and the peak value achieved for each muscle during the three trials was recorded. Finally, the data collected for each muscle during the walking trials were expressed as a percentage of the peak MVC value for the same muscle to facilitate comparison between different sites and different participants [91].

9.3.6 Randomisation, Blinding and Interventions

Given the somewhat subjective nature of many of the clinical assessments used in this study, it was important to ensure that these tests were completed by a member of the research team who was blind to each participant's group allocation. To facilitate this, participants were assigned to their group following the baseline assessments by the lead investigator (RPH) using a random allocation sequence generated by a co-investigator (GAN), who was not involved in participant allocation or assessment (block size=2; 1:1 ratio). The clinical assessments were conducted at Baseline, 12-weeks and 24-weeks by an experienced movement disorders scientist who was blinded to participant group assignment (MHC).

Following completion of the baseline assessments and group allocation, participants allocated to the Exercise intervention group completed the 12-week trunk-specific exercise program that is outlined in Section 8.3.5. Similarly, those who were randomised to the Education group received a weekly education brochure via mail or email, outlining lifestyle changes and/or strategies around the home that they might adopt to minimise their risk of falling (Section 8.3.5).

9.3.7 Statistical Analysis

As was the situation for Study 3, the withdrawal of a small number of participants from the study made it impossible to adopt an 'intention to treat' approach for this study. Therefore, analyses of the clinical and biomechanical outcomes post-intervention were based on per protocol analysis. Linear mixed model analyses were conducted to determine whether the trunk-specific exercise program was more effective than the education program at improving head and trunk symmetry, movement amplitude and muscle activation. These models included one repeated factor (Day; 3 levels), one fixed factor (Group; 2 levels) and 2 covariates (levodopa and walking speed). Walking speed and levodopa were included as covariates in these models, as walking speed is known to influence accelerations [129, 130] and levodopa is known to improve motor symptoms in PD [87, 184, 210]. When a significant main effect or interaction was identified, the Tukey's Least Significant Difference (LSD) post-hoc procedure was used to identify where the differences lay. All statistical analyses were completed in the SPSS v.22 (New York, USA) and the level of significance was set at $p<0.05$. Furthermore, the minimal detectable change (MDC) for each measure was derived to highlight the clinical importance of the presented outcomes.

9.4 Results

9.4.1 Study Population Retention and Compliance

Of the 24 participants assessed at baseline, 22 completed the 12-week intervention and two withdrew citing changes in circumstances that made them unable to commit to the project. To limit the potential for bias, participants who were unable to complete or who were excluded from completing the intervention were not reassessed at the 12- or 24-week mark and their baseline data are not presented in the subsequent analyses. Comparisons of the remaining 22 patients at baseline indicated that the Exercise and Education groups did not differ for measures of cognition, vision, neurological function or mobility. However, individuals in the Exercise group had greater body mass index (BMI) at baseline than the Education group (Table 15). In accordance with the strict inclusion and exclusion criteria adhered to throughout the participant recruitment phase, all 22 participants included in this study were free of any significant medical conditions (other than PD) that may have influence their balance and/or gait and presented with no significant physical, psychological or visual disabilities at the time of testing.

Between the 12- and 24-week assessments, an additional four participants (two Exercise, two Education) were lost to follow-up, with two receiving deep brain stimulation surgery, one not contactable via telephone or email and one unable to return for the 24-week assessment. As such, the data presented for the 24-week follow-up is based on data for the remaining 18 participants (9 Exercise; 9 Education). Average participant compliance for the exercise sessions was 90%, with individual compliance ranging from 8 (67%) to 12 (100%) of the 12 supervised sessions. Participants reported no discomfort or harmful effects associated with either intervention.

9.4.2 Clinical Outcomes

The results of the linear mixed model analyses returned significant Group effects for the PDQ-39 ($p=0.03$), UPDRS III ($p=0.02$) and levodopa daily equivalents ($p=0.02$). These findings indicated that, irrespective of day, the Education group had a significantly poorer quality of life,

experienced greater motor symptom severity and took larger amounts of levodopa compared with the Exercise group. Furthermore, the lack of any significant main effects for Day or any significant Group*Day interactions indicated that these group differences remained relatively unchanged throughout the study (Table 15).

Table 15: Mean (± SD) scores for the clinical assessments of symptom severity, disease stage, mobility, balance confidence and quality of life

	Education			Exercise			Main Effects		Interaction
	Baseline	12-Week	24-Week	Baseline	12-Week	24-Week	Group	Day	Group*Day
Mobility and Balance Confidence									
Timed Up and Go (s)	9.87 ± 1.66	9.96 ± 2.02	8.85 ± 1.90	8.78 ± 1.29	9.26 ± 1.80	8.72 ± 0.90	ns	ns	ns
Activities-specific Balance Confidence	78.35 ± 25.96	78.70 ± 23.09	89.06 ± 5.34	83.30 ± 13.78	74.15 ± 30.82	76.39 ± 31.21	ns	ns	ns
Quality of Life									
39-Item Parkinson's Disease Questionnaire	24.13 ± 11.24	22.84 ± 10.77	17.95 ± 7.78	21.33 ± 12.32	21.27 ± 14.38	16.60 ± 9.30	‡	ns	ns
Neurological Examination									
Unified Parkinson Disease Rating Scale III	21.45 ± 11.73	24.55 ± 10.15	19.50 ± 7.97	17.27 ± 14.40	16.45 ± 11.94	15.11 ± 5.80	‡	ns	ns
Hoehn & Yahr Stage Score	1.95 ± 0.69	2.14 ± 0.67	1.67 ± 0.41	1.77 ± 0.56	1.55 ± 0.69	1.56 ± 0.68	ns	ns	ns
Schwab & England Activities of Daily Living	80.91 ± 9.95	80.00 ± 7.07	85.00 ± 6.32	84.09 ± 7.69	84.55 ± 7.57	86.67 ± 8.29	ns	ns	ns
Gait and Falls Questionnaire	12.82 ± 13.50	10.36 ± 10.08	5.83 ± 4.88	8.64 ± 9.45	9.27 ± 12.19	5.44 ± 9.04	ns	ns	ns
Freezing of Gait	6.00 ± 5.92	5.27 ± 5.24	3.17 ± 2.64	4.64 ± 5.20	5.00 ± 6.00	2.89 ± 4.62	ns	ns	ns
Retropulsion Test	0.55 ± 0.69	0.55 ± 0.82	0.33 ± 0.52	0.27 ± 0.65	0.27 ± 0.65	0.11 ± 0.33	ns	ns	ns
Levodopa Daily Equivalents (mg)	868.23 ± 475.71	783.59 ± 530.36	794.00 ± 521.95	564.81 ± 327.58	569.55 ± 343.83	484.11 ± 338.37	‡	ns	ns

ns = no significant differences; **‡ =** Significant Group effect; **¥** = Significant Day effect; i = Significant difference between Baseline and 12-week; ii = Significant difference between Baseline and 24-week; iii = Significant difference between 12-week and 24-week; **Ŧ** = Significant Group*Day interaction; **a** = Significant difference between Baseline and 12-week for Education; **b** = Significant difference between Baseline and 24-week for Education; **c** = Significant difference between 12-week and 24-week for Education; **d** = Significant difference between Baseline and 12-week for Exercise; **e** = Significant difference between Baseline and 24-week for Exercise; **f** = Significant difference between 12-week and 24-week for Exercise

9.4.3 Primary Outcome: Movement Symmetry

Analysis of the AP, ML and VT head and trunk movement symmetries showed no significant Group effects. However, significant main effects for Day were returned for AP head and VT trunk symmetry (Table 16). Pairwise comparisons revealed that AP head symmetry was reduced during the 12-week assessment compared with both the baseline ($p=0.03$) and 24-week ($p=0.05$) time points. Furthermore, VT trunk symmetry was lower during the 12- ($p<0.001$) and 24-week ($p=0.03$) assessments, relative to baseline.

Post hoc analyses following Group*Day interactions revealed that AP ($p=0.01$) and VT head ($p=0.05$) symmetry and ML ($p=0.002$) trunk symmetry were reduced at 12-weeks compared with baseline for the Education group (Figure 16). Despite these findings, the reported MDCs for these outcomes suggested that the changes in AP and VT head symmetries were not clinically meaningful. Group*Day interactions were also evident for the Exercise group for AP ($p=0.02$) and VT ($p<0.001$) head and AP ($p=0.007$) trunk movement symmetry. Pairwise comparisons revealed that AP head movement symmetry improved at 24-weeks compared with the baseline ($p=0.04$) and 12-week ($p=0.02$) assessments, while VT head movement symmetry also improved at 12-weeks relative to baseline ($p=0.01$). Similar improvements were evident for the trunk segment, which showed increased AP movement symmetry at both 12- ($p<0.001$) and 24-weeks ($p=0.007$) compared with baseline. While the reported MDC values indicated that the majority of these improvements were clinically meaningful, the improvement observed in VT head symmetry at 12-weeks did not achieve a level that could be considered clinically important (Table 16).

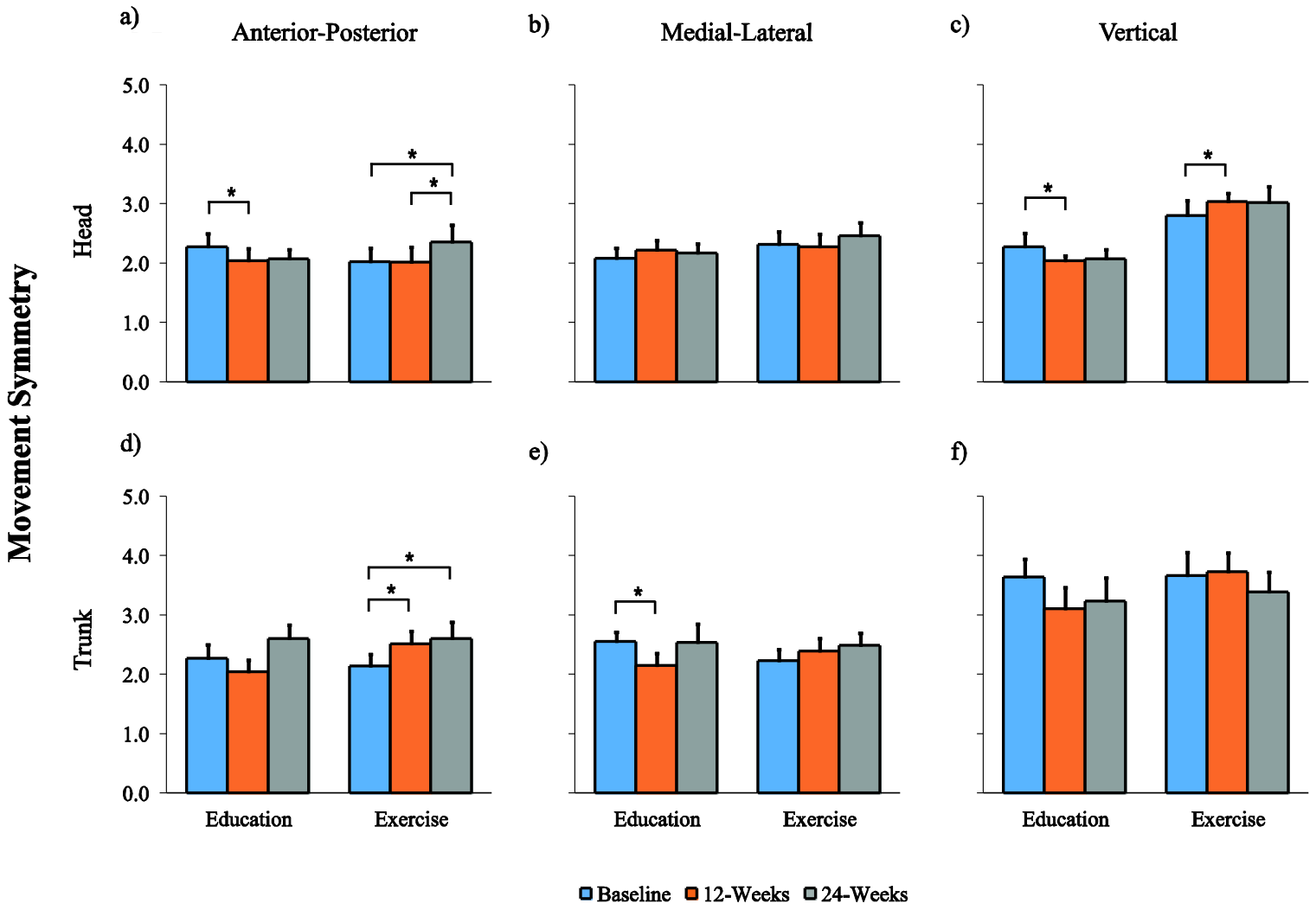

Figure 16: Mean (+1 SEM) harmonic ratios for the Exercise and Education groups.

9.4.4 Secondary Outcomes: Movement Amplitude

Analysis of the movement amplitude data (RMS accelerations) returned significant Group effects for ML head ($p=0.05$) and AP trunk ($p=0.04$) acceleration, which indicated greater movement amplitudes for the Exercise group (Table 16). Additionally, the main effect for Day indicated that AP head movement amplitude was significantly lower at 12-weeks compared with baseline, while VT head ($p<0.001$) and AP ($p<0.001$), ML ($p<0.001$) and VT ($p<0.001$) trunk movement amplitudes were all lower at baseline compared with the 12-week assessment. AP and ML trunk movement amplitude remained increased during the 24-week assessment relative to baseline, while trunk VT movement amplitude increased and head VT movement amplitude decreased relative to the 12-week assessment.

Group*Day interactions were identified for VT head and AP, ML and VT trunk movement amplitudes. Pairwise comparisons revealed greater VT head ($p<0.001$) and AP ($p<0.001$), ML ($p<0.001$) and VT ($p=0.003$) trunk movement amplitudes for the Education group at 12-weeks relative to baseline (Figure 17). Additionally, VT head ($p<0.001$) movement amplitude decreased by the 24-week assessment, AP ($p=0.01$), ML ($p=0.01$) and VT ($p<0.001$) trunk movement amplitudes all remained elevated at 24-weeks relative to baseline. The reported MDCs indicate that most of these changes were clinically relevant; however, the increased VT head movement amplitude at 12-weeks and ML trunk movement amplitude at 24-weeks fell short of clinical significance using MDC change statistics. Similar changes were highlighted in movement amplitude for the Exercise group, with VT head ($p<0.001$) movement amplitude increasing at 24-weeks relative to baseline and ML trunk movement amplitude increased at 24-weeks relative to the baseline ($p<0.001$) and 12-week ($p<0.001$) assessments.

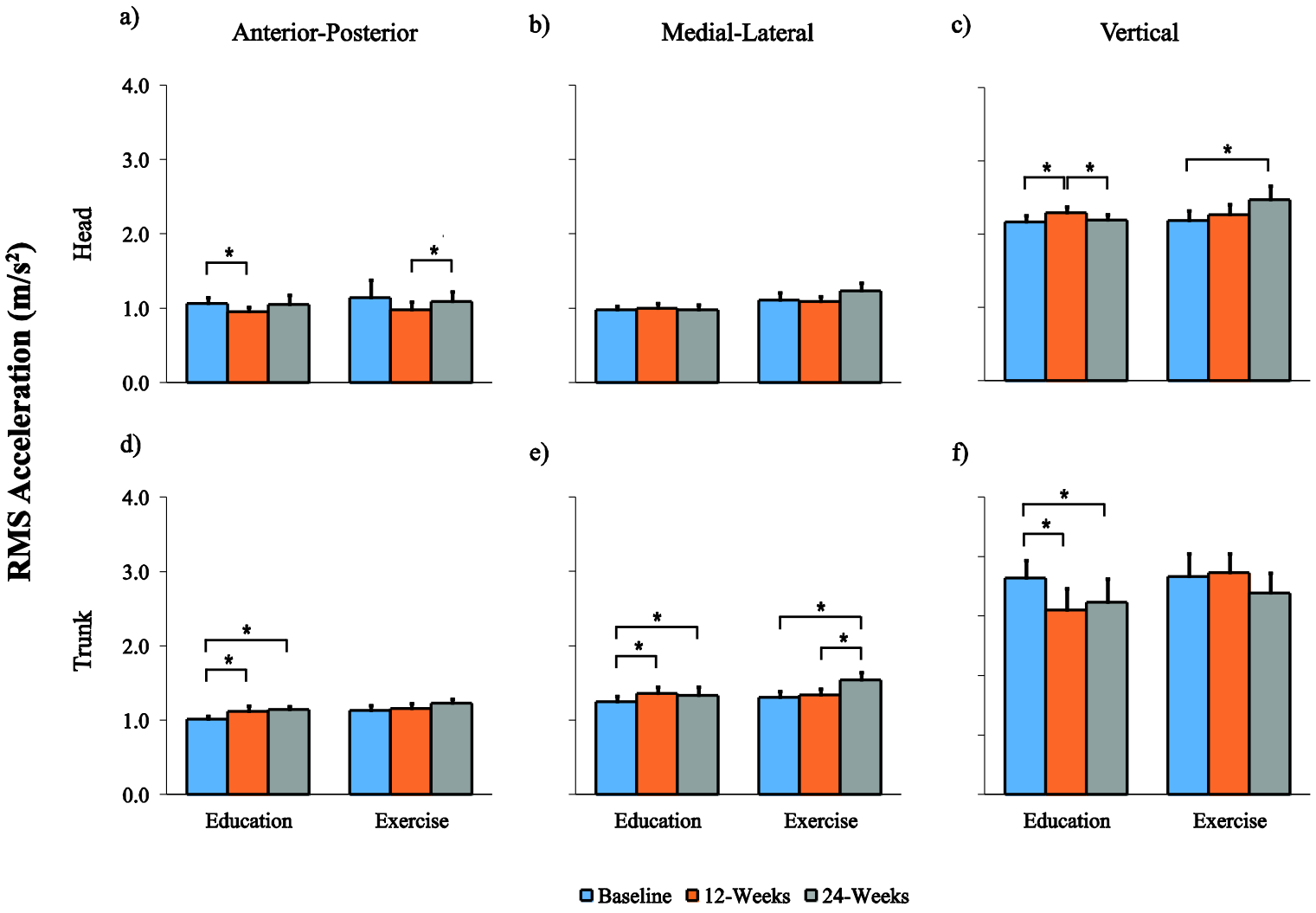

Figure 17: Mean (+1 SEM) RMS accelerations for the Exercise and Education groups.

9.4.5 Secondary Outcomes: Trunk Muscle Function

The results for the assessment of trunk muscle function revealed no significant Group effects (p>0.05). However, significant Day effects for peak (p=0.04) and baseline (p=0.02) activation of the lower erector spinae indicated that both measures were reduced at 24-weeks relative to baseline, independent of group allocation (Table 16).

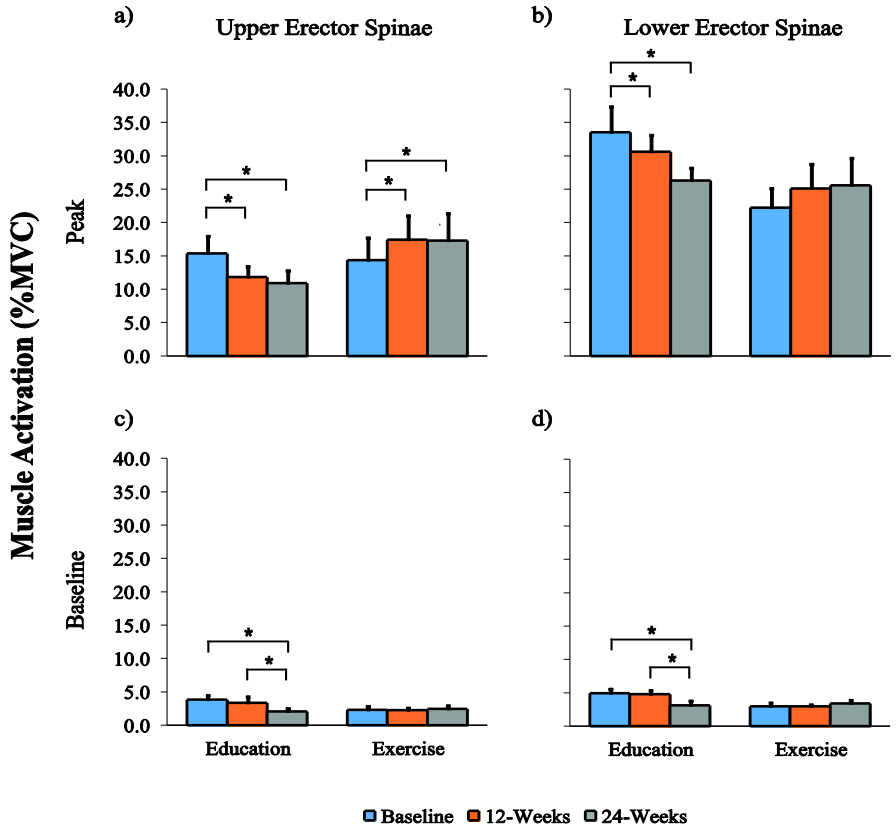

Figure 18: Mean (+1 SEM) erector spinae activity for the Exercise and Education groups.

Group*Day interactions were found for peak and baseline levels of activation for the upper and lower erector spinae muscles. Pairwise comparisons indicated that peak activation of the upper and lower erector spinae was significantly reduced at 12- and 24-weeks relative to baseline for the Education group (Figure 18). Similarly, baseline levels of upper and lower erector spinae activity were significantly reduced at 24-weeks for the Education group, relative to the baseline and 12-week assessments. In contrast, peak activation of the upper erector spinae increased at the 12- (p=0.004) and 24-week (p<0.001) time points for the Exercise

group, relative to baseline, while the other outcomes did not significantly change for this sub-group. While the results from the MDC calculations showed that the changes in upper erector spinae activity for the Exercise group post-intervention were not clinically important, the reduced peak and baseline erector spinae activity for the Education group at 24-weeks did exceed the threshold considered as clinically meaningful.

Table 16: Mean (± SD) movement symmetry, movement amplitude and muscle function for the Education and Exercise groups.

		Education			Exercise				Main Effects		Interaction
		Baseline	12-Week	24-Week	Baseline	12-Week	24-Week	95% MDC	Group	Day	Group*Day
Primary Outcome											
Movement Symmetry											
Head	AP	2.27 ± 0.80	2.04 ± 0.72	2.07 ± 0.52	2.02 ± 0.80	2.01 ± 0.90	2.35 ± 0.91	0.29	ns	**¥, i, iii**	**Ŧ, a, e, f***
	ML	2.08 ± 0.61	2.22 ± 0.59	2.17 ± 0.51	2.31 ± 0.76	2.27 ± 0.77	2.46 ± 0.70	0.24	ns	ns	ns
	VT	2.27 ± 0.81	2.04 ± 0.72	2.07 ± 0.52	2.80 ± 0.89	3.03 ± 1.10	3.02 ± 0.84	0.34	ns	ns	**Ŧ, a, d**
Trunk	AP	2.27 ± 0.81	2.04 ± 0.72	2.60 ± 0.74	2.14 ± 0.71	2.51 ± 0.75	2.60 ± 0.87	0.22	ns	ns	**Ŧ, d*, e***
	ML	2.55 ± 0.57	2.15 ± 0.73	2.54 ± 0.95	2.23 ± 0.67	2.39 ± 0.75	2.49 ± 0.66	0.22	ns	ns	**Ŧ, a***
	VT	3.64 ± 1.03	3.10 ± 1.24	3.23 ± 1.22	3.66 ± 1.35	3.73 ± 1.10	3.39 ± 1.03	0.43	ns	**¥, i, ii**	ns
Secondary Outcomes											
Movement Amplitude											
Head	AP	1.06 ± 0.32	0.95 ± 0.25	1.05 ± 0.40	1.14 ± 0.82	0.98 ± 0.38	1.09 ± 0.43	0.20	ns	**¥, i**	ns
	ML	0.98 ± 0.19	1.00 ± 0.24	0.98 ± 0.23	1.11 ± 0.36	1.09 ± 0.26	1.23 ± 0.35	0.10	‡	ns	ns
	VT	2.16 ± 0.34	2.29 ± 0.31	2.19 ± 0.25	2.18 ± 0.49	2.26 ± 0.52	2.47 ± 0.59	0.15	ns	**¥, i, iii**	**Ŧ, a, c, e***
Trunk	AP	1.01 ± 0.19	1.12 ± 0.27	1.14 ± 0.17	1.13 ± 0.26	1.16 ± 0.24	1.23 ± 0.19	0.08	‡	**¥, i, ii**	**Ŧ, a*, b***
	ML	1.25 ± 0.28	1.36 ± 0.32	1.33 ± 0.38	1.31 ± 0.28	1.34 ± 0.29	1.54 ± 0.34	0.10	ns	**¥, i, ii**	**Ŧ, a*, b, e*, f***
	VT	2.40 ± 0.38	2.59 ± 0.42	2.76 ± 0.74	2.46 ± 0.59	2.43 ± 0.54	2.75 ± 0.50	0.17	ns	**¥, i, iii**	**Ŧ, a*, b***
Muscle Function (%MVC)											
Peak	Upper ES	15.39 ± 8.77	11.81 ± 5.58	10.91 ± 5.94	14.35 ± 11.49	17.41 ± 12.39	17.30 ± 12.47	3.70	ns	ns	**Ŧ, a, b*, d, e**
	Lower ES	33.53 ± 13.09	30.59 ± 8.73	26.28 ± 13.24	22.24 ± 9.73	25.11 ± 12.37	25.59 ± 12.10	4.19	ns	**¥, ii**	**Ŧ, a, b***
Baseline	Upper ES	3.84 ± 2.45	3.34 ± 3.48	2.08 ± 1.51	2.29 ± 2.06	2.28 ± 1.41	2.45 ± 1.79	0.83	ns	ns	**Ŧ, b*, c***
	Lower ES	4.93 ± 2.46	4.78 ± 2.23	3.10 ± 2.38	2.99 ± 1.96	2.95 ± 1.12	3.40 ± 1.80	0.81	ns	**¥, i, ii**	**Ŧ, b*, c***

AP = anterior-posterior; **ML** = medial-lateral; **VT** = vertical; **MDC** = minimum detectable change; **ns** = no significant differences; **‡ =** Significant Group effect; **¥** = Significant Day effect; **i** = Significant difference between Baseline and 12-week; **ii** = Significant difference between Baseline and 24-week; **iii** = Significant difference between 12-week and 24-week; **Ŧ** = Significant Group*Day interaction; **a** = Significant difference between Baseline and 12-week for Education; **b** = Significant difference between Baseline and 24-week for Education; **c** = Significant difference between 12-week and 24-week for Education; **d** = Significant difference between Baseline and 12-week for Exercise; **e** = Significant difference between Baseline and 24-week for Exercise; **f** = Significant difference between 12-week and 24-week for Exercise. **NOTE:** An asterisk (*) after a symbol indicates that the statistically-significant difference can also be considered clinically important.

9.5 Discussion

This phase II randomised-controlled trial represents the first study to examine the efficacy of a 12-week trunk-specific exercise program for improving gait symmetry in PD. The results support the hypothesis that trunk-specific exercises may improve (or at the very least, maintain) AP head and trunk symmetry and trunk muscle function in this population. Furthermore, our results suggest that, without specifically focusing on maintaining mobility and core strength, medial-lateral trunk symmetry may decline in as little as 12 weeks.

The findings of this study are commensurate with previous research, which demonstrated improvements in vertical trunk movement symmetry for people with mild cognitive impairment following a 6-month multi-component exercise program [59]. Additionally, improvements in gait symmetry have been observed following different verbal cueing strategies in PD [137]. Our results extend existing knowledge by suggesting measures of gait symmetry, such as the harmonic ratio, may be suitable for assessing subtle changes in gait symmetry (a proxy for postural stability) when the larger cohorts required for prospective falls studies are unobtainable. Our results also suggest that the benefits offered by the exercise program can be maintained for up to 12-weeks following the cessation of a regular training regime. These findings are important, as they suggest that performing exercises that target trunk strength and mobility as little as once per week can improve movement symmetry and reduce falls risk in people with PD.

The improvements in AP head and trunk symmetry in the Exercise group were accompanied by increases in head (VT) and trunk (ML) movement amplitude following the 12-week intervention. Similar increases in movement amplitude were also evident for the trunk segment (AP, ML, VT) for the Education group. As PD is a hypokinetic disorder [248], it is not surprising that some studies [67, 129] have shown that the amplitude and speed of head and trunk movements are reduced in this population relative to age-matched controls. Collectively, these results suggest that an increase in movement amplitude would be considered an improvement for

people with PD, as it would bring their segmental accelerations closer to those values observed in age-matched controls. Despite this interpretation, the results presented for the Education group should be considered with some caution. Reference to the means and standard deviations suggests that head and trunk accelerations were generally higher for the Exercise group at baseline than for the Education group. As such, the increased accelerations recorded for the Education group during the 12- and 24-week assessments did not result in significantly greater head and/or trunk movement than the Exercise group, but rather accounted for the differences measured at baseline.

The reported changes in gait symmetry and movement amplitude were also complemented by changes in trunk muscle function. Specifically, the Education group experienced significant and clinically-important declines in trunk movement symmetry at 12-weeks that were combined with declines in peak and baseline levels of erector spinae activity at 24-weeks. In contrast, while the targeted exercise intervention resulted in statistically significant improvements in trunk muscle function for the Exercise group, these changes were not sufficient large to be considered clinically meaningful. Nevertheless, these results provide evidence to suggest that the Exercise program was successful at helping to maintain trunk muscle function for the Exercise group, which has important implications for clinical practice. For example, the phasic bilateral activation of the erector spinae during walking serves to resist the large anteriorly-directed torque imposed upon the body at heel contact [256]. As such, the maintenance of trunk muscle function in the Exercise group may help to explain the improved AP head and trunk symmetry reported for these individuals during the 12- and 24-week assessments.

As with any study, potential limitations should be considered when interpreting the outcomes. First, a slow rate of participant recruitment resulted in a relative small number of patients (from a statistical perspective) into the program. While the comparisons reported between the baseline and post-intervention (12-week) assessments are supported by an a-priori

power calculation, the loss of 2 participants from each of the groups between the 12- and 24-week assessments meant that these comparisons may be slightly underpowered. As such, the results presented for the 24-week follow-up should be interpreted with care. Second, the Education group reported increased difficulty with motor symptoms and poorer quality of life. Collectively, these factors may have impacted their motivation for the MVC trials, which would have influenced their normalised EMG results. However, it should be noted that reduced motivation during the MVC trials would be expected to result in lower maximum values and, hence larger normalised trunk muscle activity during the walking trials. As the results indicate, even if these patients were lacking motivation during one or more of the assessments, they still recorded significantly lower peak and baseline activity at 12- and/or 24-weeks.

In conclusion, our results demonstrate that walking symmetry and trunk muscle function can degrade quite rapidly in people with PD. However, by performing as little as one focussed exercise session per week it seems possible to offset these changes and statistically and clinically improve or, at the very least maintain, gait symmetry. Such improvements in function are likely to have significant implications for an individual's self-confidence and independence, which ultimately should contribute to an improved quality of life. Given these findings, exercises that target trunk muscle function should be considered when developing an exercise program that seeks to improve balance and gait symmetry and reduce falls risk in people with PD.

10.0 Overall Discussion and Conclusions

This thesis comprised four inter-related studies that sought to determine the utility of accelerometers for assessing standing and walking balance and the potential efficacy of a 12-week trunk-specific exercise program for improving static and dynamic postural stability in people with PD. Overall, this thesis produced a number of important findings. First, accelerometers have been placed on numerous anatomical landmarks to assess static and dynamic postural stability, an accelerometer placed on the trunk is the most common method used for people with PD. Similarly, while many accelerometer-based measures have been used to assess stability in different populations, the harmonic ratio has been the most commonly used for assessing gait stability in PD populations. Second, the results presented in this dissertation suggest that wearable sensors may offer additional insight into the balance and gait deficits experienced by people with PD and appear to be capable of quantifying differences that are not easily detected with common clinical assessments. Lastly, it was shown that trunk-specific exercises performed once a week may be beneficial for managing symptoms of postural instability and gait disability in people with PD. While the improvements in standing balance were not quite large enough to be considered clinically meaningful, the improvements observed during walking were substantial enough to be considered clinically important. Given that the vast majority of falls occur during dynamic tasks, such as locomotion, the improved head and trunk symmetry observed following the 12-week program may have significant implications for falls prevention in this population. The findings presented in this thesis have the potential to contribute to improved screening and treatments for symptoms of postural instability and gait disability in people with PD and should ultimately help to improve the quality of life of people living with this condition.

Parkinson's disease poses a significant financial burden to the public health system with an estimated $8.3 billion per annum for the Australian population as of 2011 [189]. However, this

burden extends far beyond the Australian population, with annual estimated costs of $23 billion USD (≈$29.3 billion AUD) in the United States [107] and £600 million (≈$1.2 billion AUD) in the United Kingdom [68]. With advances in medical science, the average age of the general population is increasing, meaning that age-related conditions, such as PD, are likely to become more prevalent [189]. Despite the significant physiological and psychological burdens that this rise in cases will impose upon those diagnosed and their loved ones, the direct and indirect costs associated with the condition's management will also increase [189]. PD is a condition that directly affects an individual's ability to be productive in their careers and can make even the simplest of everyday tasks increasingly difficult. With disease progression, the severity of motor (e.g. tremor, joint stiffness, postural instability) and non-motor (e.g. sleep disorders, cognitive problems, depression) symptoms become more severe; ultimately reducing the patient's independence and overall quality of life. Given that postural instability is the most disabling symptoms of PD [248] and that it is not well managed with traditional therapies, it is unsurprising that research continues to seek better strategies for improving these symptoms. Within this context, this program of research addressed a series of interconnected issues, which sought to develop improved methods for assessing and managing symptoms of postural instability in people with PD.

Due to the ineffectiveness of pharmacological and surgical intervention on postural instability [19], clinicians and scientists have turned to non-invasive and natural therapies such as exercise to improve postural stability in PD. Structured and progressive home-based exercise programs have been shown to improve strength [47, 85] balance [47], and motor symptoms in PD [2, 112, 139]. However, exercise interventions, to date, have also been unable to improve typical clinical balance measures [2, 84, 139], falls risk [2], and reduce the rate of falls in PD [6, 84]. This highlights the need for more high quality evidence on the ability of exercise to reduce the rate of falls in PD [85]. One of the most recent positions on the impact of exercise intervention on improving postural instability in PD concluded that programs lack sufficient focus on balance in

challenging situations and multi-component home-based exercise programs show little to no beneficial effects in improving stability [122]. This thesis has addressed this shortcoming of previous research by incorporating current best practices into a randomised controlled trial, the highest quality of research. By seeking to incorporate balancing tasks performed under more challenging conditions, the progressive exercise-based intervention adopted in this program of research would be expected to have greater transferability to similarly challenging situations in real-world settings.

The primary reliance on clinical tests of mobility and physiological function to evaluate the efficacy of their program may be a limitation of many previous exercise-based interventions. The systematic evidence generated from Study 1 identified wearable sensors as being a suitable means of assessing postural stability in people with PD and while these devices are widely used in laboratory-based studies, they have traditionally been lacking in previous high-quality randomised controlled trials [104]. Given the findings of Study 1, this program of research combined common clinical assessments with outcomes derived from wearable sensors to determine the potential benefits of this technology over common procedures. The results of Study 2 supported the hypothesis that objective measures of dynamic postural stability would provide greater insight into gait deficits than common clinical measures of mobility, gait difficulty, postural stability and balance confidence. The findings of this study suggest that previous studies that have relied solely on clinical assessments to determine the efficacy of a specific falls prevention intervention may have been limited in their capacity to report clinically-meaningful changes in postural stability. The results of Study 3 partially supported the hypothesis that a 12-week trunk-specific exercise program would be effective at significantly reducing objective measures of postural sway; although the reported changes were insufficient to be considered clinically meaningful. Similarly, the results of Study 4 supported the hypothesis that the 12-week exercise-based intervention would improve accelerometer-based measures of head and trunk symmetry during walking and influence the

activation patterns of the trunk muscles. In contrast, however, the results of this research did not support the hypothesised improvements in clinical measures of symptom severity, balance confidence and gait impairment following the 12-week exercise program. Collectively, these findings provide further support for the notion that common clinical assessments of balance, mobility and symptom severity may lack the sensitivity to detect small, yet clinically-meaningful changes in postural stability for patients with PD.

For the first time, through the rigor of a randomised controlled trial, this program of research has established that objective measures of gait symmetry, postural sway and muscle function can provide insight into the efficacy of exercise-based interventions that target improved postural stability in people with PD. The exercise intervention produced improvements in head and trunk movement symmetry (as measured with the harmonic ratio) during gait that was not only statistically significant, but clinically meaningful also. Similar improvements were recorded during the posturography assessments when the patients stood on the foam surface with their eyes closed. Under this most challenging condition, measures of postural sway decreased for the Exercise group following the 12-week intervention, suggesting an overall improvement in postural control. The improvement in head and trunk symmetry for the Exercise group were limited to the anterior-posterior (front-to back) plane of movement, which is commensurate with the findings of previous research examining the effect of verbal cueing strategies on gait symmetry in the PD population [137]. The reported improvements in movement symmetry and postural sway for the Exercise group were strengthened by the findings of increased postural sway and significant and clinically-meaningful reductions in trunk movement symmetry and erector spinae activity for those in the Education group. The lack of any significant changes in postural stability during the simpler standing balance tasks (e.g. standing on a firm surface with eyes open) is commensurate with previous research [2, 45, 121] and suggests that screening for balance deficits should involve the assessment of balance under challenging conditions. Collectively, the findings of this randomised

controlled trial highlighted that inactivity may lead to more rapid declines in postural stability and trunk muscle function and suggest that regular exercise may not only be useful for improving postural stability, but also for maintaining trunk strength and endurance.

As a phase-II randomised controlled trial (proof-of-concept), this study sought to determine the efficacy of a 12-week trunk-specific exercise intervention for the improvement of objective measures of standing balance and movement stability in people with PD. While the sample size may be considered relatively small, the results reported for the primary outcome measures were supported by a-priori sample size calculations. Nevertheless, the transferability of these findings to larger patient cohorts is unknown and, hence, further research is warranted. Additionally, a potential shortcoming of this research was that trunk muscle endurance (assessed via a front bridge static hold) was not assessed for the education group at baseline or during the 12- and 24-week assessments. Therefore, while consistent improvements in static hold times were reported for all participants in the exercise group after the intervention, it was not possible to establish what proportion of this change might simply be attributed to naturally-occurring differences between testing dates. Furthermore, it should be acknowledged that the improvements reported for the exercise group may have been enhanced if the weekly training frequency was increased from one session per week to three sessions per week (for example). While it was an ancillary aim of this program of research to answer this question [103], difficulties with participant recruitment and retention made it necessary to forfeit this aspect of the experiment and focus on the primary aim. Nevertheless, given the encouraging outcomes of this study, future research might seek to establish whether increasing the frequency of exercise leads to greater improvements in static and dynamic balance for people with PD. It should also be noted that the outcomes presented in this dissertation were based on a relatively large number of statistical comparisons made between the groups, the testing dates and testing conditions. When conducting a large number of statistical tests, the risk of reporting a significant outcome simply due to chance (i.e. a Type 1 error) is

inflated. As statistical corrections for multiple comparisons are not recommended for exploratory studies [15], this risk should be considered when reviewing the reported findings.

In addition to the abovementioned shortcomings, it is also important to acknowledge a number of potential limitations associated with the recruitment and sampling methods used for this research. First, the information letter that was sent to all potential participants informed them that they would be randomly assigned to either an exercise-based intervention or an education program. As such, it is possible that some of the participants who were randomly allocated to the education group may have taken it upon themselves to increase their physical activity levels outside of the study; potentially influencing the outcomes. Second, with any study of this nature there is always a risk that the sample will be biased towards people who are more intrinsically motivated and/or genuinely believed that they will benefit from the intervention, which may impact that representativeness of the sample. Finally, while the exercise-based intervention used in this thesis was designed to conform to the current recommendations for best clinical practice [132, 216, 221], it specifically focused on improving dynamic trunk function. Given that postural instability is generally considered a multifaceted problem, it is possible that a more general and multidisciplinary intervention would have yielded different outcomes to those presented in this research. Nevertheless, the improvements made by the participants throughout the 12-week period (as evidenced by the increased difficulty of their exercises and the longer static hold times) and the improved gait symmetry evident during the follow-up assessments seems to suggest that improving trunk control may play an important part in enhancing postural stability for people with PD.

The findings of this research are strongly relevant to current clinical practice. With the integration of inexpensive and objective measuring devices into standard clinical practice, it may be possible to measure small, yet meaningful changes in a patient's function and may facilitate early intervention for at-risk patients. Wearable sensors are relatively easy to use, require little set-up time, and can be easily implemented in real-world and clinical settings. Furthermore, this

program of research provides additional support for the benefits of regular exercise in the management of PD and its symptoms, indicating that targeted low-intensity core conditioning exercises completed as little as once a week can maintain or improve standing and walking stability. Given the promise shown by these results, future research should utilise this type of equipment to focus on larger sample size multi-site or multi-national clustered randomised control trials to investigate the assessment and effects of interventions on postural stability. To this end, improving the assessment of postural stability in PD may ultimately inform policies, clinical guidelines and practices for reducing falls in people with PD by improving postural stability and, in the long term, contribute to improving the quality of life of these individuals.

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Appendix A: Systematic Review Search Strategy

Research Question: Can wearable sensors be used to measure postural stability in people with Parkinson's disease?

Research Protocol:

Methods for Literature Search:

A targeted search was conducted on August 27, 2014 of relevant databases for articles that were published within the past 20 years (1994-2014) and reported using wearable sensors to assess elements of postural stability in people with Parkinson's disease (PD). Specifically, the databases searched were:

Pubmed

EMBASE

The Cochrane Library

Additionally, the bibliographies of the studies that met the inclusion criteria for this review were screened for relevant articles that may have been missed during the initial database searches. As potential papers were identified, they were added to an Endnote database to eliminate duplicate entries of research studies. The following outlines the complete combination of search terms that was used to search the titles and abstracts of potential papers for each of the three databases:

((((Parkinson's[Title/Abstract]) **OR** Parkinson[Title/Abstract])) **AND**
((((Walk[Title/Abstract]) **OR** Gait[Title/Abstract]) **OR** Balance[Title/Abstract]) **OR**
Stability[Title/Abstract])) **AND** (((((Acceleration[Title/Abstract]) **OR**
Accelerometer[Title/Abstract]) **OR** Gyroscope[Title/Abstract]) **OR** Inertial[Title/Abstract])
OR Sensor[Title/Abstract])

Strict Inclusion/Exclusion Criteria:

To be eligible for inclusion in the systematic review, papers were required to meet the following inclusion and exclusion criteria:

Inclusion Criteria: For inclusion, papers were required to; i) involve a PD population; ii) utilise a body-mounted wearable sensor; iii) present at least one outcome measure for balance or postural stability during standing or walking; iv) be written in English; v) include a control group or control condition (e.g. ON vs. OFF medication); or vi) be a full-text article (i.e. not a conference abstract, systematic review or meta-analysis).

Exclusion Criteria: Papers were excluded if they had; i) no control group or control condition; ii) a mixed neurological participant sample; iii), no blinding to intervention status (if applicable); or iv) a wearable sensor that was a pedometer.

Paper Review Process:

A minimum of 2 reviewers performed the initial screening of articles based on the title and abstract of the papers identified in the initial search and where discrepancies existed between the reviewers, they were discussed until a consensus was reached. The full-text of those papers that were considered potentially relevant following title and abstract screening were reviewed by 1 of the reviewers and papers that were eligible were subjected to quality assessment and data extraction. Where there were uncertainties about the relevance of a paper in the full-text review process, the second reviewer was asked to independently evaluate the study and the inclusion status of the paper was discussed until a final consensus was reached.

Quality Assessment:

The methodological quality of each included paper was assessed using a previously-developed checklist described by Downs & Black (1998). This quality assessment checklist uses 27 questions to assess the reporting of external validity, bias and other potentially confounding factors that may have existed due to the study design. Each variable on the checklist was valued at 1 point if the criterion was met, with a score of zero being awarded if the criterion was not reported. However, the criterion related to the reporting of power calculations was valued at 5 points due to its increased importance for sample size justification. The sum of the scores for each of these items was divided by the maximum possible score and multiplied by 100 to yield a percentage that provided an assessment of the manuscript's methodological quality. Manuscripts were classified as having either very low (<25%), low (<50%, but ≥25%), moderate (<75%, but ≥50%) or high (≥75%) methodological quality.

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of epidemiology and community health, 52(6), 377-384.

Methods for Data Extraction and Analysis:

The initial step for this process involved a simple descriptive evaluation of each of the studies included in this review, which is presented in Table 2 of the dissertation. Furthermore, this table included a number of important pieces of information that were extracted from these studies and included:

Demographics – Experimental groups, disease severity, disease duration
Intervention – Description of intervention (if applicable)
Sensor Details – Type and placement
Postural Stability – Measures and modality of assessment
Findings – Results of the study
Quality Score – Details regarding the methodological quality of the study

Appendix B: Systematic Review Methodological Quality Assessment

1. Reporting

1) Is the hypothesis/aim/objective of the study clearly described?			
Yes	1	No	0

2) Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results, the question should be answered 'No'.			
Yes	1	No	0

3) Are the characteristics of the patients included in the study clearly described? In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.			
Yes	1	No	0

4) Are the interventions of interest clearly described?¥ Treatments and placebo (where relevant) that are to be compared should be clearly described.			
Yes	1	No	0

5) Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided.					
Yes	2	Partially	1	No	0

6) Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. ***N.B. This question does not cover statistical tests which are considered below***			
Yes	1	No	0

7) Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described it must be assumed that the estimates used were appropriate and the questions should be answered 'Yes'.			
Yes	1	No	0

8) Have all important adverse events that may be a consequence of the intervention been reported?¥ This should be answered 'Yes' if the study demonstrates that there was a comprehensive attempt to measure adverse events.			
Yes	1	No	0

9) Have the characteristics of patients lost to follow-up been described?[¥] This should be answered 'Yes' where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered 'No' where a study does not report the number of patients lost to follow-up.			
Yes	1	No	0

10) Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			
Yes	1	No	0

2, External Validity

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

11) Were the subjects asked to participate in the study representative of the entire population from which they were recruited? The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source populations from which the patients are derived, the question should be answered as 'Unable to Determine'.			
Yes	1	No	0
Unable to Determine	0		

12) Were those subjects who were prepared to participate representative of the entire population from which they were recruited? The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.			
Yes	1	No	0
Unable to Determine	0		

13) Were the staff, places and facilities where the patients were treated representative of the treatment the majority of patients received? For the question to be answered 'Yes' the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered 'No' if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.			
Yes	1	No	0
Unable to Determine	0		

3. Internal Validity – Bias

14) Was an attempt made to blind study subjects to the intervention they have received?[¥] For studies where the patients would have no way of knowing which intervention they received, this should be answered 'Yes'.			
Yes	1	No	0
Unable to Determine	0		

15) Was an attempt made to blind those measuring the main outcomes of the intervention?¥			
Yes	1	No	0
Unable to Determine	0		

16) If any of the results of the study were based on 'data dredging,' was this made clear? Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer 'Yes'.			
Yes	1	No	0
Unable to Determine	0		

17) In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?¥ Where follow-up was the same for all study patients the answer should be 'Yes'. If different lengths of follow-up were adjusted for by, for example, survival analysis, the answer should be 'Yes'. Studies where differences in follow-up are ignored should be answered 'No'.			
Yes	1	No	0
Unable to Determine	0		

18) Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example non-parametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered 'Yes'. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered 'Yes'.			
Yes	1	No	0
Unable to Determine	0		

19) Was compliance with the intervention(s) reliable?¥ Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered 'No'. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered 'Yes'.			
Yes	1	No	0
Unable to Determine	0		

20) Were the main outcome measures used accurate (valid and reliable)? For studies were the outcome measures are clearly described, the question should be answered 'Yes'. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered 'Yes'.			
Yes	1	No	0
Unable to Determine	0		

4. Internal Validity – Confounding (Selection Bias)

21) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? For example, patients for all comparison groups should be selected from the same hospital. The question should be answered 'Unable to Determine' for cohort and case-control studies where there is no information concerning the source of patients included in the study.			
Yes	1	No	0
Unable to Determine	0		

22) Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered 'Unable to Determine'.			
Yes	1	No	0
Unable to Determine	0		

23) Were study subjects randomised to intervention groups?[¥] Studies which state that subjects were randomised should be answered 'Yes', except where the method of randomisation would not ensure random allocation. For example alternate allocation would score 'No' because it is predictable.			
Yes	1	No	0
Unable to Determine	0		

24) Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?[¥] All non-randomised studies should be answered 'No'. If assignment was concealed from patients but not from staff, it should be answered 'No'.			
Yes	1	No	0
Unable to Determine	0		

25) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered 'No' for trials if the main conclusions of the study were; i) based on analyses of treatment rather than intention to treat; ii) the distribution of known confounders in the different treatment groups was not described; or iii) the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered 'No'.			
Yes	1	No	0
Unable to Determine	0		

26) Were losses of patients to follow-up taken into account?[¥] If the number of patients lost to follow-up is not reported, the question should be answered as 'Unable to Determine'. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered 'Yes'.			
Yes	1	No	0
Unable to Determine	0		

5. Power

27) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a different of x% and y%.			
	Size of smallest intervention group	Power Estimate	Score
A	$< n_1$	70%	0
B	n_1-n_2	80%	1
C	n_3-n_4	85%	2
D	n_5-n_6	90%	3
E	n_7-n_8	95%	4
F	n+	99%	5

Overall Research Quality Score

Randomised Controlled Trials
Randomised controlled trials are assessed based on the sum of scores for all 27 items, divided by the maximum possible score (28) and multiplied by 100 to yield a percentage score that represents the overall methodological quality of the manuscript.

Reporting	/ 11	*	100	%
External validity	/ 3	*	100	%
Internal validity - bias	/ 7	*	100	%
Internal validity - selection bias	/ 6	*	100	%
Power	/ 5	*	100	%
Total score	/ 32	*	100	%

Cross-Sectional Studies
Cross-sectional studies or other studies that do not involve one or more interventions are assessed based on the sum of scores for items 1-3, 5-7, 10-13, 16, 18, 20-22, 25 and 27 (i.e. 17 items), divided by the maximum possible score for these items (18) and multiplied by 100 to yield a percentage score that represents the overall methodological quality of the manuscript.

Reporting	/ 8	*	100	%
External validity	/ 3	*	100	%
Internal validity - bias	/ 3	*	100	%
Internal validity - selection bias	/ 3	*	100	%
Power	/ 5	*	100	%
Total score	/ 22	*	100	%

Overall Quality Rating	
Quality Score	*Quality Assessment*
0 - 25%	Very Low
25.1 - 50%	Low
50.1 - 75%	Moderate
75.1 - 100%	High

Adapted From: Downs SH, Black N (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of epidemiology and community health 52: 377-384.

Appendix C: Participant Information Sheet

PARTICIPANT INFORMATION LETTER

PROJECT TITLE:	Improving postural stability in people with Parkinson's disease
PRINCIPLE INVESTIGATOR:	Dr Michael Cole
CO-SUPERVISOR:	Professor Geraldine Naughton
STUDENT RESEARCHER:	Ryan Hubble
STUDENT'S DEGREE:	Doctor of Philosophy

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?

The objective of this project is to assess the effect of different non-invasive interventions on standing and walking balance in people with Parkinson's disease. Some people with Parkinson's disease may have difficulties that affect their balance, and the results of this study could provide new information to gain a better understanding of difficulties to help develop better interventions for managing balance problems in this population. A brief description of the tests in this research is given below and we would like to ask you to consider being a part of this study. For each visit, parking will be available at the University and a detailed description of all assessments is included with this document for your consideration.

Who is undertaking the project?

This project is being conducted by Ryan Hubble and forms the basis of the Doctor of Philosophy degree that he is completing at the Australian Catholic University under the supervision of Dr Michael Cole.

Are there any risks associated with participating in this project?

The preparation and testing phases will involve short periods of standing and walking. There is a chance that you may feel tired and/or uncomfortable, but you will be given rest breaks between tests and you may ask for additional breaks if needed. Furthermore, you will be encouraged to do the tests at your own pace and a member or the research staff will always be close by during the assessments to ensure your safety.

Additionally, the testing of muscle function from the skin's surface will require small areas of your skin to be clean and lightly abraded (exfoliated) to help put small sensors on the skin's surface and provide clear results. While unlikely, it is foreseeable that some people could have a reaction to this process, but the risk of this is no greater than that experienced with similar routines in everyday life.

There is a chance that you may be randomly assigned to an exercise program for this study. The exercise program has been developed to be achievable, yet challenging, so it is expected that some of the exercises may initially be difficult for you to perform properly. Also, as a result of the exercises, you may experience some general muscular soreness known as delayed onset muscle soreness (DOMS). To ensure that the exercise program is challenging enough to promote improvement, yet gentle enough to minimise DOMS, the exercises will start at a low level of difficulty and will progressively become harder as you improve your muscular endurance. During the exercise visits, the exercise scientist will also demonstrate proper technique for performing the exercises and you will be encouraged to complete the exercises at your own pace.

What will I be asked to do?

If you agree to participate in this research, you will be randomly placed into one of three different intervention groups: exercise one day per week, exercise three days per week, or education. Before you are randomly placed into a group however, your falls risk, standing balance and walking performance will be assessed with the following tests outlined below:

1. Questionnaires and Clinical Assessments:

Clinical assessments will be performed to examine memory and attention, vision and disease severity. Questionnaires will include questions that relate to height and weight, falls, health and medical conditions, medications and mobility.

2. Quiet Stance:

To assess standing balance, you will be asked to stand as still as possible on different surfaces (firm, foam) under multiple conditions (e.g. eyes open, eyes closed).

3. Walking:

To examine how your body moves when you are walking at a comfortable speed, small match-box sized devices (accelerometers) will be placed on your head (via a sports headband) and back (using double-sided tape). Additionally, the way your muscles turn on and off during walking will also be examined from the skin's surface via a non-invasive and safe method known as 'surface electromyography'.

4. Education Group

If you are randomly placed into the education group, after your initial assessment you will maintain your normal everyday life. Once a week for 12 weeks you will receive a pamphlet with information that may be helpful at improving your balance and quality of life. After completing this protocol, you will be offered the opportunity to participate in the same exercise program as the two exercise groups.

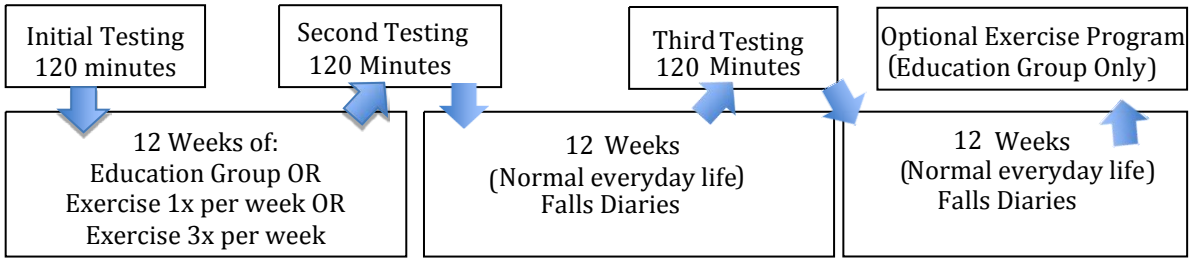
5. Exercise Groups:

If you are randomly placed into one of the exercise intervention groups, each week you will be asked to attend one supervised exercise session at Australian Catholic University Brisbane campus (McAuley at Banyo). If you are randomly placed in the exercise three times per week group, you will be asked to complete an additional two exercise sessions at home for a total of three exercise sessions per week. The exercise program will last for 12 weeks and each session will take no more than one hour to complete.

6. Follow-up Falls Calendars:

You will be asked to record any falls you experience on a daily falls calendar, which will be returned each month via a postage paid envelope over the six months following the 12-week education period.

How much time will the project take?



To participate in this research, you will be asked to visit the Australian Catholic University Brisbane campus a minimum of 3 times and up to a maximum of 15 times. Your initial visit will take up to 120 minutes to complete and will included the clinical tests and the walking and balance tests outlined above. You will be asked to return 12 and 24 weeks after this initial session to complete the same group of tasks again. The timeline above shows how your participation in this project would progress. After the initial visit, you will be randomly placed into one of three intervention groups. If you are randomly placed into the education group, you will continue your normal everyday life, but you will be sent a brochure with information that could help improve your balance and quality of life. After completing the protocol for the education group, you will have the opportunity of participating in the same exercise program as the exercise groups. This will include one 60-minute supervised exercise session a week for 12 weeks. This is completely optional but it is provided purely for your benefit. If you are placed in either exercise group, you will be asked to attend a one-hour training session at the Australian Catholic University (Brisbane Campus) once a week for 12 weeks. If you are placed in the exercise 3 times per week group, you will be asked to complete two additional sessions at home each week at a time convenient for you. The exercise program will start with a minimal difficulty level and progress as you improve with the exercises. At the end of the training session, you will be provided with the same education tips that are being provided to the education group. All groups will be asked to keep a daily diary of their activity levels, which could take as little as a couple minutes each day. After your second visit for assessment you will be asked to record any falls in a falls diary for 12 weeks before your third and final visit

for assessment. After your final assessment you will be asked to record any falls in a falls diary for another 12 weeks. Recording your falls involves ticking a few boxes on a questionnaire that may take as little as one minute or up to a couple of minutes, and then returning it to the research team via a reply-paid envelope.

What are the benefits of the research project?

The educational information that you will be provided with over the course of this study may be beneficial to you, as it could be useful in improving your balance and quality of life. Research has demonstrated that regular exercise can be effective at improving strength, balance, mobility and symptoms of tremor and rigidity for people with Parkinson's disease. As such, your involvement in the exercise program associated with this study may have a number of health benefits for you. Furthermore, your involvement in this study is expected to benefit the wider community, particularly other people with Parkinson's disease. Your participation in this study will assist in improving our understanding how exercise affects postural stability, and will help form a scientific basis for promoting effective interventions aimed at improving postural stability in this population. Ultimately this knowledge will lead to the development of well-planned interventions that may reduce the incidence of falls and fall related injuries and improve quality of life in people with Parkinson's disease. In addition, upon completion of the study, you will be given a $40 Coles group and Myer gift voucher as a token of our appreciation for your time and dedication to our research.

Can I withdraw from the study?

Taking part in this project is entirely voluntary and we will ask you to sign a written consent form (enclosed) to confirm that you agree to participate. You will also be asked to consent to being photographed and/or videotaped. For the photographs your face will not be photographed to keep your identity confidential. However, due to the need to assess head and neck movements during some of the clinical tests, your identity may not be concealed. This data is to be used for clinical training purposes only and will not be released to any individual not affiliated with this study. However, if you decide not to consent to being photographed and/or videotaped as part of this study, it will not affect your involvement in this study. Furthermore, it is important to know that you are free to withdraw consent before, during, or after the experiment without comment or penalty. Under no circumstances will you be prejudiced as a result of your actions; your participation or withdrawal of consent will not influence your present or future care or your relationship with the research staff at the Australian Catholic University.

Will anyone else know the results of the project?

All data will be kept at the Australian Catholic University, in a locked filing cabinet. Data will also be stored in password-protected files on a computer within the University and back-up copies will be held on a portable hard-drive for storage off-site. The researchers will take every care to ensure that individually identifying material will be removed from the data as soon as it is possible, in order to ensure the privacy and confidentiality of the participants. You should be aware that your identity will not be disclosed in the reporting of the research. Following completion of data collection, the results from the study will be summarised and presented in the form of scientific publications. It is important however, to reiterate that the outcomes of this research will focus on the averaged data from all participants and will not identify individual participants in any way.

Will I be able to find out the results of the project?

People who volunteer to take part in this research will be offered verbal feedback on their performance on the assessments at the end of the trial. Due to the prospective design of this research, it is likely to be incredibly time-consuming for the HDR Student Researcher to produce individualised reports for each patient. However, participants will be given the option to receive a summary of the overall findings of the research following its completion to help them better understand what they have contributed to. If you would like a summary of the results of the study, you should contact the HDR student Ryan Hubble. His contact details are included below on this form.

Who do I contact if I have questions about the project?

If you have any questions regarding this study or you require any further information about it, please do not hesitate to contact a member of the research team for this project:

Name:	Ryan Hubble
Telephone:	07 3623 7703
Email:	ryan.hubble@acu.edu.au
Postal Address:	School of Exercise Science Australian Catholic University Brisbane Campus P.O. Box 456 Virginia QLD 4014

What if I have a complaint or any concerns?

The study has been approved by the Human Research Ethics Committee at Australian Catholic University (approval number 2013 223Q). If you have any complaints or concerns about the conduct of the project, you may write to the Chair of the Human Research Ethics Committee care of the Office of the Deputy Vice Chancellor (Research). Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

Chair, HREC
c/o Office of the Deputy Vice Chancellor (Research)
Australian Catholic University
Melbourne Campus
Locked Bag 4115
FITZROY, VIC, 3065
Ph: 03 9953 3150
Fax: 03 9953 3315
Email: res.ethics@acu.edu.au

I want to participate! How do I sign up?

If you agree to participate in this project, you should contact a member of the research team to indicate your interest and sign both copies of the Consent Form. One of these copies is for you to keep for your records and you should return the other copy to the Principal Investigator during your first visit to the Australian Catholic University. Thank you for taking the time to consider this research and I look forward to discussing this research with you soon.

Yours sincerely,

Ryan Hubble
School of Exercise Science
Australian Catholic University
Brisbane Campus
1100 Nudgee Road, Banyo, QLD, 4014
Phone: 07 3623 7703
E-mail: ryan.hubble@acu.edu.au

Dr Michael Cole
School of Exercise Science
Australian Catholic University
Brisbane Campus
1100 Nudgee Road, Banyo, QLD, 4014
Phone: 07 3623 7674
E-mail: michael.cole@acu.edu.au

Full Explanation of Tests:

1. Questionnaires and Clinical Assessments:

Falls history and fear of falls; pre-existing medical conditions; current medications; memory and attention; freezing of gait and quality of life will be evaluated using a series of previously developed and evaluated questionnaires. The severity of the symptoms that you may experience will also be evaluated using standard clinical tests.

2. Quiet Stance

This test will take place while you are standing as still as possible for a 30 second period with your eyes open and closed on a firm, flat surface as well as on a foam surface. To ensure your safety, a member of the research team will be standing beside you at all times.

3. Walking

To measure your walking ability, you will be asked to walk on a firm surface at a comfortable pace. While you are walking, your movements will be measured using a small matchbox-sized measuring devices (accelerometers) that will be attached to your head using a headband and to your back using double-sided tape. The way in which your muscles turn on and off during walking will also be assessed using a non-invasive procedure known as 'surface electromyography'. This will require a small area of your skin to be gently exfoliated and cleaned using a medical-grade alcohol wipe, after which multiple small circular dots to be stuck to your skin with an adhesive suitable for sensitive skin types. To assist with the placement of this equipment on the body, it is necessary for you to be *wearing shorts and a sleeveless* shirt so we can easily place the measuring equipment on your head and back.

4. Exercise Program

You will be asked to attend a one-hour supervised group exercise session once a week for a total of 12 weeks. You will be asked to wear or bring a change of clothes that will allow you to comfortably move while completing the exercises. For your consideration, there will be multiple exercise sessions scheduled throughout the week that you may choose to attend depending on your availability. Each group exercise session will consist of a warm-up that promotes mobility of the upper body and arms, exercises that target at improving endurance of the muscles of the back and abdomen, and a cool-down period consisting of walking and light stretching. At the end of the exercise session you will receive an educational pack that will provide you with information that may help to reduce your risk of falling and contribute to an improved quality of life. There will be breaks offered during the training sessions, and you may request additional breaks if you need them. At the end of the training session you will be offered morning /afternoon tea or coffee.

5. Follow-up Falls Calendar

You will be asked to record any falls that you may have over the course of a six-month period on a questionnaire consisting primarily of tick boxes. These questionnaires will ask for information about the incidence of any falls and the circumstances surrounding their occurrence (e.g. what time of day it occurred, cause of the fall, location of the fall, injuries sustained, etc.) and will be returned to the investigative team via a postage-paid envelope once a month.

Appendix D: Participant Consent Form

CONSENT FORM
(COPY FOR PARTICIPANT TO KEEP)

TITLE OF PROJECT: *Improving postural stability in people with Parkinson's disease*
PRINCIPAL INVESTIGATOR (SUPERVISOR): Dr Michael Cole
CO-SUPERVISOR: Professor Geraldine Naughton
STUDENT RESEARCHER: Ryan Hubble

I……..... (*the participant*) have read (*or, where appropriate, have had read to me*) and understood the information provided in the Letter to Participants. Any questions I have asked have been answered to my satisfaction. I agree to participate in this research aimed at improving postural stability in people with Parkinson's disease and understand that this research will involve assessments of standing balance, walking and muscle function, realising that I can withdraw my consent at any time, without adverse consequences. I agree that research data collected for the study may be published or may be provided to other researchers in a form that does not identify me in any way.

☐ I consent to my photograph being taken during my participation in this study and understand that it may be used in academic publications as a visual description of testing procedures involved. I am consenting to this with the understanding that the investigators will not photograph my face to maintain the confidentiality of my identity.

☐ I consent to having video taken of me during my participation in this study and understand that it will be used for clinical training purposes only. I am consenting to this with the understanding that, due to the need to assess head and neck movements during some of the clinical tests, my identity may not be concealed. This data is to be used for clinical training purposes only and will not be released to any individual not affiliated with this study.

☐ I do not consent to being photographed or videoed during any of the testing procedures for this study.

☐ I understand that there is an equal chance that I may be randomly assigned to either to one of two exercise groups or an education group. If I am randomly placed into the education group, I am interested in receiving information regarding the optional exercise program aimed at improving postural stability after the completion of the study. It has also been explained to me that due to the study design, details of the training program cannot be provided until after the study is completed.

☐ I am interested in receiving a summary of the results at the end of the study. I understand that the results may take up to two years to finalise, but I will be contacted by a member of the research team to make these results available to me at the completion of the study.

NAME OF PARTICIPANT: .....

SIGNATURE: ..... DATE: ….....

SIGNATURE OF PRINCIPAL INVESTIGATOR: ……..... DATE: .....

SIGNATURE OF STUDENT RESEARCHER: ..... DATE: ……

School of Exercise Science
1100 Nudgee Road
Banyo, Queensland, 4014
T: 07 3623 7703 **F:** 07 3623 7650 **E:** ryan.hubble@acu.edu.au

Appendix E: Ethics Approval

AUSTRALIAN CATHOLIC UNIVERSITY

Human Research Ethics Committee

Committee Approval Form

Principal Investigator/Supervisor:	Dr Michael Cole
Co-Investigators:	Professor Geraldine Naughton
Student Researcher:	Mr Ryan Hubble

Ethics approval has been granted for the following project:
Improving postural stability in people with Parkinson's disease: A randomised controlled trial

For the period: 01/10/2013 - 30/06/2016

Human Research Ethics Committee (HREC) Register Number: 2013 223Q

Special Condition/s of Approval

Prior to commencement of your research, the following permissions are required to be submitted to the ACU HREC: N/A

The following standard conditions as stipulated in the *National Statement on Ethical Conduct in Research Involving Humans* (2007) apply:

(i) that Principal Investigators / Supervisors provide, on the form supplied by the Human Research Ethics Committee, annual reports on matters such as:
- security of records
- compliance with approved consent procedures and documentation
- compliance with special conditions, and

(ii) that researchers report to the HREC immediately any matter that might affect the ethical acceptability of the protocol, such as:
- proposed changes to the protocol
- unforeseen circumstances or events
- adverse effects on participants

The HREC will conduct an audit each year of all projects deemed to be of more than low risk. There will also be random audits of a sample of projects considered to be of negligible risk and low risk on all campuses each year.

Within one month of the conclusion of the project, researchers are required to complete a *Final Report Form* and submit it to the local Research Services Officer.

If the project continues for more than one year, researchers are required to complete an *Annual Progress Report Form* and submit it to the local Research Services Officer within one month of the anniversary date of the ethics approval.

Signed: K. Pashley. Date: 28/10/2013

(Research Services Officer, McAuley Campus)
U:\Ethics\Ethics Applications 2013\2013 223Q Cole\2013 223Q Approval Form.doc

Appendix F: Research Portfolio

Paper 1: (Published) Trunk muscle exercises as a means of improving postural stability in people with Parkinson's disease: a protocol for a randomised controlled trial.

From: onbehalfof+editorial.bmjopen+bmj.com@manuscriptcentral.com on behalf of editorial.bmjopen@bmj.com
To: Ryan Hubble; Michael Cole
Cc: Ryan Hubble; Michael Cole; Geraldine Naughton; p.silburn@neurosciencesqld.com.au
Subject: BMJ Open - Decision on Manuscript ID bmjopen-2014-006095.R1
Date: Tuesday, 25 November 2014 7:45:22 PM

25-Nov-2014

Dear Mr. Hubble:

It is a pleasure to accept your manuscript entitled "Trunk muscle exercises as a means of improving postural stability in people with Parkinson's disease: a protocol for a randomised-controlled trial" in its current form for publication in BMJ Open. Any final comments from the reviewer(s) are included at the foot of this letter. These will be published as supplementary information alongside your article.

In order to support making all research published in BMJ Open fully open access, an article-processing charge is levied. This charge supports the peer review process, production costs (typesetting, copy editing, etc.), and the costs of maintaining the content online and marketing it to readers.

Therefore, your payment of £675 (excluding any applicable VAT) for accepted manuscript bmjopen-2014-006095.R1 is now due.

If you reviewed for the journal within 12 months of submitting this paper, or you are an editorial board member, please contact the editorial office (editorial.bmjopen@bmjgroup.com) about your discount . Information regarding waivers and discounts is included in our instructions for authors; however, we anticipate that most authors will have the resources to pay.

You can choose to pay by card or invoice, using our secure 3rd party online system..

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Once your article is published online you will be able to keep track of usage. Each article published in BMJ Open has individual usage statistics which are updated daily and can be accessed from the Article Usage Statistics link in the Services section of the right hand column on each page of the article. In this column you can also sign up to be alerted about any e-letter responses to your article.

Thank you for your contribution, and we hope that you will continue to submit to the journal in future.

Sincerely,
Richard Sands, managing editor
Editorial Office, BMJ Open
editorial.bmjopen@bmj.com
http://bmjopen.bmj.com

Reviewer(s)' Comments to Author:
Reviewer Name Marialuisa Gandolfi
Institution and Country Neuromotor and Cognitive Rehabilitation Research Centre (CRRNC)
Department of Neurological and Movement Sciences
University of Verona
Neurorehabilitation Unit – Azienda Ospedaliera Universitaria Integrata
University Hospital

BMJ Open

Trunk muscle exercises as a means of improving postural stability in people with Parkinson's disease: a protocol for a randomised controlled trial

Ryan P Hubble,[1] Geraldine A Naughton,[2] Peter A Silburn,[3] Michael H Cole[1]

To cite: Hubble RP, Naughton GA, Silburn PA, *et al*. Trunk muscle exercises as a means of improving postural stability in people with Parkinson's disease: a protocol for a randomised controlled trial. *BMJ Open* 2014;4:e006095. doi:10.1136/bmjopen-2014-006095

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2014-006095).

Received 14 July 2014
Revised 16 October 2014
Accepted 25 November 2014

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ABSTRACT

Introduction: Exercise has been shown to improve clinical measures of strength, balance and mobility, and in some cases, has improved symptoms of tremor and rigidity in people with Parkinson's disease (PD). However, to date, no research has examined whether improvements in trunk control can remedy deficits in dynamic postural stability in this population. The proposed randomised controlled trial aims to establish whether a 12-week exercise programme aimed at improving dynamic postural stability in people with PD; (1) is more effective than education; (2) is more effective when training frequency is increased; and (3) provides greater long-term benefits than education.

Methods/design: Forty-five community-dwelling individuals diagnosed with idiopathic PD with a falls history will be recruited. Participants will complete baseline assessments including tests of cognition, vision, disease severity, fear of falling, mobility and quality of life. Additionally, participants will complete a series of standing balance tasks to evaluate static postural stability, while dynamic postural control will be measured during walking using head and trunk-mounted three-dimensional accelerometers. Following baseline testing, participants will be randomly-assigned to one of three intervention groups, who will receive either exercise once per week, exercise 3 days/week, or education. Participants will repeat the same battery of tests conducted at baseline after the 12-week intervention and again following a further 12-week sustainability period.

Discussion: This study has the potential to show that low-intensity and progressive trunk exercises can provide a non-invasive and effective means for maintaining or improving postural stability for people with PD. Importantly, if the programme is noted to be effective, it could be easily performed by patients within their home environment or under the guidance of available allied health professionals.

Trial registration number: The protocol for this study is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613001175763).

Strengths and limitations of this study

- This study has been designed as a randomised controlled trial, which is currently considered the best methodological approach for evaluating the efficacy of a specific intervention.
- The proposed study will be the first to assess whether dynamic postural stability during walking can be improved or maintained in people with Parkinson's disease who regularly perform specific exercises to improve trunk mobility and endurance.
- This study seeks to assess changes in static and dynamic balance using continuous measures rather than graded clinical tests that are based on Likert scales, as these may be more sensitive for detecting improvements in postural stability for this patient group.
- While it would be important to examine whether improvements in postural stability are associated with a reduction in falls, the large sample size required to achieve this goal (approximately 120 participants per group) is prohibitive.
- Owing to the nature of the chosen intervention, the findings may only be applicable to patients who experience mild-to-moderate symptoms and are healthy enough to perform the exercises. As such, alternate interventions may be necessary for individuals who present with more advanced symptoms.

INTRODUCTION

Prospective studies indicate that the incidence of falls are much greater for people with Parkinson's disease (PD) than for age-matched controls, with up to 68% of people with PD falling at least once each year and up to 50% of these individuals experiencing recurrent falls.[1 2] The increased falls risk in this population is compounded by an increased risk of injury, as differences in the postural responses of people with PD place them at a greater risk of sustaining a significant fall-related injury than age-matched controls.[3] Falls and fall-related injuries often lead to a fear of falling, reduced mobility, poorer muscle strength and loss of independence, all of which ultimately influence

an individual's mortality, morbidity and quality of life.[4] Biomechanical research involving healthy younger adults[5] has shown that the trunk segment plays an important role in modulating gait-related oscillations and maintaining head stability; an important goal of the human postural control system. However, the increased axial rigidity that is evident in people with PD[6] significantly impairs the trunk's capacity to attenuate these movement-related forces, which inadvertently reduces head stability and impairs the clarity of the visual and vestibular information used in balance control. In the early stages of the disease, the symptoms of PD are typically managed using any number of antiparkinsonian medications. However, these medications are unfortunately not always effective at improving symptoms of axial rigidity[6] and often lead to undesirable side effects including dopamine-induced dyskinesias or motor fluctuations that have the potential to increase the risk of falls in people with PD. As such, there is a clear need for alternative therapies that can be easily implemented, have low running costs and have the potential to improve postural control, segmental mobility and falls risk in this population.

It is important for individuals to be able to effectively control their body's segments to maintain postural stability and limit the risk of falling during both static and dynamic activities of daily living. Older adults demonstrate poorer postural stability during tasks requiring dynamic postural control (eg, walking and turning), which can place them at an increased risk of falling.[7] Age-related declines in dynamic postural control may be further exacerbated with the presence of PD, which would exacerbate the decreased balance and higher falls rate evident in this population.[1 8 9]

Given that the head and trunk comprise 60% of the overall mass of the body,[10] it seems reasonable to suggest that one's ability to precisely coordinate trunk movements would contribute significantly to attenuating movement-related oscillations and maintaining postural stability during these activities. An examination of segmental stability for different regions of the upper body in a healthy population showed that trunk movements were smaller than those of the head and neck during walking.[11] However, separate research suggests that the trunk has a more irregular movement pattern than the head during gait.[5] The authors argued that the trunk may serve to attenuate forces during dynamic tasks to stabilise the head, and preserve the quality of the visual and vestibular feedback required for postural control. If an individual has increased axial rigidity[6] and is unable to adequately control the trunk segment during dynamic tasks, then the exaggerated movements of the trunk may have a direct impact on head stability and overall balance.

A common method used to evaluate head and trunk stability during dynamic tasks is the harmonic ratio (HR), which provides a measure of the stability of gait-related accelerations by evaluating the stride-to-stride regularity of the harmonics within the acceleration signal.[12] Walking patterns that produce higher HRs will be characterised by a more regular acceleration profile over successive gait cycles (ie, less stride-to-stride variability); hence, the gait pattern is deemed to be more stable.[13] People with PD who fall are known to have increased mediolateral (ML) and anteroposterior (AP) movements of the trunk during sitting,[14] less regular pelvic movements (lower HRs)[15] and increased ML head movement during gait.[1 16] Collectively, these studies suggest that some of the falls experienced by people with PD may be related to a reduced capacity for these individuals to adequately coordinate the body's segments during dynamic tasks. As such, there is a clear need to evaluate the efficacy of different non-invasive interventions aimed at maintaining and/or improving trunk mobility and control to improve postural stability in this population. To date, few studies have investigated the efficacy of different non-invasive methods for improving balance and reducing falls risk in this high-risk population.[17–21]

It is widely recognised that exercise is an effective means of maintaining or improving cardiovascular and musculoskeletal health, both of which are critical for preserving physiological functioning and independence. Furthermore, some modes of exercise have been shown to be effective at improving standing balance,[22 23] symptoms of anxiety and depression[24 25] and reducing fall rates[26] and risk of falling[22 27] in otherwise healthy individuals. A number of previous studies have also provided evidence to support the short-term benefits of exercise for improving clinical measures of mobility,[15 17 28–30] postural stability,[15 17 28–30] quality of life,[31] cognitive function[31 32] and symptom severity in people with PD.[29 30] Current evidence suggests that when programmes include more challenging balance exercises, they may offer greater benefits for balance and mobility.[17] For example, tai chi is a specific form of exercise known to challenge the balance system. Previous research has shown tai chi can improve measures of static postural stability in people with PD.[33] However, it is important to note that the results of a recent systematic review suggest that other forms of exercise may also provide similar benefits to balance in this population.[34]

While this systematic evidence supports that exercise improves clinical measures of balance, mobility and disease severity, many of the improvements did not achieve a level that would be considered a minimally clinically important change. Furthermore, most of the balance and mobility assessments used in previous studies have relied on Likert scales to assess function, which may limit their ability to discriminate between people with PD who fall and those who do not. As such, it is possible that the incorporation of biomechanical measures of dynamic postural stability may improve our capacity to accurately detect improvements or declines in balance for this population, which would facilitate better identification of patients who are at a higher risk of falling. However, the investigators are unaware of any

previous research that has investigated whether exercise can improve quantitative measures of dynamic postural stability in people with PD. A possible explanation for this may be that such a study would require the use of complex measuring equipment that is typically only available in a laboratory setting, making it a higher order of investigation and difficult to assess in a clinical environment.

As such, the proposed randomised controlled trial aims to establish whether a 12-week exercise programme aimed at improving dynamic postural stability in people with PD; (1) is more effective than education; (2) is more effective when training frequency is increased; and (3) provides greater long-term benefits than education. It is hypothesised that the both exercise programmes will improve dynamic postural stability more than education, however training at an increased frequency will yield better improvements for the people with PD.

METHODS

The proposed randomised controlled trial will be conducted in 2014/2015 and seeks to improve the mobility and endurance of the trunk and its supporting musculature. This study protocol was developed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[35]

Participants

Forty-five participants diagnosed with idiopathic PD, based on the UK Brain Bank Criteria[36] and who have a history of two or more near-misses and/or one fall or more in the previous 12 months will be recruited from: (1) neurology clinics, (2) community support groups, (3) and a pre-existing database of people with PD who have expressed an interest in participating in research. Prospective participants will be sent an information letter outlining the details of the study and inviting them to contact a member of the research team if they are interested in participating in the research. On contacting a member of the research team, prospective participants will be screened to ensure that they all meet the requirements of the study and, if they are deemed eligible for inclusion, a time will be scheduled to conduct the baseline assessments. Participants will be excluded if they: (1) are unable to stand and walk independently without the use of a walking aid, (2) have any significant visual (Bailey-Lovie high-contrast visual acuity >0.30 logMAR) or cognitive impairment (Addenbrooke's cognition examination score <82), (3) have uncontrolled hypertension, (4) are taking psychotropic medications, (5) have any significant limitations due to osteoporosis, (6) have had any orthopaedic surgery within the previous year, (7) have any serious neck, shoulder or back injuries; including spinal fusions, or (8) have received deep brain stimulation surgery to manage their symptoms. For the purposes of this study, a fall will be defined as 'any coming to the ground or lower level not as the result of a major intrinsic event or overwhelming hazard' and a near miss will be defined as 'an event on which an individual felt that they were going to fall but did not actually do so'.[18] All volunteers will be asked to provide written informed consent in accordance with the Declaration of Helsinki prior to participation in the study.

To determine a suitable sample size, a power calculation was completed based on the HR, the primary measure of this study. The sample size was calculated using ML head accelerations from a previous study that assessed differences in dynamic postural stability in PD compared with healthy controls using the HR.[37] On the basis of this calculation, it was concluded that a minimum of 11 participants per group is needed to confidently report any significant changes in dynamic postural stability (diff=0.05, SD=0.04, Cohen's d=1.25, Power=80%, p=0.05). Given the longitudinal nature of the research, 15 individuals will be recruited per intervention group to accommodate a 25% rate of attrition. The experimental procedures for this study have been approved by the Australian Catholic University Human Research Ethics Committee. To ensure participants are assessed under similar conditions during each testing session, all procedures will be scheduled to start within 1–2 h of the participants taking their medication. This will ensure the participants are comfortable and safe during the assessments and that the results are representative of how the individuals might perform such tasks in the real world.

Clinical measures

Individuals who provide consent to participate in this study will be asked to attend an initial session at the Australian Catholic University (Brisbane) during which a series of baseline assessments will be performed. This battery of tests will include clinical assessments of: (1) cognitive function (Addenbrooke's Cognitive Examination (ACE)),[38] (2) visual acuity (Bailey-Lovie high-contrast visual acuity[39]), (3) disease severity (Unified Parkinson's Disease Rating Scale (UPDRS), the modified Hoehn & Yahr (H&Y) scale,[40] the Schwab & England Activities of Daily Living Scale[41] and the PD Gait and Falls Questionnaire (PD-GFQ)[42]), (4) fear of falling (Activity-specific Balance Confidence Scale[43]), (5) mobility (Timed Up and Go[44]) and (6) quality of life (Parkinson's disease questionnaire 39 (PDQ-39)).[45] The PD-GFQ is a 16-item tool that assesses the extent of any falls and gait difficulties experienced by people with PD and incorporates six questions that are summed to give the freezing of gait (FOG) score.[42] The ACE was selected to assess cognitive function, as it incorporates the Mini Mental State Examination and has been shown to have high sensitivity and specificity for detecting dementia (cut-off <82 gives 82% sensitivity and 100% specificity). The other assessments were selected as they have been shown to be both reliable and valid,[38 46–49] and have been used previously to assess individuals with PD.[15 50]

Postural stability measures

To evaluate dynamic postural stability, participants will be asked to walk along a 10 m walkway at a comfortable self-selected pace for four trials and will be offered a rest break between trials to minimise the risk of fatigue. While completing this task, movement patterns of the head and trunk will be measured using two microelectromechanical system three-dimensional accelerometers (Noraxon Inc, Scottsdale, Arizona, USA) sampling at a rate of 500 Hz. Prior to testing, the accelerometers will be statically calibrated using the methods described previously.[51] Calibration involves aligning each sensing axis of the accelerometer perpendicular to a horizontal surface to determine a conversion factor that describes gravitational acceleration (1 gravitational unit or 1 g). Following static calibration, an accelerometer will be firmly attached over the occipital protuberance of the skull via a sport headband and another will be attached directly to the skin using double-sided tape over the spinous process of the 10th thoracic vertebra (T10). To detect gait events, such as heel strike and toe off during the gait cycle, two pressure-sensitive footswitches (Noraxon Inc) will be placed bilaterally under the calcaneus, the distal end of the first phalange and the distal end of the first and fifth metatarsals of the foot.

Static postural stability will be assessed while participants are standing quietly on a portable force plate that is sampling data at an effective rate of 200 Hz (Advanced Mechanical Technology Inc, USA). Participants will complete two 30 s trials that will involve standing as still as possible for each of the following conditions: (1) on a firm surface with eyes open, (2) on a firm surface with eyes closed, (3) on a foam surface with eyes open and (4) on a foam surface with eyes closed. Before start of each trial, participants will be asked to look straight ahead at a cross that will be placed on the wall at eye level with their arms resting at their sides and their feet 10 cm apart. Measurements derived from the force plate data will include: peak RMS displacement of the centre of pressure and postural sway velocity in the AP and ML directions.

In addition to the acceleration profiles that will be collected for the head and trunk, muscle activation patterns for the thoracic and lumbar erector spinae will be measured at 1500 Hz using a wireless Noraxon surface electromyography (EMG) system (Noraxon Inc). In healthy individuals, the erector spinae muscles show a phasic increase in activation just after heel-contact to counter forward trunk flexion during walking.[52] The erector spinae muscles were chosen for evaluation because individuals with PD are known to have decreased trunk muscle performance than age-matched controls,[53] which may influence their capacity to control trunk motion during walking. Prior to applying the surface electrodes over the muscles of interest, the skin will be prepared with an abrasive gel (Nuprep; Weaver Company, Aurora, Colorado, USA), and then cleaned thoroughly with an isopropyl alcohol wipe to minimise impedance at the electrode-skin interface and improve clarity of the myoelectric signal.[54] For individuals with excessive hair over the muscles of interest, the area will be shaved in order to maximise the fidelity of the myoelectric signal and ensure the best possible adherence to the skin. After skin preparation, four pairs of Ag/AgCl pregelled surface electrodes (AMBU Blue Sensor, Ballerup, DK; 34 mm diameter, 10 mm^2 sensing area) will be placed with a centre-to-centre interelectrode distance of 34 mm. Specifically, these electrode pairs will be placed bilaterally 5 cm lateral to the spinous process of the T10 vertebral body and 2 cm lateral to the spinous process of the third lumbar (L3) vertebral body.[55]

To facilitate comparisons between the different testing dates and the different participant groups, the EMG data will be normalised to the muscle activity levels recorded for the participants during a maximal voluntary contraction (MVC) of the erector spinae. To perform the MVC, the participants will lie prone/prostrate on a padded table with their hips flexed and their feet on the floor. The participant will then be asked to complete three practice trials to learn the movement before performing three maximal efforts that involve simultaneously extending both hips to raise the legs to a horizontal position to activate the erector spinae muscle group. A restraining force will be applied to the legs of the participants to make sure that their legs remain horizontal (180°) while performing the test to produce the MVC. This method was chosen in preference to the traditional Biering-Sorensen test, due to the potential difficulties that older participants may have with this movement.[55]

All data collection will be performed using the MyoResearch XP software to ensure that the data from the different systems remain synchronised. Participants will be re-tested using the assessments outlined above: (1) after the 12-week intervention to establish the immediate effects of the exercise programme on postural stability and (2) 12 weeks after the completion of the intervention to evaluate the retention of any benefits over the longer term (ie, 24 weeks following baseline). The battery of assessments and the time points at which they will be taken are summarised in table 1 and the flow of recruitment, data collection and follow-up procedures are outlined in figure 1.

Data analyses

Data from the raw accelerations will be low-pass filtered using a bi-directional fourth order Butterworth filter with a cut-off frequency of 30 Hz.[56] Measurements derived from the accelerometry data will include: (1) peak acceleration (root mean square (RMS)) and (2) HR, both of which will be calculated for the AP, ML and vertical (VT) axes of the head and trunk accelerometers separately. The HR has been used previously to evaluate dynamic postural instability in people with PD[15 37] and will be used in this study to provide an indication of how

Table 1 The primary, secondary and tertiary outcomes measures and the time points at which they will be assessed during the study

	Outcome measures	Baseline (week 0)	Postintervention (week 12)	Final assessment (week 24)
Primary outcome measure				
Dynamic postural stability	Harmonic ratio (AP, ML, VT)	X	X	X
Secondary outcome measures				
Static postural stability	Peak RMS displacement (AP, ML)	X	X	X
	Sway velocity (AP, ML)	X	X	X
Bilateral trunk muscle function	Peak RMS activity (ES at T10 and L3 levels)	X	X	X
Tertiary outcome measures				
Disease severity	UPDRS III	X	X	X
	FOGQ	X	X	X
	ABC scale	X	X	X
	Schwab and England Activities of daily living	X	X	x
	PDQ-39	X	X	X
Other variables	Intervention compliance	X	X	x
	Adverse events	X	X	X
	Daily levodopa equivalents	X	X	X
	International physical activity questionnaire		X	X
Screening measures				
Cognitive function	Addenbrooke's cognitive examination	X		
Visual function	Bailey-Lovie high-contrast visual acuity	X		

ABC Scale, Activities-Specific Balance Confidence Scale; AP, anteroposterior; ES, erector spinae; FOGQ, Freezing of Gait Questionnaire; ML, mediolateral; PDQ-39, Parkinson's Disease Questionnaire 39; UPDRS III, Motor Subscale of Unified Parkinson's Disease Rating Scale; VT, Vertical.

well the movement patterns of the head and trunk are controlled during normal gait.

Raw EMG data will be high-pass filtered at 100 Hz to remove heart rate artefact from the signal and then full-wave rectified and low-pass filtered (4th order Butterworth filter) at 20 Hz.[57] Following filtering of the data, the RMS of the muscle activity throughout the walking trials will be calculated over a 50 ms[57] moving average window, with a 25 ms overlap.[55] To facilitate comparisons between participants and across testing days, the activation levels of the trunk muscles will be normalised to the peak RMS amplitude of the muscle activity recorded during the MVC trials. The peak normalised RMS muscle activities derived from three complete gait cycles for each leg from each of the four trials (n=12 gait cycles per leg) will then be averaged and these data will be used for all subsequent analyses.

Randomisation and blinding

After completion of the baseline assessments, participants will be randomised using a computerised random number generator (block size=3) in a 1:1:1 ratio to one of the three intervention groups: (1) exercise 1 day/week, (2) exercise 3 days/week or (3) education. To minimise the possibility of introducing issues related to inter-rater reliability and/or biasing the outcomes, the clinical assessments will be conducted by an individual who is trained to administer the tests, but who will not be involved with the recruitment and allocation of participants to intervention groups and will also be blinded to intervention status. Furthermore, another member of the research team responsible for processing and analysing the data related to the assessment of static and dynamic postural stability will recruit and assign participants to intervention groups, however will be blinded to the group allocation of the participants during data analysis.

Intervention

At baseline, all participants will receive a 10–15 min one-off presentation outlining the evidence that supports exercise as an effective means of improving movement and postural stability in people with PD. Participants in the education group will be encouraged to continue their day-to-day lives, as usual, but will receive a weekly multidisciplinary education package that will include a health tip that will explain how, for example, exercise, nutrition and/or sleep quality may influence their falls risk and quality of life. The education group represents what would normally be seen in everyday life, with the education brochures created using scientific evidence drawn from pre-existing research and freely-available information sheets produced by government and not-for-profit organisations.

Participants assigned to the exercise groups will complete a low-level supervision, 12-week exercise programme aimed at improving trunk mobility and

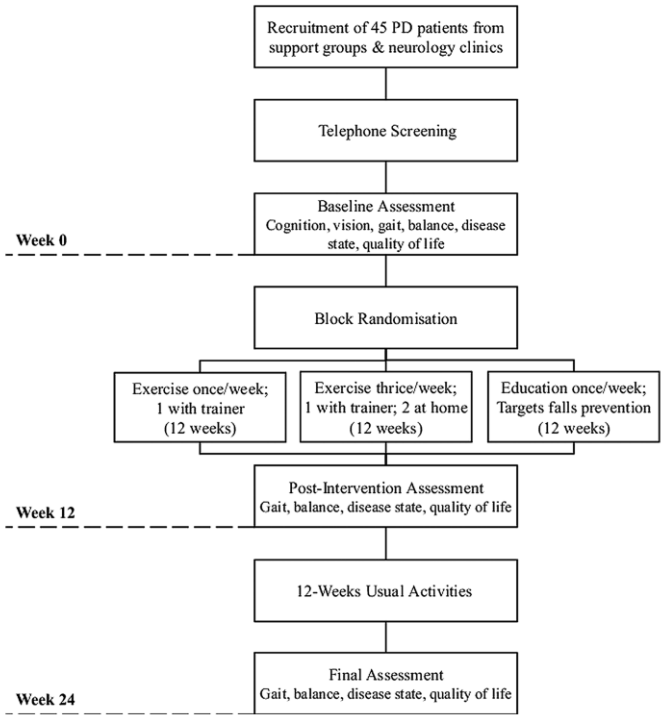

Figure 1 Study outline. Flow chart depicting the order of recruitment and testing procedures for the outlined study.

endurance, which will involve one supervised session each week with a trained Exercise Scientist at the University. The group exercising once per week will receive the intervention during the weekly supervised session, while the group exercising three times per week will be asked to complete the protocol at home on two other days of the week, for a total of three training days per week. The exercise programme consists primarily of exercises that have previously been used in two different exercise-based interventions involving older adults[58] and people with PD,[59] that focused on improving trunk muscle strength and endurance. Importantly, the programme was designed to conform to the current recommendations for best clinical practice with respect to the implementation of exercise-based interventions for improving postural stability.[27 33 60] Specifically, the programme includes movements focusing on improving trunk mobility, exercises that target muscular strength and endurance, tasks that aim to develop balance under challenging situations (ie, on an unstable surface) and ambulating over different terrains in a real-world environment. The programme will progress in complexity to accommodate individuals with different physical capabilities. The primary movements used for the programme are outlined in table 2. Hold times for the endurance exercises begin at 5 s and repetitions begin at 10 or as many as achievable by the participant. In addition, as the participant progresses in the programme, a round and flat air filled disc will be incorporated to create an unstable surface and create a balance challenging environment during the exercises. For the walking portion of the programme, this will be completed on an outdoor walking path that specifically incorporates varying degrees of incline and decline, stairs and multiple surface types to simulate walking during activities of daily living. The various challenges offered by this walking course will serve to improve the participants' capacity to safely and effectively ambulate in predictable and unstable real-world environments.

To facilitate monitoring of activity levels during the 12-week intervention and the 12-week sustainability periods, all participants will be asked to record their weekly activity levels using the International Physical Activity Questionnaire (IPAQ)[61] during these periods. The IPAQ is a questionnaire that has been shown to be both a valid and reliable tool for quantifying activity levels in different populations.[62 63] In addition, compliance to the intervention protocol and any adverse events will also be monitored and reported by the researchers.

Statistical analysis

Continuous data will first be checked for normal distribution and, where applicable, log transformation will be applied to the data. To assess for any significant differences between the groups with respect to the continuous demographic variables (eg, age, height, weight,) a one way

Table 2 Summary of the specific tasks, repetitions and progressions for each of the exercises

Task	Movement	Repetitions/progression
Trunk mobility Warm-up	Lateral bends	10 to the left 10 to the right
	Torso totations	10 to the left 10 to the right
	Small arm circles	10 forward 10 backward
	Large arm circles	10 forward 10 backward
	Torso rotations with high and low reaching	10 reaching up to left, down to right 10 reaching up to right, down to left
Trunk endurance	Abdominal hollowing Side bridging Front bridging Bird dog	Increase difficulty of exercise by: ▶ Increased hold times ▶ Movement complexity ▶ Introduce unstable support surface
Mobility	Walking over surfaces of varying incline/decline, density and up and down stairs	8–10 min of walking on an outdoor walking path
Active cool down	Hamstring stretch	2 sets of 20 s holds
	Quadriceps stretch	2 sets of 20 s holds
	Gastrocnemius/soleus stretch	2 sets of 20 s holds
	Triceps stretch	2 sets of 20 s holds
	Pectoral stretch	2 sets of 20 s holds

analysis of variance (ANOVA) will be used, while the χ^2 test will be used to identify any significant differences in the frequency of categorical data (eg, gender, Hoehn & Yahr scale). If a significant difference is found from the ANOVA, the Tukey's honestly significant difference test will be used to perform post hoc comparisons among the three groups. If the assumptions of normality (Shapiro-Wilks test) or homogeneity of variance (Levene's test) are still violated after log transformation, the non-parametric Kruskal-Wallis testing will replace the ANOVA. Analysis of the outcome measures for static and dynamic postural stability will be based on intention to treat principles. To assess the acute (12 weeks) and long-term (24 weeks) effects of the intervention on measures of postural stability, a repeated measures analysis of covariance (RM-ANCOVA) will be conducted, with the baseline value for each outcome measure and disease severity entered as covariates. To determine covariates, variables of age and disease severity will be graphed in relation to baseline measures of postural stability to identify any linear relationships. All statistical analyses will be completed in the Statistical Package for the Social Sciences (SPSS V.21.0) and the level of significance will be set at $p<0.05$.

DISCUSSION

For people with PD, the increased risk of falls and fall-related injuries has the potential to significantly influence an individual's psychological, physiological and socioeconomic state; ultimately impacting their quality of life. Although oral medications are known to improve many of the motor and non-motor symptoms associated with PD, late-stage symptoms such as gait difficulties and postural instability are not always responsive to this therapeutic intervention.[64] As postural instability and gait difficulties contribute significantly to the high risk of falls in patients with PD, there is a strong need for further research examining additional non-invasive interventions that target the improvement of segmental control and postural alignment in this population.

To date, a number of studies have demonstrated that an exercise intervention can improve strength,[65 66] measures of static postural stability[67] and motor symptoms[17 28 68] in people with PD. In contrast, a separate study reported no significant improvements in self-reported disability or clinical measures of balance, mobility or quality of life for people with PD following a 6-week home-based exercise intervention.[18] Although these clinical tests have been widely used to assess falls risk in people with PD, they may lack the sensitivity to provide real insight into the falls risk of this population. Specifically, it has been shown that the Tinetti Balance and Gait Assessment, Berg Balance Scale, Timed Up and Go, Functional Reach and Physiological Profile Assessment (PPA) of falls risk achieve only moderate sensitivities (65–69%), specificities (62–69%) and accuracies (53–68%) when predicting prospective falls for people with PD.[50] Continuous biomechanical measures, such as those provided by force platforms and accelerometers may help to resolve this problem by increasing the sensitivity of outcome measures to more accurately detect changes in motor performance.

From the perspective of maintaining balance, the trunk is believed to play an important role in maintaining head stability during dynamic tasks. During walking, forces are transmitted upwards from the feet following heel contact, which requires the legs, trunk and neck to act as shock absorbers to attenuate the load and maintain smooth

movement patterns for the head.[5] However, individuals with PD are known to have deficits in trunk control and trunk muscle function,[53] which may impair their capacity to perform this role and increase their risk of falling. The findings of previous research tend to support this notion, indicating that people with PD who fall have greater ML head movement while walking on firm[1] and compliant[16] surfaces and poorer pelvic control[15] during unconstrained gait. As such, interventions aimed at improving trunk muscle functioning may help to improve postural stability and reduce falls for individuals with PD.

The intervention for this study was specifically developed to achieve this goal and will incorporate a series of safe and progressive exercises that were adapted from two previous studies examining the effects of exercise on balance and trunk muscle performance. The findings of these studies demonstrated that progressive exercises targeting improvements in the function of the deeper trunk muscles were effective in improving clinical measures of balance in older women who were at a high risk of falling.[58] Similar exercises, when combined with aerobic exercises and stretching, were shown to significantly improve the strength and mobility of the trunk muscles in individuals with PD, but the authors did not report whether these improvements were associated with any changes in postural stability.[59]

As with any study of this nature, there are a number of limitations that have the potential to influence the outcomes of the proposed exercise-based intervention. First, to ensure the comfort and safety of the participants throughout the data collection and exercise (if applicable) sessions, participants will complete the baseline, follow-up and training sessions while on-medication. As such, it is possible that dopamine-induced side effects of the medication may influence their performances on some of the laboratory and/or clinical assessments. However, details regarding medications will be collected and participants will be asked to report any changes in medications during the study period. If differences are identified between the groups with respect to disease duration, disease severity or medications, these variables will be entered as covariates in the statistical model. Second, the sample size for this study may seem small compared with other studies that have used exercise-based interventions to reduce falls in older adults[69] or people with PD.[18] However, as supported by the presented power calculation, the target sample size of 15 participants per group is adequate to detect differences in our chosen primary outcome measure and will accommodate an attrition rate of 25%.

In conclusion, there is a growing body of evidence to suggest that regular exercise has the potential to reduce the risk of falling in people with PD[17] and may even help to reduce the number of falls experienced by some individuals.[18] This study will be the first to examine whether a 12-week training programme aimed at improving trunk mobility and endurance has the potential to improve measures of postural stability in this population. If found to be effective, this training programme will provide a safe and inexpensive exercise-based therapy option that will help to maintain and/or improve postural stability and ultimately contribute to improving quality of life for people with Parkinson's disease.

Contributors RPH and MHC designed the study, obtained funding and completed extensive preparation to develop the study protocol. MHC will oversee the execution of the study and will be responsible for administering the clinical tests and assisting with recruitment of participants. RPH will be responsible for the day-to-day management of the study, data collection, data analysis and interpretation of the findings. GAN provided important assistance with the development of the study protocol and will be responsible for participant allocation. PAS will be involved in assisting with participant recruitment and with the interpretation of the clinical relevance of the study's outcomes. RPH and MHC developed the initial draft of this manuscript and all authors contributed to the refinement and finalisation of the submitted manuscript.

Funding This project is supported by research funding provided by the Australian Catholic University (grant number 2013000584). Furthermore, Dr Michael H. Cole was supported by an Australian National Health and Medical Research Council Early Career Research Fellowship (grant number 1006481).

Competing interests None.

Ethics approval Australian Catholic University Human Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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BMJ Open

Trunk muscle exercises as a means of improving postural stability in people with Parkinson's disease: a protocol for a randomised controlled trial

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BMJ Open 2014 4:
doi: 10.1136/bmjopen-2014-006095

Study 1 (Published) “Wearable sensor use for assessing standing balance and walking stability in people with Parkinson’s disease: A systematic review.”

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RESEARCH ARTICLE

Wearable Sensor Use for Assessing Standing Balance and Walking Stability in People with Parkinson's Disease: A Systematic Review

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OPEN ACCESS

Citation: Hubble RP, Naughton GA, Silburn PA, Cole MH (2015) Wearable Sensor Use for Assessing Standing Balance and Walking Stability in People with Parkinson's Disease: A Systematic Review. PLoS ONE 10(4): e0123705. doi:10.1371/journal.pone.0123705

Academic Editor: Walter Maetzler, University of Tuebingen, GERMANY

Received: December 8, 2014

Accepted: March 6, 2015

Published: April 20, 2015

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This project was supported by research funding provided by the Australian Catholic University (Research Grant #2013000584), which funded a 3-year International PhD scholarship for Mr Ryan P. Hubble. Dr Michael H. Cole was also supported by an Australian National Health and Medical Research Council Early Career Researcher Fellowship (Project #GNT1016481). The funding body played no role in the design of this study and did not contribute to the

Abstract

Background

Postural instability and gait disability threaten the independence and well-being of people with Parkinson's disease and increase the risk of falls and fall-related injuries. Prospective research has shown that commonly-used clinical assessments of balance and walking lack the sensitivity to accurately and consistently identify those people with Parkinson's disease who are at a higher risk of falling. Wearable sensors provide a portable and affordable alternative for researchers and clinicians who are seeking to objectively assess movements and falls risk in the clinical setting. However, no consensus currently exists on the optimal placements for sensors and the best outcome measures to use for assessing standing balance and walking stability in Parkinson's disease patients. Hence, this systematic review aimed to examine the available literature to establish the best sensor types, locations and outcomes to assess standing balance and walking stability in this population.

Methods

Papers listed in three electronic databases were searched by title and abstract to identify articles measuring standing balance or walking stability with any kind of wearable sensor among adults diagnosed with PD. To be eligible for inclusion, papers were required to be full-text articles published in English between January 1994 and December 2014 that assessed measures of standing balance or walking stability with wearable sensors in people with PD. Articles were excluded if they; i) did not use any form of wearable sensor to measure variables associated with standing balance or walking stability; ii) did not include a control group or control condition; iii) were an abstract and/or included in the proceedings of a conference; or iv) were a review article or case study. The targeted search of the three electronic databases identified 340 articles that were potentially eligible for inclusion, but following title, abstract and full-text review only 26 articles were deemed to meet the inclusion criteria. Included articles were assessed for methodological quality and relevant data from the papers were extracted and synthesized.

data collection, analysis, decision to publish or the preparation of this manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Results

Quality assessment of these included articles indicated that 31% were of low methodological quality, while 58% were of moderate methodological quality and 11% were of high methodological quality. All studies adopted a cross-sectional design and used a variety of sensor types and outcome measures to assess standing balance or walking stability in people with Parkinson's disease. Despite the typically low to moderate methodological quality, 81% of the studies reported differences in sensor-based measures of standing balance or walking stability between different groups of Parkinson's disease patients and/or healthy controls.

Conclusion

These data support the use of wearable sensors for detecting differences in standing balance and walking stability between people with PD and controls. Further high-quality research is needed to better understand the utility of wearable sensors for the early identification of Parkinson's disease symptoms and for assessing falls risk in this population.

PROSPERO Registration

CRD42014010838

Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disorder that results from the loss of neurons within the basal ganglia that produce dopamine, an important neurotransmitter involved in the regulation of movement. As medical advances have extended the life expectancy of the average person, clinical and experimental methods need to progress as well in order to improve the management of the symptoms associated with the disease. It is well understood that deficits in balance and gait are common and disabling features of PD that significantly increase an individual's risk of falling [1]. Subsequently, many clinical assessments have been developed to evaluate these symptoms in this population. The most common assessments include the Berg Balance Scale [2, 3], the Tinetti Gait and Balance assessment [2], the Timed up and Go test [2, 4] and the postural instability and gait disability (PIGD) score derived from the Unified Parkinson's Disease Rating Scale (UPDRS) [2, 5]. These assessments are suited to clinical settings because they require little equipment to conduct and provide almost immediate outcomes that can be reported to the patient. However, prospective research shows these tests have poor sensitivity and specificity for identifying prospective fallers in the PD population [2] and may not be sufficiently sensitive to detect changes in balance and walking in people with PD who have mild to moderate disease severity [6–9].

Given the inherent short-comings of the aforementioned clinical tests, previous research has sought to improve the objectivity of these measures to enhance their ability to track symptom progression and evaluate patient risk. Camera-based three-dimensional motion analysis systems have been commonly used in laboratory settings to examine the walking patterns of people with PD [10–12]. However, the methods associated with these assessments are often time-consuming and require specific expertise and expensive motion capture systems that are impractical for smaller clinical spaces. Wearable sensors, such as accelerometers or inertial measurement units (IMUs), offer a more portable, flexible and moderately-priced alternative to camera-based motion analysis systems. Moreover, wearable sensors do not require excessive

space for normal operation and outcome measures can be output almost immediately without the need for significant post-processing procedures. Given these strengths, research has recently sought to improve the sensitivity of clinical assessments, such as the Timed Up and Go test, by incorporating accelerometers or IMUs to provide continuous measures of walking [13–17]. The results of this research demonstrated that it was possible to detect differences in the performances of people with PD compared with controls by instrumenting the Timed Up and Go test with a wearable sensor [13–17].

Wearable sensors have recently shown good test-retest reliability for assessing individuals with PD, particularly for acceleration-based measures calculated in the time domain (e.g. jerk; the first time derivative of acceleration) [13]. Furthermore, a growing body of literature supports the use of wearable sensors to assess standing balance or walking for; i) people with PD and controls [13, 14, 18–29]; ii) PD fallers and non-fallers [30, 31]; iii) people with different PD sub-types [17, 32–35]; iv) carriers and non-carriers of the LRRK2 gene [36]; and v) people at high risk of developing PD (HRPD) [37, 38]. Results from these studies demonstrate that outcomes derived from wearable sensors are effective for detecting differences in standing balance between HRPD patients, people with PD and controls [38]. When combined in a logistic regression model, it was evident that outcome measures derived from wearable sensors can discriminate HRPD patients from controls using an instrumented functional reach test [37]. Furthermore, three-dimensional accelerometers positioned on the head, trunk or pelvis, have highlighted less rhythmic walking patterns for people with PD who retrospectively reported falling than patients without falls [30, 31]. Collectively, these results suggest that wearable sensors may not only be useful for evaluating changes in a patient's balance or gait patterns, but may also offer a means of screening individuals for various risk factors associated with PD or falls. Nevertheless, scientifically-rigorous prospective research is needed before stronger recommendations can be provided regarding the use of these devices as predictive instruments for clinical populations.

Despite the expanding body of evidence to support the use of wearable sensors for assessing function in people with PD, it is important to recognise that this area of science is still developing. Furthermore, the adoption of such varying methodological approaches in the existing literature makes it difficult to determine which type of sensor is the best to use and which placements and outcome measures are optimal to maximise the utility of these devices. As such, it was the purpose of this systematic review to examine the available literature that utilised wearable sensors to measure standing and walking balance in people with PD and provide a summary of the best sensor types, locations and outcomes based on a consensus of the literature.

Methods

This review was registered with the International Prospective Register of Systematic Reviews on September 3, 2014 (PROSPERO Registration: CRD42014010838). The search strategy and study protocol are available at http://www.crd.york.ac.uk/PROSPEROFILES/10838_STRATEGY_20141106.pdf.

Search Strategy

An electronic database search of titles and abstracts was performed in January 2015 using PubMed, EMBASE and the Cochrane Library to identify articles measuring standing balance and walking stability with any kind of wearable sensor among adults diagnosed with PD. The following terms were used for the literature search: 'Parkinson', 'Parkinson's', 'walk', 'gait', 'balance', 'stability', 'sensor', 'gyroscope', 'inertial', 'acceleration' and 'accelerometer'. Specifically, papers that were included in this review were required to have the term 'Parkinson or Parkinson's' AND ('walk' OR 'gait' OR

'balance' OR 'stability') AND ('sensor' OR 'gyroscope' OR 'inertial' OR 'accelerometer' OR 'acceleration') located within the title and/or abstract. In addition to the systematic electronic database search, a targeted search of the bibliographies of relevant articles was also performed to identify any additional studies for inclusion. The research protocol for this systematic review is included as Supporting Information and outlines the procedures followed and the exact search strategy used for this study (S1 File).

Selection Criteria

Only original, full-text articles published in English between January 1994 and December 2014 that assessed standing balance or walking stability with wearable sensors in people with PD were included in this review. Articles were excluded if they; i) did not use any form of wearable sensor to measure variables associated with standing balance or walking stability; ii) did not include a control group or control condition; iii) were an abstract and/or included in the proceedings of a conference; or iv) were a review article or case study. All studies that met the inclusion criteria were considered for review, irrespective of their research design (cross-sectional, randomised controlled trial, etc). After the initial literature search was completed, two assessors (RPH, MHC) independently screened each of the papers based on their title and abstract and made a decision on the suitability of the paper for inclusion in the review. Once both reviewers had completed this process, any and all discrepancies between the two assessments were discussed until a consensus was reached regarding each paper. Full-text articles were retrieved for all of the papers selected for inclusion based on the title and abstract review process and the full-text of these articles was reviewed for suitability by one assessor (RPH). A flow diagram illustrating the study selection process is provided in Fig 1.

Data Extraction and Quality Assessment

Upon selection of the articles for inclusion, one assessor (RPH) extracted and collated information concerning the type and number of participants, their mean age, disease duration and symptom severity, as well as the type and location of the wearable sensor(s) used and the major findings of each study (Table 1). The included studies presented a range of outcomes that sought to gain a better insight into the deficits of standing balance and walking stability evident in people with PD and these included; i) the root mean square (RMS) of segmental accelerations; ii) the harmonic ratio; iii) jerk (the first derivative of acceleration); iv) step or stride variability; v) step or stride regularity/symmetry; and vi) other less commonly-used measures of stability.

In addition to extracting and compiling these data, a quality assessment was performed by using a modified version of a previously-developed 27-item quality checklist, designed to accommodate both randomised and non-randomised studies [14]. To evaluate the overall methodological quality of each paper, 25 of the criteria on the quality assessment tool were assigned a score of one point if the criterion was met or a zero if the criterion was not met. If it was not possible or unreasonably difficult for the assessors to determine whether the information required for a particular criterion had been provided by the authors, a score of zero was given for that criterion. Of the remaining two questions on the quality checklist, one question evaluating whether potentially confounding variables had been reported by the authors was assessed on a 2-point scale, where the study was given 2 points if confounders were clearly described, 1 point if they were partially described or 0 points if they were not described. The final methodological aspect of the studies that was evaluated was statistical power, which was more heavily weighted than the other criteria and assessed on a 5-point scale. Studies that achieved a statistical power of $\leq$70% for the standing balance or walking stability measures were given a score of zero, while those that achieved powers of 80, 85, 90, 95 or 99% were assigned scores of 1 to 5,

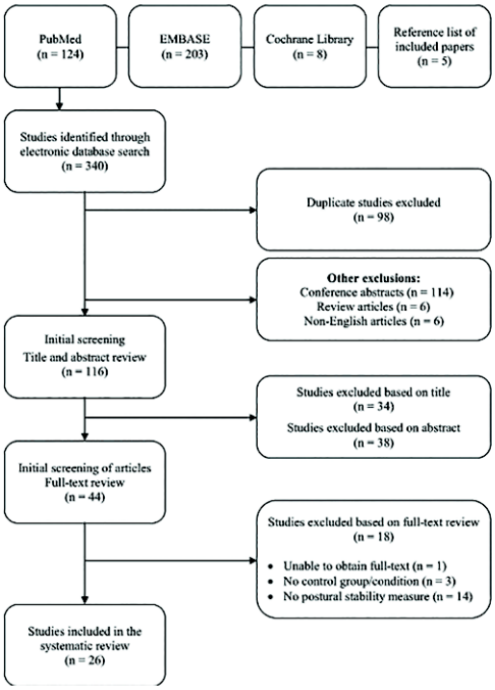

Fig 1. Flow diagram outlining the progression of the study's systematic search strategy and review process, which led to the identification of the articles included in the review.

doi:10.1371/journal.pone.0123705.g001

respectively. Where an appropriate statistical power calculation was not provided by the authors, it was necessary to evaluate the statistical power of each study based on the data presented by the authors. If a statistical power calculation was not reported and the raw data were not presented, the paper was given a score of zero for this criterion. After each paper was assessed against these criteria, the scores were summed and divided by the maximum total points to yield a final score that represented the percentage of total possible points earned. This percentage score was used to evaluate the overall quality of the study using quartiles to classify the methodological quality of the article as either very low (≤25%), low (>25%, but ≤50%), moderate (>50%, but ≤75%) or high (>75%). The methodological quality assessment tool (S2 File) and the scoring of each of the studies included in this review (Table A in S2 File) are provided as Supporting Information.

Results

The initial database search identified 335 articles that were potentially eligible for inclusion in this review. Of the 335 studies identified, 98 were excluded as duplicates, 114 were conference abstracts, six were review articles and six were written in a language other than English. The remaining 115 papers were screened by title and abstract, which resulted in 34 being excluded, based on title and 38 being excluded based on abstract. A manual search was conducted of the bibliographies of those papers that were considered appropriate for full-text review, which

Table 1. Summarises the major characteristics of the research design, analyses and outcomes for the studies that met the inclusion criteria for this review.

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Baston 2014 [24]	PD = 5 (62.0±8.0) PSP = 7 (68.0±5.0) Control = 7 (68.0 ±7.0)	***UPDRS III*** PD = 34.0±14.0	Not Reported	Inertial Sensor Freq: 128 Hz L5 Shank	RMS acceleration *Anteroposterior (AP)*	Dynamic Posturography	No significant difference between PD and controls for AP acceleration during all conditions of the Sensory Organisation Test (SOT). PD had reduced AP accelerations for conditions 4 and 5 of the SOT compared with the PSP group.
Fazio 2012 [16]	PD = 17 (60–85) Ataxia = 24 (20–85) Control = 24 (20–85)	***UPDRS III*** PD = 22.5±3.6	Not Reported	3D Accelerometer Freq: 20 Hz Sternum Front pelvis Back pelvis	RMS acceleration *For sum of sternum accelerations For sum of front pelvis accelerations For sum of back pelvis accelerations* RMS Jerk *For sum of sternum accelerations*	Gait	PD patients had lower Jerk scores compared with controls, but were not significantly different to ataxic patients. PD had significantly lower RMS accelerations for the sternum and two pelvis locations compared with the ataxic and control participants.
Gago 2014 [32]	IPD = 10 (73 [61–79]) VPD = 5 (77 [63–84])	***MDS-UPDRS III*** IPD = 30 [15–53] VPD = 44 [33–57]	IPD 6.0 [5.0–10.0] VPD 5.0 [3.0–9.0]	3D Accelerometer Freq: 113 Hz Lower back	Length of sway Maximum sway distance **Mean sway distance** Maximum linear velocity	Quiet Stance	Idiopathic PD (IPD) patients had significantly increased length and maximum distance of sway during normal stance while on medication. Sway length and maximum distance was also greater for the IPD group when eyes were closed compared with open during the Romberg test off medication. Compared with the IPD patients, vascular PD (VPD) patients had increased mean distance of sway during normal stance and greater maximal distance of sway compared with the IDP patients during the Romberg test with eyes closed off medication.
Hasmann 2014 [37]	PD = 13 (65.0±9.4) HRPD = 31 (62.6 ±5.0) Control = 13 (63.9±7.3)	***UPDRS III*** PD = 26.8±11.0 HRPD = 3.0±3.0 Control = 0.2±0.6	PD 4.5 ±2.8	3D Accelerometer Freq: Not reported Lower back	Mean acceleration *Anteroposterior (AP) Mediolateral (ML)* Jerk *Anteroposterior (AP) Mediolateral (ML)*	Functional Reach	Compared with controls, PD had increased mean acceleration in the AP and ML directions, but the groups did not differ significantly with respect to AP or ML Jerk scores.
Herman 2014 [17]	PD PIGD = 31 (65.0±7.7) PD TD = 32 (64.6 ±11.6)	***UPDRS III—OFF*** PIGD = 38.7±10.5 TD = 39.5±12.5 ***UPDRS III—ON*** PIGD = 33.3±10.0 TD = 33.4±11.8	PIGD 5.7 ±3.7 TD 5.4±3.2	3D Accelerometer Freq: 100 Hz Lower back	Harmonic ratio (HR) *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)* Stride regularity Stride timing variability	Gait	For usual walking, PIGD patients had reduced stride regularity and reduced vertical HRs compared with the TD group while off medication. Accelerometer-derived measures from a 3-day period of in-home activity monitoring revealed that the PIGD group had reduced stride regularity and lower harmonic ratios in both the AP and VT directions compared with the TD group.

(*Continued*)

Table 1. (*Continued*)

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Latt 2009 [30]	***PD Fallers vs. Non-Fallers:*** Non-Faller = 33 (63.0 ±4.0) Faller = 33 (67.0±2.0) Control = 33 (67.0 ±4.0)	***Hoehn & Yahr*** Non-faller = 1 (1–1) Faller = 3 (3–4) ***UPDRS III*** Non-faller = 12.0±3.0 Faller = 21.0±3.0	PD NF 7.0 ±2.0 PD F 9.0±2.0	3D Accelerometer Freq: 200 Hz Head Sacrum	Harmonic ratio (HR) *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* RMS acceleration *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Step timing variability	Gait	Compared with controls and PD non-fallers, fallers had increased step timing variability. With the exception of AP head accelerations, PD fallers had significantly reduced head and pelvis accelerations compared with non-fallers and controls. Controls had higher AP head accelerations compared with PD fallers, and PD non-fallers had lower ML accelerations for the pelvis than controls. PD fallers had lower AP and VT HRs for the head and lower AP, ML and VT HRs for the pelvis compared with non-fallers and controls. PD non-fallers had lower VT HRs for the head and pelvis and lower AP HRs for the head compared with controls. Non-fallers also had greater ML HRs for the head compared with fallers.
Lowry 2010 [39]	PD = 7 (70.3±8.5)	***Hoehn & Yahr*** PD = 2.4±0.5	PD 6.2 ±4.7	3D Accelerometer Freq: 200 Hz L3	Harmonic Ratio (HR) *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)*	Gait	Cognitive cueing (thinking "big step" during the swing phase) and verbal cueing (assessor saying "big step" during the swing phase) both improved AP HR compared with preferred gait (without cues).
Lowry 2009 [19]	PD = 11 (68.0±7.7) Control = 11 (69.0 ±8.8)	***Hoehn & Yahr*** PD = 1.9±0.8	PD 5.2 ±4.0	3D Accelerometer Freq: 200 Hz L2	Harmonic Ratio (HR) *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Stride timing variability Stride length variability	Gait	PD and controls did not differ significantly with respect to stride length variability, stride timing variability or AP, ML and VT HRs. After normalising these data to walking speed, PD patients had lower AP and ML HRs compared with controls.
Maetzler 2012 [36]	PD = 12 (61.5±2.2) HRPD = 20 (61.9 ±1.5) Control = 14 (63.9±1.9)	***Hoehn & Yahr*** PD = 2.0±0.0 ***UPDRS III—OFF*** PD = 26.5±10.9 HRPD = 3.3±2.4 Control = 1.1±1.7	PD 4.3 ±2.6	Inertial Sensor Freq: 100 Hz L3/ L4	RMS acceleration *Anteroposterior (AP)* *Mediolateral (ML)* Jerk *Anteroposterior (AP)* *Mediolateral (ML)* Frequency with 95% of signal (F95) *Anteroposterior (AP)* *Mediolateral (ML)* Mean sway velocity	Quiet Stance	The PD and control groups did not differ significantly for AP or ML RMS accelerations or Jerk scores, even when vision was occluded and/or somatosensory feedback was reduced. However, the high risk of PD (HRPD) group had greater AP and ML RMS accelerations than PD patients and controls while standing on a foam surface with eyes closed and greater scores than PD when standing on a firm surface with eyes closed. The HRPD group also had greater AP and ML Jerk scores than the PD and controls group during the foam eyes closed task. Groups did not differ with respect to F95 or mean sway velocity.

(*Continued*)

Table 1. (*Continued*)

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Mancini 2011 [28]	PD = 13 (60.4±8.5) Control = 12 (60.2 ±8.2)	***Hoehn & Yahr*** PD = 1.8±0.6 ***UPDRS III*** PD = 28.2±11.2	PD 14.3 ±6.9	Inertial Sensor Freq: 50 Hz L5	RMS Acceleration *Resultant of AP and ML* Jerk *Resultant of AP and ML* Frequency with 95% of signal (F95) *Resultant of AP and ML* Mean sway velocity	Quiet Stance	Compared with controls, the PD group had significantly greater RMS accelerations, Jerk scores and mean sway velocity measures while standing on a firm surface with eyes open, but not with eyes closed. Groups did not differ with respect to the F95 measure.
Mancini 2012 [13]	***Study 1*** PD = 13 (60.4±8.5) Control = 12 (60.2 ±8.2) ***Study 2*** PD = 17 (67.1±7.3) Control = 17 (67.9 ±6.1)	***Study 1 UPDRS III*** PD = 28.1±11.2 ***Study 2 UPDRS III*** PD = 28.3±10.4	Not Reported	Inertial Sensor Freq: 50 Hz L5	RMS Acceleration *Resultant of AP and ML* Jerk *Resultant of AP and ML* Frequency with 95% of signal (F95) *Resultant of AP and ML* Mean sway velocity Length of sway Mean sway distance Sway area	Quiet Stance	Compared with controls, the PD group had significantly higher RMS accelerations, Jerk scores, sway distances and sway areas, but the groups did not differ with respect to the F95 measure, mean sway velocities or length of sway.
Mancini 2012 [29]	PD = 13 (60.4±8.5) Control = 12 (60.2 ±8.2)	***Hoehn & Yahr*** PD = 1.8±0.2(SEM) ***UPDRS III*** PD = 26.6±3.5 (SEM)	Not Reported	Inertial Sensor Freq: 50 Hz L5	RMS acceleration *Anteroposterior (AP) Mediolateral (ML)* Jerk *Anteroposterior (AP) Mediolateral (ML)* Frequency with 95% of signal (F95) *Anteroposterior (AP) Mediolateral (ML)* Mean sway velocity *Anteroposterior (AP) Mediolateral (ML)*	Quiet Stance	For RMS accelerations, a significant main effect for group showed that PD participants had greater ML accelerations than controls, while the AP axis fell marginally short of statistical significance. PD participants also had higher AP and ML Jerk scores at baseline, but ML Jerk was also larger for the PD patients at the 3–6 and 12-month follow-up time points. There were also significant main effects for group for ML F95 values and mean sway velocity along the ML axis, indicating that the PD group had larger values for both of these measures compared with control.
Mirelman 2013 [30]	***PD LRRK2 Gene:*** Carrier = 50 (62.6 ±9.6) Non-Carrier = 50 (60.2 ±11.3)	***Hoehn & Yahr*** Carrier = 2–3 Non-Carrier = 2–3 ***UPDRS Total*** Carrier = 27.9±14.2 Non-Carrier = 26.9 ±13.3	Carrier 4.4 ±3.3 Non-Carrier 6.1 ±6.1	3D Accelerometer Freq: Not reported Lower back	***Preferred vs. Fast speed vs. Dual-task:*** Stride timing variability Step regularity (step-to-step consistency) Width of dominant frequency *Anteroposterior (AP)*	Gait	Carriers of the LRRK2 gene had greater stride timing variability and less step regularity than non-carriers during preferred speed, fast speed and dual-task (serially subtracting 3s) walking. Carriers also had greater gait variability during preferred and fast walking, as evidenced by the greater width of the dominant frequency. Significant group by condition interactions suggested that the carriers had a greater increase in stride timing variability and a greater width of the dominant frequency with increased task complexity (i.e. dual tasking) compared with non-carriers.

(*Continued*)

Table 1. (*Continued*)

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Palmerini 2013 [14]	PD = 20 (62.0±7.0) Control = 20 (64.0 ±6.0)	***Hoehn & Yahr*** PD = 2.4±0.2	PD 5.2 ±4.1	3D Accelerometer Freq: 100 Hz L5	RMS acceleration *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Normalised Jerk *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Harmonic ratio (HR) *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Phase coordination index	Timed Up and Go	During the gait and turning portions of the Timed Up and Go test, PD patients had significantly lower AP and ML normalised Jerk scores than control participants. Similarly, during the gait component of the test, PD participants also had lower AP and VT HRs compared with controls. The two groups did not differ significantly for any of the other accelerometer-based measures.
Palmerini 2011 [40]	PD = 20 (62.0±7.0) Control = 20 (64.0 ±6.0)	***Hoehn & Yahr*** PD = <2.5 ***UPDRS-III*** PD = 26.6±7.1	Not Reported	3D Accelerometer Freq: 100 Hz L5	High Frequency Power *Anteroposterior (AP)* *Mediolateral (ML)* Frequency Dispersion *Anteroposterior (AP)* *Mediolateral (ML)* Sway Range *Anteroposterior (AP)* *Mediolateral (ML)*	Quiet Stance	Compared with controls, the PD group had significantly higher high frequency power in the ML direction during the dual task condition and significantly lower AP frequency dispersion scores while standing on a foam surface. AP sway range was not significantly different between groups. A wrapper feature selection approach determined that ML high frequency power on a firm surface with eyes open, AP frequency dispersion on a foam surface with eyes open and AP sway range on foam surface with eyes closed represented the best candidate subset to distinguish PD from controls.
Rocchi 2014 [33]	PD PIGD = 40 (64.5±6.9) PD TD = 26 (67.6±9.9) Control = 15 (78.2 ±3.9)	***UPDRS III*** PD PIGD = 38.3±10.9 PD TD = 43.3±13.4	PD PIGD 5.1±3.6 PD TD 5.7 ±2.8	3D Accelerometer Freq: 100 Hz Lower back	***Feet together vs. Semi-tandem:*** Centroidal frequency (CF) *Anteroposterior (AP)* Length of sway *Anteroposterior (AP)* *Mediolateral (ML)* *2-dimensional (2D)* Mean sway velocity *Anteroposterior (AP)* *Mediolateral (ML)*	Quiet Stance	The TD group had significantly lower CF values than controls for all experimental tasks and the PIGD group also had lower CF values than controls for all conditions except semi-tandem stance with eyes closed. The TD and PIGD groups did not differ with respect to CF during any of the experimental tasks. CF values were influenced by foot position for the two PD groups (PIGD and TD) with greater values recorded during semi-tandem stance. Results were similar for sway velocity and length of sway, with all groups typically showing higher values with eyes closed compared with eyes open. The groups did not differ for sway velocity or length of sway for the feet together or semi-tandem stance trials with eyes open, but the PIGD and TD groups had lower values compared with controls during the EC conditions.

(*Continued*)

Table 1. (*Continued*)

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Sant'Anna 2011 [27]	PD = 11 (60.0±8.6) Control = 11 (61.0 ±7.8)	***Hoehn & Yahr*** PD = 1.6±0.6 ***UPDRS-PIGD*** PD = 0.7±1.1	PD 1.1 ±1.1	1D Gyroscopes Freq: 200 Hz Anterior shank 2D Gyroscopes Freq: 200 Hz Wrist	Symbolic symmetry index (SI_{symb}) Symmetry index (SI_{index}) Gait asymmetry (SI_{GA}) Symmetry angle (SI_{angle}) Maximum angular velocity ratio (SI_{ratio}) Trend symmetry (SI_{trend}) LCEA symmetry magnitude (SI_{LCEA})	Gait	Of the symmetry measures derived from the gyroscopes placed on the shanks and wrists, only the SI_{index}, SI_{GA}, SI_{ratio} and SI_{symb} values for the wrist sensors were significantly higher for PD participants. Evaluation of the area under the Receiver Operating Characteristic (ROC) curves for these four outcomes showed that only SI_{ratio} and SI_{symb} were able to differentiate PD from controls, but the higher Intra-class Correlation Coefficients for SI_{symb} indicated that this outcome was more robust for differentiating between the two cohorts.
Sejdić, 2014 [20]	PD = 10 (≥65 years) Neuropathy = 11 (≥65 years) Control = 14 (≥65 years)	***Hoehn & Yahr*** PD = 2–3	Not Reported	3D Accelerometer Freq: 100 Hz L3	Lyapunov exponent (LE) *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)* Harmonic ratio (HR) *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)* Entropy rate *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)* Cross entropy rate *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)*	Gait	There were no significant differences between the groups for AP, ML or VT Lyapunov exponents, but PD patients had less gait rhythmicity in the vertical direction (decreased VT HRs) compared with healthy controls. With respect to the entropy measure, the PD and peripheral neuropathy groups both had significantly greater ML values than controls, but there were no group differences for cross entropy rate.
Sekine 2004 [21]	PD = 11 (66±9.6) Control = 10 (66.3 ±5.3)	***Hoehn & Yahr*** PD = 1–2	Not Reported	3D Accelerometer Freq: 1024 Hz L5/ S1 region	Fractal Brownian Motion *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)*	Gait	The fractal values for the AP, ML and VT directions were significantly higher for the individuals with PD compared with controls. Also, the AP, ML and VT fractal dimensions were all significantly negatively correlated with walking speed for the PD group, but not controls.

(*Continued*)

Table 1. (*Continued*)

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Sekine 2004 [54]	Mild PD = 11 (66.0 ±9.6) Severe PD = 5 (57.4±19.1) Control = 10 (66.3 ±5.3)	***Hoehn & Yahr*** Mild PD = 1–2 Severe PD = 3–4	Not Reported	3D Accelerometer Freq: 1024 Hz L5/ S1 region	Vertical patterns *Anteroposterior (AP) Mediolateral (ML)* Vertical *(VT)* Circular patterns *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)* Horizontal patterns *Anteroposterior (AP) Mediolateral (ML) Vertical (VT)*	Gait	Controls did not differ significantly from the mild or severe PD groups for AP, ML or VT vertical patterns. Circular patterns were different between the groups, with both mild and severe PD participants having larger values than controls in the AP and VT directions, while severe PD patients also had higher AP circular patterns than mild PD patients. Severe PD patients had greater short horizontal patterns than controls in all three directions and lower long horizontal patterns in the AP and VT than controls. Severe PD patients also had greater short horizontal patterns in the AP, ML, VT than mild PD patients and mild PD patients had lower values than controls for long horizontal patterns in the AP and VT directions.
van Emmerik 1999 [29]	PD = 27 (53.7 ±10.6) Control = 11 *(not reported)*	***Hoehn & Yahr*** PD = 1.5 ±0.6 ***UPDRS III*** PD = 16.7±6.2	PD 2.3 ±1.4	1D Accelerometer Freq: 104 Hz Shank	Stride timing variability Relative phase analysis	Gait	Stride timing variability was not significantly different between PD and controls, but variability significantly decreased for both groups as walking velocity increased. Continuous relative phase was also larger for controls compared with PD patients between walking speeds of 0.2 and 1.4 m/s.
Weiss 2011 [22]	PD = 22 (65.9±5.9) Control = 17 (69.9 ±8.8)	***Hoehn & Yahr*** PD = 2.5±0.4 ***UPDRS III*** PD = 23.6±9.4	PD 4.8 ±3.8	3D Accelerometer Freq: 256 Hz Lower back	Stride timing variability Width of the dominant harmonic	Gait	Stride timing variability was significantly higher for PD patients compared with healthy controls. Similarly, the width of the dominant harmonic of the power spectral density of the locomotor band of the acceleration signal was significantly greater for PD patients, both on and off medication, compared with controls. Furthermore, the width of the dominant harmonic was greater for patients when off medication compared with on medication.

(*Continued*)

Table 1. (*Continued*)

Article	Experimental Groups N (Mean Age ± SD)	Disease Severity	Disease Duration (Years)	Sensor Type (Placement)	Postural Stability Measures	Modality	Findings
Weiss 2014 [35]	***PD Freezer vs. Non-Freezer:*** Non-Freezer = 44 (66.5 ±8.8) Freezer = 28 (64.4±8.7)	***Hoehn & Yahr*** Non-Freezer = 2.4 ±0.5 Freezer = 3.2 ±0.8 ***UPDRS III—OFF*** Non-Freezer = 42.3 ±12.9 Freezer = 46.2 ±12.2 ***UPDRS III—ON*** Non-Freezer = 35.6 ±12.8 Freezer = 36.3 ±11.7	Non-Freezer 6.7±2.2 Freezer 7.5±4.5	3D Accelerometer Freq: Not reported Lower back	Harmonic ratio (HR) *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Stride regularity *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Width of dominant frequency *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)*	Gait	Freezers had decreased AP, ML and VT harmonic ratios and stride regularity compared with non-freezers. PD freezers also had a significantly greater width of the dominant frequency in the VT and AP directions. Harmonic ratios and stride regularity were significantly correlated with the new freezing of gait questionnaire (NFOG-Q) and the width of the dominant frequency in the VT and AP direction were also significantly correlated with this clinical test.
Weiss 2014 [31]	***PD Fallers vs. Non-Fallers:*** Non-Faller = 67 (64.0 ±9.8) Faller = 40 (66.5±8.2)	***Hoehn & Yahr*** Non-Faller = 2.4 ±0.5 Faller = 2.9 ±0.8	Non-Faller 5.2±3.1 Faller 6.1 ±4.0	3D Accelerometer Freq: 100 Hz Lower back	Harmonic ratio (HR) *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Stride regularity *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)* Width of dominant frequency *Anteroposterior (AP)* *Mediolateral (ML)* *Vertical (VT)*	Gait	During a 3-day assessment of gait and mobility, fallers exhibited reduced HRs in both the AP and VT directions. PD fallers also had less VT stride regularity than non-fallers and a greater width of the dominant frequency for the AP and VT directions.
Yang 2011 [26]	PD = 5 (78.0±9.8) Control = 5 (26.0 ±3.1)	***Hoehn & Yahr*** PD = 2–3	Not Reported	3D Accelerometer Freq: 50 Hz Lateral pelvis	Step regularity Stride regularity Step symmetry	Gait	There were no significant differences observed in step regularity, stride regularity or step symmetry between PD patients and controls.
Zampieri 2009 [36]	PD = 12 (60.4±8.5) Control = 12 (60.2 ±8.2)	***Hoehn & Yahr*** PD = 1.6±0.5 ***UPDRS III*** PD = 20.0±8.4	PD 1.1 ±1.1	1D Gyroscopes Freq: 200 Hz Anterior shank 2D Gyroscopes Freq: 200 Hz Wrist Inertial Sensor Freq: 200 Hz Sternum	Stride length variability Stride timing variability	Timed Up and Go	PD and control groups did not differ with respect to stride length variability or stride time variability.

PD: Parkinson's disease; **PSP:** Progressive supranuclear palsy; **IPD:** Idiopathic Parkinson's disease; **VPD:** Vascular Parkinson's disease; **HRPD:** People at high-risk of Parkinson's disease; **UPDRS:** Unified Parkinson's Disease Rating Scale; **MDS-UPDRS:** Movement Disorders Society's revision of the Unified Parkinson's Disease Rating Scale; **Freq:** Sampling frequency of wearable sensor

doi:10.1371/journal.pone.0123705.t001

identified five additional papers for consideration. Following full-text review of the remaining 44 studies, a further 18 studies were excluded, including one that was unattainable, three that had no control group or condition and 14 that had no sensor-based measure of standing balance or walking stability. The remaining 26 articles were selected for inclusion in this systematic review.

Study Design and Methodological Quality

All 26 studies included within this review had a cross-sectional research design with a broad aim of using different types of wearable sensors to observe or identify differences in standing balance or walking stability for Parkinson's disease compared with controls or a control condition (e.g. on medication vs. off medication, PD subtypes). Given their cross-sectional nature, ten items were excluded from the methodological quality checklist, as they specifically targeted qualities that are unique to intervention studies. The decision to exclude these criteria was made to ensure that the overall quality of the studies included in this review was not unfairly biased by these items that were not relevant to their chosen design.

Based on the appraisal of methodology quality, eight papers were identified as being of low methodological quality (range = 31.8% to 50.0%), 15 papers were of moderate methodological quality (range = 54.5% to 72.7%) and three papers were of high methodological quality (range = 77.3% to 90.9%). In general, the reviewed papers performed poorly on criteria addressing external validity (e.g. representativeness of the sample), internal validity (e.g. identification of and adjustment for potential confounders) and statistical power (e.g. no power calculation and insufficient details to make an informed appraisal).

Sensor Type and Placement

Multiple wearable sensor types were used within the included articles to assess measures of standing balance and walking stability. Of these studies, 69% reported using three-dimensional accelerometers [14, 17–23, 30–37, 39, 40], 27% used inertial sensors [13, 24–28, 38], and 4% used other types of sensors [28, 29]. Similarly, there were multiple protocols described with respect to the placement of the wearable sensors on the human body. Of the 26 included studies, 85% reported placing a wearable sensor on either the lumbar or sacral region of the trunk [13, 14, 17–22, 24–27, 31–40] and 15% reported placing devices on other body landmarks (e.g. head, shank, wrist) [23, 28–30]. Details on the studies included in this review that reported using each specific type and placement of sensors are summarised in Table 1.

Assessment of standing balance and walking stability

Of the 26 included studies, 65% used wearable sensors to assess walking during clinical tests, such as the Timed up and Go Test [14, 28] or during assessments of straight-line walking at a self-selected speed [17–23, 27, 29–31, 34–36, 39]. A wide range of sampling frequencies was used to assess walking stability in the reviewed studies, with authors reporting sampling frequencies ranging between 20 and 1024 Hz. The remaining nine studies (35%) assessed standing balance using an instrumented functional reach test [37], dynamic posturography [24] or one of many pre-existing clinical tests conducted during quiet stance (i.e. the Romberg test, tandem stance, semi-tandem stance, standing with eyes open and eyes closed) [13, 25, 26, 32, 33, 38, 40]. Understandably, the wearable sensors used in these studies were generally set to collect data at a slower rate to those used for assessing the dynamic tasks, with reported sampling frequencies ranging from 50 to 128 Hz.

The included studies reported multiple outcomes of standing balance and walking stability that were calculated from the signals provided by the wearable sensors (e.g. accelerations). Of

these outcomes, the most commonly-reported measures of standing balance included postural sway velocity (23% of studies) [13, 25, 26, 32, 33, 38], RMS accelerations (19% of studies) [13, 24–26, 38] and jerk (19% of studies) [13, 25, 26, 37, 38]. The most commonly-reported measures of walking stability included, the harmonic ratio (31% of studies) [14, 17, 19, 20, 22, 30, 35, 39] and stride timing variability (27% of studies) [17, 19, 22, 28–30, 36]. A summary of the studies reporting each of the outcome measures of standing balance and walking stability is provided in Table 2.

Discussion

The purpose of this systematic review was to examine the existing literature to determine the best types of wearable sensors and the most appropriate anatomical placements and outcome measures to assess deficits in balance and gait between people with PD and controls. Using the methodological quality assessment tool adapted from Downs and Black [41], it was determined that the overall quality of scientific reporting in this area is largely of low to moderate quality. In general, the reviewed papers were lacking details concerning the representativeness of the study population (external validity), the approaches adopted to identify and account for confounding variables (internal validity) and an appropriate justification for the chosen sample size. Interestingly, 62% of the included studies received a score of zero for all of the criteria related to at least two of these three areas, while one study (4%) received a score of zero for all three of these areas. The heavier weighting attributed to the sample size criterion is indicative of the importance of ensuring that a study has sufficient statistical power to identify a difference where one exists and, hence, minimise the likelihood of incorrectly accepting the null hypothesis (i.e. Type II error) [42]. Of the 26 studies included in this review, not one reported the results of a sample size calculation, but 13 (50%) had fewer than 15 participants in each of their groups [13, 19–21, 23–28, 32, 34, 39] and three others (12%) had at least one group with fewer than this number [29, 37, 38]. While it is important to emphasise that a large sample size is not always required to address a specific research question, reporting the outcome of an appropriate a-priori statistical power calculation is beneficial for determining the overall rigor of the reported findings.

Of the other methodological aspects that were poorly reported, the lack of appropriate detail regarding the influence of confounding variables was quite substantial, as failure to account for these factors may result in a study observing a significant change that is simply the manifestation of another variable not adequately controlled for [43]. For example, it is widely recognised that gait and balance variables are influenced by walking speed [44–48] and age [49–51], hence if groups differ for either or both of these variables, appropriate adjustments should be made to account for this. Of the reviewed studies, 15 (58%) described the principal confounder(s) of their research and reported having made adjustments to their outcomes to account for these variable(s) [17, 19, 22, 26–32, 35, 36, 38–40]. Of the remaining studies, four (15%) provided a description of the potential confounders, but lacked clear descriptions of how they were accounted for in their analyses [14, 21, 34, 37], while seven (27%) neither reported nor accounted for their potential confounders [13, 18, 20, 23–25, 33]. In the study by Fazio et al [18], it was reported that people with PD had significantly lower accelerations and jerk scores than ataxic patients and healthy controls. However, the age of the patients in the PD group (n = 17) ranged from 60–85 years, while the ataxic patients (n = 24) and controls (n = 24) were aged between 20 and 85 years, with more than 60% of these participants aged less than 60 years. Furthermore, the authors reported that the PD and ataxic patients walked significantly slower than the control participants. Given the differences in age and walking speed between the cohorts, it is difficult to determine whether the reported differences in acceleration profiles were indicative of disease-related changes or whether they were

Table 2. Summarises and defines the sensor-based measures of standing balance and walking stability used in the studies included in this review.

Outcome Measure	Definition of Measure	Articles
Standing Balance or Walking Stability		
Mean acceleration	The average of the anteroposterior (AP), mediolateral (ML) or vertical (VT) accelerations during a specific phase of the movement. Provides an indication of the rate of change in the velocity of the body during this phase. Under static conditions, larger values would represent poorer control.	[37]
Root mean square (RMS) acceleration	Taking the RMS of the accelerations makes all values of the time series positive, to yield an average positive amplitude for AP, ML or VT accelerations. Like mean accelerations, RMS accelerations provides an indication of the rate of change in velocity, but is more robust for data that has both positive and negative values.	[13,14,18,24–26,30,38]
Jerk	Time series of the first derivative of acceleration (third derivative of displacement), representing the rate of change of acceleration. It is calculated from the raw AP, ML or VT accelerations. During steady movements, the body should be neither accelerating nor decelerating rapidly, hence Jerk scores should be smaller for more stable people.	[13,25,26,37,38]
Root mean square (RMS) Jerk	Similar to RMS accelerations, RMS Jerk mathematically converts all values to a positive number and provides an average value for the AP, ML and VT Jerk time series. In lay terms, the RMS Jerk provides a single value that describes the jerkiness of the movement.	[18]
Normalised Jerk	RMS Jerk score divided by overall movement time. Provides similar information to RMS Jerk, but takes into account differences in task duration for different populations.	[14]
Standing Balance		
Maximum sway distance	The resultant of AP and ML displacement is calculated for an inertial measurement unit placed at the height of the centre of mass (COM; 55% of height). Maximum sway distance is the single largest value recorded throughout the trial. Provides insight into the extremes of postural sway.	[32]
Mean sway distance	The resultant of AP and ML displacement is calculated for an inertial measurement unit placed at the height of the COM (55% of height). Mean sway distance is the average of all resultant values recorded throughout the trial. Larger values represent poorer postural control.	[13,32]
Sway Range	The overall range of displacement of the centre of mass (COM; estimated from an inertial measurement unit positioned on the trunk) in the anteroposterior (AP) and mediolateral (ML) directions. Larger values represent an increased amount of postural sway.	[40]
Length of sway	The total distance travelled by the COM on the transverse plane. Increased length of sway indicates more sway per unit of time and, hence, reduced postural control.	[13,32,33]
Mean sway velocity	The first integral of the AP, ML or VT acceleration signals. Higher sway velocities represent more erratic postural adjustments and, hence, poorer postural control.	[13,25,26,33,38]
Sway area	The elliptical area that encapsulates the sway path derived from the AP and ML accelerations. Larger sway areas represent an increased volume of sway, which may suggest poorer balance.	[13]
F95	The frequency below which 95% of the acceleration signals power is present. Higher frequencies would represent a larger number of postural adjustments to maintain balance during the trial.	[13,25,26,38]
Centroidal frequency	The frequency at which the power of the signal above and below are exactly balanced (i.e. the centre point). The centroidal frequency can be calculated for the AP, ML and VT axes separately. Lower frequencies represent poorer postural control.	[33]
High frequency power	Percentage of the acceleration signal that is present between 4 and 7 Hz. A greater proportion of data in this high frequency band represents increased postural adjustment and postural sway.	[40]
Frequency dispersion	A unitless frequency-based measure of variability. Values closer to zero would represent more regular patterns of sway, while values closer 1 represent a greater degree of variability.	[40]
Walking Stability		
Harmonic Ratio	A measure of the stability of gait-related accelerations by evaluating the stride-to-stride regularity of the harmonics within the acceleration signal. Walking patterns that produce higher ratios have more regular acceleration profiles over successive gait cycles (i.e. less stride-to-stride variability); hence, the gait pattern is deemed to be more stable.	[14,17,19,20,30,31,35,39]
Step and stride regularity	The regularity of the AP, ML or VT acceleration profiles from step-to-step or stride-to-stride. Higher regularity scores represent a more rhythmic and consistent walking pattern and is often said to reflect a more stable gait pattern.	[17,23,31,35,36]
Step symmetry	Ratio of step regularity to stride regularity. A ratio closer to 1 represents greater symmetry between the left and right steps, while values closer to 0 indicate poorer symmetry.	[23]

(*Continued*)

Table 2. (*Continued*)

Outcome Measure	Definition of Measure	Articles
Step and stride timing variability	The standard deviation (SD) or the coefficient of variation ((SD/mean)*100) of all step or stride times collected during a trial. Greater variability represents a less rhythmic walking pattern that is often said o reflect a less stable gait pattern.	[17,19,22,28–30,36]
Stride length variability	The standard deviation (SD) or the coefficient of variation ((SD/mean)*100) of all stride lengths collected for the left and right leg collected throughout a trial. Greater variability represents a less predictable and, hence, less stable walking pattern.	[19]
Lyapunov exponent	A non-linear measure that assesses the sensitivity of the system to perturbations in the AP, ML or VT directions. The Lyapunov exponent provides an indication of the local dynamic stability of the gait pattern, with lower values representing increased local stability during gait.	[20]
Entropy rate	Assesses the regularity of the AP, ML and VT accelerations. Values range from 0, which represents no regularity (maximum randomness) to 1, which represents maximum regularity.	[20]
Cross entropy rate	Non-linear measure of asynchrony between two related time series. Used to assess how well the pattern of AP acceleration (for example) can predict ML accelerations. Higher values indicate more synchronisation between the acceleration patterns and, hence, a more stable gait pattern.	[20]
Width of the dominant frequency	The width of the dominant harmonic of the power spectral density of the acceleration signal. Greater widths, represent greater dispersion and greater variability of the gait pattern.	[22,31,35,36]
Relative phase analysis	A graphic-based analysis that plots the angular position of a segment against the angular velocity of the same segment. Relative phase analysis provides a measure of the coordination between two adjoining segments (e.g. pelvic and trunk) and the overall stability of this pattern.	[29]
Phase coordination index (PCI)	Stable walking has step times that are approximately half the length of the gait cycle (i.e. 180° of a 360° cycle). Deviation from this expectation is considered an inaccuracy. The PCI is a summary measure that combines this value representing the accuracy with the coefficient of variation, representing consistency, hence the PCI is considered a measure of gait coordination.	[14]
Symmetry index (SI_{Index})	The SI_{Index} compares movements from one side (e.g. injured) to the other side (e.g. uninjured). Perfect symmetry is represented by zero and larger numbers represent more asymmetry.	[27]
Gait asymmetry (SI_{GA})	Mean swing time is calculated for both left and right legs. Gait asymmetry is the natural log (ln) of the swing time of the leg with the shortest swing time divided by the swing time of the leg with the longer swing time. Values closer to zero represent a symmetrical movement pattern.	[27]
Symmetry angle (SI_{angle})	Measures the relationship between discrete values obtained from the left and right side and is derived when the right-side value is plotted against the left-side value to create a line that forms an angle with the x-axis. Angles that deviate from 45° represent some degree of asymmetry.	[27]
Maximum angular velocity ratio (SI_{ratio})	Ratio of the maximum angular velocity of the left leg (averaged over all gait cycles) to maximum angular velocity of the right leg (averaged over all gait cycles). Values that are closer to zero represent better symmetry between the left and right sides of the body.	[27]
Trend symmetry (SI_{trend})	Translated data from the left and right sides of the body are used to derive eigenvectors. Trend symmetry assesses the ratio of the variability *about* the eigenvector (y-axis) to the variability *along* the eigenvector (x-axis). A value of zero represents perfect symmetry.	[27]
LCEA symmetry magnitude (SI_{LCEA})	Applies a latency corrected ensemble average (LCEA) to assess the correlation between the magnitudes of the signals collected from the left and right sides of the body using a cross-correlation approach. Larger values represent a greater degree of symmetry.	[27]
Fractal Brownian Motion	Fractal measures provide an indication of the complexity of the AP, ML, VT accelerations during walking. Higher values represent more complex walking patterns, hence walking patterns that are more difficult to coordinate and control effectively.	[21]
Vertical Patterns	A time-frequency pattern of the energy of the acceleration signal for AP, ML and VT directions. Vertical patterns represent impulse type activities during the walking cycle.	[34]
Circular Patterns	A time-frequency pattern of the energy of the acceleration signal for AP, ML and VT directions. Circular patterns characterise irregular burst like patterns during the walking cycle.	[34]
Horizontal Patterns	A time-frequency pattern of the energy of the acceleration signal for AP, ML and VT directions. Horizontal patterns represent long-term smooth and regular activities.	[34]

doi:10.1371/journal.pone.0123705.t002

simply representative of age-related and/or speed-related factors. Identifying all potential confounders in this type of research and reporting how they have been accounted for in the analyses is critical to ensuring that any changes in outcome can be confidently attributed to the treatment or disease of interest. Collectively, the results of the methodological quality assessment identified

that issues related to internal and external validity, as well as statistical power are typically poorly reported in the literature. It should be emphasised that this does not suggest that the authors did not consider some or all of these factors, but rather suggests that these areas should be given more attention in the reporting of future research. To improve the overall methodological quality of research in this area, it is recommended that scientists use existing research reporting guidelines (e.g. CONSORT, STROBE) when designing and planning the reporting of their studies.

Despite the outlined shortcomings in the reporting of the methods, 81% of the studies described differences between different PD groups and/or a healthy control group for one or more of their sensor-based measures of standing balance or walking stability [13, 14, 17–22, 25–27, 29–37, 39, 40]. However, contradictory findings reported in separate studies suggest that some of the reported outcomes may be more robust than others. For example, two studies that compared PD patients with controls using a standing balance assessment reported no significant differences between the groups for jerk scores [37, 38], while three others reported significantly greater jerk scores for PD patients [13, 25, 26]. Similarly, two studies reported no differences between people with PD and controls for RMS accelerations [24, 38], while three studies reported significantly greater RMS accelerations for PD patients [13, 25, 26]. Sway velocity was another common measure used to evaluate standing balance, but similarly only three studies [25, 26, 33] reported differences between people with PD and controls, while the remaining three did not [13, 32, 38]. It is interesting to note, however, that contradictory findings were presented by the three studies reporting differences between patients and controls for sway velocity, as one study reported reduced values for PD patients while standing with eyes closed [33], while the others reported greater values for people with PD while standing with eyes open [25, 26], but not eyes closed [26]. While each of the studies that assessed standing balance derived their outcomes from a wearable sensor positioned on the trunk [13, 24–26, 32, 33, 37, 38], there were some methodological differences that may explain the discrepancies observed between the studies' reported outcomes. The studies unable to report significant differences in jerk scores, RMS accelerations and sway velocities assessed standing balance using a semi-tandem stance test [38], the Sensory Organisation Test [24], the Romberg test [32] or an instrumented version of the functional reach test [37]. In contrast, the studies that reported significant differences for jerk, RMS accelerations and sway velocities assessed participants during quiet standing with the heels separated by 10 cm [13, 25, 26] or while they stood with their feet together or in a semi-tandem stance with their eyes open and closed [33]. Given the available evidence, it seems that the best recommendation for clinicians seeking to assess standing balance using wearable sensors would be to calculate RMS accelerations or jerk scores from trunk accelerations collected while patients stand with their eyes open and their heels 10 cm apart. However, a degree of caution may be required when considering this recommendation, as three of the four studies that reported differences in standing balance for people with PD appear to have used the same patient cohort, due to the reported demographics being the same for each study [13, 25, 26]. As such, it is possible that the overall interpretation of the existing literature in this area may be biased and the transferability of the findings may be more limited than they appear.

In addition to the nine studies that used wearable sensors to assess standing balance, the remaining 65% used these devices to assess walking stability. These studies reported numerous outcome measures derived from the acceleration signals, but the Harmonic Ratio (HR) was the most commonly-reported measure and was calculated for the head [30] and lumbosacral region [14, 17, 19, 20, 30, 31, 35, 39]. The HR seems to be a sensitive and versatile measure of walking stability, as the reviewed literature reports differences between people with PD and controls [14, 19, 20, 30], PD freezers and non-freezers [35], PD fallers and non-fallers [30, 31], PD patients with different dominant symptoms [17] and different methods of cueing for people with PD [39]. Stride timing variability was the second most common outcome

measure for the studies that assessed walking stability, but careful review of the included studies suggested that it may not be a dependable measure for discriminating between different populations. Of the seven studies that reported this outcome, three described differences in stride timing variability between PD fallers and non-fallers [30], PD patients and controls [22, 30] or carriers and non-carriers of the LRRK2 gene mutation [36]. In contrast, four studies reported no differences between PD patients and controls [19, 28, 29] or patients with different sub-types of PD [17]. A common characteristic of those studies reporting differences for the HR and stride timing variability was that they each assessed walking stability during straight line walking. As such, it is recommended that clinicians who wish to assess walking stability using wearable sensors calculate the HR from trunk accelerations collected while patients walk in a straight line at a self-selected speed. While there is some evidence to support the use of stride timing variability to assess walking stability, it would only be recommended as a secondary measure due to the inconsistencies evident within the current literature.

While it was not the primary focus of this review to evaluate the effects of anti-parkinsonian medications, such as levodopa, on measures of standing balance and walking stability, it is an important factor that warrants consideration. It is widely recognised that levodopa improves symptoms of PD (based on the UPDRS) [17, 32], spatiotemporal gait characteristics (e.g. stride length) [52, 53] and performance on clinical tests of balance, such as the Berg Balance scale [54]. Of the studies included in this review, five (19%) reported assessing standing balance or walking stability while patients were not medicated [14, 24, 33, 38, 40], 9 (35%) assessed patients on-medication [18–21, 30, 31, 35, 36, 39] and three (12%) assessed patients in both on and off states [17, 22, 32]. Of the remaining studies, six (22%) assessed patients who were not yet being medicated for PD [13, 25–29], while three (12%) did not report whether their participants were on or off medication at the time of testing [23, 34, 37]. Interestingly, of the studies not reporting differences in standing balance or walking stability between different groups of PD patients and/or healthy controls, two assessed patients while they were off medication [24, 38], while the other did not report whether patients were assessed on or off medication [23]. Of the three studies that assessed patients on and off medication, only two statistically compared their presented outcomes for the two conditions [22, 32]. For a group of idiopathic PD patients, it was reported that the length and maximal distance of postural sway was significantly increased during normal stance, when patients were assessed on medication [32], which would typically be interpreted as a greater amount of sway during the medicated state. During walking, Weiss et al. [22] reported a significant reduction in the width of the dominant harmonic in the acceleration signal when patients were tested on medication, which represented less variability in the gait patterns of medicated patients. While there is a clear need for further research in this area, the presented findings suggest that wearable sensors can be effectively used to evaluate changes in standing balance and walking stability for different patients who are assessed with or without anti-parkinsonian medication.

Considering that 66% of individuals with PD fall at least once in a given year [11, 55] and nearly 50% of these falls occur during locomotion [56, 57], assessing walking stability and falls risk is critical to ensure that high-risk patients can be easily identified by clinicians. However, to date, there is a paucity of research evaluating the capacity for wearable sensors to identify people with PD who are at a higher risk of prospectively falling. Two of the studies included in this review compared people with PD who retrospectively reported having no falls (non-fallers) to those who reported falling at least once (fallers) in the previous 12 months [30, 31]. Both of these studies reported that PD fallers had less rhythmic movements for the pelvis or lower trunk (as assessed using the HR) in both the anterior-posterior (forward-backward) and vertical directions compared with PD non-fallers [30, 31] and controls [30]. While their retrospective nature makes it difficult to determine whether these deficits contribute to the patients falling or whether they are perhaps a consequence of an increased fear of future falls, the

results of these studies provide some support for the use of wearable sensors for screening patients for falls risk. Nevertheless, further prospective research is needed to confirm whether sensor-based measures of standing balance or walking stability are suitable for the assessing falls risk and predicting future falls in this population.

There are a number of limitations that should be considered when interpreting the results of this review of literature. First, the results of the methodological quality assessment included in this systematic review are based on the assessor's (RPH) interpretation of each of the studies. Often, the results reflect the quality of the reporting of the research and, hence, should not be seen as a critique of the significance of the research and its outcomes. Second, given the relatively small number of studies published in this area and the wide variety of research questions addressed using wearable sensors, it is difficult to make strong recommendations regarding the most appropriate equipment, placements and outcomes for assessing standing balance and walking stability in people with PD. In light of these limitations, the results presented in this systematic review should be considered preliminary and additional work will be required as this field of science continues to evolve.

In conclusion, wearable sensors provide a light-weight, portable and affordable alternative to more expensive three-dimensional motion analysis systems and are effective for detecting changes in standing balance and walking stability among people with PD. However, it appears that some outcome measures may be more useful than others for discriminating patient cohorts from controls. Specifically, measures of jerk and RMS acceleration for the trunk appear to be the best sensor-based measures of standing balance, even under less challenging conditions (i.e. feet apart on a firm surface with eyes open). For assessments of walking stability, a trunk-mounted wearable sensor can be used to assess the rhythmicity of dynamic gait patterns using the HR calculated for the three axes of motion. While some studies have provided support for other more complex frequency-based measures of postural stability, additional research is essential to objectively assess the utility of these measures for the PD population. Future research should give careful consideration to the internal and external validity of their methods and provide an appropriate sample size calculation to support their study, as these aspects could have been better reported in the existing literature.

Supporting Information

S1 File. Systematic search strategy and procedures.
(DOCX)

S2 File. The quality of methodological reporting assessment tool and the outcomes of this assessment for each of the included studies.
(DOCX)

Acknowledgments

This project was supported by research funding provided by the Australian Catholic University (Project code #2013000584). Dr Michael H. Cole was also supported by an Australian National Health and Medical Research Council Early Career Researcher Fellowship (Project #GNT1016481)

Author Contributions

Conceived and designed the experiments: RPH MHC. Performed the experiments: RPH MHC. Analyzed the data: RPH MHC. Contributed reagents/materials/analysis tools: MHC GAN PAS. Wrote the paper: RPH MHC GAN PAS. Review and critical feedback on manuscript: MHC GAN PAS.

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Study 2 (Published) “Assessing stability in mild and moderate Parkinson’s disease: Can clinical measures provide insight?”

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Gait & Posture 49 (2016) 7–13

Contents lists available at ScienceDirect

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Full length article

Assessing stability in mild and moderate Parkinson's disease: Can clinical measures provide insight?

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ARTICLE INFO

Article history:
Received 26 January 2016
Received in revised form 3 May 2016
Accepted 3 June 2016

Keywords:
Parkinson's disease
Motor control
Falls
Quality of life
Postural stability

ABSTRACT

This cross-sectional study aimed to investigate the relationship between accelerometer-derived measures of movement rhythmicity and clinical measures of mobility, balance confidence and gait difficulty in people with Parkinson's disease (PD). Twenty-nine independently-living PD patients (Hoehn & Yahr Stages 1–3) with no history of significant injury or orthopaedic/deep brain stimulation surgery were recruited from a database of patients who had expressed an interest to participate in research. Participants completed clinical assessments of mobility, postural stability, balance confidence and symptom severity, while head and trunk rhythmicity was evaluated during gait using accelerometers. Following data collection, patients were stratified based on disease stage into either a Mild (Hoehn & Yahr Stage 1) or Moderate (Hoehn & Yahr Stages 2–3) PD group. The results highlighted that the Moderate PD group had poorer quality of life, reduced balance confidence and increased gait and falls difficulty. Furthermore, for these patients, gait disability and the number of previous falls were both negatively correlated with multiple components of head and trunk rhythmicity. For the Mild PD group, six-meter walk time was positively correlated with ML head rhythmicity and linear regression highlighted a significant predictive relationship between these outcomes. For the Mild and Moderate PD groups, balance confidence respectively predicted anterior-posterior trunk rhythmicity and vertical head rhythmicity. While these findings demonstrate that falls history and the Gait and Falls questionnaire provide moderate insight into head and trunk rhythmicity in Moderate PD patients, objective and clinically-feasible measures of postural instability would assist with the management of these symptoms.

1. Introduction

Postural instability is one of the most disabling symptoms of Parkinson's disease (PD) and significantly increases the risk of falling [1]. The costs of falls and falls-related injuries are not well established for many countries [2], but Australian estimates indicate that approximately AUD$27.5 million was spent on injuries associated with falls and falls-related injuries in 2010 [3]. Given the significant physical and financial burden associated with falls in PD, a clear need exists to develop an improved capacity to assess symptoms of postural instability to assist with their early identification and treatment. For people with PD, symptoms of postural instability are often accompanied by a decline in the patient's mobility [4]. Traditionally, clinical tests like the Timed up and Go (TUG) [5] and 10-m [4] (or 6-m [6]) walk tests have been used to assess changes in mobility for a range of healthy [7] and pathological [4] populations. Given the ease with which they can be administered and their widespread use in hospitals and other clinical settings, it is not surprising that such tests are often used to assess the efficacy of exercise interventions aimed at improving mobility and/or preventing falls in people with PD [8]. However, despite their widespread use for the assessment of people with PD [9], research suggests that some of these clinical tests are not always able to identify differences in mobility between people with PD and age-matched controls [10,11]. Therefore, while the TUG and 6-meter walk tests are widely acceptable as clinical tests

Abbreviations: ABC, Activities-Specific Balance Confidence Scale; ACE, Addenbrooke's Cognitive Examination; PD, Parkinson's disease; TUG, Timed up and Go test; UPDRS, Unified Parkinson's Disease Rating Scale.

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http://dx.doi.org/10.1016/j.gaitpost.2016.06.002
0966-6362/

of mobility, there seems to be a need for further investigations to determine whether such clinical tests have the capacity to identify changes in postural stability in people with PD.

The improved availability and affordability of wearable sensors has now made it feasible to develop and/or enhance clinical assessments to incorporate more objective measures of walking stability. For example, research has shown that by placing a wearable sensor on a patient's body during the performance of the TUG test, the objectivity of the assessment can be significantly improved [11]. Specifically, research utilising this adaptation of the TUG test has reported differences in the amplitude, rhythmicity and smoothness of segmental motion (as measured using RMS accelerations, harmonic ratios and jerk, respectively) for people with PD compared with age-matched controls [12]. Of the numerous accelerometer-based outcomes reported in the literature, the harmonic ratio (HR) is the most commonly reported for people with PD [13] and provides a measure of gait rhythmicity by assessing the ratio of in-phase accelerations to out-of-phase accelerations within a given gait cycle [14]. Additionally, the HR has been shown to have the capacity to discriminate PD patients with a history of falling from patients who have not previously fallen [15]. Despite its frequent use in the research setting, more traditional tests of mobility continue to prevail in daily clinical practices. As such, this study aimed to determine whether the results of common clinical tests of mobility, balance confidence and gait difficulty correlate with laboratory-based measures of postural stability to determine whether these assessments offer insight into deficits in postural stability for people with PD. It was hypothesised that clinical measures of mobility, gait difficulty, postural stability and balance confidence would not be related to movement rhythmicity and, therefore, offer limited insight into dynamic postural stability.

2. Methods

2.1. Participants

Thirty participants diagnosed with idiopathic PD, based on the UK Brain Bank Criteria were recruited. Patients with a history of two or more near-misses and/or at least one fall in the previous 12 months were contacted via a pre-existing database of people with PD who had expressed an interest to participate in research. Prospective participants received an information letter outlining the study's details and inviting them to contact a member of the research team if they were interested in volunteering. Participants were excluded if they were; (i) unable to stand and walk independently; (ii) significantly visually (Bailey-Lovie high contrast visual acuity >0.30 logMAR) or cognitively impaired (Addenbrooke's cognition examination score <82); (iii) known to have uncontrolled hypertension; (iv) taking psychotropic medications; (v) significantly limited by osteoporosis; (vi) a recipient of orthopaedic surgery within the previous year; (vii) suffering serious neck, shoulder or back injuries (including spinal fusions); or (viii) a recipient of deep brain stimulation surgery to manage their symptoms. Experimental procedures were approved by the University's Human Research Ethics Committee and volunteers provided written informed consent. An a-priori sample size calculation based on a p-value of 0.05, a power of 80% and a large effect size ($\rho = 0.6$) indicated that at least 13 participants were required per group to examine the relationships between the clinical tests and harmonic ratios.

2.2. Experimental protocol

Individuals attended a single testing session during which a battery of tests was performed including clinical assessments of; (i) cognition (Addenbrooke's Cognitive Examination (ACE)); (ii) visual acuity (Bailey-Lovie high contrast visual acuity); (iii) symptom severity (Unified Parkinson's Disease Rating Scale (UPDRS), the modified Hoehn & Yahr (H&Y) scale, the Schwab & England Activities of Daily Living Scale, the PD Gait and Falls questionnaire and the Freezing of Gait (FOG) questionnaire); (iv) balance confidence (Activity-specific Balance Confidence (ABC) scale); and (v) quality of life (39-item Parkinson's Disease Questionnaire (PDQ-39)). A measure of postural instability and gait disability (PIGD) was also calculated for each participant by summing items 27–30 of the UPDRS motor sub-section [16]. The ACE was used to assess cognition, as it incorporates the Mini Mental State Examination and has high sensitivity and specificity for detecting dementia (cut-off score of <82 gives 82% sensitivity and 100% specificity). These assessments were selected due to their established reliability, validity [17,18] and previous use in assessing individuals with PD [19]. In addition to the clinical assessments, participants were also asked to report any falls and/or near misses experienced in the previous year. For this study, a fall was defined as "any coming to the ground or other lower level not as the result of a major intrinsic event or overwhelming hazard [20]". A near miss was defined as "an event on which an individual felt that they were going to fall but did not actually do so [20]".

Following the questionnaire-based assessments, participants completed five barefoot trials of the TUG test. Participants were seated in a 42 cm high chair with their feet flat on the floor, their back flat against the backrest and their arms resting on the armrests, which were situated 20 cm above the seat. Upon the word 'GO,' participants were required to stand from the chair and walk at a brisk, but comfortable pace to a line on the floor three meters away, turn around and return to the chair to sit down. The time taken to complete the test was recorded using a stopwatch. Following the TUG test, participants completed 6 barefoot walking trials at a comfortable pace along a 10-m firm walkway. In accordance with the established procedures of the 6-m walk test (6MWT), walking speed was assessed over the middle 6-m distance using a dual beamed timing gait system (SWIFT Performance Equipment, Alstonville, Australia) that was positioned at hip height.

Gait rhythmicity was assessed during the 6MWT using two microelectromechanical (MEMS) three-dimensional accelerometers (1500 Hz; Noraxon Inc., Scottsdale, AZ) to provide insight into the patients' dynamic postural control. Each accelerometer was statically-calibrated prior to attachment by aligning each of its sensing axes perpendicular to a horizontal surface to establish the exact value of gravitational acceleration (i.e. 1 gravitational unit or 1 g) [14]. Following static calibration, one accelerometer was firmly attached to a sport headband and positioned over the occipital protuberance and the second accelerometer was firmly attached using double-sided tape to the skin overlying the spinous process of the 10th thoracic vertebra (T10) and reinforced with Micropore. During the 6MWT trials, 3D head and trunk accelerations were wirelessly telemetered to a Telemyo DTS unit, which was connected to a laptop computer running the MyoResearch XP (v1.08) software.

2.3. Data analysis

Raw accelerations were transformed to represent a horizontal-vertical orthogonal coordinate system [14]. Transformation was necessary, as accelerometers measured data relative to a local (or internal) rather than global coordinate system. As such, positioning sensors on body segments often results in two or more of the sensing axes being influenced by gravitational accelerations, which can make it difficult to identify the proportion of the signal attributable to movement-related accelerations [14]. After data

transformation, accelerations were filtered using a bi-directional fourth-order low-pass Butterworth filter with a cut-off frequency of 30 Hz [21]. Given 99% of accelerations during walking occur at or below 15 Hz [22], the cut-off frequency of 30 Hz was sufficient to ensure higher frequencies, unrelated to movement, were attenuated without influencing the gait-related accelerations. Filtered and transformed accelerations for the anteroposterior (AP), mediolateral (ML) and vertical (VT) axes were then used to derive the HRs for head and trunk segments, separately. To calculate the harmonic ratios, the time-series data were divided into individual gait cycles by identifying the positive peaks in the VT trunk accelerations, which coincided with heel contact. Using a custom Matlab program (version R2015), AP, ML and VT harmonic ratios were calculated for four consecutive gait cycles identified in the central portion of each 6MWT trial. As the HR provides a ratio of the in-phase to out-of-phase accelerations during gait, larger values are considered to represent more regular movement patterns, while lower values represent less regular movements [14].

2.4. Statistical analysis

Following processing, data were sub-divided based on each patient's H&Y stage score. Patients who had mild symptoms affecting one side of the body only (H&Y Stage 1) were combined to form a Mild PD group, while data for patients presenting with Mild (H&Y Stage 2) to Moderate (H&Y Stage 3) bilateral symptoms were combined to form a Moderate PD group. To assess for any significant differences between the groups with respect to the continuous demographic variables and clinical assessments, a one-way analysis of variance (ANOVA) was used, while the Chi-square tests were used to identify any differences in the frequency of categorical data. If the assumptions of normality (Shapiro–Wilks test) and/or homogeneity of variance (Levene's test) were violated, the equivalent non-parametric Mann-Whitney was used for the continuous variables [23].

Bivariate correlations were used to establish the relationship between clinical tests of mobility and stability and laboratory-based measures of dynamic postural control. To determine the appropriateness of the parametric Pearson's correlation coefficient, the normality of the continuous measures was assessed using the Shapiro-Wilk test and where a p-value less than 0.05 was returned, the non-parametric Spearman's Rho test was used. Linear regression analyses examined whether clinical measures of mobility, postural stability, balance confidence and gait difficulty were capable of explaining a significant proportion of the variance in head and trunk rhythmicity during walking. Statistical analyses were performed in SPSS version 22 (New York, USA) with significance set at $p < 0.05$.

3. Results

Of the thirty participants recruited, one was excluded prior to completing the assessments due to deficits in cognitive function (i.e. ACE total score <82). Based on the neurological assessment, the remaining 29 patients had mild to moderate symptoms of PD, were independently living and most (90%) were taking anti-parkinsonian medication. Patients comprising the Moderate PD group were shown to have more severe motor symptoms ($p = 0.004$) and reported poorer balance confidence ($p < 0.001$), poorer quality of life ($p = 0.001$), a greater incidence of freezing of

Table 1
Demographic information and results for the assessments of mobility, balance confidence, quality of life and symptom severity for the Mild and Moderate PD groups.

	All PD (n = 29)	Mild PD (n = 13)	Moderate PD (n = 16)	Test	p-value
Demographics					
Male	21 (72.4%)	8 (61.5%)	13 (81.3%)	3	0.238
Age (years)	64.7 ± 6.4	62.8 ± 7.1	66.3 ± 5.4	1	0.147
Height (cm)	171.7 ± 8.0	170.6 ± 8.9	172.6 ± 7.3	1	0.504
Mass (kg)	80.4 ± 20.1	78.8 ± 20.2	81.7 ± 20.7	1	0.709
Body Mass Index (kg/m^2)	27.0 ± 5.3	26.8 ± 5.1	27.2 ± 5.6	1	0.853
Cognition and Vision					
Addenbrooke's Cognitive Exam	91.7 ± 6.1	92.5 ± 5.2	91.1 ± 6.8	1	0.527
High Contrast Visual Acuity (LogMAR)	0.0 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	2	0.475
Balance Confidence and Quality of Life					
Previous Fallers	23 (79.3%)	11 (84.6%)	12 (75.0%)	3	0.525
Previous Falls	1.4 ± 2.0	1.2 ± 1.5	1.6 ± 2.4	2	0.846
Activities-specific Balance Confidence (%)	77.8 ± 24.8	93.2 ± 6.6	65.4 ± 27.4	2	**<0.001**
39-Item Parkinson's Disease Questionnaire	23.5 ± 15.3	14.9 ± 6.9	30.4 ± 16.9	2	**0.001**
Mobility					
Timed Up and Go Total Time (s)	9.4 ± 1.5	9.0 ± 1.2	9.8 ± 1.7	1	0.202
6-Meter Walk Test (s)	4.7 ± 0.6	4.8 ± 0.5	4.7 ± 0.7	1	0.647
Neurological Examination					
Disease Duration (years)	6.7 ± 5.3	4.9 ± 1.1	8.1 ± 6.8	2	0.288
Unified Parkinson's Disease Rating Scale (Part III)	14.4 ± 11.5	9.1 ± 2.3	18.8 ± 14.1	2	**0.004**
Hoehn & Yahr Stage Score	1.7 ± 0.7	1.0 ± 0.0	2.2 ± 0.4	2	**<0.001**
Schwab & England Activities of Daily Living Scale	86.6 ± 7.5	90.0 ± 4.1	83.8 ± 8.5	2	0.056
Freezing of Gait Score	4.9 ± 5.2	2.7 ± 2.9	6.7 ± 6.0	2	**0.040**
Postural Instability and Gait Disorder Score	1.9 ± 1.6	0.8 ± 1.0	2.7 ± 1.6	2	**0.002**
Retropulsion Test	0.5 ± 0.7	0.2 ± 0.4	0.8 ± 0.9	2	0.083
Levodopa (mg/day)	618.3 ± 432.1	545.2 ± 350.7	677.8 ± 491.7	1	0.421
Dopamine Agonists	6 (20.7%)	2 (15.4%)	4 (25.0%)	3	0.468
Catechol-O-Methyl Transferase Inhibitors	9 (31.0%)	4 (30.8%)	5 (31.3%)	3	0.885
Monoamine Oxidase Inhibitors	10 (34.5%)	3 (23.1%)	7 (43.8%)	3	0.194
Benzodiazepine	1 (3.4%)	1 (7.7%)	0 (0.0%)	3	0.274

Note: Test 1 = One-way analysis of variance; Test 2 = Mann-Whitney U test; Test 3 = Chi-square test

gait ($p = 0.040$) and increased postural instability and gait difficulty ($p = 0.002$) compared with the Mild PD group (Table 1).

3.1. Correlation analyses

Tests of normality indicated that a number of the continuous outcome measures were not normally distributed, hence the non-parametric Spearman's Rho test was used to assess the relationships between the clinical tests and the accelerometer-based measures of walking rhythmicity (Table 2). For the whole PD sample, previous falls were shown to be positively correlated with the gait and falls questionnaire ($\rho = 0.508$, $p = 0.005$) and negatively correlated with the 6-m walk time ($\rho = -0.466$, $p = 0.011$) and all harmonic ratios for the head ($\rho = -0.448$ to -0.513, $p \leq 0.02$) and

Table 2
Spearman's Rho correlations between the clinical balance and mobility tests and the objective measures of walking rhythmicity for the entire PD cohort and the Mild and Moderate PD sub-groups.

			All PD		Mild PD		Moderate PD	
			Spearman's Rho	p-value	Spearman's Rho	p-value	Spearman's Rho	p-value
Retrospective Falls	6-Meter Walk Time		**−0.466**	**0.011***	−0.344	0.250	**−0.531**	**0.034***
	Timed Up and Go Total Time		−0.169	0.381	−0.194	0.526	−0.193	0.474
	Retropulsion Test		0.008	0.965	0.077	0.802	0.055	0.839
	Gait & Falls Questionnaire		**0.508**	**0.005***	0.274	0.365	**0.600**	**0.014***
	Activities-Specific Balance Confidence Scale		0.039	0.839	**0.555**	**0.049***	0.038	0.889
	Harmonic Ratio (Head)	AP	**−0.465**	**0.011***	−0.521	0.068	**−0.537**	**0.032***
		ML	**−0.448**	**0.015***	−0.320	0.286	**−0.579**	**0.019***
		VT	**−0.513**	**0.004***	−0.436	0.137	**−0.693**	**0.003***
	Harmonic Ratio (Trunk)	AP	**−0.524**	**0.004***	**−0.611**	**0.027***	−0.430	0.097
		ML	**−0.437**	**0.018***	−0.272	0.369	**−0.595**	**0.015***
		VT	**−0.623**	**<0.001***	−0.436	0.137	**−0.766**	**0.001***
6-Meter Walk Time	Gait Speed		**−1.000**	**<0.001***	**−1.000**	**<0.001***	**−1.000**	**<0.001***
	Timed up and Go Total Time		**0.519**	**0.004***	0.287	0.343	**0.624**	**0.010***
	Retropulsion Test		0.082	0.672	−0.286	0.344	0.268	0.315
	Gait & Falls Questionnaire		−0.134	0.487	−0.034	0.913	−0.158	0.560
	Activities-Specific Balance Confidence Scale		−0.197	0.307	−0.228	0.453	−0.474	0.064
	Harmonic Ratio (Head)	AP	0.163	0.397	0.571	0.571	0.174	0.520
		ML	**0.416**	**0.025***	**0.573**	**0.041***	0.365	0.165
		VT	0.035	0.857	0.174	0.571	−0.026	0.922
	Harmonic Ratio (Trunk)	AP	0.020	0.918	0.025	0.936	0.038	0.888
		ML	0.313	0.099	0.446	0.126	0.194	0.471
		VT	0.003	0.988	0.209	0.492	−0.091	0.737
Timed Up and Go Total	Gait Speed		**−0.519**	**0.004***	−0.287	0.343	**−0.624**	**0.010***
	Retropulsion Test		0.320	0.091	−0.171	0.577	0.413	0.112
	Gait & Falls Questionnaire		0.352	0.061	0.539	0.058	0.257	0.336
	Activities-Specific Balance Confidence Scale		**−0.565**	**0.001***	−0.472	0.104	**−0.708**	**0.002***
	Harmonic Ratio (Head)	AP	0.358	0.057	0.440	0.133	0.035	0.897
		ML	0.326	0.084	0.225	0.459	0.169	0.531
		VT	0.297	0.118	0.324	0.280	0.107	0.692
	Harmonic Ratio (Trunk)	AP	0.053	0.783	0.280	0.354	−0.187	0.488
		ML	0.278	0.145	0.473	0.103	−0.075	0.782
		VT	0.110	0.570	0.110	0.721	−0.097	0.720
Retropulsion Test	Gait Speed		−0.082	0.672	0.286	0.344	−0.268	0.315
	Gait & Falls Questionnaire		**0.434**	**0.019***	0.087	0.777	0.349	0.185
	Activities-Specific Balance Confidence Scale		**−0.595**	**0.001***	−0.143	0.641	**−0.652**	**0.006***
	Harmonic Ratio (Head)	AP	−0.297	0.118	−0.285	0.345	**−0.499**	**0.049***
		ML	−0.143	0.458	−0.513	0.073	−0.422	0.104
		VT	0.119	0.540	−0.057	0.853	−0.051	0.851
	Harmonic Ratio (Trunk)	AP	−0.102	0.597	0.342	0.253	−0.275	0.303
		ML	0.089	0.645	0.228	0.454	−0.173	0.523
		VT	0.116	0.550	0.114	0.711	−0.064	0.814
Gait & Falls Questionnaire	Gait Speed		0.134	0.487	0.034	0.913	0.158	0.560
	Activities-Specific Balance Confidence Scale		**−0.555**	**0.002***	0.007	0.982	**−0.521**	**0.038***
	Harmonic Ratio (Head)	AP	−0.176	0.360	0.067	0.827	**−0.526**	**0.036***
		ML	−0.107	0.579	0.079	0.799	**−0.538**	**0.032***
		VT	−0.042	0.828	0.163	0.595	−0.496	0.051
	Harmonic Ratio (Trunk)	AP	**−0.425**	**0.022***	−0.115	0.708	**−0.642**	**0.007***
		ML	−0.201	0.296	0.129	0.674	**−0.510**	**0.044***
		VT	−0.267	0.162	0.022	0.942	**−0.638**	**0.008***
Activities-Specific Balance Confidence Scale	Gait Speed		0.197	0.307	0.228	0.453	0.474	0.064
	Harmonic Ratio (Head)	AP	−0.119	0.540	0.025	0.936	−0.032	0.905
		ML	−0.256	0.181	0.014	0.964	0.159	0.557
		VT	−0.322	0.088	0.061	0.844	−0.291	0.274
	Harmonic Ratio (Trunk)	AP	−0.014	0.944	−0.505	0.078	0.126	0.641
		ML	−0.209	0.277	−0.356	0.233	−0.153	0.572
		VT	−0.158	0.414	0.168	0.583	−0.112	0.680

AP = Anteroposterior, ML = Mediolateral, VT = Vertical, * = Significant correlation.

trunk ($\rho = -0.437$ to -0.623, $p \leq 0.02$). The sub-group analyses indicated that these relationships were further strengthened for the Moderate PD patients, when patients with milder symptoms were considered separately. Specifically, the bivariate correlations revealed that previous falls were moderately positively correlated with gait and falls difficulty ($\rho = 0.600$, $p = 0.014$) and moderately negatively correlated with 6-meter walk time ($\rho = -0.531$, $p = 0.034$) and all head ($\rho = -0.537$ to -0.693, $p \leq 0.05$) and most trunk ($\rho = -0.595$ to -0.766, $p \leq 0.015$) HRs. In contrast, the number of previous falls was moderately positively correlated with balance confidence ($\rho = 0.555$, $p = 0.049$) and moderately negatively correlated with AP trunk rhythmicity ($\rho = -0.611$, $p = 0.027$) for the Mild PD patients.

Analysis of the two mobility assessments demonstrated that the 6-meter walk time negatively correlated with gait speed ($\rho = -1.000$, $p < 0.001$) and positively correlated with TUG total time ($\rho = 0.519$, $p = 0.004$) and mediolateral head HR ($\rho = 0.416$, $p = 0.025$). The sub-group analyses showed that the 6-meter walk time was moderately positively correlated with TUG total time ($\rho = 0.624$, $p = 0.010$) for the Moderate PD group, while ML head rhythmicity was moderately positively correlated with the 6-meter walk time ($\rho = 0.573$, $p = 0.041$) for the Mild PD group. For the whole PD cohort, TUG total time was negatively correlated with gait speed ($\rho = -0.519$, $p = 0.004$) and balance confidence ($\rho = -0.565$, $p = 0.001$), but the sub-group analyses revealed that these relationships only remained significant for the Moderate PD group (gait speed: $\rho = -0.624$, $p = 0.010$; ABC: $\rho = -0.708$, $p = 0.002$).

Similar to clinical tests of mobility, the retropulsion test was negatively correlated with balance confidence ($\rho = -0.595$, $p = 0.001$) and positively associated with the Gait and Falls questionnaire ($\rho = 0.434$, $p = 0.019$). Additionally, the Gait and Falls questionnaire was moderately negatively correlated with balance confidence ($\rho = -0.555$, $p = 0.002$) and AP trunk rhythmicity ($\rho = -0.425$, $p = 0.022$). The sub-group analyses indicated that the retropulsion test was moderately negatively correlated with balance confidence ($\rho = -0.652$, $p = 0.006$) and AP head rhythmicity ($\rho = -0.499$, $p = 0.049$) for the Moderate PD group. Furthermore, for the Moderate PD group, the gait and falls questionnaire was moderately negatively correlated with balance confidence ($\rho = -0.521$, $p = 0.038$) and most head ($\rho = -0.526$ to -0.538, $p < 0.05$) and all trunk ($\rho = -0.510$ to -0.642, $p < 0.05$) HRs. No other relationships were observed between the questionnaires and the objective measures of walking stability (Table 2).

3.2. Regression analysis

The linear regression analyses performed for the entire PD cohort indicated that, of all of the clinical assessments conducted, the 6MWT and ABC scale were the only tests that were able to predict any component of head or trunk rhythmicity. Specifically, the 6MWT predicted ML head HRs ($p = 0.041$) and the ABC scale predicted VT head HRs ($p = 0.032$). Similar results were returned for the regression analyses conducted for the two sub-groups, with the 6MWT predicted ML head HRs ($p = 0.036$) for the Mild PD group and the ABC scale predicted AP trunk HRs ($p = 0.012$) and VT head HRs ($p = 0.047$) for the Mild and Moderate PD groups, respectively (Table 3).

4. Discussion

The purpose of this study was to examine whether common clinical tests of mobility, postural stability, balance confidence and gait difficulty were capable of providing insight into walking stability in people with PD. The results indicated that individuals with moderate disease severity reported experiencing poorer balance confidence, greater postural instability and gait difficulty and poorer quality of life than patients with milder symptoms. Interestingly, however, the Moderate and Mild PD groups had similar results for the clinically-administered assessments, including the retropulsion test, TUG and 6MWT. Similar findings were evident for the correlation analyses, which indicated that while the outcomes of the clinically-administered tests were not correlated with the measures of head and trunk rhythmicity, those patients in the Moderate PD group who reported a greater number of previous falls and/or greater difficulties with gait and falls also had poorer head and trunk rhythmicity. These findings were similar to previous research that has shown that PD fallers with moderate symptoms had poorer head and pelvis rhythmicity during gait than patients with milder symptoms who had not previously fallen [15]. Collectively, these findings suggest that clinical measures of balance, mobility, gait difficulty and balance confidence may not provide insight into the walking rhythmicity of individuals with milder symptoms. However, for patients who have more advanced symptoms, it seems that the assessments that rely more on a patient's self-reported difficulties may provide better insight into the gait rhythmicity of these patients. These findings would appear to have important clinical implications and suggest that objectively evaluating a patient's mobility without considering their perceived difficulties may inadvertently result in important information regarding falls risk being overlooked. Nevertheless, it is widely recognised that self-report assessments can be limited by patients over- or under-reporting their difficulties, hence more objective tests would greatly benefit the clinical assessment of postural stability in people with PD.

The retropulsion test is one of the most commonly used clinical assessment of postural stability for people with PD and is incorporated into the motor sub-section of the UPDRS [24]. Despite its widespread use and its apparent capacity to assess a patient's stability under static conditions, previous research has highlighted its inability to discriminate PD fallers from non-fallers [25] or single fallers from recurrent fallers in cohorts with and without PD [26]. While our findings largely agreed with these studies, it is important to highlight that the retropulsion test was significantly correlated with AP head rhythmicity in individuals with moderate symptom severity. Given that the retropulsion test examines a patient's postural response to a firm backward pull on their shoulders, it is perhaps not surprising that those who scored more poorly on the retropulsion test also demonstrated poorer AP head control during gait (i.e. lower AP head HRs). The poor relationship between the retropulsion test and the continuous measures of head and trunk rhythmicity may be explained, at least in part, by a number of factors. First, the retropulsion test is somewhat limited by its use of a Likert scale that ranges from zero (normal response) to four (unable to stand without assistance). Specifically, for a patient's score to change from a zero to a one for the retropulsion test, they must demonstrate a retropulsive gait pattern and recover without assistance. Given the marked heterogeneity of PD symptoms, it is very likely that some patients will develop difficulties that affect their gait and balance, but do not manifest in the form of a retropulsive gait pattern during the retropulsion test. A second factor that may influence the applicability of the retropulsion test to dynamic situations could be the fact that it assesses postural stability during quiet stance rather than under dynamic conditions. Given that only 32% of falls occur during standing [27], it is possible that the retropulsion test may be limited in its capacity to explain the factors contributing to the 66% of falls that occur during ambulation and transfer events [27].

Another interesting finding of this study was that the number of previous falls experienced by patients in the Mild PD group was significantly positively correlated with balance confidence, suggesting that individuals who fell more had greater balance

Table 3
Results of the linear regression analyses conducted between the clinical balance and mobility tests and the objective measures of walking rhythmicity for the entire PD cohort and the Mild and Moderate PD sub-groups.

		All PD			Mild PD			Moderate PD		
		Unstandardised beta (B)	Standardised Beta (β)	p-value	Unstandardised beta (B)	Standardised Beta (β)	p-value	Unstandardised beta (B)	Standardised Beta (β)	p-value
Retrospective Falls										
	AP	−0.499	−0.179	0.354	−0.668	−0.316	0.293	−0.491	−0.153	0.572
Harmonic Ratio (Head)	ML	−0.478	−0.164	0.395	−0.301	−0.125	0.683	−0.787	−0.236	0.379
	VT	−0.671	−0.271	0.155	−0.469	−0.287	0.342	−1.074	−0.331	0.211
	AP	−0.755	−0.238	0.214	−0.868	−0.352	0.239	−0.671	−0.191	0.479
Harmonic Ratio (Trunk)	ML	−0.437	−0.135	0.486	−0.218	−0.100	0.746	−0.729	−0.181	0.502
	VT	−0.683	−0.321	0.089	−0.506	−0.319	0.288	−0.934	−0.374	0.154
6-Meter Walk Time										
	AP	0.121	0.154	0.424	0.148	0.222	0.465	0.142	0.160	0.553
Harmonic Ratio (Head)	ML	**0.348**	**0.382**	**0.041***	**0.500**	**0.585**	**0.036***	0.423	0.398	0.127
	VT	0.064	0.086	0.657	0.160	0.299	0.322	−0.003	−0.003	0.993
	AP	0.036	0.183	0.846	0.030	0.040	0.897	0.040	0.037	0.892
Harmonic Ratio (Trunk)	ML	0.237	0.238	0.214	0.296	0.404	0.171	0.224	0.180	0.504
	VT	0.005	0.008	0.966	0.177	0.330	0.270	−0.076	−0.110	0.684
Timed Up and Go Total										
	AP	0.663	0.363	0.053	0.676	0.459	0.115	0.535	0.265	0.321
Harmonic Ratio (Head)	ML	0.577	0.272	0.153	0.263	0.139	0.651	0.547	0.226	0.400
	VT	0.516	0.301	0.113	0.255	0.215	0.482	0.664	0.291	0.274
	AP	0.036	0.016	0.933	0.413	0.246	0.418	−0.256	−0.104	0.701
Harmonic Ratio (Trunk)	ML	0.713	0.309	0.103	0.817	0.503	0.080	0.423	0.149	0.581
	VT	0.302	0.214	0.265	0.138	0.116	0.705	0.273	0.174	0.519
Retropulsion Test										
	AP	−0.243	−0.271	0.155	−0.128	−0.267	0.378	−0.491	−0.483	0.058
Harmonic Ratio (Head)	ML	−0.124	−0.199	0.538	−0.259	−0.419	0.154	−0.402	−0.330	0.212
	VT	0.085	0.101	0.603	0.028	−0.072	0.815	−0.007	−0.006	0.982
	AP	−0.107	−0.098	0.612	0.153	0.280	0.354	−0.308	−0.249	0.352
Harmonic Ratio (Trunk)	ML	0.059	0.052	0.790	0.044	0.084	0.785	−0.109	−0.077	0.778
	VT	0.051	0.074	0.703	0.020	0.053	0.864	−0.069	−0.087	0.748
Gait & Falls Questionnaire										
	AP	−3.309	−0.207	0.282	0.238	0.052	0.866	−8.161	−0.449	0.081
Harmonic Ratio (Head)	ML	−2.575	−0.154	0.425	0.765	0.147	0.631	−8.745	−0.465	0.070
	VT	−0.774	−0.055	0.779	0.557	0.158	0.607	−5.408	−0.295	0.268
	AP	−6.204	−0.341	0.071	−0.096	−0.018	0.954	−9.312	−0.469	0.067
Harmonic Ratio (Trunk)	ML	−3.315	−0.178	0.355	0.180	0.038	0.902	−8.699	−0.383	0.143
	VT	−2.140	−0.175	0.363	−0.402	−0.117	0.703	−5.602	−0.397	0.127
Activities-Specific Balance Confidence Scale										
	AP	−6.767	−0.199	0.300	−3.088	−0.329	0.272	−3.881	−0.108	0.691
Harmonic Ratio (Head)	ML	−9.947	−0.281	0.140	−4.230	−0.397	0.180	−4.687	−0.126	0.642
	VT	**−12.013**	**−0.399**	**0.032***	−0.922	−0.127	0.679	**−18.297**	**−0.504**	**0.047***
	AP	−6.616	−0.171	0.374	**−7.332**	**−0.669**	**0.012***	−7.555	−0.192	0.475
Harmonic Ratio (Trunk)	ML	−6.457	−0.164	0.395	−4.123	−0.424	0.149	−4.191	−0.093	0.731
	VT	−8.144	−0.315	0.096	−0.745	−0.106	0.731	−8.898	−0.319	0.229

AP = Anteroposterior, ML = Mediolateral, VT = Vertical, * = Significant correlation.

confidence. This finding is in contrast with a growing body of literature that supports the use of the ABC scale for assessing balance confidence in people with PD and for identifying patients who are at an increased risk of future recurrent falls [28,29]. While the uncharacteristically high balance confidence reported for individuals in the Mild PD group may have been influenced by their higher level of motor functioning (i.e. lower UPDRS scores) and the improved quality of life reported for these patients, it remains unclear what attributes of the disease most influence one's perceived risk of falling. As such, there is a need for future research to examine how self-reported balance confidence changes with disease progression and to establish what symptoms are most likely to influence one's fear of falling.

As with any study, our results should be considered in the context of a couple of limitations. First, our sample size, particularly once stratified based on disease severity, may be considered quite small from a statistical perspective. While the two groups were at least the size of the minimum group size determined in our a-priori sample size calculation, further research involving larger cohorts would be warranted. Second, the patients involved in this study were typically of mild to moderate disease severity (Hoehn & Yahr Stages 1–3), hence the transferability of our findings may be limited to similar patient cohorts.

5. Conclusion

Although existing tests of mobility, postural stability, balance confidence and gait difficulty provide little insight into movement rhythmicity in individuals with mild symptom severity, this study suggests that falls history and the Gait and Falls questionnaire may provide some insight into head and trunk rhythmicity in

individuals with moderate symptom severity. Nevertheless, given that these measures rely on accurate patient recall, the development and implementation of objective and clinically-feasible measures of postural instability and gait disability would help to improve the management of these symptoms in people with PD.

Conflict of interest

The authors report no potential conflict of interest with respect to this research or the submitted manuscript.

Financial disclosure related to research covered in this article

- RH was supported by an Australian Catholic University Postgraduate Award for this study.
- Professor Peter A. Silburn is a consultant neurologist with Neurosciences Queensland and has received research support from the Australian National Health and Medical Research Council (NHMRC), the Australian Research Council (ARC) and the University of Queensland.
- Professor Geraldine A. Naughton has received funding from the Australian NHMRC, the ARC and the Australian Catholic University.
- Dr Michael H. Cole received funding from the Australian NHMRC and the Australian Catholic University.

Author roles

Authors RH and MC were involved with the research project conception, organization and execution, statistical analysis design, execution and review and critique, and the manuscript review and critique. RH was involved with writing the first draft of the manuscript. PS was involved with the organization of the project and the review and critique of the manuscript. GN was involved with the review and critique of the manuscript.

Funding source for study

This study was supported by research funding provided by the Australian Catholic University (Project #2013000584). The funding body did not contribute to data collection or data analysis and played no part in the decision to prepare and publish this manuscript.

Acknowledgements

The authors wish to thank the participants who volunteered their time to contribute to this research project. We also want to thank Dr. Tim Blackmore and Eamon Conway for their help with developing the Matlab programs used for processing the acceleration data collected for this study.

Conflict of interest

The authors report no potential conflict of interest with respect to this research or the submitted manuscript.

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Study 4 (Under Review) “Exercise improves gait symmetry in Parkinson disease: A blind phase II randomised-controlled trial.”

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To: Ryan Hubble
Subject: Movement Disorders - Paper submitted: MDS-16-0307.R1

09-Jun-2016

Dear Mr. Hubble:

Your revised manuscript entitled "Exercise improves gait symmetry in Parkinson disease: A blind phase II randomised-controlled trial" has been successfully submitted online and is presently being given full consideration for publication in Movement Disorders.

Your manuscript ID is MDS-16-0307.R1. Please mention this manuscript ID in all future correspondence.

Thank you for submitting your manuscript to Movement Disorders.

Sincerely,

Movement Disorders Editorial Office

AUSTRALIAN CATHOLIC UNIVERSITY

Statement of the Contribution of Authors

The following is a description of the contribution of the main and co-authors for each of the published/submitted manuscripts supporting this thesis.

1) ***"Trunk muscle exercises as a means of improving postural stability in people with Parkinson's disease: a protocol for a randomised controlled trial."***

Author	Roles	Contribution
Ryan Hubble	Conception of study design Preparation of initial draft of manuscript	60%
Dr Michael Cole	Conception of study design Revision of manuscript	25%
Professor Geraldine Naughton	Assisted with study design Revision of manuscript	10%
Professor Peter Silburn	Revision of manuscript	5%

2) ***"Wearable sensor use for assessing standing balance and walking stability in people with Parkinson's disease: A systematic review."***

Author	Roles	Contribution
Ryan Hubble	Conceived and designed experiments Performed experiments Analysed the data Preparation of initial draft of manuscript	60%
Dr Michael Cole	Conceived and designed experiments Performed experiments Analysed the data Contributed reagents/materials/analysis tools Revision of manuscript	25%
Professor Geraldine Naughton	Contributed reagents/materials/analysis tools Revision of manuscript	10%
Professor Peter Silburn	Contributed reagents/materials/analysis tools Revision of manuscript	5%

3) "Assessing stability in mild and moderate Parkinson's disease: Can clinical measures provide insight?"

Author	Roles	Contribution
Ryan Hubble	Conceived and designed experiments Performed experiments Analysed the data Preparation of initial draft of manuscript	60%
Dr Michael Cole	Conceived and designed experiments Performed experiments Analysed the data Revision of manuscript	25%
Professor Geraldine Naughton	Contributed reagents/materials/analysis tools Revision of manuscript	10%
Professor Peter Silburn	Contributed reagents/materials/analysis tools Revision of manuscript	5%

4) "Exercise improves gait symmetry in Parkinson disease: A blind phase II randomised-controlled trial"

Author	Roles	Contribution
Ryan Hubble	Conceived and designed experiments Performed experiments Analysed the data Preparation of initial draft of manuscript	60%
Dr Michael Cole	Conceived and designed experiments Performed experiments Analysed the data Revision of manuscript	25%
Professor Geraldine Naughton	Contributed reagents/materials/analysis tools Revision of manuscript	10%
Professor Peter Silburn	Contributed reagents/materials/analysis tools Revision of manuscript	5%

I hereby declare that my contribution to each of the four published/submitted manuscripts, as outlined above, to be accurate and true.

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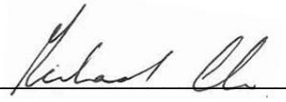
Signature:  Date: 29/07/2016

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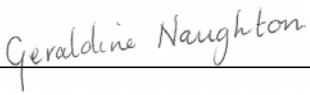
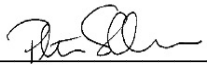
Signature:  Date: 31/07/2016

Co-Author: Professor Peter A. Silburn

Signature:  Date: 02/08/2016