FALL RISK FACTORS AND EXERCISE IN PARKINSON'S DISEASE

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SUPERVISOR'S STATEMENT

This is to certify that the thesis entitled "**FALL RISK FACTORS AND EXERCISE IN PARKINSON'S DISEASE**" submitted by **NATALIE ELIZABETH ALLEN** in fulfilment of the requirements for the degree of Doctor of Philosophy is in a form ready for examination.

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I, **NATALIE ELIZABETH ALLEN**, hereby declare that the work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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ABSTRACT

Many people with Parkinson's disease fall frequently and recurrently. The consequences of falls can be devastating, far reaching and costly. Unfortunately, medications for Parkinson's disease do not appear to prevent falls. The overall aim of the studies in this thesis was to evaluate and explore exercise interventions with the potential to reduce fall risk in people with Parkinson's disease.

Leg muscle weakness, freezing of gait and reduced balance are risk factors for falls which are potentially remediable with exercise in people with Parkinson's disease. However, there is a paucity of research into the effects of exercise training on fall risk in this group. A randomised controlled trial with blinded assessment was conducted to assess the effect on fall risk of a six-month exercise program which targeted these risk factors compared with usual care in people with Parkinson's disease. Forty-eight participants with Parkinson's disease who had fallen or were at risk of falling were randomised to the exercise or control group. The exercise group attended a monthly exercise class and performed exercises at home, such that exercises were performed three times per week. Both groups received falls prevention advice. The primary outcome measure was a Parkinson's disease fall risk score (% risk of falling) – an algorithm consisting of weighted contributions from knee extensor muscle strength of the weaker leg, balance in standing and freezing of gait. Secondary outcome measures included measures of the targeted risk factors as well as physical abilities, fear of falling and quality of life. The exercise group showed a 7% greater improvement than the control group in the Parkinson's disease falls risk score, but this was not statistically significant (95% Confidence Interval (95% CI) -20 to 5) and the clinical relevance of this small reduction is uncertain. There were statistically significant improvements in the

exercise group compared to the control group for two secondary outcomes which were not part of the falls risk score: Freezing of Gait Questionnaire (mean between-group difference = -2.8, 95% CI -5.4 to -0.3) and timed sit to stand (mean between-group difference = -1.9 s, 95% CI -3.6 to -0.2). There were non-significant trends toward greater improvements in the exercise group for other measures that were not part of the falls risk score, including muscle strength (stronger leg $P = 0.06$), fast walking speed ($P = 0.21$) and fear of falling ($P = 0.10$), but not for balance or quality of life. The exercise group had no major adverse events. Therefore, a minimally-supervised exercise program for mobile people with Parkinson's disease who are at risk of falling might reduce overall risk of falling and improve muscle strength and can improve freezing and sit to stand speed. The results of this study have informed the implementation of a larger randomised controlled trial to assess whether this relatively small reduction in fall risk translates into actual falls prevented.

Reduced balance is a commonly experienced risk factor for falls in people with Parkinson's disease. However, the effect of exercise and motor training on balance in people with Parkinson's disease was unclear and had not been subjected to meta-analysis. A systematic review with random effects meta-analysis was conducted to determine the effects of exercise and motor training on balance-related activity performance in people with Parkinson's disease. Meta-regression was used to investigate if the total dose of exercise and the presence of highly-challenging balance training are associated with the size of the effect of intervention on balance-related activities. Seven electronic databases were searched in September 2009. Trials were included if they were published randomised controlled trials of an intervention designed for people with Parkinson's disease that compared exercise and/or motor training with a

no intervention or placebo control group, and were evaluated with a measure of balance. The primary outcome measures were balance-related activity performance and falls. The balance-related activity performance measure involved pooling the single most comprehensive balance measure from each trial and included (in order of priority): the Berg Balance Scale, the Timed Up and Go, gait velocity/time, turning time, sit to stand time, Functional Reach and single leg stand time. The outcomes were included in this order to prioritise outcomes the author considered to be the most global measures of balance or balance-related activity performance. Secondary outcome measures included these individual balance measures as discrete measures as well as step/stride length and cadence. The balance-related activity performance meta-analysis included 15 trials with 747 participants and the falls meta-analysis included 2 trials with 250 participants. The pooled estimate of the effect showed that exercise and motor training significantly improved balance-related activity performance (Hedges' $g = 0.34$, 95% CI 0.11 to 0.57, $P = 0.004$) but there was no evidence of an effect on the proportion of fallers (risk ratio = 1.02; 95% CI 0.66 to 1.58, $P = 0.94$). Exercise and motor training was found to have a small positive effect on gait velocity and step/stride length as well as a moderate effect on turning time. The greatest relative effects of exercise and motor training on balance-related activity performance tended to occur in programs with highly-challenging balance training ($P = 0.16$), but there was no evidence of an association with the total dose of exercise ($P = 0.98$). There were non-significant trends towards improvement for most other outcome measures. Therefore, exercise and motor training can improve the performance of balance-related activities in people with Parkinson's disease. However, further research is required to determine if falls can be prevented using exercise approaches in this population.

While leg muscle weakness is a risk factor for falls in people with Parkinson's disease, muscle strength is not commonly considered to be affected by the disease process and muscle weakness is usually not apparent on clinical examination. However, people with Parkinson's disease often report feeling weak. One of the reasons for this discrepancy is the presence of bradykinesia (slowness of movement), making it difficult to ascertain if people with Parkinson's disease are truly weak, or just slow to develop muscle force. The measurement of muscle power (force × velocity of contraction) has the potential to clarify the relationship between muscle weakness and bradykinesia in people with Parkinson's disease. Furthermore, in the general older population, muscle power appears to be a better predictor of falls and physical activity performance than muscle strength. While modern variable resistance technology has the ability to measure muscle strength without the interference of bradykinesia, as well as muscle power, these measurements had never been reported in people with Parkinson's disease. A descriptive study with two parts was conducted utilising this technology.

Part one aimed to determine if the leg extensor muscles of people with mild to moderate Parkinson's disease are weaker and/or less powerful than a neurologically-normal control group, and determine the relative contributions of force and movement velocity to muscle power in people with Parkinson's disease. The leg extensor muscle strength (N) and power (W) of 40 participants with Parkinson's disease and 40 neurologically-normal participants of similar age and gender were assessed. The Parkinson's disease group were 16% weaker (mean between-group difference = 172N, 95% CI 28 to 315) and 22% less powerful (mean between-group difference = 124 W, 95% CI 32 to 216) than the control group. Muscle power was disproportionately reduced at light to medium loads due to reduced movement speed, whereas at heavy loads this bradykinesia was no

longer apparent. These results suggest that reduced muscle power at lighter loads arises from weakness and bradykinesia combined, but at heavier loads arises primarily from weakness.

Part two aimed to examine the relationship of muscle strength/power with walking speed and past falls in people with Parkinson's disease. Walking velocity over 10 m and the number of falls experienced in the prior 12 months was recorded for the 40 aforementioned participants with Parkinson's disease. Muscle power was found to explain more than half the variance in walking velocity ($R^2 = 0.54$) and remained significantly associated with walking velocity in models which included a measure of Parkinson's disease severity. Furthermore, participants with low muscle power were 6 times more likely to report multiple falls in the prior 12 months than those with high muscle power (Odds Ratio = 6.0, 95% CI 1.1 to 33.3), although this association between falls and power was no longer significant in models which included Parkinson's disease severity. However, muscle power was consistently found to explain as much or more of the variation in walking velocity, and was more strongly associated with past falls, than muscle strength. Adequate leg extensor muscle power therefore seems likely to be important for maximising mobility and reducing fall risk in people with Parkinson's disease. A Parkinson's disease fall risk score that includes leg muscle power instead of strength should be trialled, and the effect of muscle power training on walking speed and falls in people with Parkinson's disease warrants investigation.

Overall, the research presented in this thesis provides three pieces of evidence related to exercise and fall risk in people with Parkinson's disease. Firstly, exercise interventions can improve freezing of gait and are likely to improve muscle weakness and balance in people with Parkinson's disease. Improvements in these potentially remediable risk

factors for falls may lead to a reduction in the overall risk of falling in this group. Secondly, it appears that muscle weakness and reduced muscle power are due, in part, to the disease process itself. Finally, reduced muscle power is likely to also be a risk factor for falls in Parkinson's disease and may be more important to address with exercise interventions than muscle weakness. These results provide evidence to assist clinicians and researchers in devising exercise programs for people with Parkinson's disease. Any reduction in falls in this group will improve the quality of life of people with Parkinson's disease and their carers and help to reduce pressure on health care systems.

PUBLICATIONS AND PRESENTATIONS

Parts of the work presented in this thesis have been published and/or presented in the following forums:

PUBLISHED PAPERS

Allen NE, Canning CG, Sherrington C, Fung VSC (2009) Bradykinesia, muscle weakness and reduced muscle power in Parkinson's disease. *Movement Disorders* 24(9):1344-1351.

Allen NE, Sherrington C, Canning CG, Fung VSC (2010) Reduced muscle power is associated with slower walking velocity and falls in people with Parkinson's disease. *Parkinsonism and Related Disorders* 16(4):261-264.

Allen NE, Canning CG, Sherrington C, Lord SR, Latt MD, Close JCT, O'Rourke SD, Murray SM, Fung VSC (2010) The effects of an exercise program on fall risk factors in people with Parkinson's disease: A randomized controlled trial. *Movement Disorders* 25(9):1217-1225. (This paper was selected by the Movement Disorders Society for use in their Internet Journal Continuing Medical Education program).

PUBLISHED ABSTRACTS

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CONFERENCE PRESENTATIONS - ORAL

Allen NE, Canning CG, Sherrington C, Fung VSC (2007) Muscle strength and power in Parkinson's disease. Biennial FHS Postgraduate Research Student Conference, Sydney, Australia.

Allen NE, Canning CG, Sherrington C, Fung VSC, Murray SM, O'Rourke SD (2009) Support-group based exercise to address risk factors for falls in people with Parkinson's disease: a randomised controlled trial. Australian Physiotherapy Association National Neurology Group Conference, Sydney, Australia. (Won award for best presentation by a student researcher).

Allen NE, Canning CG, Sherrington C, Fung VSC, Murray S, O'Rourke S (2009) Exercise effects on fall risk in Parkinson's disease. Biennial FHS Postgraduate Research Student Conference, Sydney, Australia.

INVITED TALKS

Allen NE, Canning CG, Sherrington C (2009) Research update on mobility and fall risk in people with Parkinson's disease. Australian Physiotherapy Association Gerontology Group, Sydney, Australia.

Allen NE, Canning CG, Sherrington C (2010) Exercise reduces fall risk in people with Parkinson's disease. Parkinson's New South Wales Awareness Week Seminar, Sydney, Australia.

CONFERENCE PRESENTATIONS - POSTER

Allen NE, Canning CG, Sherrington C, Fung VSC (2008) Muscle strength and power are reduced in people with Parkinson's disease (preliminary data). Twelfth International Congress of Parkinson's Disease and Movement Disorders, Chicago, USA.

Allen NE, Canning CG, Sherrington C, Fung VSC (2008) Muscle power is reduced and is associated with falls in people with Parkinson's disease. Third Australian and New Zealand Falls Prevention Conference, Melbourne, Australia.

Allen NE, Canning CG, Sherrington C, Fung VSC (2008) Muscle power is reduced and is related to past falls in people with Parkinson's disease. The National Parkinson's Conference, Sydney, Australia. (Won the Inaugural Parkinson's NSW Student Prize).

Allen NE, Canning CG, Sherrington C, Fung VSC (2008) Muscle power is reduced and is associated with falls in people with Parkinson's disease. From Cell to Society 6 – The University of Sydney Faculties of Health Research Conference, Leura, Australia. (Won a University of Sydney Faculties of Health Research Conference 2008 poster prize).

Allen NE, Sherrington C, Paul SS, Canning CG (2010) Exercise and motor training can improve balance in Parkinson's disease: Systematic review. 4th Australian and New Zealand Falls Prevention Society Conference, Otago, New Zealand.

Allen NE, Canning CG, Sherrington C, Fung VSC, Murray SM, O'Rourke SD (2010) Exercise for fall risk factors in Parkinson's disease: A randomised controlled trial. 4th Australian and New Zealand Falls Prevention Society Conference, Otago, New Zealand.

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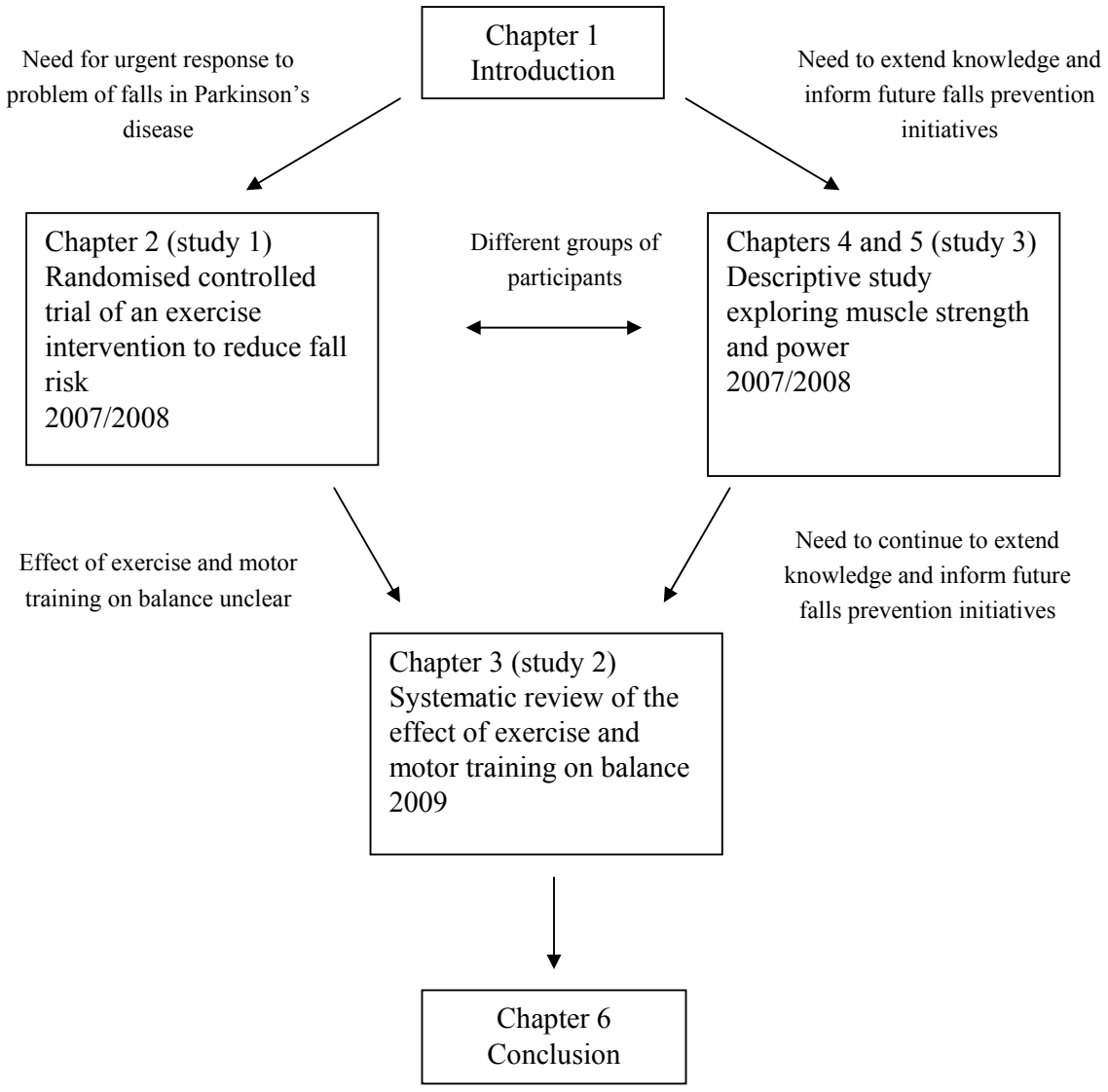
PREFACE

This thesis consists of three studies and is arranged into six chapters. Chapter 1 is an introduction to the thesis and provides an overview of the relevant literature regarding falls and fall risk factors in Parkinson's disease. Chapter 2 (Study 1) presents a randomised controlled trial with blinded assessment that evaluated an exercise program designed to reduce fall risk in people with Parkinson's disease. This study is based on current knowledge of potentially remediable risk factors for falls in Parkinson's disease and seeks to respond quickly to the pressing problem of frequent falls in people with Parkinson's disease. This paper is presented as published in *Movement Disorders.*

Chapters 3, 4 and 5 (Studies 2 and 3) seek to extend our knowledge and to inform the future development of falls prevention exercise programs for people with Parkinson's disease. Chapter 3 is a report of a systematic review with meta-analysis that investigated the effect of exercise and motor training on balance-related activity performance in people with Parkinson's disease. It is presented in the format required by *Movement Disorders*, where it has been submitted for peer review. A descriptive study exploring muscle strength and power in Parkinson's disease is presented in Chapters 4 and 5. Chapter 4 is presented as published in *Movement Disorders* and describes the effect of Parkinson's disease on leg extensor muscle strength and power. Chapter 5 is presented as published in *Parkinsonism and Related Disorders* and describes the relationships between leg extensor muscle strength and power with walking speed and past falls in people with Parkinson's disease. Chapter 6 concludes the thesis and contains a discussion of clinical implications and directions for future research in the area of falls prevention in Parkinson's disease.

Each chapter contains its own reference list. Appendices which were published as online supplementary material are presented at the end of the relevant chapter, and additional, unpublished work from the descriptive study is presented as an appendix at the end of Chapter 5. Other appendices are presented at the end of the thesis. Ethical approval from The University of Sydney Human Ethics Committee was granted prior to data collection for the two studies involving participants that are presented in this thesis.



Flow chart explaining order of presentation of studies.

CHAPTER 1

Introduction

OVERVIEW OF CHAPTER 1

This chapter provides a background and rationale for the studies contained in this thesis. It begins with an introduction to Parkinson's disease, outlining the pathophysiology of the disease, common impairments and activity limitations, as well as pharmaceutical and surgical management of the disease. Falls and fall risk in people with Parkinson's disease are then addressed, including the prevalence and impact of falls, exercise for falls, fall risk, risk factors for falls and exercise for potentially-remediable risk factors for falls. Specific impairments which have not traditionally been considered to be major motor impairments or risk factors for falls in Parkinson's disease, specifically muscle strength and power, are then addressed. The Chapter concludes by presenting the detailed aims of the thesis in evaluating and exploring interventions with the potential to reduce fall risk in people with Parkinson's disease.

INTRODUCTION TO PARKINSON'S DISEASE

Pathophysiology

Parkinson's disease is a chronic, progressive, neurodegenerative disease for which there is no known cure. It is the second most common neurodegenerative disease, exceeded only by dementia.[1, 2] The most common age of onset is after 50, though it can affect younger individuals.[3] While in a small number of cases Parkinson's disease is genetic, in most cases the cause of Parkinson's disease is unknown.[1, 2]

Traditionally, Parkinson's disease was believed to result from a pathological process beginning in the substantia nigra of the basal ganglia. However, recent work provides evidence that degeneration begins in the dorsal motor nucleus of the vagal nerve and olfactory nucleus, followed by the lower brain stem, then the basal ganglia and forebrain

and finally extending into the cortex.[4, 5] The loss of dopaminergic neurones from the substantia nigra is thought to be responsible for many of the motor symptoms of Parkinson's disease, with the disease becoming apparent when around 80 percent of the nerve cells in the substantia nigra have degenerated.[6] However, some impairments (both motor and non-motor) respond poorly to dopaminergic medications and are thought to be due to degeneration of other parts of the brain.[7]

Impairments and activity limitations

The World Health Organization's International Classification of Functioning, Disability and Health (ICF)[8] provides a useful model for understanding the symptoms and impact of Parkinson's disease. In this model, functioning and disability are both umbrella terms, where functioning encompasses all body functions, activities and participation while disability encompasses impairments, activity limitations and participation restrictions. The ICF consists of two parts, each with two components.

Part 1. Functioning and Disability

a) Body Functions and Structures

b) Activities and Participation

Part 2. Contextual Factors

c) Environmental Factors

d) Personal Factors

World Health Organization (2001), p 10[8]

Under this framework, impairments are *"…problems in body function or structure such as a significant deviation or loss"* and activity limitations are *"…difficulties an individual may have in executing activities."* (World Health Organization (2001), p 10)[8]. These ICF concepts will be used throughout this thesis.

Parkinson's disease has traditionally been characterised by four cardinal features – bradykinesia (slowness of movement), rigidity, tremor and postural instability (ie reduced balance not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction).[9] Additionally, freezing is considered to be a classic feature of Parkinson's disease.[10] For a diagnosis of Parkinson's disease to be made there must be a presence of bradykinesia and at least one of the other cardinal features. A good response to levodopa medication further confirms the diagnosis.[9]

The term bradykinesia means slowness of movement, but is often used synonymously with akinesia (lack of movement) and hypokinesia (reduced amplitude of movement). It affects all motor activities and is responsible for the slow, shuffling gait, absence of arm swing and lack of facial expression typical of the person with Parkinson's disease.[11-13] Bradykinesia appears to primarily be caused by failure of the basal ganglia to adequately support cortical mechanisms preparing for and executing movement, resulting in slowed development of muscle force when initiating movement.[14]

The rigidity present in Parkinson's disease causes the individual to feel tightness and stiffness in their joints and muscles, and can contribute to discomfort and pain. There is an increased resistance to passive joint movement in both the extensor and flexor muscles which is present even during slow velocity stretch,[15] though it does have a

velocity-dependent component.[16] Rigidity may be accompanied by the cogwheel phenomenon (a regular interruption at a 5 to 6 Hz frequency), likely due to underlying tremor.[10]

The tremor associated with Parkinson's disease is a resting tremor of about 4 to 6 Hz. It usually diminishes or ceases during intended movements,[17] is exacerbated by emotional stress and is absent while the individual is asleep.[18] Tremor typically affects the hands, feet, lips, chin and jaw.[10] Postural tremor (tremor while voluntarily maintaining a position against gravity) and/or action tremor can also be present and tends to be more prominent and disabling than resting temor.[10]

Balance (or postural stability) is a "*generic term to describe the dynamics of body posture to prevent falling*" (Winter 1995, p 3).[19] Balance requires maintenance of the body's centre of mass within the limits of the base of support while sitting or standing, or control of it while moving to a new base of support while walking or running.[19] Postural adjustments are task and context specific muscle activations used to maintain balance.[20] Postural adjustments can be broadly categorised into two groups: anticipatory and ongoing postural adjustments, and reactive postural adjustments. Anticipatory and ongoing postural adjustments occur immediately prior to and during a volitional movement, as an integral part of that movement.[21] Reactive postural adjustments occur in response to an external perturbation, such as being pushed or bumped.[21]

Most people with Parkinson's disease will develop reduced balance at some stage,[22] and balance problems tend to worsen with increased disease severity.[23, 24] Balance is often tested clinically using the postural stability item of the Unified Parkinson's Disease

Rating Scale (UPDRS),[25] where the individual is rapidly pulled backwards at the shoulders. Those with poor balance reactions either do not respond and must be caught by the assessor, or take an abnormally large number of backward steps to recover. Balance is also required for reaching and other tasks where the individual must control movements of their body to achieve a task without falling.[26] While reduced balance is considered to be a motor impairment on its own, other problems including bradykinesia, rigidity, dyskinesia, shuffling gait, narrowed base of support, stooped posture and cognitive impairment can all compound the balance problem and impede task performance.[27] Individuals with poor balance are more likely to fall, have poor mobility, difficulty performing daily activities and reduced quality of life.[27, 28] A more detailed review of balance in Parkinson's disease can be found in Appendix 1.

Freezing refers to difficulty starting or continuing movement and is a disabling and frustrating problem experienced by many people with Parkinson's disease.[10, 29] Freezing most commonly affects gait, however it can also interfere with other tasks such as writing and speaking.[29] Freezing of gait has recently been defined as:

> *"…an episodic inability (lasting seconds) to generate effective stepping in the absence of any known cause other than parkinsonism or high-level gait disorders. It is most commonly experienced during turning and step initiation but also when faced with spatial constraint, stress, and distraction. Focused attention and external stimuli (cues) can overcome the episode."*
>
> Giladi and Nieuwboer (2008), p *S*424[30]

Freezing of gait is a complex phenomenon which is estimated to affect around 7% of people with early and 60% of people with advanced disease.[31-34] It is considered to be a

common cause of falls in people with Parkinson's disease as it tends to occur abruptly, resulting in the feet staying in the one spot while momentum carries the body forwards.[24, 29, 33, 35] A more detailed review of freezing of gait can be found in Appendix 2.

Dyskinesia is a common motor side-effect of the dopamine replacement medications (levodopa and dopamine agonists) generally used to treat Parkinson's disease.[36, 37] Dyskinesias are involuntary, purposeless movements, often writhing in nature. Dyskinesias usually coincide with the peak dose of medication, but can occur at the beginning of the medication effect and again when the medication is wearing off.[36, 37] When medication is not effective, dyskinesia can also manifest as prolonged muscle spasms and persistent postures of the body, also known as dystonia.[36, 37] The incidence of dyskinesia increases with the number of years of treatment with levodopa, and occurs in around 90% of people treated for more than 10 years.[36] While for many people dyskinesia is mild and non-disabling, it can become severe and painful[36] and is likely to contribute to falls.[38-40]

There are a wide range of non-motor impairments also associated with Parkinson's disease. These include cognitive and emotional impairments, autonomic dysfunction, sleep disorders and sensory abnormalities.[10, 41] Cognitive impairment affects around 25% of people with newly diagnosed Parkinson's disease, with impairments most prominent in attention/executive function and memory.[42] Around 30% of people will go on to develop Parkinson's disease with dementia.[43] Neuropsychiatric symptoms such as depression, anxiety, apathy and psychosis will affect most people with Parkinson's disease at some stage during the course of their disease[44] and can be as debilitating as

the motor symptoms.[10] Fatigue is also a common and troubling symptom of Parkinson's disease and can occur independently of depression and sleep disorders.[45]

While the impairments and activity limitations of Parkinson's disease are often described individually, they frequently influence and exacerbate each other.[27] For example, freezing of gait is not thought to be caused by bradykinesia.[33] However, freezing of gait that is associated with a forward loss of balance is postulated to be due to difficulty linking postural adjustments with stepping.[46] In turn, bradykinesia is believed to be responsible for the slow and small postural adjustments found in people with Parkinson's disease.[46-51] It therefore appears that bradykinesia may exacerbate freezing of gait indirectly by interfering with postural adjustments.

The individual experience of Parkinson's disease is variable, with people experiencing the motor and non-motor impairments in various combinations and to differing extents. However, many of the impairments of Parkinson's disease can predispose the individual to falls. For this reason, the reduction of fall risk in people with Parkinson's disease presents a complex and unique challenge.

Pharmaceutical and surgical management

The mainstay of medical management for Parkinson's disease since the 1960s is levodopa medication, which works to restore dopamine levels in the brain.[2, 18] Many motor symptoms, including bradykinesia, tremor and rigidity, respond well to levodopa for the first five to seven years of treatment.[2, 52] However, as the disease progresses, motor fluctuations (observed as vacillation between periods of being ON, being ON with levodopa-induced dyskinesia and being OFF) occur.[2, 53] ON periods denote the

time when the Parkinson's medication is working well and movement is free and easy without excessive slowness, rigidity or tremor. In contrast, during an OFF period, medication effects have worn off and the benefits on movement, slowness, rigidity and tremor are no longer present. These shortcomings of levodopa therapy have led to the development of many other medications aimed at prolonging the effects of levodopa, reducing dyskinesias and ending sudden, unpredictable OFF periods.[2, 53] The pharmaceutical management of Parkinson's disease is therefore complex and requires careful tailoring for each individual.

Despite advances in the pharmaceutical management of Parkinson's disease, medications used to treat Parkinson's disease do not appear to prevent people with Parkinson's disease falling.[54, 55] This is largely because some motor impairments, including postural instability and freezing of gait, respond poorly to levodopa.[2, 54, 56, 57] Furthermore, as medication improves mobility without improving postural instability and freezing of gait, it may render some individuals with Parkinson's disease at an increased risk of falling.[27]

In recent years surgery in the form of deep brain stimulation of the subthalamic nucleus or the globus pallidus internus has increasingly been employed to manage symptoms in carefully selected people with more advanced disease.[52, 53] Deep brain stimulation is effective in treating the symptoms that respond well to levodopa, such as bradykinesia, tremor and rigidity,[52] as well as improving motor fluctuations by reducing OFF time and dyskinesias.[58] For this reason, people with a history of a good response to levodopa, whose disability is largely due to motor complications and who have good cognition make the best candidates for deep brain stimulation.[53] However, motor impairments that

respond poorly to levodopa, including postural instability and freezing of gait when ON, also tend to respond poorly to deep brain stimulation.[52, 59-61] This result suggests that falls similarly may not be reduced by subthalamic or globus pallidus internus stimulation, and some authors suggest that individuals experiencing frequent falls due to postural instability should be excluded from deep brain stimulation surgery.[52] Non-pharmacological and non-surgical interventions, such as exercise, may therefore, hold the key to falls reduction in people with Parkinson's disease.

FALLS AND FALL RISK IN PARKINSON'S DISEASE

Prevalence of falls

People with Parkinson's disease fall frequently and recurrently. They are twice as likely to fall as people with other neurological conditions, and are nine times more likely to experience recurrent falls than healthy individuals of the same age.[38, 62] A meta-analysis of six prospective studies of falling in Parkinson's disease[63] found that 46% of participants fell in a 3 month period. Of the participants who had not fallen in the previous 12 months, 21% fell in the 3 month follow-up period. In one of these studies with a 12 month follow-up, over two thirds of participants fell, with half falling more than once.[64] Further, in a survey of 100 people with Parkinson's disease, 13% reported falling more than once a week.[55] Given that there were at least 54,700 Australians with Parkinson's disease in 2005,[1] there are likely to be over 800,000 falls each year due to Parkinson's disease in Australia alone. Furthermore, it is estimated that from 2005 to 2030 the prevalence of Parkinson's disease in developed countries will almost double.[65] Therefore, the incidence of Parkinson's disease-related falls can be expected to have an even bigger impact on health care systems around the world in the coming decades.

Impact of falls

The consequences of people with Parkinson's disease falling are significant and far-reaching, affecting the person with Parkinson's disease, their family and the community. Falls frequently result in injury, causing pain and requiring costly medical intervention. They also contribute to increased fear of falling, reduced activity levels, poor quality of life and caregiver stress.

People with Parkinson's disease regularly injure themselves when they fall. While most of these injuries are soft tissue damage, more serious injuries are common, with fractures occurring more frequently in people with Parkinson's disease than in healthy individuals of the same age.[38, 66-69] Overall, the relative risk of fracture is doubled in those with Parkinson's disease, with the greatest increase in risk being for hip fracture.[66, 67] This increased risk for hip fracture is thought to be due to abnormally directed arm movements in response to loss of balance. People with Parkinson's disease have been found to adduct their arms against their body instead of using their arms to reach for support or to break their fall.[54, 70] Consequently, the person with Parkinson's disease has an increased chance of landing on, and so possibly fracturing, his/her hip.

The financial cost of falls amongst people with Parkinson's disease is high. Falls and related fractures are a common reason for hospital admission in Australia. A study of 761 hospital admissions for people with Parkinson's disease[71] found that only 15% of these were primarily for management of the patient's Parkinson's disease. Of the remaining admissions, falls and related fractures were the most frequent cause for admission, accounting for almost 13% of admissions. Furthermore, the treatment of fractures in people with Parkinson's disease poses a significant economic burden on the individual and the health care system. The costs associated with treating fractures in people with Parkinson's disease are close to double, and for treating a fractured hip are close to triple the costs for treating fractures in healthy older people.[67]

Frequent and injurious falls often lead to fear of falling, which is a widespread problem for people with Parkinson's disease. While some individuals at a high risk of falls are not fearful of falling, community-dwelling people with Parkinson's disease overall have

a greater fear of falling than healthy individuals of the same age.[38, 72] A 6 month prospective study of ambulant community residents found 46% of people with Parkinson's disease were fearful of falling, compared to 7% of healthy people of the same age. Furthermore, falls were more likely to lead to an increased fear of future falls in the Parkinson's disease group.[38]

Fear of falling reduces people's activity levels and quality of life. While cautious behaviour and avoidance of hazardous activities can help to lower the individual's risk of falling, too much restriction of activities can lead to decline in function and mobility, social isolation and poor quality of life.[28, 38] In the afore-mentioned prospective study of people with Parkinson's disease, 96% of people who reported fear of falling also reported restricting their physical activity levels.[38] This is likely to contribute to the substantial correlation ($R^2 = 0.74$) between reduced quality of life and higher fear of falling found amongst people with Parkinson's disease.[28]

Carers of recurrent fallers with Parkinson's disease report high levels of stress caused by fear of the person falling. A postal survey of 116 caregivers found that those caring for a person with Parkinson's disease who had fallen, had poorer quality of life and higher levels of caregiver burden than carers of people who had not fallen.[73] A study of carers of recurrent fallers with Parkinson's disease[74] found that carers experienced high demands on their physical, psychological and social wellbeing. The carers often injured themselves trying to help the person with Parkinson's disease up from the floor, were fearful of leaving the person unattended and felt unable to leave the house.

Falls are clearly a major problem for people with Parkinson's disease, their carers and healthcare systems. As falls do not appear to be prevented by Parkinson's disease medication or surgery,[52, 54, 55] there is a pressing need to evaluate and explore exercise interventions with the potential to reduce falls in people with Parkinson's disease.

Exercise for falls

A substantial amount of research has explored the effects of exercise on falls in the general older population.[75, 76] Meta-analyses have consistently shown that exercise can prevent falls in this group,[75, 76] resulting in an estimated 17% reduction in fall rates.[76] In particular, exercise programs combining 2 or more types of exercise into either an individually prescribed home-based program or a group program have been shown to be effective.[75, 77-81] Many different types of exercise have been explored, including balance, strength, cardiovascular and flexibility exercises. While all of these types of exercise have the potential to provide beneficial health outcomes, specificity of training means that these beneficial effects will vary depending on the type of exercise completed. For falls prevention, programs which combine a higher total dose of exercise (> 50 hours over trial period) with exercises that challenge balance have been shown to be the most effective in reducing falls rates.[76] Importantly, this research is informing the implementation of successful falls prevention exercise programs for the general older population throughout the developed world.

While it is clear that exercise can reduce falls in the general older population, there is no such evidence regarding falls in people with Parkinson's disease. Only three published randomised controlled trials to date have reported the effect of exercise on falls in people with Parkinson's disease.[82-84] The first trial[82] found no effect on falls from a

fully-supervised eight week program of treadmill walking and training steps in response to perturbations on a treadmill. However, the trial was too small (n = 18) to be able to detect an effect on falls if one had existed.

The second trial[83] investigated the effect of a three week home-based program of rhythmical cueing of gait and gait-related activity. There was no effect on fall rates, however the trial did not target fallers and did not aim to reduce falls. Rather, fall rates were measured to check that the intervention group participants' increased activity was not leading to an increase in falls. However, results did show increased confidence for not falling, along with improved balance and gait as well as reduced freezing in participants for whom freezing was a problem.

The third trial[84] did target fallers with Parkinson's disease and showed promising results. This six week home-based program incorporated a broad range of exercises including strengthening, range of movement, balance and walking exercises as well as strategies to reduce falls and improve movement and movement initiation. Results showed a trend towards a reduction in fall events (unadjusted difference between exercise and control groups = -9% (95% CI = -25% to 8%)) and a significant reduction in near-falls (unadjusted difference between exercise and control groups = -15% (95% CI = -30% to -1%)). Notably, all three trials[82-84] involved a relatively short duration of intervention and are well short of the total dose of exercise (> 50 hours) found to be more effective in reducing falls in the general older population.[76] It is likely that people with Parkinson's disease would also receive greater benefits from higher-dose programs involving several months of exercise.

Fall risk

Ideally, studies of falls prevention interventions use fall rates as the primary outcome measure. However, studies with falls outcomes require a large sample size, which can be difficult to achieve in people with specific health problems, such as Parkinson's disease. As an alternative, some studies of older people have used a fall risk score as the primary outcome measure to give an indication of the likely effects on falls themselves.[85, 86] In order to develop effective exercise programs for reduction of fall risk in people with Parkinson's disease, it is first important to identify and understand potentially modifiable risk factors for falls.

Risk factors for falls

Risk factors for falls in the general older population include impaired gait, reduced balance, lower limb weakness, polypharmacy, foot problems, peripheral sensory deficits and visual and hearing deficits.[40, 87-90] As Parkinson's disease tends to affect people over 50 years of age, these risk factors will also apply to many people with Parkinson's disease. However, the impairments associated with Parkinson's disease mean that there are also disease-specific risk factors in this population.[40]

The identification of risk factors for falls in Parkinson's disease has received increasing attention in recent years[38-40, 64, 91-95] and many different risk factors have been proposed. A meta-analysis of six prospective studies of falling in Parkinson's disease[63] reported that the best predictor of falling was two or more falls in the previous year. However, participants without a history of falls still had a 21% risk of future falls. This result highlights the importance of identifying fall risk factors that are potentially remediable and detectable before the first fall.

Several studies have reported that lower limb muscle weakness (ie a deficit in maximal force production), freezing of gait and reduced balance are risk factors for falls in Parkinson's disease.[39, 40, 93, 94] In particular, a prospective study of risk factors for falls in 113 people with Parkinson's disease[94] found that these three factors were independent risk factors for falls, regardless of whether previous falls had occurred or not. Lower limb muscle weakness, freezing of gait and reduced balance are all potentially remediable with exercise and able to be detected before the onset of falls. It is therefore logical to target these three risk factors for falls with exercise. Furthermore, an algorithm to calculate fall risk using measures of these three risk factors has been developed.[94] Therefore, the randomised controlled trial presented in Chapter 2 of this thesis investigates the effect on fall risk of a sustainable, six-month exercise program for people with Parkinson's disease which targets these three risk factors and applies this fall risk score.

Exercise for potentially-remediable fall risk factors

Muscle weakness

High intensity resistance training improves muscle strength and the functional abilities of people with Parkinson's disease.[96-101] People with mild to moderate Parkinson's disease have been reported to achieve similar increases in muscle strength as neurologically-normal people of the same age after progressive resistance training.[96, 98] In addition, increases in muscle strength were accompanied by improved gait velocity,[98, 101] stride length,[98] Timed Up and Go time,[101] 6 minute walk test distance[96] and stair descent time.[96] Moreover, resistance training combined with balance training has been shown to result in greater improvements in balance in people with Parkinson's disease

than balance training alone.[97] These results suggest that muscle strength training may play an important role in falls prevention in people with Parkinson's disease, and requires further investigation.

To date, published studies examining the effect of resistance training in people with Parkinson's disease have utilised specialised strength training equipment, requiring participants to attend and be supervised at a gym facility or clinic to use them.[96-101] However, simpler, cheaper methods of applying resistance, such as weighted vests or belts, have been used successfully in older people[102-104] and in people with multiple sclerosis.[105] The randomised controlled trial presented in Chapter 2 evaluated these pragmatic, readily accessible methods for applying resistance in people with Parkinson's disease.

Freezing of gait

The main intervention used to address freezing of gait is cueing. Cueing refers to the use of external temporal or spatial stimuli to assist the initiation and continuation of walking.[83] Cueing is known to engender immediate improvements in gait speed and step length in people with Parkinson's disease.[106, 107] It is also known that freezing of gait episodes can quickly be overcome with cues. However, most research has looked at the effect of a single intervention session,[108-113] so the longer term, therapeutic effect of cueing on freezing of gait is less clear.[114]

Freezing of gait episodes often occur during gait initiation and when turning during walking.[115] A few small descriptive studies have assessed the effect of cueing in these situations.[47, 111-113] Overall, these studies suggest that visual cues may be of most benefit

during gait initiation as they encourage an increase in step size, and that auditory cues may be of most benefit when turning as they reduce asymmetry and help to maintain timing.[114] However, there is currently no evidence that these improvements will reduce freezing during gait initiation or turning.

Nieuwboer et al[83] is the only large, high quality randomised controlled trial to address the effect of cueing intervention on freezing of gait in people with Parkinson's disease. In this trial 153 participants, 63 of whom experienced freezing, undertook 9 sessions over 3 weeks of training in the use of auditory (beeps through an ear-piece) or somatosensory (vibrations to the wrist) cues. Cueing training was incorporated into functional situations at the participant's home and participants who experienced freezing practised using the cue in circumstances that tended to provoke their freezing. Results did not show an overall effect on freezing. Nonetheless, the sub-group who did experience freezing problems reported a 1.3 point mean between-group difference in the Freezing of Gait Questionnaire ($P = 0.007$, scale from 0 to 24) at post-test, suggesting that cueing training can improve freezing of gait in those for whom freezing is a problem. This study was therefore used as a model for the delivery of cueing training to participants for whom freezing was a problem in the randomised controlled trial presented in Chapter 2.

Reduced balance

Balance is an inherent part of most daily activities and so can be observed during the performance of those activities. Balance can be assessed with tasks specifically designed to make controlling the centre of mass over the base of support difficult (eg, coordinated stability test).[116] However, many daily activities, such as reaching or turning around, also require control of the centre of mass over the base of support and are challenging for people with balance impairment. Therefore balance can also be assessed clinically by measuring the performance of these balance-demanding activities.

Balance is able to be improved in the general older population,[76, 117] and is considered to be potentially remediable in people with Parkinson's disease.[40, 94] However, the effect of exercise on balance in people with Parkinson's disease is unclear. Randomised trials to date have used a diverse range of intervention strategies and outcome measures.[82-84, 97, 118-123] While some studies have reported promising results,[82, 97, 119-121, 123] many of these studies are small and/or of poor methodological quality.

There does not appear to be a single intervention type or measure that consistently shows improvement in people with Parkinson's disease and several high quality studies have measured a number of balance outcomes, but have found improvement in only one or two.[83, 84, 118] Ashburn et al[84] conducted a randomised controlled trial of a six week home-based program for fallers with Parkinson's disease, which incorporated strength, range of movement, balance and walking exercises as well as strategies to improve movement and reduce falls. Results showed no statistically significant effect on the Berg Balance Scale, the Timed Up and Go, the chair stand test or the Functional Reach test.

Nieuwboer at al[83] reported a randomised cross-over trial of a three week home-based program of rhythmical cueing, aimed at improving step length, walking speed and balance and reducing freezing of gait. Results did not show any effect on Functional Reach or Timed Up and Go. The single leg and tandem stand times also did not improve, though there was a significantly reduced chance of failing (not reaching 30s) in these tests after intervention. There was significant improvement in a Posture and Gait score (UPDRS[25] items 13-15 (falling, freezing when walking, walking) and 29-30 (gait, postural stability) after intervention. However, improvements were temporary with the effects of intervention declining by the 6 week follow-up.

Morris et al[118] conducted a randomised controlled trial comparing the effects of two weeks of movement strategy training with exercise in hospitalised people with Parkinson's disease. The movement strategy training involved using cognitive strategies including focused attention and external cues when performing tasks such as walking, turning, standing up from a chair and negotiating obstacles. The exercise program included conventional exercises aimed at improving strength, range of movement, posture, general fitness and ability to perform everyday activities. A battery of previously published balance tests[124] was conducted. This battery includes the balance pull test, tandem stand time, single leg stand time and Functional Reach. The only reported difference between the groups was in the balance pull test (response to an unexpected backwards perturbation) which improved in the movement strategy group, but did not improve in the exercise group. The between-group difference in the balance pull test was diminished by the 3-month follow-up. Furthermore, neither group showed improvement in the Timed Up and Go test.

There is, therefore, no consensus as to the most effective form of exercise to address balance impairment in people with Parkinson's disease. In the general older population, highly-challenging balance exercises, characterised by movement of the centre of mass, narrowing of the base of support and minimization of upper limb support, have been shown to be the most effective.[76] The balance training provided in the randomised controlled trial presented in Chapter 2 was therefore based on these principles.

Despite the lack of clarity regarding the effect of exercise on balance in Parkinson's disease, there has only been one systematic review to specifically address this issue.[125] Dibble et al[125] concluded that there was moderate evidence that exercise improved balance and the performance of balance-demanding activities, and limited evidence that exercise reduced falls. This review, however, did not include any meta-analysis. Furthermore, of systematic reviews exploring the effectiveness of exercise for people with Parkinson's disease,[106, 107, 114, 125-137] only two published papers[136, 137] have included any meta-analysis, and to date no reviews have reported a meta-analysis of balance outcome measures. Chapter 3 presents the first systematic review with meta-analyses to assess the effects of exercise on balance-related activity performance in people with Parkinson's disease.

Summary of falls and fall risk in Parkinson's disease

Falls are a major problem for people with Parkinson's disease and do not appear to be prevented with modern medical management. There is a paucity of research examining the effects of exercise training on falls in people with Parkinson's disease and such research requires large sample sizes in order to achieve the statistical power required to detect an effect on falls. Furthermore, trials to date have involved a relatively short duration of intervention which may not be sufficient to improve fall rates. Despite this, some promising results have been reported. The use of a fall risk score offers an alternative outcome measure capable of providing an indication of the likely effects on falls. Muscle weakness, freezing of gait and reduced balance are fall risk factors in Parkinson's disease which are potentially remediable with exercise and for which a fall risk score algorithm has been developed. The randomised controlled trial presented in Chapter 2 used this algorithm to assess the effect on fall risk of a sustainable, 6 month-exercise program which targeted muscle strength, freezing of gait and balance.

While balance is often considered to be potentially remediable in people with Parkinson's disease, published research revealed the effect of exercise on balance in people with Parkinson's disease is unclear. The systematic review with meta-analysis presented in Chapter 3 clarifies the effects of exercise on balance-related activity performance in people with Parkinson's disease.

MUSCLE STRENGTH AND POWER IN PARKINSON'S DISEASE

Muscle strength

Progressive loss of muscle strength with increasing age is widely acknowledged. A longitudinal study[138] of the lower limb muscle strength of men and women (initially aged 46 to 78 years) reported an average 14% decline in knee extensor strength and an average 16% decline in knee flexor strength over 10 years. This reduction in muscle strength is accompanied by a reduction in muscle mass, both of which are believed to be mainly due to a loss of muscle fibres with age.[139]

It is unclear whether or not Parkinson's disease leads to muscle weakness over and above that caused by ageing. Although people with Parkinson's disease often report feeling weak,[140] this weakness is usually not apparent during clinical examination.[141, 142] Furthermore, attempts to quantify muscle strength in people with Parkinson's disease have yielded mixed results, and it remains uncertain as to whether people with Parkinson's disease are weaker than neurologically-normal people of the same age.

Measurement of muscle strength

The uncertainty surrounding muscle weakness in Parkinson's disease is partly due to bradykinesia. It can be argued that what appears to be muscle weakness is actually a slowness to develop muscle force. It is thought that bradykinesia results from inadequate generation of muscle force when initiating movement, caused by failure of the basal ganglia to adequately support cortical mechanisms preparing for and executing movement.[14] The abnormal force generation patterns seen in people with Parkinson's disease support this hypothesis. Electromyographic studies of rapid arm movements in people with Parkinson's disease have found a reduced rate of rise of agonist

electromyographic activity, as well as an increased number of agonist bursts and an increase in agonist/antagonist co-contraction.[143-147] Furthermore, there is a reduced rate of force production and release during isometric muscle contractions.[144, 148-150] These abnormalities in force generation patterns appear to be an underlying component of bradykinesia. However, they also have the potential to influence the results of muscle strength testing.

Isokinetic strength testing involves movement at a constant predetermined velocity, so it is likely to be influenced by bradykinesia.[142] Studies of isokinetic strength have consistently reported muscle weakness in Parkinson's disease compared to healthy control groups.[141, 151, 152] The fact that muscle strength – when measured isokinetically – deteriorates as the speed of muscle contraction increases,[153, 154] is evidence of the influence of bradykinesia on this type of measurement.

Isometric muscle strength testing has been described as a more "pure" form of strength testing as it does not involve movement.[142] Provided the individual with Parkinson's disease is given adequate time to generate force, isometric muscle testing will give a more accurate picture of the maximum force the individual is able to produce. Studies comparing the isometric muscle strength of people with Parkinson's disease before and after taking antiparkinsonian medication have found muscle strength is improved after medication.[146, 150, 155] However, studies of isometric muscle strength in people with Parkinson's disease compared to a neurologically-normal control group, have yielded variable results. Some studies have reported no difference in strength,[141, 142, 144, 156, 157] while others found that weakness was present in the Parkinson's disease group.[146, 158, 159]

Until recently it has been difficult to measure muscle strength in a way that is both accurate and functionally relevant. Measures of muscle strength taken on the basis of the weight a person can lift do not provide an accurate measure of the force they are exerting. Since force = mass x acceleration, when a weight is lifted, the force required changes with even small changes in acceleration. In order to measure muscle force in a way that is reproducible and accurate, traditional measures have sought to control movement speed, resulting in the use of isokinetic and isometric techniques. Unfortunately, however, these techniques are not functionally relevant as they do not provide strength measures which reflect the way human muscles are predominantly used for most everyday activities. As a consequence, the relevance of isokinetic and isometric muscle strength testing is unclear.

Recent advances in technology have led to the development of a pneumatic variable resistance machine (Keiser Sports Health Equipment, Fresno CA). As the machine is able to vary the resistance, it allows muscle strength to be measured while the participant lifts the load at his/her own speed. In this way it provides an accurate and reproducible muscle strength measure[160] that reflects the individual's ability to use their muscles in a functional way. Furthermore, this technique can allow for the fact that when lifting very heavy loads at the limits of their strength, all people will lift slowly, regardless of whether they have Parkinson's disease or not. This form of measurement should, therefore, be useful for measuring muscle strength without the interference of bradykinesia in people with Parkinson's disease. This variable resistance technology has been used for testing the muscle strength of older people.[160-163] Chapter 4 presents the results of the first published study to use this technology to measure the leg extensor muscle strength of people with Parkinson's disease.

Impact of muscle weakness on physical activity performance and falls

Despite the limitations of traditional measures of strength measures, when muscle weakness has been present in people with Parkinson's disease, it has been shown to have a detrimental effect on their ability to perform physical activities. A descriptive study[152] of 30 people with Parkinson's disease and 30 age- and gender-matched healthy controls found that people with Parkinson's disease were weaker than the healthy group in their trunk, hip and ankle flexor and extensor muscles. This weakness was related to reduced walking speed in the Parkinson's disease group, whereas no relationship was found between strength and walking speed in the healthy group. Muscle weakness in Parkinson's disease has also been reported to affect ability to stand up from a chair. A study of elderly women with mild to moderate Parkinson's disease[158] found that the women took longer to stand up than a healthy control group and that performance was slowest in women with Parkinson's disease who also had weak extensor leg muscles. A similar small study of men with mild Parkinson's disease[151] also reported increased time to stand up and overall hip and knee extensor muscle weakness when the men had not taken their Parkinson's disease medication. Additionally, slowness to complete the Timed Up and Go test has been reported to be associated with leg extensor muscle weakness in people with Parkinson's disease.[164] These studies suggest that reduced leg muscle strength may contribute to reduced walking speed and difficulty standing up from a chair – both problems that commonly affect people with Parkinson's disease and potentially could result in a situation where the individual is at risk of falling.

Leg muscle weakness has in fact been found to be predictive of falls in people with Parkinson's disease.[94] In a 12 month prospective study of 112 people with Parkinson's disease, participants who fell were found to have weaker knee and ankle muscles than

those who did not fall. Furthermore, reduced knee extensor muscle strength was found to be an independent predictor of falls. The authors[94] suggested that leg extensor muscle strength was particularly important in falls prevention in order to prevent collapse of the supporting leg[165] and to facilitate balance control.[166, 167] The study presented in Chapter 5 further explores the associations between leg extensor muscle strength and walking speed and past falls in people with Parkinson's disease.

Muscle power

Muscle power quantifies the ability to use muscles quickly, and can be defined as force x speed of muscle contraction. Adequate muscle power is required for many daily activities, such as standing up from a chair, walking and reacting quickly in order to prevent a fall. While muscle power is related to muscle strength, measures of muscle power incorporate the speed at which force is applied and so are likely to provide a better picture of the individual's ability to use their muscles in everyday life.[168] Muscle power is able to be measured in a reliable and valid way[160, 169] using the same pneumatic variable resistance equipment (Keiser Sports Health Equipment, Fresno CA) that can be used to measure muscle strength.

Impact of reduced muscle power on physical activity performance and falls

Beyond the fifth decade of life, muscle power is lost at a faster rate than strength (3% to 4% vs 1% to 2% per year).[170] In both healthy and disabled older people, this loss of power has been found to have a greater influence on the performance of physical activity than loss of strength. A study of 45 older people with mobility limitations[161] found that leg extensor power predicted physical activity performance. Furthermore, leg extensor power accounted for 2 to 8% more of the variance in physical activity

performance than leg extensor strength. A large study of over 800 older people, most of whom had mild to moderate mobility limitations, subsequently confirmed these results.[171] Leg extensor power consistently explained more of the variance in the performance of physical activity than leg extensor strength, such that people with low power were 2 to 3 times more likely to have a mobility limitation than people with low strength (odds ratio for poor performance if leg power was low = 8.9, 95% CI 4.0 to 20.1; odds ratio for poor performance if leg strength was low = 2.9, 95% CI 1.5 to 5.6). Similarly, a study of 100 healthy older people[170] found that leg extensor power was more highly correlated with the ability to stand up from a chair and to ascend a tall step than leg extensor strength. Muscle power, therefore appears to be a better predictor of the performance of physical activity than muscle strength in the general older population.

In addition to influencing the performance of physical activities, loss of muscle power has been found to be related to falls. A study of 403 healthy older women[172] measured lower limb extensor power and collected data on falls and related injuries prospectively for one year. This study found that women with lower limb extensor power asymmetry were 1.7 times more likely to have one injurious fall and 2.4 times more likely to have recurrent injurious falls compared to women without power asymmetry. Another study examining lower limb muscle strength and power in 35 community-dwelling female fallers and non-fallers aged 65 and over found that out of seven strength measures, fallers were weaker in only one (concentric ankle dorsiflexion).[173] Fallers, however, were 24% less powerful in their least powerful leg than non-fallers. Both fallers and non-fallers were asymmetrical in their lower limb strength and power, however fallers were more asymmetric than non-fallers in power only. Therefore reduced lower limb

extensor muscle power, and particularly asymmetry of extensor power, appears to be more predictive of falls, especially injurious falls, than traditional strength measures in older women.

The ability to generate muscle force at a high velocity appears to be a critical factor in determining mobility and preventing a fall. Muscle power measurements taken with low resistance (and therefore fast muscle contraction) have been found to have as much or more influence on measures of physical activity performance than power measurements taken at higher resistance (and therefore slower muscle contraction). This is despite the fact that the measures at higher resistance gave a higher peak power reading. A study compared power generated at 40% of the one repetition maximum (1RM) (ie, low resistance and fast muscle contraction) with power generated at 70% of 1RM (ie, high resistance and slower muscle contraction) in disabled older adults.[163] Absolute power generated at 40% of 1RM was lower overall but explained more of the variability in walking speed and the same amount of variability in the time taken to climb stairs and to stand up from a chair than power generated at 70% 1RM. This suggests that it is not just the force of muscle contraction, but also the speed at which it can be generated that determines performance of physical activities, particularly in tasks where a lower percentage of maximal strength, but rapid muscle contraction is required, such as walking. This may also be the case in recovering from a loss of balance to prevent a fall.

The well established influence of extensor muscle power on physical activity performance and falls in older people shows a clear need for muscle power to be investigated in people with Parkinson's disease. Furthermore, as muscle power

incorporates speed of movement as well as the force generated, measurement of muscle power and analysis of its components has the potential to provide information about the relative contributions of weakness and bradykinesia to physical activity performance and falls in people with Parkinson's disease. Chapters 4 and 5 present the first published study to explore the effect of Parkinson's disease on leg extensor muscle power as well as the relationships between leg extensor power and walking speed and falls in this population.

Summary of muscle strength and power in Parkinson's disease

The effect of Parkinson's disease on muscle strength (force) is difficult to assess due to the presence of bradykinesia. The measurement of muscle power (force × speed of muscle contraction) has the potential to help clarify the relationship between muscle strength and bradykinesia. Furthermore, in the general older population, muscle power appears to be a better predictor of falls and physical activity performance than muscle strength. The muscle power of people with Parkinson's disease has never been reported. Technology now exists to measure muscle strength without interference from bradykinesia and to measure muscle power. The descriptive study presented in Chapters 4 and 5 utilised this technology to clarify the effect of Parkinson's disease on leg extensor muscle strength and power (Chapter 4) and to investigate associations between leg extensor muscle strength and power with walking speed and past falls in this population (Chapter 5).

AIMS OF THE THESIS

The overall aim of this thesis is to evaluate and explore interventions with the potential to reduce fall risk in people with Parkinson's disease. This thesis contains three studies conducted by the candidate and presented as four journal articles, each of which may be read independently. The specific aims for each study are:

Study 1: to determine if a six-month randomised controlled trial of an exercise program which targets potentially remediable risk factors for falls in people with Parkinson's disease improves: (i) performance in measures of fall risk and (ii) physical abilities, fear of falling and quality of life (Chapter 2).

Study 2: to systematically review the literature to examine whether exercise and motor training improves balance-related activity performance in people with Parkinson's disease and to determine if the total dose of exercise and the presence of highly-challenging balance training is associated with the magnitude of any improvement in balance-related activity performance (Chapter 3).

Study 3: (i) to determine if people with mild to moderate Parkinson's disease are weaker and/or less powerful than a neurologically-normal control group and to determine the relative contributions of force and movement velocity to muscle power in people with Parkinson's disease (Chapter 4) and (ii) to investigate the relationships between leg extensor muscle strength and power with walking speed and past falls in people with mild to moderate Parkinson's disease (Chapter 5).

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CHAPTER 2

The effects of an exercise program on fall risk factors in people with Parkinson's disease: A randomised controlled trial

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A supplementary file (Intervention Details) was published online with this publication. It is placed as an appendix at the end of this chapter.

The exercise program used in this study is presented in Appendix 3.

An example of a participant exercise instruction and recording sheet is presented in Appendix 4.

Statement from co-authors confirming authorship contribution of the PhD candidate

As co-authors of the paper *The effects of an exercise program on fall risk factors in people with Parkinson's disease: A randomised controlled trial*, we confirm that Natalie Elizabeth Allen has made the following contributions:

- conception, organisation and execution of the research
- acquisition of funding
- analysis and interpretation of the findings
- writing the paper and critical appraisal of content
- revising the paper for important intellectual content

Colleen G Canning	C. G. Canning	Date: 8/9/10
Catherine Sherrington	Catherine	Date: 31/8/10
Stephen R Lord	SR Lord	Date: 31/8/10
Mark D Latt	Mark Latt	Date: 18/08/2010
Jacquleine CT Close		Date: 3.9.10
Sandra D O'Rourke		Date: 9.9.10
Susan M Murray		Date: 8.9.10
Victor SC Fung	Vic Fung	Date: 8.9.10

The published paper and online supplementary file were included in the thesis here.

CHAPTER 3

Exercise and motor training improves balance-related activity performance in Parkinson's disease: systematic review and meta-analysis

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Guidelines for publication in *Movement Disorders* are outlined in Appendix 5.

Statement from co-authors confirming authorship contribution of the PhD candidate

As co-authors of the paper *Exercise and motor training improves balance-related activity performance in Parkinson's disease: Systematic Review and meta-analysis*, we confirm that Natalie Elizabeth Allen has made the following contributions:

- conception and design of the review
- conducted the search strategy
- screened the search output and extracted the data
- assessed the risk of bias in the data
- writing the review and critical appraisal of content
- revising the review for important intellectual content

Catherine Sherrington _____ Date: 10/9/10

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Balance and Falls in Parkinson's Disease: A Meta-analysis of the Effect of Exercise and Motor Training

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Abstract

This systematic review with meta-analysis aimed to determine the effects of exercise and motor training on the performance of balance-related activities and falls in people with Parkinson's disease (PD). Sixteen randomized and quasi-randomized controlled trials that assessed the efficacy of exercise and/or motor training against no intervention or placebo intervention were included. The primary outcome measures were balance-related activity performance (15 trials) and falls (2 trials). The pooled estimate of the effect of exercise and motor training indicated significantly improved balance-related activity performance (Hedges' g = 0.34, 95% confidence interval (CI) = 0.11 to 0.57, P = 0.004) but there was no evidence of an effect on the proportion of fallers (risk ratio = 1.02; 95% CI 0.66 to 1.58, P = 0.94). Balance-related activity performance improved to a greater extent in the trials of programs involving highly-challenging balance training but the difference in effect sizes was not statistically significant (P = 0.158). Exercise and motor training can improve the performance of balance-related activities in people with PD. However, further research is required to determine if falls can be prevented in this population.

Keywords: Parkinson's disease, exercise, motor training, balance

INTRODUCTION

Falls are a major problem for many people with Parkinson's disease (PD).[1] Reduced balance is known to be an important risk factor for falls in this population.[2-4] Balance requires maintenance of the body's centre of mass within the limits of the base of support while sitting or standing, and control of the centre of mass while moving to a new base of support during walking or running.[5] Balance is often assessed with tasks designed to make controlling the centre of mass over the base of support difficult.[6] However, many daily activities, such as walking or standing up from a chair, are also balance-related as they require control of the centre of mass while moving to a new base of support. Therefore balance can be measured indirectly by tests of the individual's ability to perform balance-related activities, particularly in individuals with impaired mobility.[7]

Most people with PD will ultimately develop reduced balance,[8] which worsens with disease progression.[9, 10] Reduced balance is associated with falls, poor mobility, disability and reduced quality of life in people with PD.[2, 11-13] There is therefore a pressing need to explore interventions which may improve balance in this population.

The effect of exercise and motor training on balance in people with PD is unclear. Research to date has used a range of interventions and outcome measures designed to target and reflect balance.[14-23] Nonetheless, meta-analysis is able to combine studies with broadly similar interventions and outcomes, and therefore provide a comprehensive summary of the available evidence.[24] Two published meta-analyses have addressed the effect of exercise on PD but did not focus on balance outcomes.[25, 26] One published review article specifically addressed the effects of exercise on balance,[27] but did not include a meta-analysis.[28]

Therefore, to examine whether exercise and motor training improves balance-related activity performance and falls in people with PD, we conducted meta-analyses of randomized and quasi-randomized controlled trials that assessed the efficacy of these interventions against no or placebo intervention. Meta-regression was used to investigate if the total dose of exercise and the presence of highly-challenging balance training were associated with the size of estimates of the effect of intervention on balance-related activity performance.

METHODS

Data Sources and Searches

A literature search was conducted on September 24th 2009 to identify studies of the effects of exercise and motor training in people with PD. Databases searched were MEDLINE, EMBASE, AMED, PsycINFO, the Cochrane Central Register of Controlled Trials and CINAHL. The electronic search strategies are available as Supporting Information on the website. The search was supplemented with searches of the Physiotherapy Evidence Database (PEDro; http://www.pedro.org.au) and examination of trials included in previously published systematic reviews. [25-27, 29-41]

Study Selection

Included trials were published randomized (or quasi-randomized, i.e., not truly random but intended to produce similar groups) controlled trials of interventions for people with PD. The intervention was required to be exercise or motor training, or a multi-faceted intervention where most of the intervention was exercise or motor training and there was an aim (explicit or implicit) to improve performance of balance-related activities for at least 50% of the intervention (including cueing, strength and fitness

training). The effects of the intervention were required to be compared with a no intervention or placebo control group (including social support or 'interest' talks) and the ongoing effects of the intervention were evaluated with a measure of balance or a balance-related activity. Trials evaluating the effect of whole body vibration were excluded as this was not considered to be exercise or motor training.

To determine eligibility, trial titles and abstracts were screened independently by two investigators (NEA and CGC). If it was clear that the trial did not meet the inclusion criteria, it was excluded. The full article was obtained for the remaining trials. Further eligibility assessment was then independently conducted for these trials by two investigators (NEA and SSP), using a standardised form containing the details of the inclusion criteria. Differences of opinion regarding trial eligibility were resolved by discussion with the remaining two investigators (CGC and CS).

Data Extraction and Quality Assessment

A data extraction sheet was developed, pilot-tested on 5 randomly selected included trials and modified accordingly. For each trial, one investigator (NEA) extracted all data and a second investigator (CS) checked the extracted data. Discrepancies were resolved by discussion. Care was taken to identify duplicate reports of trials. Published data only were used.

Information extracted from each trial comprised a description of participants, details of the exercise and motor training program and details of outcome measures. The risk of bias from reported methodology for each trial was evaluated by one investigator (NEA) in consultation with the other investigators using the Cochrane risk of bias tool.[24] This tool was used to assess and report the quality of the included trials but trials were not excluded on the basis of this assessment.

Data Synthesis and Analysis

The primary outcome measures were determined a priori; these were balance-related activity performance and proportion of fallers. The balance-related activities analysis involved the pooling of the most comprehensive balance measure from each trial.[24] The measure from each trial was chosen prior to analysis according to the following order of priority: the Berg Balance Scale,[42] the Timed Up and Go,[43] gait velocity/time, turning time, sit to stand time, Functional Reach[44] and single leg stand time. Where a trial reported results for more than one of these outcomes, only the outcome of the highest priority was used.

Secondary outcome measures included individual balance-related activity performance measures. These were the Berg Balance Scale, the Timed Up and Go, turning time, sit to stand time, Functional Reach, single leg stand time, gait velocity/time, step/stride length and gait cadence.

Trials with two different intervention groups had each intervention included in a separate comparison, with the number of participants in the control group divided equally between the comparisons and the control group mean and standard deviation left unchanged.[24] Where a trial included two similar intervention groups, they were combined to create a single pair-wise comparison with the control group.[24] For cross-over studies, first phase data only was used.[24] All data used was that collected immediately post-intervention. Where the median and inter-quartile range were reported and the study sample size exceeded 70, the median was used as an approximation of the mean and the inter-quartile range was assumed to equal 1.35 standard deviations.[24, 45]

Random effects meta-analyses were conducted using Comprehensive Meta-Analysis software (Version 2, Biostat, Englewood NJ). The standardized mean difference (Hedges' g) was calculated for all meta-analyses except for the proportion of fallers,

which was calculated as a risk ratio. Hedges' *g* was calculated by the computer software using either the pre and post mean and standard deviations *or* the mean change and standard deviation data. For secondary outcomes, an estimate of the difference in mean outcome scores in the original unit of measurement was calculated by multiplying Hedges' *g* by the largest included trial's standard deviation at baseline.[24] Statistical heterogeneity was quantified with the I^2 and Q statistics. Publication bias for the primary outcome measures were assessed using Egger's test to determine if there is any evidence of a relationship between sample size and effect size.[46]

Two separate pre-specified univariate random effects meta-regressions were conducted to assess the associations between the total number of hours of intervention in the trials and the presence of highly-challenging balance training (yes or no/unclear), and estimates of the effect of intervention on balance-related activity performance. Highly-challenging balance training was defined as involving all of: movement of the centre of mass, narrowing of the base of support and minimizing upper limb support.[47] Sensitivity analysis was conducted to determine the effect of omitting studies for which the content of the balance training was unclear. All meta-regression analysis was conducted using the 'metareg' command in Stata (Version 10, College Station, TX).

RESULTS

Trial Flow and Study Characteristics

Searching identified 2,798 records, of which 19 were potentially appropriate for inclusion in a meta-analysis (Figure 1).[48] Three trials were excluded from the meta-analyses[49-51] because the balance measures they reported were not able to be pooled with any others. The characteristics of the included trials[14, 15, 18, 19, 21, 22, 52-62] are summarized in Table 1. The risk of bias assessment[24] for each included study is summarized in Table

2 and shows that 7 of the 16 trials were judged to fulfil the criteria for at least 3 of the 5 domains, suggesting they were of moderate to high quality. The quality of a further 8 trials was unclear as there was insufficient information in the publication to permit judgment regarding adherence to each domain.

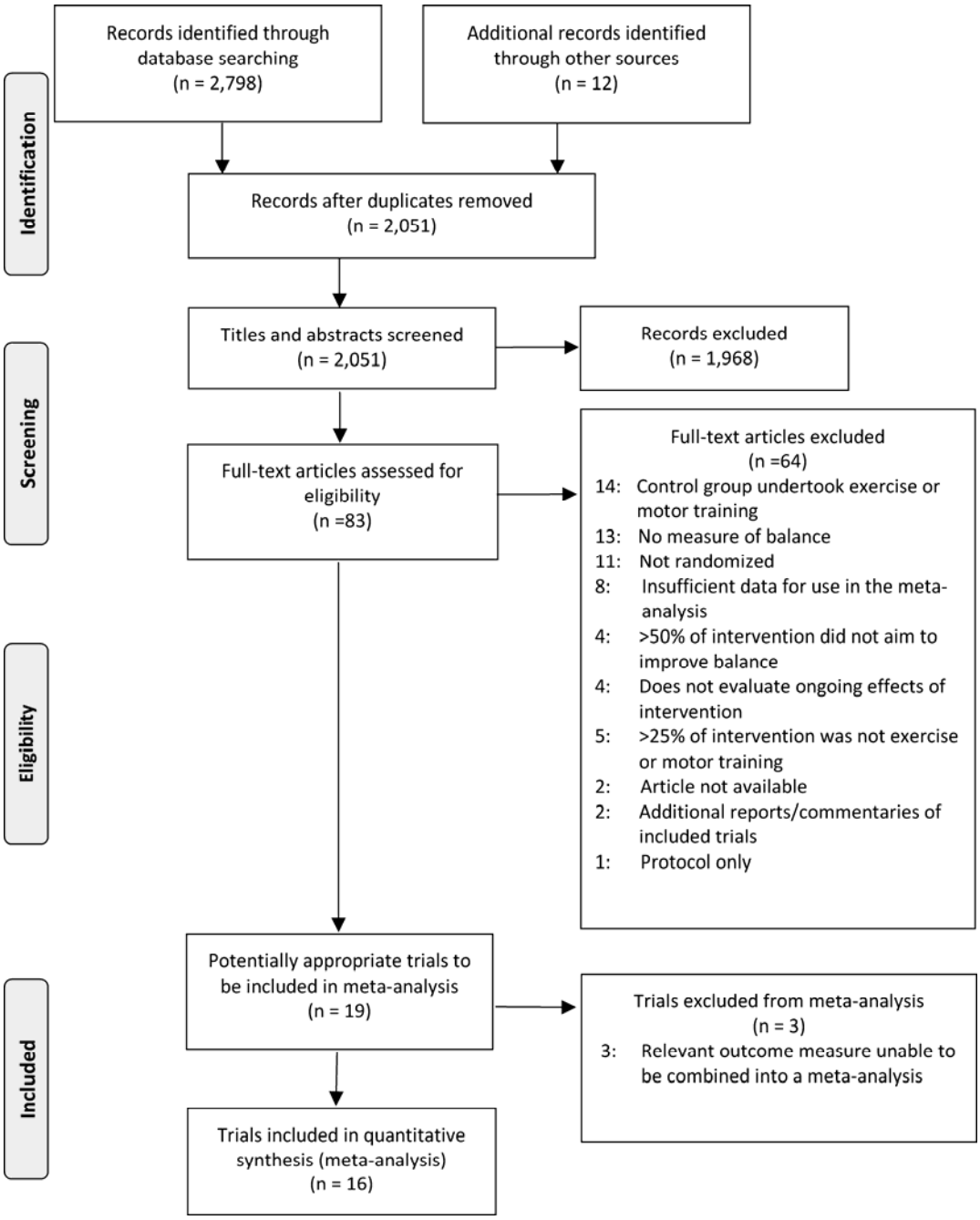

FIG. 1. PRISMA flow diagram[48] showing flow of information through the review.

TABLE 1. *Characteristics of the 16 included trials*

First author, year and experimental intervention type	Control Intervention	Data extracted	Initial sample size	Age (years, mean ± SD)	Disease severity	Assessed ON or OFF	Location and delivery of experimental intervention	Duration of Intervention (weeks)	Hours of Intervention (approx)	Highly-challenging balance training	Task training (cueing)	Fitness training	Task training (movement strategy)	Strength training	Stretching / ROM exercise	Walking over ground / exercises	Walking treadmill
Ashburn 2007 exercise and strategy	usual care	falls – number of fallers other - pre and post mean and SD	142	72.1 ± 9.2	moderate	ON	home, individual	6	33	U	N	N	**Y**	U	**Y**	**Y**	N
Blackinton 2002 exercise	support group meetings	pre and post mean and SD	15	66.5 ± 12.8	mild to moderate	ON	facility, group + home individual	6	15	**Y**	**Y**	N	N	U	**Y**	**Y**	N
Caglar 2005 exercise	no intervention	pre and post mean and SD	30	65.9 ± 9.4	mild to moderate	ON	facility group + home individual	9	63	U	N	N	**Y**	N	**Y**	**Y**	N
Cakit 2007 treadmill walking	not reported	pre and post mean and SD	54	71.8 ± 6.4	mild to moderate	ON	facility, delivery not reported	8	8	N	N	N	N	N	**Y**	N	**Y**
Ellis 2005 (duplicated as de Goede 2004) physiotherapy	no intervention	pre and post mean and SD	68	64 ± 8.6	mild to moderate	ON	facility, group	6	18	U	**Y**	N	**Y**	U	**Y**	**Y**	**Y**
Fisher 2008 treadmill walking OR physiotherapy	education classes	pre and post mean and SD	30	62.9 ± 11.9	mild	ON	facility, delivery not reported	8	18 18	N U	N N	**Y** N	N **Y**	N U	N **Y**	N **Y**	**Y** N
Hackney 2008 Tai Chi	no intervention	mean change, SD difference	33	63.8 ± 9.2	mild to moderate	ON	not reported	10 to 13	20	**Y**	N	N	N	N	N	N	N
Hackney 2009 partnered dance	no intervention	pre and post mean and SD	58	67.1 ± 9.3	mild to moderate	ON	facility, group	10 to 13	20	**Y**	N	N	N	N	N	N	N
Kurtais 2008 treadmill walking	taught ROM and flexibility exercises but no ongoing intervention	pre and post mean and SD	30	64.8 ± 8.3	mild to moderate	ON	facility, delivery not reported	6	12	N	N	**Y**	N	N	**Y**	N	**Y**
Lehman 2005 [a] walk with verbal cues	no intervention	pre and post mean and SD	11	75.8 ± 4.2	mild	ON	not reported	2	5	N	**Y**	N	N	N	N	**Y**	N
Mak 2008 cued sit to stand OR exercise	no intervention	pre and post mean and SD	60	64.1 ± 7.9	mild to moderate	ON	not reported	4	4 6	N N	**Y** N	N N	**Y** **Y**	N **Y**	N **Y**	N N	N N
Nieuwboer 2007 cueing training	no intervention	falls – number of fallers other - pre and post mean and SD	153	68.3 ± 7.8	mild to moderate	ON	home, individual	3	4.5	N	**Y**	N	**Y**	N	N	**Y**	N
Protas 2005 treadmill walking and step training	no intervention	pre and post mean and SD	18	72.5 ± 7.8	mild to moderate	ON	facility, individual	8	24	**Y**	N	N	N	N	N	N	**Y**
Sage 2009 aerobic exercise OR SAFEx	no intervention	pre and post mean and SD	53	65.9 ± 9.5	mild to moderate	ON	facility, group	12	18 20 to 34	N **Y**	N N	**Y** N	N N	N N	N **Y**	N **Y**	N N
Schenkman 1998 exercise	no intervention	mean change, SD difference	51	70.9 ± 6.7	mild to moderate	ON	location not reported, individual	10	22.5 to 30	N	N	N	**Y**	N	**Y**	N	N
Thaut 1996 walk with auditory cues OR walk without cues	no intervention	pre and post mean and SD	37	71.1 ± 7.0	mild to moderate	ON	home/ community, individual	3	10.5 10.5	N N	**Y** N	N N	N N	N N	N N	**Y** **Y**	N N

ROM, range of movement; **Y**, yes; N, no; U, unclear - insufficient information to categorize; [a] , part 2 of trial only; SAFEx, sensory attention focused exercise; Highly-challenging balance training, intervention described as involving all of: movement of the centre of mass, narrowing of the base of support and minimizing upper limb support; Task training (cueing), the use of cues specifically mentioned; Fitness training, aimed to maintain heart rate at 60% or more of maximum heart rate; Task training (movement strategy), the practice of strategies to facilitate functional movement specifically mentioned; Strength training, intervention described as involving added resistance to exercise; Stretching/ROM exercises, short or long duration stretches and/or range of movement exercises were specifically mentioned; Walking over ground/exercises, a walking program or walking exercises specifically mentioned; Walking treadmill, walking on a treadmill specifically mentioned

TABLE 2. *Review authors' judgments for the Cochrane risk of bias checklist[24] for the 16 trials included in the review*

First author and year	Outcomes of interest for meta-analysis	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?
Ashburn 2007		Y	Y		Y	Y
	Berg Balance Score			Y		
	Falls			Y		
	Functional Reach			Y		
	Sit to stand time*			Y		
	Timed Up and Go*			Y		
Blackinton 2002		U	U		U	U
	Functional Reach			Y		
	Gait velocity (preferred pace)			Y		
	Single leg stand time			Y		
	Timed Up and Go (expanded)			Y		
	Sit to stand time*			Y		
Caglar 2005		N	U		Y	U
	Gait velocity (preferred pace)			Y		
	Number of steps (preferred pace)			Y		
	Turn time			Y		
Cakit 2007		U	U		U	U
	Berg Balance Score			U		
	Gait velocity (maximal pace on treadmill)			U		
Ellis 2005 (duplicated in de Goede 2004)		Y	N		Y	U
	Gait velocity (preferred pace on treadmill)			Y		
Fisher 2008		Y	Y		Y	U
	Cadence (preferred pace)			Y		
	Gait velocity (preferred pace)			Y		
	Stride length (preferred pace)			Y		
	Sit to stand time*			Y		
Hackney 2008		Y	U		Y	U
	Berg Balance Score			Y		
	Gait velocity (preferred pace)			Y		
	Single leg stand time			Y		
	Stride length (preferred pace)			Y		
	Timed Up and Go			Y		
Hackney 2009		Y	U		Y	U
	Berg Balance Score			Y		
	Gait velocity (pace not reported)			Y		
	Stride length (pace not reported)			Y		
	Timed Up and Go			Y		
Kurtais 2008		U	U		Y	U
	Gait velocity (preferred pace)			Y		
	Single leg stand time			Y		
	Sit to stand time			Y		
	Turn time			Y		
Lehman 2005[a]		U	U		Y	U
	Step length (preferred pace)			U		
Mak 2008		Y	U		Y	U
	Sit to stand time			Y		
Nieuwboer 2007		Y	Y		Y	U
	Cadence (preferred pace)			Y		
	Falls			U		
	Functional Reach			Y		
	Gait velocity (preferred pace)			Y		
	Step length (preferred pace)			Y		
	Single leg stand time			Y		
	Timed Up and Go			Y		
Protas 2005		U	U		Y	U
	Cadence (fast pace)			Y		
	Gait velocity (fast pace)			N		
	Stride length (fast pace)			Y		
	Falls*			Y		
Sage 2009		U	U		U	U
	Cadence (preferred pace)			N		
	Gait velocity (preferred pace)			N		
	Step length (preferred pace)			N		
	Timed Up and Go			N		
Schenkman 1998		U	U		U	N
	Functional Reach			N		
	Gait velocity (preferred pace)			N		
	Turn time			N		
Thaut 1996		U	U		Y	U
	Cadence (preferred pace)			U		
	Gait velocity (preferred pace)			U		
	Stride length (preferred pace)			U		

Y, yes; N, no; U, unclear; *, outcome unable to be included in a meta-analysis as no or insufficient data given; [a] , part 2 of trial only.

Balance-Related Activity Performance

Fifteen trials[14, 15, 18, 19, 21, 22, 52-57, 59-62] with outcomes associated with the performance of balance-related activities reported a total of 19 comparisons, involving 747 participants. The pooled estimate of the effect size was statistically significant in favour of intervention (Figure 2). There was evidence of small sample bias (Egger's test of the intercept B0 = 1.72, 95% CI 0.17 to 3.27, $t = 2.34$, degrees of freedom (df) = 17, $P = 0.016$). The funnel plot of precision and Hedges' g showed a disproportionate number of smaller studies with a larger positive effect suggesting some publication bias (available as Supporting Information on the website).

There was a moderate level of heterogeneity in the estimates ($I^2 = 51\%$, Q = 36.7, $df = 18$, $P = 0.006$). Meta-regression was used to investigate if differences in the total number of intervention hours and the presence of highly-challenging balance exercises contributed to this heterogeneity. Results showed that there was no association between the total number of intervention hours and the effect of intervention on performance of balance-related activities (effect of dose on Hedges' $g = -0.0002$, 95% CI -0.019 to 0.019, $P = 0.982$). There was a larger effect on balance-related activity performance in the 5 comparisons where interventions included highly-challenging balance exercises (Hedges' $g = 0.64$, 95% CI 0.14 to 1.15, $P = 0.015$) than in the 14 comparisons which did not, or where the content of the balance exercises was unclear (Hedges' $g = 0.24$, 95% CI -0.03 to 0.51, $P = 0.076$). However, the difference between the effects in these two groups of comparisons did not reach statistical significance (effect of highly-challenging balance training on Hedges' $g = 0.40$, 95% CI 0.17 to 0.97, $P = 0.158$). Sensitivity analysis showed that removing the comparisons in which the content of the balance training was unclear (Table 1) had minimal effect on this result (difference in Hedges' $g = 0.41$, 95% CI 0.25 to 1.07, $P = 0.201$).

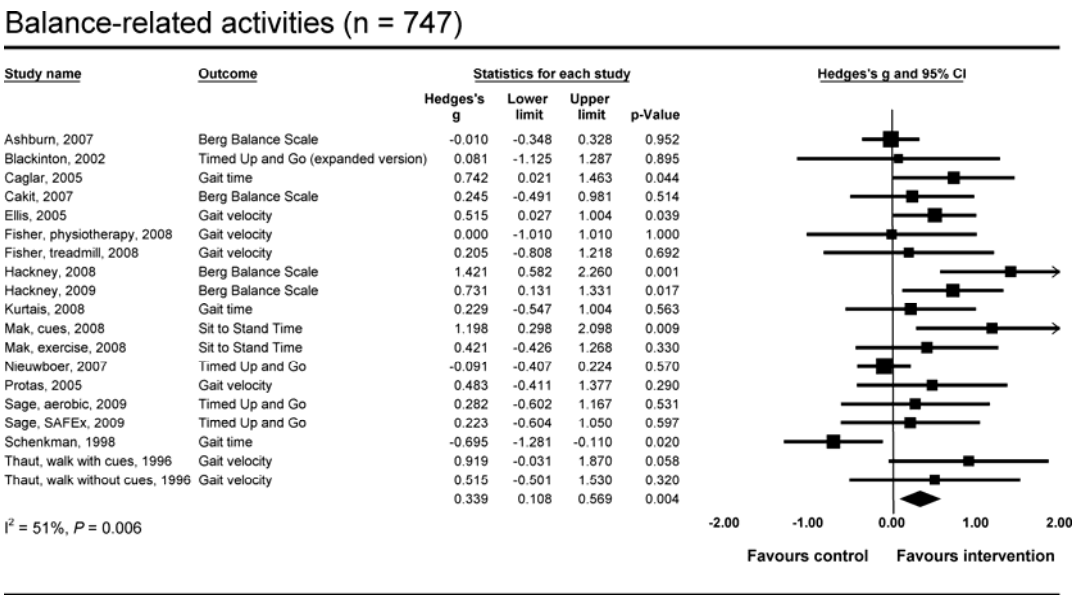

FIG. 2. Forest plot from the meta-analysis of exercise and motor training on measures of balance-related activity performance showing estimates of effect size with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

Falls

The proportion of fallers was reported in two trials,[14, 22] involving a total of 250 participants. There was no evidence of an effect from intervention (Figure 3), and there was a moderate level of heterogeneity in the estimates (I^2 = 49%, Q = 2.0, df = 1, P = 0.16).

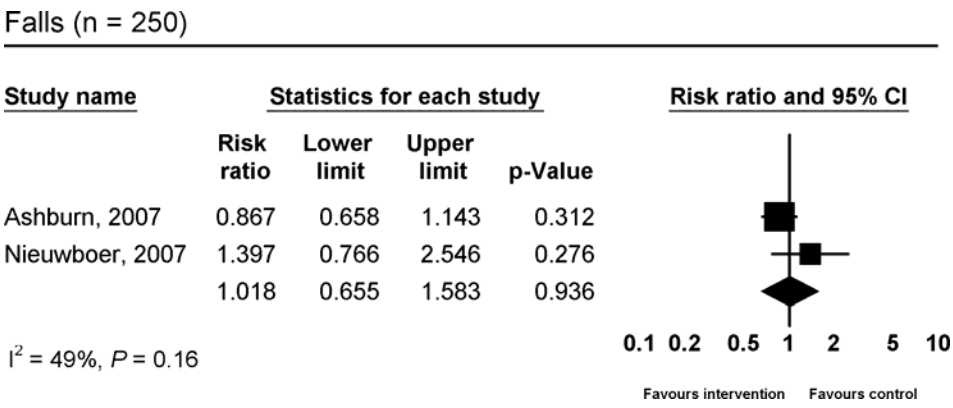

FIG. 3. Forest plot from the meta-analysis of exercise and motor training on falls showing estimates of effect size with 95% confidence intervals. Relative weight for each trial is indicated by the size of the corresponding square.

Secondary Outcome Measures

Forest plots and approximate mean differences for the Berg Balance Scale,[14, 18, 19, 21] Timed Up and Go,[18, 19, 22, 52, 60] turning time,[52, 53, 57, 61] sit to stand time,[57, 59] Functional Reach[14, 22, 52, 61] and single leg stand time[19, 22, 52, 57] are presented in Figure 4. The pooled estimates (Hedges' *g*) of effect size are all in the direction of showing favorable effects of intervention, however this favorable result only reached statistical significance for turning time (Figure 4C), representing a mean difference of approximately 1.3 s when turning 360 degrees.

Variation in the estimates was minimal for turning time (I^2 = 0%, Q = 0.74, *df* = 3, *P* = 0.90), Functional Reach (I^2 = 0%, Q = 2.983, *df* = 3, *P* = 0.39) and single leg stand time (I^2 = 0%, Q = 2.573, *df* = 3, *P* = 0.46). There were low to moderate levels of heterogeneity in the estimates of the effect of intervention on sit to stand time (I^2 = 37%, Q = 3.16, *df* = 2, *P* = 0.21) and Timed Up and Go (I^2 = 42%, Q = 8.7, *df* = 5, *P* = 0.12). The Berg Balance Scale estimates showed a high level of heterogeneity (I^2 = 75%, Q = 12.1, *df* = 3, *P* = 0.007).

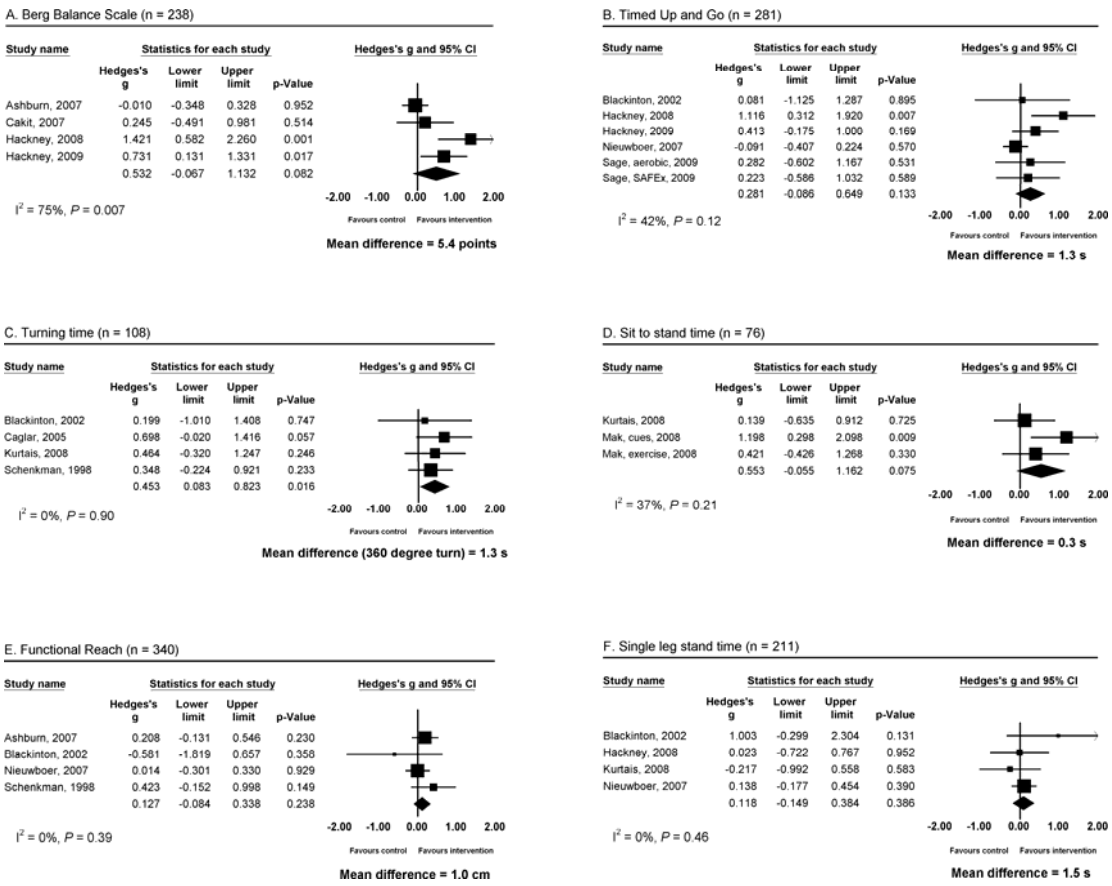

FIG. 4. Forest plots from the meta-analyses of exercise and motor training on secondary outcomes not relating to gait showing estimates of effect size with 95% confidence intervals and approximate mean differences. A. Berg Balance Scale; B. Timed Up and Go; C. turning time; D. sit to stand time; E. Functional Reach and F. single leg stand time. Relative weight for each trial is indicated by the size of the corresponding square.

Forest plots and approximate mean differences for the variables relating to gait are presented in Figure 5. The pooled estimates of the effect size for gait velocity/time[15, 18, 19, 21, 22, 52-57, 60-62] and step/stride length[15, 18, 19, 22, 53, 56, 58, 60, 62] were statistically significant in favor of intervention (Figure 5A and B). For gait velocity this represented an improvement with intervention of approximately 0.05 m/s at preferred pace, which translates to a 0.7 s improvement over 10 m (based on a preferred walk velocity of 0.845m/s). For step/stride length this represented an improvement in step length at preferred pace of approximately 3 cm. Similarly, there was a favorable trend towards a reduction in cadence[15, 22, 56, 60, 62] after intervention compared with control (Figure 5C). There was very little heterogeneity in the estimates of the effect of intervention on gait (gait velocity/time I^2 = 14%, Q = 17.46, df = 15, P = 0.29; step/stride length I^2 = 0%, Q = 6.07, df = 11, P = 0.87; cadence I^2 = 0%, Q = 3.499, df = 7, P = 0.84).

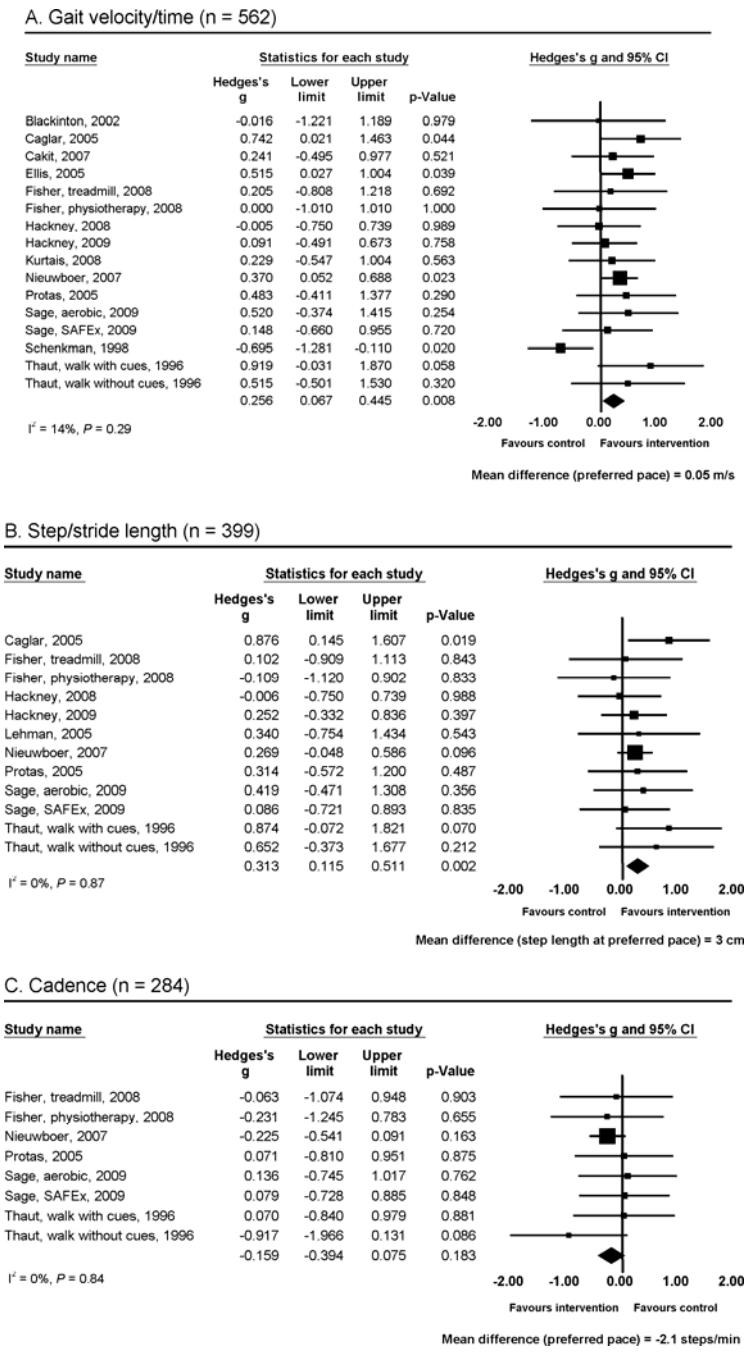

FIG. 5. Forest plots from the meta-analyses of exercise and motor training on secondary outcomes relating to gait showing estimates of effect size with 95% confidence intervals and approximate mean differences. A. gait velocity/time; B. step/stride length and C. cadence. Relative weight for each trial is indicated by the size of the corresponding square.

DISCUSSION

This systematic review provides evidence that exercise and motor training can improve performance of balance-related activities in people with PD. However, it remains unclear whether exercise and motor training can reduce falls in this population. Exercise and motor training were found to have a small positive effect on balance-related activity performance, gait velocity and step/stride length, as well as a moderate effect on turning time. The meta-regression results suggest that the inclusion of highly-challenging balance training may improve the efficacy of intervention on balance-related activity performance but this requires further investigation.

This is the first systematic review to conduct meta-analyses of the effect of exercise and motor training on the performance of balance-related activities. The results of this review uphold and quantify the results of the recent narrative review suggesting positive effects from exercise on balance in PD.[27] In the current review, the measure of balance-related activity performance included 15 trials with a total of 747 participants. While the overall quality of 8 of the included trials was unclear, the remaining 7 trials were of moderate to good quality (Table 2). However, the included trials do show some evidence of publication bias, with some small studies having a relatively large positive effect size. These results should therefore be interpreted cautiously and generalized only to people with mild to moderate PD.

There was no evidence from this review that exercise and motor training can reduce falls in people with PD. However, of the two trials included in the meta-analysis on falls, one did not include highly challenging balance exercises and did not aim to reduce falls,[22] while the type of balance training used in the other trial was unclear.[14] However, results of this review do suggest that exercise and motor training may improve balance, and balance is known to be an important risk factor for falls in this population.[2-4]

Furthermore, exercise has been shown to reduce falls in the general older population.[47, 63] For these reasons, further research is required to determine if falls can be prevented in people with PD.

As expected, there was a moderate to high level of heterogeneity in the meta-analyses of this review. We suggest that despite this heterogeneity, random effects meta-analysis is appropriate as all included studies had broadly similar outcomes and interventions, i.e. they targeted balance-related activities.[64] We used meta-regression to investigate whether this heterogeneity could be explained by differences in exercise program design and found an indication of a bigger effect of exercise on balance-related activity performance if highly-challenging balance training was included. However, this difference in the effect in trials with and without highly-challenging balance training did not reach statistical significance. There were not enough trials to conduct meta-regression analyses on the secondary outcome measures but the high level of heterogeneity in the Berg Balance Scale analysis may reflect the fact that of the four pooled trials, only two included highly-challenging balance training.[18, 19]

These results suggest that therapists should consider including highly-challenging balance training in exercise programs for people with PD. Although many forms of exercise and motor training improve the performance of balance-related activities in this population, exercise which specifically involves movement of the centre of mass, narrowing of the base of support and minimizing upper limb support may produce the best results. While this result is encouraging, the progressive nature of PD means that balance training would be required to be ongoing. Providing highly-challenging balance training in a sustainable way for this population is problematic as it is difficult to achieve the required level of challenge while maintaining safety in group or semi-supervised home-based programs. Future research working towards the development of

effective programs which are sustainable for the long term would be an important step in solving this problem.

Most of the effect sizes found in these meta-analyses were small to moderate (Hedges' g = 0.2 to 0.5) but do represent a meaningful improvement in the outcome measure (e.g. a 0.05 m/s improvement in gait velocity has been shown to be meaningful in older adults.)[65] Larger effects have been found to occur with more intense interventions following stroke[66] and in the general older population,[47] and this may also be true of people with PD. Trials included in the current review averaged 18 hours of intervention over 7 weeks. This overall low dose of intervention may also explain why the total dose of exercise was not associated with the effect of intervention on performance of balance-related activities. Future research needs to examine the effect of using a higher dose of intervention on balance outcomes and the performance of balance-related activities.

In conclusion, exercise and motor training can improve the performance of balance-related activities in people with PD. We recommend that highly-challenging balance exercises be part of rehabilitation programs for people with PD. It is now important to develop effective, sustainable programs that people with PD can participate in for the long term, and to assess the effect of these programs on falls rates. The development of such programs may have a widespread and ongoing impact in improving the quality of life of people with PD and their families as well as easing demands on healthcare systems.

AUTHORS' ROLES

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Allen: 1A, 1B, 1C, 2A, 2B, 3A, 3B; **Sherrington:** 1A, 1B, 1C, 2A, 2B, 3B; **Paul:** 1C, 2C, 3B; **Canning:** 1A, 1B, 1C, 2A, 2C, 3B.

FULL FINANCIAL DISCLOSURE

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Stock ownership in medically related fields - none

Intellectual property rights - none

Consultancies - none

Expert testimony - none

Advisory boards -none

Employment -none

Partnerships -none

Contracts - none

Honoraria -none

Royalties -none

Grants - none

Other:

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The University of Sydney Faculty of Health Sciences Postgraduate Research Scholarship

The George Burniston-Cumberland Foundation Fellowship

The Parkinson's NSW Research Student Award

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Partnerships - none

Contracts - none

Honoraria - none

Royalties – Cambridge University Press (book called Falls in Older People)

Grants:

Sherrington C. NHMRC Senior Research Fellowship, 2010 – 2014, $508,000, (ID 632 929)

Paul SS, Canning CG, **Sherrington C**, Fung VSC. Leg muscle power and balance-demanding activities in people with Parkinson's disease. The Physiotherapy Research Foundation. 2010-2011 $9,598

Cameron ID, Crotty M, Grey L, Kurrle S, Luscz M, Scuffham P, Whitehead C, Lord S, Giles L, Halbert J, **Sherrington C**, Bartlett H, Rungie M, Hudd S. Transition care: innovation and evidence. NHMRC Health Services Research Grant, 2006-2010, $2,900,000. (ID 402791)

Canning C, **Sherrington C**, Lord SR, Fung V, Close JC, Latt M. Exercise therapy for prevention of falls in people with Parkinson's disease: a randomised controlled trial. NHMRC Project Grant, 2008-2010, $574,000. (ID 512326)

Lord SR, Sturnieks D, Fitzpatrick R, Rogers M, **Sherrington C.** Impaired stepping as a risk factor for falls in older people. NHMRC Project Grant 2008-2010, $541,650. (ID: 510110)

Sherrington C, Clemson L, Lord SR, Howard K, Moseley AM, Vogler CM. Exercise self-management to improve long-term functioning and prevent falls after hip fracture. NHMRC Project Grant 2009-2012, $809,875 (2009 $190,750; 2010 $255,500; 2011 $270,250; 2012 $93,375), (ID 570886)

Lord SR, Smith ST, **Sherrington C.** A novel, home-based volitional step training program for fall prevention. NHMRC Project Grant 2009-2011, $286,450 (2009 $114,250; 2010 $84,500; 2011 $87,700) (ID 568724)

Herbert RD, Moseley AM, Maher CG, **Sherrington C,** Elkins MR. PEDro Supporting decisions about physiotherapy with high quality evidence. Motor Accidents Authority of New South Wales. 2008 $68,248, 2009 $68,248, 2010 $68,248

Other – none

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Contracts - none

Honoraria - none

Royalties - none

Grants:

Canning CG, Sherrington C, Lord SR, Fung V, Close JC, Latt M. Exercise therapy for prevention of falls in people with Parkinson's disease: a randomised controlled trial. NHMRC Project Grant 2008-2010, $574,000. (ID 512326)

Paul SS, **Canning CG**, Sherrington C, Fung VSC. Leg muscle power and balance-demanding activities in people with Parkinson’s disease. The Physiotherapy Research Foundation. 2010-2011 $9,598

Other - none

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Appendix – Online Supplementary Information

SEARCH STRATEGIES

Search filters developed by the Scottish Intercollegiate Guidelines Network (SIGN; http://www.sign.ac.uk/methodology/filters.html) to identify randomized trials were included in the search strategies. There were no restrictions on language or publication date.

Search Strategy: MEDLINE (1950 to present) (OVID)

1 Parkinson's disease.mp. or exp Parkinson Disease/
2 (Parkinson$ adj1 disease).mp.
3 1 or 2
4 exp Accidental Falls/
5 fall$.mp.
6 exp Exercise/
7 rehabilitation.mp. or exp Rehabilitation/
8 exp "Physical Therapy (Specialty)"/ or exp Physical Therapy Modalities/ or physical therapy.mp.
9 exp Postural Balance/
10 exp Resistance Training/
11 exp Motor Activity/
12 exp Cues/
13 exercis$.mp.
14 train$.mp.
15 therap$.mp.
16 physiother$.mp.
17 physical ther$.mp.
18 balanc$.mp.
19 strength$.mp.
20 11 or 7 or 17 or 18 or 16 or 13 or 6 or 9 or 12 or 14 or 15 or 8 or 4 or 10 or 19 or 5
21 3 and 20
22 exp Deep Brain Stimulation/
23 exp Drug Evaluation/
24 exp Drug Approval/
25 exp Antiparkinson Agents/
26 exp Stem Cells/
27 exp Gene Therapy/
28 exp Alzheimer Disease/
29 27 or 25 or 22 or 28 or 24 or 26 or 23
30 21 not 29
31 randomized controlled trials as topic/
32 randomized controlled trial/
33 random allocation/
34 double-blind method/
35 Single-Blind Method/
36 clinical trial/
37 exp clinical trials as topic/

38 (clinic$ adj trial$1).tw.
39 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
40 placebos/
41 placebo$.tw.
42 randomly allocated.tw.
43 (allocated adj2 random).tw.
44 35 or 33 or 32 or 39 or 40 or 36 or 41 or 42 or 38 or 34 or 37 or 43 or 31
45 30 and 44
46 limit 45 to humans

Search Strategy: EMBASE (1980 to present) (OVID)

1 Parkinson's disease.mp. or exp Parkinson disease/
2 (Parkinson$ adj1 disease).mp.
3 1 or 2
4 exp falling/
5 fall$.mp.
6 exp exercise/ or exp treadmill exercise/ or exp leg exercise/
7 exp kinesiotherapy/
8 rehabilitation.mp. or exp rehabilitation/
9 physiotherapy.mp. or exp physiotherapy/
10 exp physical education/
11 exp balance disorder/
12 exp body equilibrium/
13 exp "physical activity, capacity and performance"/
14 exp muscle strength/
15 exp motor activity/
16 exp motor control/
17 exp association/
18 exercis$.mp.
19 train$.mp.
20 therap$.mp.
21 physiother$.mp.
22 "physical ther$".mp.
23 balanc$.mp.
24 strength$.mp.
25 11 or 21 or 7 or 17 or 22 or 18 or 23 or 16 or 13 or 6 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 24 or 10 or 19 or 5
26 25 and 3
27 exp brain depth stimulation/
28 exp drug analysis/
29 exp drug research/
30 exp drug approval/ or exp drug monitoring/
31 exp antiparkinson agent/
32 exp stem cell/
33 exp gene therapy/
34 exp Alzheimer disease/
35 27 or 33 or 32 or 28 or 34 or 30 or 29 or 31
36 26 not 35
37 clinical trial/
38 randomized controlled trial/
39 exp randomization/
40 single blind procedure/
41 double blind procedure/
42 crossover procedure/
43 placebo/
44 randomi?ed controlled trial$.tw.
45 RCT.tw.

46 random allocation.tw.
47 randomly allocated.tw.
48 allocated randomly.tw.
49 (allocated adj2 random).tw.
50 single blind$.tw.
51 double blind$.tw.
52 ((treble or triple) adj blind$).tw.
53 placebo$.tw.
54 prospective study/
55 53 or 48 or 42 or 46 or 44 or 50 or 39 or 40 or 51 or 41 or 47 or 38 or 52 or 49 or 37 or 45 or 43 or 54
56 36 and 55
57 limit 56 to human

Search Strategy: AMED (1985 to present) (OVID)

1 exp Parkinson disease/ or Parkinson's disease.mp.
2 (Parkinson$ adj1 disease).mp.
3 1 or 2
4 exp Exercise/ or exp Rehabilitation/
5 physical therapy.mp.
6 physiotherapy.mp.
7 exp Kinematics/
8 exp Accidental falls/
9 fall$.mp.
10 exp Resistance training/
11 exp Motor skills/
12 exp Cues/
13 exercis$.mp.
14 train$.mp.
15 therap$.mp.
16 physiother$.mp.
17 physical ther$.mp.
18 balanc$.mp.
19 strength$.mp.
20 11 or 7 or 17 or 18 or 16 or 13 or 6 or 9 or 12 or 14 or 15 or 8 or 4 or 10 or 19 or 5
21 3 and 20
22 exp Neurosurgery/
23 deep brain stimulation.mp.
24 exp Drug therapy/
25 exp Antiparkinson agents/
26 exp germ cells/
27 exp gene therapy/
28 exp Alzheimers disease/
29 27 or 25 or 22 or 28 or 24 or 26 or 23
30 21 not 29
31 exp Clinical trials/
32 exp Randomized controlled trials/
33 exp Double blind method/
34 exp Placebos/
35 exp Random allocation/
36 exp Comparative study/
37 (clinical trial$ or randomi$ed controlled trial or controlled clinical trial).pt.
38 (crossover or cross-over or cross over).tw.
39 (random$ or placebo$ or (clin$ adj1 trial$)).ab,ti.
40 ((singl$ or doubl$ or trebl$ or tripl$) adj1 (blind$ or mask$)).ab,ti.
41 35 or 33 or 32 or 39 or 40 or 36 or 38 or 34 or 37 or 31
42 30 and 41

Search Strategy: PsycINFO (1806 to present) (OVID)

1 Parkinson's disease.mp. or exp Parkinsons Disease/
2 (Parkinson$ adj1 disease).mp.
3 1 or 2
4 exp Falls/
5 fall$.mp.
6 exp Physical Activity/
7 exp Rehabilitation/ or rehabilitation.mp.
8 physical therapy.mp. or exp Physical Therapy/
9 exp Equilibrium/
10 exp Athletic Training/ or exp Training/
11 exp Physical Strength/
12 exp Physical Fitness/
13 exp Motor Coordination/
14 exp Perceptual Motor Learning/
15 exp Cues/
16 exercis$.mp.
17 train$.mp.
18 therap$.mp.
19 physiother$.mp.
20 physical ther$.mp.
21 balanc$.mp.
22 strength$.mp.
23 11 or 21 or 7 or 17 or 22 or 18 or 16 or 13 or 6 or 9 or 12 or 20 or 14 or 15 or 8 or 4 or 10 or 19 or 5
24 3 and 23
25 exp Electrical Brain Stimulation/
26 exp Drug Therapy/
27 antiparkinson agent.mp.
28 exp Stem Cells/
29 exp Gene Therapy/
30 exp Alzheimers Disease/
31 27 or 25 or 28 or 30 or 26 or 29
32 24 not 31
33 exp Placebo/
34 exp Experiment Controls/
35 exp Clinical Trials/
36 (crossover or cross-over or cross over).tw.
37 (random$ or placebo$ or (clin$ adj1 trial$)).ab,ti.
38 35 or 33 or 34 or 36 or 37
39 38 and 32
40 limit 39 to human

Search Strategy: Cochrane Central Register of Controlled Trials (dates not provided) (OVID)

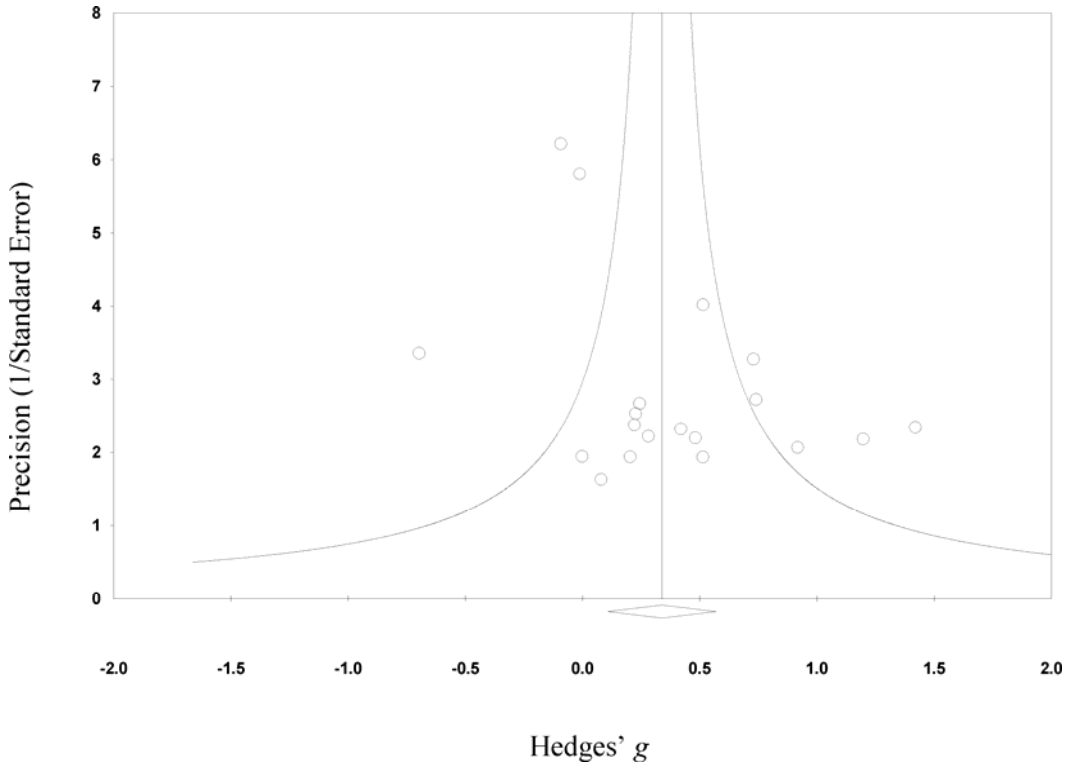
1 Parkinson's disease.mp. or exp Parkinson Disease/
2 (Parkinson$ adj1 disease).mp.
3 1 or 2
4 exp Exercise Movement Techniques/
5 exp Rehabilitation/
6 exp Physical Therapy Modalities/ or physical therapy.mp.
7 exp Accidental Falls/
8 fall$.mp.
9 exp musculoskeletal equilibrium/
10 exp Muscle Strength/
11 exp Motor Activity/
12 exp Cues/
13 exercis$.mp.
14 train$.mp.
15 therap$.mp.
16 physiother$.mp.
17 physical ther$.mp.
18 balanc$.mp.
19 strength$.mp.
20 11 or 7 or 17 or 18 or 16 or 13 or 6 or 9 or 12 or 14 or 15 or 8 or 4 or 10 or 19 or 5
21 3 and 20
22 exp Deep Brain Stimulation/
23 exp Drug Evaluation/
24 exp Antiparkinson Agents/
25 exp Stem Cells/
26 exp Gene Therapy/
27 exp Alzheimer Disease/
28 27 or 25 or 22 or 24 or 26 or 23
29 21 not 28

Search Strategy: CINAHL (1982 to present) (EBSCO)

S1	("Parkinson's disease") or (MH "Parkinson Disease")
S2	""Parkinson* disease""
S3	S1 or S2
S4	(MH "Accidental Falls")
S5	""fall*""
S6	(MH "Exercise+")
S7	(MH "Rehabilitation+")
S8	(MH "Physical Therapy+")
S9	(MH "Balance Training, Physical") or (MH "Balance, Postural")
S10	(MH "Posturography")
S11	(MH "Therapeutic Exercise+") or (MH "Exercise Therapy: Ambulation (Iowa NIC)") or (MH "Exercise Therapy: Balance (Iowa NIC)") or (MH "Exercise Therapy: Joint Mobility (Iowa NIC)") or (MH "Exercise Therapy: Muscle Control (Iowa NIC)")
S12	(MH "Motor Activity+") or (MH "Motor Skills+")
S13	(MH "Cues")
S14	(MH "Physical Fitness+")
S15	""exercis*""
S16	""train*""
S17	""therap*""
S18	""physiother*""
S19	""physical ther*""
S20	""balanc*""
S21	""strength*""
S22	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21
S23	S3 and S22
S24	(MH "Deep Brain Stimulation")
S25	(MH "Antiparkinson Agents+")
S26	(MH "Stem Cells+")
S27	(MH "Gene Therapy")
S28	(MH "Alzheimer's Disease")
S29	S24 or S25 or S26 or S27 or S28
S30	S23 not S29
S31	(MH "Clinical Trials+")
S32	PT clinical trial
S33	(MH "Placebos")
S34	(MH "Random Assignment")
S35	(MH "Control Group")
S36	(MH "Crossover Design")
S37	""randomi*ed control* trial*""
S38	""singl* blind*""
S39	""doubl* blind*""
S40	""tripl* blind*""
S41	""trebl* blind*""
S42	""singl* mask*""

S43 ""doubl* mask*""
S44 ""tripl* mask*""
S45 ""trebl* mask*""
S46 "random*"
S47 ""placebo*""
S48 ""clin* trial""
S49 S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48
S50 S30 and S49
S51 (MH "Animals+")
S52 S50 not S51

FUNNEL PLOT ASSESSING PUBLICATION BIAS



Supplemental FIG. 1. Funnel plot of precision by Hedges' *g* for meta-analysis of the effect of exercise and motor training on balance-related activity performance.

CHAPTER 4

Bradykinesia, muscle weakness and reduced muscle power in Parkinson's disease

Chapter 4 has been published as:

Allen NE, Canning CG, Sherrington C, Fung VSC (2009) Bradykinesia, muscle weakness and reduced muscle power in Parkinson's disease. *Movement Disorders* 24(9): 1344-1351.

A supplementary file (Methods used to measure muscle strength and power) was published online with this publication. It is placed as an appendix at the end of this chapter.

Statement from co-authors confirming authorship contribution of the PhD candidate

As co-authors of the paper *Bradykinesia, muscle weakness and reduced muscle power in Parkinson's disease*, we confirm that Natalie Elizabeth Allen has made the following contributions:

- conception, organisation and execution of the research
- analysis and interpretation of the findings
- writing the paper and critical appraisal of content
- revising the paper for important intellectual content

Colleen G Canning _____ Date: 8/9/10

Catherine Sherrington _____ Date: 16/9/10

Victor SC Fung _____ Date: 8.9.10

The published paper and online supplementary file were included in the thesis here.

CHAPTER 5

Reduced muscle power is associated with slower walking velocity and falls in people with Parkinson's disease

Chapter 5 has been published as:

Allen NE, Sherrington C, Canning CG, Fung VSC (2010) Reduced muscle power is associated with slower walking velocity and falls in people with Parkinson's disease. *Parkinsonism and Related Disorders* 16(4):261-264.

Unpublished findings from this study are placed as an appendix at the end of this chapter. They were not included in the publication due to the journal's word count limitations.

Statement from co-authors confirming authorship contribution of the PhD candidate

As co-authors of the paper *Reduced muscle power is associated with slower walking velocity and falls in people with Parkinson's disease*, we confirm that Natalie Elizabeth Allen has made the following contributions:

- conception, organisation and execution of the research
- analysis and interpretation of the findings
- writing the paper and critical appraisal of content
- revising the paper for important intellectual content

Catherine Sherrington _____ Date: 16/9/10

Colleen G Canning _____ Date: 8/9/10

Victor SC Fung _____ Date: 8.9.10

The published paper was included in the thesis here.

Appendix - Unpublished findings

Introduction

Some details of the statistical analysis conducted for this project were unable to be included in the journal article due to the journal's word count limitations. These additional details include further results of the regression analysis analysing associations between muscle power/strength and walking velocity as well as muscle power/strength and past falls. Additionally, a regression analysis of the associations between asymmetry of leg extensor muscle power/strength and past falls is presented.

Asymmetry of muscle power appears to be an important risk factor for falls in the general older population.[1,2] Many people with Parkinson's disease present with asymmetrical symptoms. However, it remains undetermined if asymmetry of lower limb extensor muscle strength or power is predictive of falls in people with Parkinson's disease. Consequently we aimed to determine if there is an association between asymmetry of leg extensor muscle strength or power and falls in people with Parkinson's disease.

Methods

The methods used for this study have been described in Chapters 4 and 5. Muscle strength and peak power asymmetry were measured as the difference between the legs as a percentage of the stronger leg.

Statistical Analysis

Associations between muscle strength / peak power asymmetry and past falls were explored using univariate logistic regression models. Participants were categorised as

having had 0-1 falls or multiple falls (≥ 2 falls). Muscle strength and peak power asymmetry were dichotomised into two equal groups to give a "low" and "high" grouping for each variable. Data were analysed using SPSS statistical software (Version 14, Chicago IL).

Results

Associations between UPDRS motor score and strength/power

Only 3% of the variability in muscle strength was explained by UPDRS motor score ($p = 0.268$, $R^2 = 0.03$). UPDRS motor score explained 6-9% of the variability in muscle power (peak power p=0.14, $R^2 = 0.06$, power at 30% 1RM $p = 0.06$, $R^2 = 0.09$).

Associations between strength/power and walking velocity

Muscle power explained up to 33% of the variance in comfortable walking velocity, but up to 54% of the variance in maximal walking velocity. Muscle power was a greater predictor of walking velocity than muscle strength at both walking velocities (Table 1). For comfortable walking velocity, the UPDRS motor score explained 6-11% more variability than muscle power. For maximal walking velocity the opposite was true, with 19-23% more variance explained by muscle power than the UPDRS. Age and height both explained less variance than muscle strength, power or the UPDRS motor score for both walking velocities.

Maximal power at 30% 1RM explained more of the variance in both comfortable and maximal walking velocities than peak power. For this reason, maximal power at 30%1RM was used for the remaining analysis of walking velocity.

Table 1. *Associations between predictor variables and walking velocity from univariate linear regression models*

	R^2 (p)	Coefficient (95% CI)	SD of predictor variable	Change in 10m velocity (m/s) per SD
Comfortable walking velocity				
Leg power at peak power (W)	0.28 (0.001)	0.0007 (0.0003 to 0.0011)	186.3	0.14
Leg power at 30% 1RM (W)	0.33 (<0.001)	0.001 (0.0005 to 0.0014)	150.8	0.15
Leg strength (N)	0.26 (0.001)	0.0004 (0.0002 to 0.0007)	305.7	0.13
UPDRS motor	0.39 (<0.001)	-0.0169 (-0.0238 to -0.01)	9.52	-0.16
Age (y)	0.04 (0.2)	-0.0068 (-0.0173 to 0.0038)	7.83	-0.05
Height (m)	0.14 (0.02)	1.0379 (0.1792 to 1.8967)	0.09	0.09
Maximal walking velocity				
Leg power at peak power (W)	0.50 (<0.001)	0.0014 (0.001 to 0.0019)	186.3	0.27
Leg power at 30% 1RM (W)	0.54 (<0.001)	0.0018 (0.0013 to 0.0024)	150.8	0.28
Leg strength (N)	0.43 (<0.001)	0.0008 (0.0005 to 0.0011)	305.7	0.25
UPDRS motor	0.31 (<0.001)	-0.0219 (-0.0327 to -0.011)	9.52	-0.21
Age (y)	0.12 (0.03)	-0.017 (-0.0318 to -0.0021)	7.83	-0.13
Height (m)	0.24 0.001	2.0243 (0.8417 to 3.207)	0.09	0.19

CI, confidence interval; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; 1RM, 1 repetition maximum

When a second predictor variable was added to the models (Table 2), the model explaining the largest amount of variance in walking velocity included leg muscle power and UPDRS motor score, explaining 66% of the variance in maximal walking velocity. The associations between muscle power/strength and walking velocity remained statistically significant at both walking velocities after adjusting for UPDRS motor score. The adjusted models show a one standard deviation change in muscle power at 30% 1RM produced a larger change in 10m velocity than a one standard deviation change in muscle strength at maximal walking velocity.

The associations between muscle power/strength and walking velocity also remained statistically significant after adjusting for age or height. Neither age nor height made a significant independent contribution in the multivariate models.

Table 2. *Associations between predictor variables and walking velocity from multivariate linear regression models*

	Model R^2 (Model p)	Coefficients of predictor variables (95% CI)	p of predictor variables	SD of predictor variables	Change in 10m velocity (m/s) per SD
Comfortable walking velocity					
Leg power at 30% 1RM (W) adjusted for UPDRS motor	0.56 (<0.001)	0.0007 (0.0003 to 0.0011)	0.001	150.75	0.11
		-0.0134 (-0.0197 to -0.0071)	<0.001	9.52	-0.13
Leg strength (N) adjusted for UPDRS motor	0.56 (<0.001)	0.0003 (0.0002 to 0.0005)	0.001	305.67	0.11
		-0.0149 (-0.021 to -0.0088)	<0.001	9.52	-0.14
Maximal walking velocity					
Leg power at 30% 1RM (W) adjusted for UPDRS motor	0.66 (<0.001)	0.0016 (0.0011 to 0.0021)	<0.001	150.75	0.24
		-0.0144 (-0.0225 to -0.0063)	0.001	9.52	-0.14
Leg strength (N) adjusted for UPDRS motor	0.62 (<0.001)	0.0007 (0.0005 to 0.001)	<0.001	305.67	0.22
		-0.0178 (-0.0261 to -0.0096)	<0.001	9.52	-0.17

CI, confidence interval; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; 1RM, 1 repetition maximum

Associations between strength/power and falls

Participants with low peak power or low maximal power at 30% 1RM were 6 times more likely to have experienced multiple falls in the past year than participants with high power measurements (Table 3). Participants with a high UPDRS motor score were also 6 times more likely to have experienced multiple falls in the past year than participants with a low UPDRS motor score. There was an association between low strength and past multiple falls, but this did not reach statistical significance. There was no association between older age and past multiple falls.

In multivariate models, the association between power and falls was not statistically significant after adjustment for UPDRS motor score (low maximal power at 30% 1RM, OR = 1.0, 95% CI 0.99 to 1.0, p=0.09). However UPDRS motor score continued to have an independent relationship with falls (high UPDRS motor score, OR = 1.1, 95% CI 1.0 to 1.3, p=0.028) in the model with both power at 30% 1RM and UPDRS motor score as predictor variables. In contrast, the association between power and falls remained statistically significant after adjustment for age (low maximal power at 30% 1RM OR = 5.9, 95% CI 1.05 to 33.03, p=0.04), which did not make an important contribution to the model (OR = 1.0, 95% CI 0.9 to 1.1, p = 0.86).

Table 3. *Associations between dichotomized predictor variables and multiple falls in the past year from univariate logistic regression models*

Dichotomized Predictors	Odds Ratio (95% CI)	*P*
Low peak power	6.0 (1.08 to 33.27)	0.04
Low maximal power at 30% 1RM	6.0 (1.08 to 33.27)	0.04
Low strength	3.1 (0.66 to 14.14)	0.15
High UPDRS motor score	6.0 (1.08 to 33.27)	0.04
Older age	1.0 (0.24 to 4.18)	1.0

CI, confidence interval; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; 1RM, 1 repetition maximum

Strength measured in Newtons, Power measured in Watts.

Association between asymmetry of muscle strength/peak power and falls

No clear conclusion could be reached about the association between high strength asymmetry and high peak power asymmetry and past multiple falls (Table 4).

Table 4. *Associations between dichotomised predictor variables and multiple falls in the past year from univariate logistic regression models*

Dichotomised Predictors	Odds Ratio (95% CI)	*P*
High peak power asymmetry	1.7 (0.4 to 7.34)	0.47
High strength asymmetry	1.7 (0.4 to 7.34)	0.47

CI, confidence interval

Power measured in Watts, Strength measured in Newtons.

Asymmetry measured as the difference between the legs as a percentage of the stronger leg.

Conclusion

Additional unpublished detail of the regression analyses has been presented. Given the low association between the UPDRS motor score and muscle power and the fact that the UPDRS eliminates the association between muscle power and past falls, it is likely that other factors contributing to the UPDRS motor score are more strongly associated with past falls.

In the present study there was no evidence for an association between falls and leg extensor muscle strength or peak power asymmetry in people with Parkinson's disease. The sample size of the present study may have been too small to detect these

relationships and so the possibility of an association between falls and muscle strength or power asymmetry should not be discounted.

References

1. Skelton DA, Kennedy J, Rutherford OM (2002) Explosive power and asymmetry in leg muscle function in frequent fallers and non-fallers aged over 65. *Age and Ageing* 31: 119-125.
2. Portegis E, Sipila S, Pajala S, Lamb SE, Alen M, Kaprio J, Koskenvuo M, Rantanen T (2006) Asymmetrical lower extremity power deficit as a risk factor for injurious falls in healthy older women. *Journal of the American Geriatrics Society* 54(3): 551-553.

CHAPTER 6

Conclusion

OVERVIEW

This thesis reports the results of three studies that were conducted with the broad aim of evaluating and exploring interventions with the potential to reduce fall risk in people with Parkinson's disease. The aim of the first study was to compare a six-month exercise program which targeted potentially remediable risk factors for falls with usual care in a randomised controlled trial involving people with Parkinson's disease who had fallen or were at risk of falling (Chapter 2). Participants randomised to the exercise group showed a 7% (not statistically significant) reduction in fall risk, though the clinical relevance of this small reduction is unclear. The exercise group did, however, display improvements in freezing of gait and sit to stand time, as well as trends towards improvement in knee extensor muscle strength, fast walking speed and fear of falling. These outcomes were achieved safely at home using a pragmatic, minimally-supervised exercise program, with no exercise participants falling while carrying out the exercises.

The aim of the second study was to rigorously examine the current evidence for the effectiveness of exercise and motor training on the performance of balance-related activities in people with Parkinson's disease via a systematic review with meta-analyses (Chapter 3). The review found evidence that exercise and motor training can improve performance of balance-related activities in people with Parkinson's disease. Furthermore, it appears that the inclusion of highly-challenging balance training may enhance the effect of intervention on the performance of balance-related activities. However, further research is required to determine if exercise and motor training can reduce falls in people with Parkinson's disease.

The final study had two parts which were presented separately (Chapters 4 and 5). The aims of the first part were to determine if people with mild to moderate Parkinson's disease are weaker and/or less powerful than a neurologically-normal control group and to determine the relative contributions of force and movement velocity to muscle power in people with Parkinson's disease (Chapter 4). The leg extensor muscles of the Parkinson's disease group were 16% weaker and 22% less powerful than the control group. Muscle weakness was found to contribute to reduced muscle power at all loads. However, muscle power was disproportionately reduced at light to medium loads due to decreased movement speed, suggesting that bradykinesia (ie, slowed muscle contraction) was making an additional contribution to reduced power over and above weakness at light and medium, but not heavy, loads. This is likely to be important as many daily activities, including stepping to prevent a fall, appear to depend on the ability to use muscles quickly at light to medium loads.

The second part of the final study investigated the relationships between leg extensor muscle strength and power with walking speed and past falls in people with mild to moderate Parkinson's disease (Chapter 5). Muscle power was consistently found to explain as much or more of the variation in walking velocity, and was more strongly associated with past falls, than muscle strength. More than half the variance in walking velocity was explained by muscle power, and this association remained significant in models which included the severity of Parkinson's disease motor symptoms. Furthermore, participants with low muscle power were six times more likely to report multiple falls in the prior 12 months than those with high muscle power, though this association between falls and power was no longer significant in models which included the severity of Parkinson's disease motor symptoms. Sound leg extensor muscle power

therefore seems likely to be important for maximising mobility in people with Parkinson's disease, though its value in reducing falls requires further prospective investigation.

CLINICAL IMPLICATIONS AND SUGGESTIONS FOR FUTURE RESEARCH

Several important themes with implications for the provision of exercise programs and future research into exercise to reduce fall risk and prevent falls in people with Parkinson's disease arise from the work presented in this thesis. Firstly, targeted exercise may reduce overall fall risk and is able to improve muscle strength, freezing of gait and performance of balance-demanding activities in people with Parkinson's disease. However, the ability of exercise to reduce falls in this population remains unclear. Secondly, many people with Parkinson's disease who are at risk of falling but who have sufficient cognition are able to exercise safely at home. Finally, reduced muscle power is also likely to be a risk factor for falls and the effect of muscle power training on falls and fall risk warrants investigation.

The high prevalence of falls[1-5] and the persistence of falls despite advances in medical care[5-10] underscore the importance of the development of effective exercise interventions to reduce falls in people with Parkinson's disease. Work presented in this thesis suggests that exercise may reduce fall risk in Parkinson's disease by improving remediable fall risk factors, namely leg muscle strength, freezing of gait and balance. The exercise program employed in the randomised controlled trial (Chapter 2) resulted in the exercise group achieving a 7% (not statistically significant) reduction in fall risk, falling well short of the 20% reduction anticipated from studies with the general older population.[11, 12] However, the exercise group did show a strong trend towards an improvement in knee

extensor muscle strength using weighted vests and an improvement in freezing of gait using cueing intervention modelled on that described in the successful RESCUE trial.[13] The exercise program did not provide evidence for an improvement in standing and leaning balance, but did provide evidence for an improvement in the performance of balance-related activities, with significantly faster sit to stand time and a trend towards faster walking speeds. Furthermore, results from the systematic review (Chapter 3) confirmed that exercise, particularly highly-challenging balance exercise, can improve the performance of balance-related activities in people with Parkinson's disease. These results suggest that physiotherapists should prescribe carefully designed exercise programs that target these remediable fall risk factors for people with Parkinson's disease who are at risk of falling.

A limitation of the randomised controlled trial presented in Chapter 2 is the Parkinson's disease fall risk score that was used as the primary outcome measure. This fall risk score was designed to identify individuals at risk of falling[14] rather than detect change in fall risk. One consequence of this is that the score components are constrained, utilising knee extensor muscle strength of only the weaker leg, balance measured as coordinated stability and freezing of gait measured as a yes/no response. While the exercise group did show trends towards improvements in knee extensor muscle strength and significant improvements in freezing of gait, the strength improvement was largest for the stronger leg and the improvements in freezing of gait were detected using the Freezing of Gait Questionnaire,[15] as the yes/no response was not sensitive enough to detect this improvement. It is recommended that this fall risk score be re-examined and significantly modified before use as a primary outcome measure in future intervention studies.

There was a small amount of data missing from the randomised controlled trial (Chapter 2) as three intervention group participants dropped out and were unavailable for post-intervention testing. However, the treatment of missing outcome data in randomised trials is controversial and there are limitations of current imputation methods.[16] Thus it was decided a priori not to impute missing data.

While knee extensor muscle strength did show a trend towards improvement following the exercise intervention in the randomised controlled trial (Chapter 2), these improvements were small and did not reach statistical significance. This result may have been in part due to the use of a strain gauge to measure knee extensor muscle strength. While these tools were calibrated and are reliable,[17] they measure muscle strength on a relatively small scale and so might give less precise results than more sophisticated equipment, such as variable resistance machines, which measure strength on a larger scale (Study 3, Chapters 4 and 5). However, as the randomised controlled trial was a pragmatic, largely home-based trial, measurements were made in participants' homes, necessitating the use of portable equipment. It would be interesting for future work into the effects of pragmatic strength training with weighted vests to compare the amount of improvement measured with the strain gauge against that measured with a variable resistance machine.

The lack of improvement in standing and leaning balance after the exercise intervention employed in the randomised controlled trial (Chapter 2) was surprising and perplexing, particularly as measures of performance of balance-related activities did improve. This apparent lack of improvement in balance outcomes may have been due to the nature of

outcome measures. The balance outcome measures used are commonly used in people with Parkinson's disease and in the general older population for both research and clinical purposes. Furthermore, the coordinated stability test, postural sway and maximal balance range in standing have all recently been found to improve with exercise in older people following discharge from hospital.[12] However, these measures may be less suitable to detect improvements in people with Parkinson's disease. For example, while increased postural sway has been found to be associated with increased disease severity and increased fall risk,[18-22] people with Parkinson's disease can present with an abnormal increase *or* decrease in postural sway.[18, 23, 24] Similarly, coordinated stability and maximal balance range may be problematic measures in people with Parkinson's disease since people with Parkinson's disease have difficulty estimating their limits of stability.[25]

The measures used in the trials included in the systematic review presented in Chapter 3 may provide insights regarding outcome measures to be included in future intervention studies. The primary outcome measure of balance-related activity performance involved pooling one balance measure from each trial. The list of measures to pool for meta-analysis was derived by first listing all the balance-related outcome measures described in the included trials. This list was then examined and outcomes were placed in order of priority, with higher priority given to those outcomes the author considered to be the most global measures of balance or balance-related activity performance. The meta-analysis of this primary outcome measure did show that exercise and motor training can improve balance-related activity performance. The Berg Balance Scale[26] was given top priority in this list, and the meta-analysis of the Berg Balance Scale on its own (as a secondary outcome measure) showed a strong trend toward improvement after

intervention. The failure of the meta-analysis on the Berg Balance Scale to reach statistical significance is likely to be related to the high level of heterogeneity in the analysis, which may have been because only two of these trials included highly-challenging balance exercises. These results suggest that outcome measures that assess balance globally may be more useful for assessing the effects of intervention on balance in people with Parkinson's disease.

While it appears likely that exercise can reduce fall risk in Parkinson's disease, the effect of exercise on actual falls remains unclear. Few randomised controlled trials have reported the effect of exercise on falls in people with Parkinson's disease,[13, 27, 28] and the results of these studies do not provide evidence of an effect on fall rates. Fall risk scores and assessments of the effect of exercise on fall risk factors provides useful interim information that is likely to give an indication of the effect on falls themselves. The randomised controlled trial presented in this thesis (Chapter 2) showed a 7% (not statistically significant) reduction in fall risk, evidence for improvement in sit to stand time and freezing of gait and a trend towards an improvement in muscle strength. Furthermore, the systematic review with meta-analysis found that exercise and motor training can improve the performance of balance-related activities in people with Parkinson's disease. However, this review did not find any evidence that exercise and motor training can reduce falls in people with Parkinson's disease (Chapter 3). Ultimately, evidence of exercise leading to a decrease in falls is important to secure funds to implement ongoing exercise programs designed to reduce falls in this population. Further research is required to determine if the reduction in fall risk and improvement in fall risk factors reported in this thesis can translate into actual falls prevented. The study presented in Chapter 2 of this thesis has informed the

development of a larger trial, currently in progress, designed to determine the effect of exercise on falls in people with Parkinson's disease as well as the cost effectiveness of the exercise program from the health provider's perspective.[29]

There appears to be a dose-response relationship between exercise and falls in the general older population.[30] However, no evidence of such a relationship was found between the dose of exercise and motor training and improvement in balance-related activities in people with Parkinson's disease (Chapter 3). This finding may have been due to the overall low dose of intervention prescribed in the trials included in the meta-analysis (average 18 hours). Future research is needed to examine the effect of using a higher dose of intervention on the performance of balance-related activities.

People with Parkinson's disease require exercise programs that are not only effective, but are pragmatic, safe and sustainable. The work presented in this thesis provides evidence that people with Parkinson's disease who have fallen or who are at risk of falling are able to exercise safely at home (with the assistance of carers when needed) using a pragmatic, minimally-supervised exercise program that targets potentially remediable risk factors for falls (Chapter 2). However, caution must be taken when applying these results clinically. The randomised controlled trial presented in this thesis included only participants who had sufficient cognition, whose Parkinson's medications were stable and who did not have a co-existing medical condition that could make independent exercise unsafe. Furthermore, participants were monitored monthly and changes to their program (progressions or regressions) made accordingly. Therefore, while therapists can be encouraged that carefully designed home-based exercise programs can be prescribed for many people with Parkinson's disease, care needs to be

taken to ensure that the program is regularly reviewed and that the person with Parkinson's disease and their carer will be safe. The use of such pragmatic, sustainable exercise programs is important given the ongoing, degenerative nature of Parkinson's disease and the limitations of healthcare systems.

Effective yet safe balance exercises are particularly difficult to prescribe in a home-based, minimally-supervised program. The results of the systematic review and meta-analysis (Chapter 3) found that highly-challenging balance training is likely to result in the best improvements in the performance of balance-related activities in people with Parkinson's disease. Such exercises involve movement of the centre of mass, narrowing of the base of support and minimisation of upper limb support. Furthermore, reactive balance training (responding to unexpected perturbations) may prove beneficial for people with Parkinson's disease.[27, 31, 32] Both these types of balance training interventions necessitate the individual performing activities at the limit of their ability to balance, and so if not performed carefully with the correct equipment or supervision, will place the individual at risk of falling. This tension between the need for home-based balance training to be challenging yet safe may explain the lack of improvement in standing and leaning balance found in the randomised controlled trial (Chapter 2). While the balance training component of the trial was designed to be highly-challenging, the results suggest that participants did not perform it at a high enough level of difficulty to affect an improvement. The need for balance training to be challenging yet safe and sustainable poses a difficult issue which requires further investigation. Future trials providing more supervision of the exercise program and/or monitoring of the level of perceived challenge when performing balance exercises may help to clarify the

challenge of balance exercise and the association between challenge and the amount of improvement, and may be the first step forward in solving this issue.

This thesis also identifies reduced muscle power as a new risk factor for reduced mobility and falls, which may be amenable to remediation (Chapters 4 and 5). Muscle weakness is not usually apparent during routine clinical examination of people with Parkinson's disease.[33, 34] However, the descriptive study presented in Chapter 4 shows that people with Parkinson's disease are likely to have appreciably reduced leg muscle power and strength. Furthermore, it appears that leg muscle power and strength are important determinants of walking speed and falls in this population (Chapter 5). Of the two measures, muscle power was found to be more strongly associated with both walking speed and falls history than muscle strength. For this reason, a Parkinson's disease fall risk score that includes leg muscle power instead of strength warrants examination and the effect of muscle power training in this population warrants investigation.

In the general older population, muscle power training (high velocity, lower resistance) has been found to improve physical performance[35, 36] and balance[37] as well as to increase movement velocity.[33] People with Parkinson's disease have been shown to increase muscle strength with appropriate progressive resistance exercise.[32, 38-42] Similarly the randomised controlled trial presented in Chapter 2 showed a trend towards an increase in knee extensor muscle strength after strength training with weighted vests. However, the descriptive study presented in Chapters 4 and 5 showed that people with Parkinson's disease have reduced leg muscle power which, when lifting light to moderate loads, was associated with reduced movement speed. Moreover, this reduced

muscle power was found to explain as much or more of the variation in walking velocity, and was more strongly associated with past falls, than muscle strength. While muscle strength training would be likely to improve muscle power by virtue of an improvement in strength, power training also has the potential to increase movement velocity (ie, reduce bradykinesia) and so further increase muscle power. Therefore, further research is needed to determine the effect of muscle power training on people with Parkinson's disease, particularly on balance impairment, performance of balance-related activities, movement velocity and falls. If muscle power training with specialised equipment is found to be beneficial for people with Parkinson's disease, then more clinically-accessible techniques for measuring and training muscle power in this population will need to be explored. Leg muscle power has been successfully measured in the general older population using a stair climbing protocol which is likely to be suitable for people with Parkinson's disease,[43] and home-based muscle power training could be trialled using the weighted vests that were found to be safe for home-based strength training.

The measurement of muscle power allows for the separate recording of muscle force and speed of muscle contraction, and so provides information about the influence of bradykinesia during rapid muscle contractions. The descriptive study presented in Chapter 4 found that muscle power measures taken with light to medium loads appear to be affected by decreased movement speed (bradykinesia), while power measures taken with heavy loads appear to be unaffected. This apparent absence of bradykinesia when lifting heavy loads could be further explored by recording muscle electromyography during power testing to determine if the abnormalities associated with bradykinesia change with different loads. Alternatively, it could be explored by measuring muscle

power using randomly varying loads. In the descriptive study presented in Chapter 4, participants knew that the load was increasing with each subsequent lift. This may have resulted in a subconscious increase in volitional drive when lifting the heavy loads, resulting in a situation similar to that seen in paradoxical kinesia where individuals are able to increase their movement speed under extreme circumstances. Improved understanding of the relationship between muscle strength, muscle power and bradykinesia has the potential to inform and enhance exercise interventions for this population, particularly in the areas of falls prevention and balance, where the ability to use muscles quickly is paramount.

FINAL REMARKS

Overall, the studies presented in this thesis provide promising evidence that fall risk in people with Parkinson's disease is likely to be reduced through appropriately designed exercise interventions. Moreover, reduced leg extensor muscle power is probably an important, previously unconsidered, risk factor for falls in this population. These results provide important information to assist clinicians and researchers when designing exercise interventions for people with Parkinson's disease who are at risk of falling. It is now important to assess the effect of exercise interventions on fall rates and to further develop effective, sustainable programs that people with PD can participate in for the long term. Any reduction in falls in this group will improve the quality of life of people with Parkinson's disease and their carers and help to reduce pressures on healthcare systems.

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APPENDICES

APPENDIX 1

Balance in Parkinson’s disease

BALANCE IMPAIRMENT

The underlying mechanisms underlying balance impairment in Parkinson's disease are complex and remain unclear. Traditionally, reduced balance in Parkinson's disease was thought to be due to erroneous motor programming of postural corrections within the basal ganglia.[1] However, recent work has found central somatosensory deficits which may also contribute to reduced balance.[2-4] In fact, people with Parkinson's disease have been found to have a tendency to overestimate the distance they can reach forwards without losing their balance.[5] It may be that somatosensory deficits lead to an abnormal perception of body position, resulting in individuals with Parkinson's disease overestimating their limits of stability and so contributing to an increased likelihood of falling.[1, 5]

Balance impairment in Parkinson's disease is often described and assessed in terms of the individual's response to perturbations (eg in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score).[6] However, the impact of Parkinson's disease on balance in standing is broader and more variable than that and can be considered under three circumstances: while standing (ongoing postural adjustments); during volitional movement (anticipatory and ongoing postural adjustments) and in response to a perturbation (reactive postural adjustments).

Standing

Balance while standing is often measured by postural sway. In neurologically-normal adults, postural sway increases with age[7] and amongst the older population, fallers sway more than non-fallers.[8, 9]

Studies of postural sway in people with Parkinson's disease have yielded inconsistent results. Most studies have found an increase in sway compared with healthy control groups, with sway in the mediolateral direction seeming to be more affected than anteroposterior sway.[10-15] Additionally, the increase in sway that occurs under eyes closed compared to eyes open conditions has been found to be greater in people with Parkinson's disease than healthy controls.[10] Other studies, however, have reported similar postural sway in people with and without Parkinson's disease.[16, 17] This discrepancy is likely to be due to differences in medication status, disease severity and testing procedures.

Medication status has been shown to affect postural sway measures, with an increase in sway observed in the ON state.[14, 18, 19] The simplest explanation for increased sway in the ON state is the presence of dyskinesia. A study of the postural sway of 11 people with advanced Parkinson's disease and levodopa-induced dyskinesia[19] found a 125% increase in net centre of pressure displacement when participants were ON with dyskinesia compared to when they were OFF. However, increased sway when ON has also been reported in people with Parkinson's disease who do not experience dyskinesia. Maurer et al (2003)[14] measured postural sway and intersegmental upper body-lower body stiffness in eight people with Parkinson's disease without levodopa-induced dyskinesia. Results showed increased sway but decreased intersegmental stiffness when participants were ON compared to OFF. The authors suggested that levodopa reduced rigidity, and in doing so revealed a balance impairment which was not responsive to levodopa.

The suggestion that postural sway might be reduced by rigidity when OFF medication has support from previous work. A study of eight people with moderate to advanced Parkinson's disease tested OFF medication found a smaller postural sway area in the Parkinson's disease group compared to healthy controls.[20] Furthermore, postural stiffness in standing has been found to correlate with postural instability.[21] Medication status, therefore is likely to affect postural sway, particularly in individuals with marked rigidity and/or who experience levodopa-induced dyskinesias. Accordingly, an abnormal increase or decrease in postural sway may be evident in people with Parkinson's disease.

Despite studies of postural sway in Parkinson's disease yielding variable results, increased postural sway has been found to be related to increased disease severity and increased fall risk.[10-13, 22] Recent work[13] examined people with Parkinson's disease at different stages of the disease process while OFF their medication. Results showed participants with more advanced disease had increased sway, while those with early disease who had never used dopaminergic medication exhibited normal postural sway. Another study compared the postural sway of people with Parkinson's disease who had fallen with those who had not fallen.[22] The fallers were found to have more sway in both the mediolateral and anteroposterior direction than the non-fallers, under eyes open and eyes closed testing conditions. Furthermore, increased postural sway was found to be an independent risk factor for falls in this study.

As Parkinson's disease severity increases, individuals tend to stand with a narrow base of support and a flexed posture.[23, 24] The reason why individuals with Parkinson's disease adopt body postures which would ostensibly increase their instability is unclear,

however recent work suggests that these postures may compensate for difficulty initiating walking.[25, 26]

A narrow base of support is inherently more unstable than a wider one, however people with Parkinson's disease typically stand and walk with the feet close together.[27] When healthy adults are perturbed while standing with feet close together, they modify the size and direction of postural forces produced. In contrast, people with Parkinson's disease are less likely to make these modifications,[28] further increasing their risk of falling. However, people with Parkinson's disease have been shown to have more difficulty initiating a step from wide stance (feet shoulder width apart) than from narrow stance, due to difficulty making a large enough anticipatory postural adjustment.[25] This suggests that the narrow base of support adopted by people with Parkinson's disease may be a compensatory strategy for difficulty shifting their weight laterally to step.[25]

Standing with a flexed posture is associated with a forward shift in the centre of foot pressure in people with moderate to severe Parkinson's disease.[10, 17] Furthermore, the magnitude of this forward shift increases with disease severity.[10, 17] Surprisingly, however, the centre of foot pressure is shifted backwards in people with mild disease.[17] This backwards shift is likely to have a destabilising effect and predispose the individual to losing balance backwards. It has been suggested that the forward shift in centre of foot pressure and hence the flexed posture seen later in the disease may, therefore, be an adaptive response to prevent falling backwards.[10, 17]

It appears however, that standing with a flexed posture is intrinsically unstable and so may contribute to reduced balance in Parkinson's disease.[26] Bloem et al (1999)[29]

investigated the responses of healthy people to toe-up rotational perturbations while mimicking a Parkinsonian flexed posture. Results showed that a flexed posture did minimise the backwards excursion of the centre of mass in response to this type of rotational perturbation. However, a similar experiment by Jacobs et al (2005)[26] analysed responses to multidirectional horizontal perturbations. They reported that a flexed posture decreased postural stability in healthy people. The authors suggested that the discrepancy between this and Bloem et al's (1999)[29] result was due to the context-specific nature of postural responses. Specifically, for a toe-up rotation, a flexed posture would improve stability as knee flexion would reduce the stretch on the gastrocnemius muscle and so reduce the amount of (destabilising) reflexive plantar flexion.[26, 29] In contrast, a flexed posture may hinder responses to horizontal perturbations as it may make it more difficult to relocate the centre of mass over a shifted base of support.[26] The authors speculated that flexed posture, similar to a narrowed base of support, may be a compensatory strategy to aid step initiation by facilitating forward movement of the centre of mass.[26]

Volitional Movements

Volitional movements require anticipatory postural adjustments to be made to stabilise the body's centre of mass over the base of support, or to move it over a new base of support.[30-32] In healthy adults, the size and timing of these postural adjustments appear to be proportionate to the anticipated magnitude of the destabilising force.[30]

Anticipatory postural adjustments in Parkinson's disease appear to be normal in terms of the general sequence of muscle activations.[33-36] However, abnormalities have been found in terms of the timing, speed and size of muscle activations. When rising onto the

toes, both people with Parkinson's disease and neurologically-normal people first contract the tibialis anterior (to move the body mass forward) and quadriceps (to stabilise the knee) in order to prepare for the gastrocnemius muscle to raise the heels.[33] However, the relative timing of the tibialis anterior and gastrocnemius contractions has been found to be more variable and less forceful in people with Parkinson's disease than in neurologically-normal people, resulting in a slower, less forceful postural adjustment and less stability while balancing on the toes.[36] Similar results have been found with rapid arm raising tasks, with anticipatory postural adjustments prior to raising the arm inconsistently present and small compared to healthy adults.[34, 37-39]

It has been suggested that these inconsistent and small adjustments seen prior to rapid arm rising may simply be because the individuals with Parkinson's disease were moving their arm more slowly.[34, 37, 38] Indeed, the presence and timing of postural adjustments have been shown to be dependent on the speed of the arm lift. When the arm is lifted rapidly, postural muscles are activated in a consistent sequence. Even in normal adults, when the arm is lifted slowly, the sequence of muscle activation is more variable and some postural muscles do not show activity at all.[30] This is likely to be because less stabilisation force is required during slow movements.[30]

While people with Parkinson's disease do tend to move more slowly than normal adults, they continue to display small postural adjustments even when rapid movement speed is achieved.[39] Postural adjustments in preparation for rapid arm rising were studied in 10 people with relatively mild Parkinson's disease while OFF medication. Results showed anticipatory postural adjustments were consistently present, but were smaller than the healthy control group. This was despite the fact that the Parkinson's disease group did

not have reduced movement speed or duration.[39] Therefore, even when the speed and size of the movement were accounted for, the size of the postural adjustment was reduced, suggesting that small postural adjustments in Parkinson's disease are not entirely due to slow movement speed.

Self initiated stepping tasks, both in forwards[25, 40-42] and sideways directions,[43] have also been used to assess anticipatory postural adjustments in people with Parkinson's disease. These studies have shown small and slow postural adjustments[25, 40-44] along with shorter steps[25, 40, 44] in people with Parkinson's disease compared to healthy controls. Furthermore, people with Parkinson's disease have been shown to have reduced propulsive force production during postural adjustments prior to stepping, particularly when OFF medication.[40] These small and slow adjustments are likely to have delayed unloading of the swing leg and so contributed to the reduced step length.[40] Overall, it therefore appears that bradykinesia influences the size and speed of postural adjustments in preparation for movement as well as the size and speed of the intended movement.

External Perturbations

A significant threat to balance occurs when there is an unexpected external perturbation. Most of the research that has looked at the effect of external perturbations in people with Parkinson's disease has analysed responses to movement of the support surface on which participants are standing. In considering these results, therefore, it is important to bear in mind that these types of perturbations may evoke different responses to the pushes or bumps that are more commonly encountered in daily life.

Much work has focused on responses of the muscles around the ankles which serve to maintain stability. These responses are reflexive as they occur earlier than voluntary reaction times would allow, regardless of whether or not the perturbation was predictable.[45] Neurologically-normal adults standing on a moveable platform display stereotypical, but modifiable reflex responses to platform perturbations.[46-48] If the platform remains horizontal, but moves backwards, the resultant increase in dorsiflexion stretches the calf muscles, eliciting a short and medium latency reflex contraction in those muscles, which serves to stabilise the person. These muscle contractions around the ankle are then followed by muscle contractions in more proximal muscles, with muscles contracting in a distal to proximal sequence with minimal co-contraction.[47] If a rotational toe-up perturbation is used to achieve the dorsiflexion, then the calf muscles will still contract in response to the stretch. However, under this condition the calf muscles contraction is destabilising, and so is followed by a longer latency contraction in the tibialis anterior muscle in order to maintain balance.[46, 48] Furthermore, repeated trials of rotational perturbations lead to a diminished contraction response in the calf muscles, hence normal reflex responses are modulated to produce a more efficient way of responding to the perturbation.[46]

When people with Parkinson's disease are subjected to unexpected external support surface perturbations, most show similar muscle activation latencies to that of neurologically-normal adults[17, 23, 48-52] Loss of balance is, therefore not due to a delayed response, but an ineffective response.[20] These responses have several distinguishing features, including increased size of destabilising responses, inflexibility of response and excessive co-contraction of agonist and antagonist muscles.

Research has consistently found abnormalities in the size of reflex responses in the leg muscles of people with Parkinson's disease. When people with Parkinson's disease are subjected to a rotational toe-up perturbation, they exhibit an enlarged destabilising reflex contraction of the stretched calf muscles.[17, 23, 53-55] Furthermore, the size of these reflex contractions has been found to correlate with disease severity, with the largest abnormality in people with more advanced disease.[23] These reflex contractions are especially large in response to the first perturbation, and so may underlie falls from unexpected postural disturbances in people with Parkinson's disease.[27, 56] Less consistently, some studies have also found a reduction in the stabilising response of the anterior tibial muscles, which would further exacerbate the tendency to fall.[54, 55]

Much work has shown the postural reflex responses of people with Parkinson's disease to be inflexible, even when ON medication. When sitting, there is normally no reflex response in the anterior tibial muslces in response to rapid ankle dorsiflexion, as it is not required to maintain balance.[57] In contrast, reflex contraction in the anterior tibial muscles has been shown to occur in seated people with Parkinson's disease.[58] People with Parkinson's disease are also unable to modify their postural responses to perturbations when standing on a narrow beam or when sitting on a high stool compared to when standing on a flat surface, while healthy adults change their strategy to use more proximal muscles.[20] Furthermore, people with Parkinson's disease have been found to be slower than healthy adults to change postural responses when perturbation characteristics change (toes-up vs backward horizontal perturbation),[59] or when instructions change ("give in to" or "resist" the perturbation).[55, 59] Moreover, when allowed to hold on with the hands during a perturbation in standing, healthy adults suppress medium and long latency ankle muscle activations, while people with

Parkinson's disease do not.[17] It seems, therefore, that people with Parkinson's disease are less able to modulate their postural reflex responses to suit different body positions, tasks or environmental situations.[27]

Excessive abnormal co-contraction of agonist and antagonist postural muscles in response to external perturbations has been consistently found in people with Parkinson's disease.[20, 23, 48-50] Specifically, antagonist muscles tend to be activated too early and with excessive magnitude resulting in co-contraction rather than reciprocal contraction of agonist and antagonist postural muscles in the legs and trunk.[48-50] People with Parkinson's disease also have excessive background muscle activity,[48-50] which may reflect compensatory stiffening due to fear of falling.[48, 50] Furthermore, the rigidity of Parkinson's disease may interfere with the intrinsic ability of muscles to dampen body sway.[23, 60, 61] These factors all contribute to increased postural stiffness in people with Parkinson's disease.[50]

This postural stiffness is likely to contribute to falls in people with Parkinson's disease. Stiffening has the advantage that it helps to maintain the centre of mass within a small area, reducing the risk of exceeding the limits of stability,[20, 62] and may somewhat improve resistance to external perturbations.[49] On the other hand, the increased stiffness reduces the visco-elastic properties of the body which normally aid in absorbing perturbations[27] and impedes rapid generation of muscle torque.[36, 49] Furthermore, people with Parkinson's disease have a reduced ability to appropriately increase muscle activation when perturbations occur while standing with feet close together,[50] and bradykinesia reduces the speed at which postural muscle forces are produced.[18, 36, 40, 49] Resultantly, people with Parkinson's disease with severe balance impairment have very

small limits of stability, and exceeding these limits is likely to result in the individual falling like a log.[20, 27]

Taking a step is a common reaction to a threat to stability, and if the centre of mass is perturbed outside of the limits of stability, compensatory stepping is crucial in preventing a fall.[63] The compensatory steps of people with Parkinson's disease have been found to be later, slower and shorter than neurologically-normal people of the same age.[52, 64] These abnormalities appear to be associated with bradykinesia[64] and would reduce the chances of the person with Parkinson's disease successfully recovering their balance and averting a fall.

Recent work has suggested that people with Parkinson's disease have difficulty initiating compensatory steps. King and Horak (2008)[64] studied the stepping responses to a lateral platform perturbation in 13 people with Parkinson's disease compared with a neurologically-normal control group. Results showed that the control group were consistently able to take successful compensatory steps to avoid a fall, but the Parkinson's disease group "fell" in 24% of trials when ON medication and 35% of trials when OFF medication. Two successful stepping strategies were observed: a side step with the leg on the opposite side to the perturbation in order to widen the base of support; or a crossover step with the leg un-weighted by the effect of the perturbation. The side step was the most commonly used strategy in both groups. This strategy requires the individual to rapidly increase the vertical force under the stepping leg in order to unload it by shifting the centre of mass toward the stance leg. Moreover, this needs to be accomplished at a time when the perturbation itself is tending to load the stepping leg and unload the stance leg. Results showed that the healthy control group

were able to consistently achieve this lateral weight shift prior to stepping. In contrast, only half the participants in the Parkinson's disease group used a lateral weight shift prior to stepping, and most of these individuals were not able to use the strategy consistently. Furthermore, trials where there was an absence of lateral weight shift were associated with a "fall". This suggests that some participants with Parkinson's disease had difficulty generating the lateral weight shift required to initiate successful compensatory stepping.

King and Horak's (2008)[64] study also provides evidence that people with Parkinson's disease can have difficulty selecting appropriate and consistent postural responses. Participants in the healthy control group consistently used either the side step or crossover step strategy, whereas many participants in the Parkinson's disease group changed strategy from trial to trial, or used a different strategy when OFF as compared to ON. It was these participants who had the highest "fall" rates, falling on 57% to 100% of trials. Furthermore, some participants with Parkinson's disease used strategies that were often unsuccessful. Two Parkinson's disease participants failed to step at all and fell like a log. The remaining participants most often used a side stepping strategy, resulting in falls in 17% of trials when OFF medication. However, when a crossover step strategy was used, falls occurred in 75% of trials when OFF medication. Furthermore, in some trials the participant first took a very small side step, followed by a crossover step and then a "fall". The authors proposed that this variability in response suggests that people with Parkinson's disease may have difficulty pre-selecting a consistent strategy, resulting in a delayed or inadequate response, and consequently more falls.

Balance impairment in Parkinson's disease is therefore complex and multifaceted. Overall, the postural adjustments of people with Parkinson's disease tend to be variable, delayed, slow and small, combined with reflex responses that can be destabilising and inflexible. Furthermore, while balance impairment is a cardinal sign of Parkinson's disease, it also appears to be influenced by other impairments including bradykinesia and rigidity. For most people with Parkinson's disease, balance impairment will worsen as the disease progresses. It is therefore an important risk factor for falls in this population.

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APPENDIX 2

Freezing of Gait

FREEZING OF GAIT

People with Parkinson's disease who experience freezing of gait often report that they feel that their feet are 'glued' to the floor and they are unable to start or continue walking.[1-3] The most common manifestations of freezing of gait are moving forward with very small steps and leg trembling with no effective forward movement.[4] Freezing of gait usually occurs when the person with Parkinson's disease is in the OFF state, though ON state freezing does occur in some people.[5] Complete akinesia with no observable movement of the legs is less common and more likely to occur when OFF medication.[4]

Freezing of gait is associated with disease progression and significantly contributes to disability and falls in people with Parkinson's disease. Freezing in early disease is usually brief, causing only mild difficulty and rarely leading to falls.[2, 4] However, as the disease progresses, freezing occurs more often and for longer, lasting up to a minute or more.[6] This can lead to restriction of physical activity and limited walking in the community.[7] Furthermore, as freezing episodes tend to be sudden and unpredictable, and as many people with Parkinson's disease have impaired balance, freezing can often disturb balance enough to result in a fall.[1-3, 8]

It is well recognised that freezing of gait can be exacerbated by environmental, task and emotional constraints.[7] People with Parkinson's disease are more likely to freeze in environments which appear busy (eg, in a crowd), or are restricted in space (eg, a narrow doorway or a cluttered room.[2, 7, 9] Long or complex tasks, or performing a second task while walking, can trigger a freezing episode in some people.[1, 2, 10] Stressful situations (eg, crossing a busy road) and anxiety also make freezing worse in people

who are prone to this problem.[7, 11] Conversely, moderate emotional stress in situations where people can focus their attention on walking (eg at the doctor's office) can improve freezing.[11] This fact makes freezing of gait a difficult impairment to assess, treat and research.

Gait Abnormalities Associated With Freezing of Gait

The underlying mechanisms responsible for freezing of gait are unclear.[12] Freezing of gait does not appear to be due to bradykinesia or rigidity.[3] However, several gait abnormalities are suggested to be associated with freezing episodes. These include hypokinesia,[7] gait festination,[7] difficulty linking postural adjustments with stepping,[13] and abnormalities of rhythmicity, symmetry and coordination.[14]

Gait hypokinesia has been suggested to contribute to freezing, particularly during gait initiation.[7] Hypokinesia refers to reduced amplitude of movement. Gait hypokinesia is a common characteristic in people with Parkinson's disease, and has been found to be due to an abnormality in the regulation of stride length.[15] Specifically, for a given speed, people with Parkinson's disease walk with a shorter stride length and a higher cadence than healthy adults. Furthermore, when required to walk at a specific cadence, stride length remains short, resulting in slowed walking speed.[15] This is thought to be due to a mismatch between movement amplitude selected by the cortex and the actual size of lower limb movements during walking.[16] As the preferred walking speed of people with Parkinson's disease is slower than normal, gait hypokinesia leads to slow, short stepped walking.[15] When severe, movement amplitude is scaled down so far that step initiation fails to occur, resulting in a freezing episode.[7] The small and slow postural adjustments which impede the weight transference required to unload the swing

leg prior to self-initiated stepping[13, 17-21] provides evidence for the involvement of gait hypokinesia in freezing during gait initiation.[7]

Gait festination has been suggested to contribute to freezing during a walking sequence.[7] Gait festination refers to a progressive shortening of stride length associated with a high cadence and reduction of walking speed.[7, 22] An exponential increase in cadence along with a decrease in stride length has been found to occur during both festination and in the three steps prior to freezing, suggesting that some freezing episodes may be due to a combination of an inability to maintain stride length and control cadence.[22] This is thought to be due to abnormalities in the timing of motor cue production in the globus pallidus, with freezing occurring when these phasic cues become very slow or absent.[7, 23] Freezing associated with festination therefore occurs when steps during walking become increasingly shorter and faster, ultimately resulting in a freezing episode.[7, 23]

It is likely that hypokinesia and festination occur together for some people who experience freezing.[7, 23] "Frozen" gait (likely to be festination)[22] has been associated with an incomplete weight shift from one foot to the other.[24] This is similar to that attributed to hypokinesia[7] during self-initiated stepping.[13, 17-21] It therefore seems possible that hypokinesia may be exacerbating festination in some people.[23]

Recent work has provided evidence that freezing associated with a forward loss of balance may due to an inability to combine postural adjustments with stepping.[13] Jacobs et al (2009)[13] compared the postural adjustments in response to a forward loss of balance in 10 people with Parkinson's disease and marked freezing problems with 10 healthy adults. Results showed that the healthy people usually responded with one weight-

shifting postural adjustment, followed by a step. In contrast, people with Parkinson's disease exhibited multiple postural adjustments in 69% of trials when OFF medication and in 40% of trials when ON medication. These trials with multiple postural adjustments were associated with freezing (ie, late step onset or no step followed by a fall), along with alternating trembling of the knees. However, the multiple postural adjustments were not delayed in onset and the weight shift was of normal size, suggesting that these freezing episodes were not caused by hypokinesia. The authors propose that the leg trembling often seen during freezing episodes is due to multiple postural adjustments and that when freezing is associated with a forward loss of balance it may be due to an inability to link a normal postural adjustment to the motor pattern for stepping.[13]

The gait of people with Parkinson's disease who experience freezing is less rhythmic, less symmetric and less coordinated than the gait of those who do not freeze.[14] While hypokinesia, festination and difficulty linking postural adjustments with stepping can be observed at or near the time of the freezing episode, problems with rhythmicity, symmetry and coordination are apparent even between freezing episodes.[14] This suggests that freezing may be an extreme form of this disturbed gait pattern.[2] Alternatively, these gait disturbances may predispose an individual to freezing by making it more likely that another disturbance (eg, cognitive loading) will exacerbate the already disturbed gait and so trigger a freezing episode.[14] Whatever the relationship between these gait disturbances and freezing, it seems that those people with Parkinson's disease who have reduced coordination of their left to right stepping pattern are more prone to freezing.[14]

Gait rhythmicity is typically assessed by measures of stride-to-stride variability. The stride-to-stride variability of people with Parkinson's disease has been found to be higher than healthy adults,[25] even in the early stages of the disease.[26] However, people with Parkinson's disease who experience freezing of gait have even higher levels of stride-to-stride variability than those who do not freeze.[27] This difference in variability between freezers and non-freezers is apparent even when the two groups are similar in terms of average stride time, cadence and clinical characteristics.[27] Interestingly, high stride variability is also associated with falls in people with Parkinson's disease.[28] As freezing of gait is associated with falls as well, it seems possible that there may be one pathological mechanism contributing to the two problems.[2]

Gait asymmetry (a comparison of the swing time of each leg)[29] and bilateral discoordination (coordination between left and right stepping phases)[30] have also been found to be increased in people with Parkinson's disease who freeze, compared to those who do not.[14, 29, 31] Furthermore, these impairments in the bilateral function of gait have not been found to be related to asymmetry in Parkinson's disease symptoms.[29, 31] Notably, freezing of gait is common during gait initiation and turning,[28] both of which require the left and right legs to be used in an asymmetric manner.[14] Reduced symmetry and bilateral coordination may therefore predispose some people to freeze during these tasks.[14]

In summary, freezing of gait is a debilitating and frustrating symptom of Parkinson's disease for which the underlying mechanism is unclear. The intermittent, sudden and unpredictable nature of freezing means that freezing episodes place an extra challenge on the individual's ability to balance. Given that many people with Parkinson's disease

have impaired balance, freezing of gait can instigate falls and so is an important risk factor for falls in this population.

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APPENDIX 3

The Parkinson's disease version of the Weight-bearing Exercise for Better Balance exercise program (PD-WEBB)

The Weight-bearing Exercises for Better Balance exercise program (WEBB) is designed to be a challenging, safe, evidence-based physiotherapy program for older people. The randomised controlled trial presented in this thesis used the Parkinson's disease version of the WEBB (PD-WEBB), which included cueing strategies to reduce freezing in Parkinson's disease.

The WEBB was developed by Dr Catherine Sherrington, Dr Colleen Canning, Dr Catherine Dean, Ms Natalie Allen (the PhD candidate) and Ms Karyn Blackman.

For easy reference, an abridged version of the PD-WEBB has been included in this appendix. For full details, please refer to the website at: http://webb.org.au/.

The cueing intervention used in this study was based on that used in the RESCUE trial.[1] Details of the cueing intervention varied according to the needs of each participant. Trainers referred to the following resources when planning cueing interventions:

1 Nieuwboer A, Kwakkel G, Rochester L, Jones D, Van Wegen E, Willems A, Chavret F, Hetherington V, Baker K, Lim I (2007) Cueing training in the home improves gait-related mobility in Parkinson's disease: The RESCUE trial. *Journal of Neurology, Neurosurgery and Psychiatry* 78: 134-140.

2 RESCUE Consortium (2005) Using cueing to improve mobility in Parkinson's disease. A CD-Rom for therapists. [http://hces.unn.ac.uk/rescue/pubs/cd-rom.htm]

Exercises

Warm-up

1. High stepping on the spot

Aims: warm-up, enhance co-ordination, endurance

Prescription Principles:

Making it harder:

- Step higher
- Step for longer

Making it easier:

- place a table beside the person for hand support

To enhance co-ordination and endurance

- Minimise hand support
- Aim to increase time without using hand support

Co-ordination exercises

2. Standing with a decreased base

Aims: enhance co-ordination

Prescription Principles:

Making it harder:

- Feet together and level
- Semi-tandem stance
- Tandem stance
- Stand on one leg
- Maintain position for longer
- Close eyes
- Stand on different surfaces eg foam rubber mat

Making it easier:

- place a table beside the person for hand support

To enhance co-ordination

- Minimise hand support
- Aim to increase repetitions done without hand support




3. Graded reaching in standing

Aims: enhance co-ordination

Prescription Principles:

Making it harder:

- Foot placement- narrower, step standing
- Reaching further
- Reaching in different directions
- Reaching down to a stool or the floor
- Reaching for heavier objects
- Reaching for a full cup of water
- Standing on a softer surface eg foam rubber mat
- Stepping while reaching

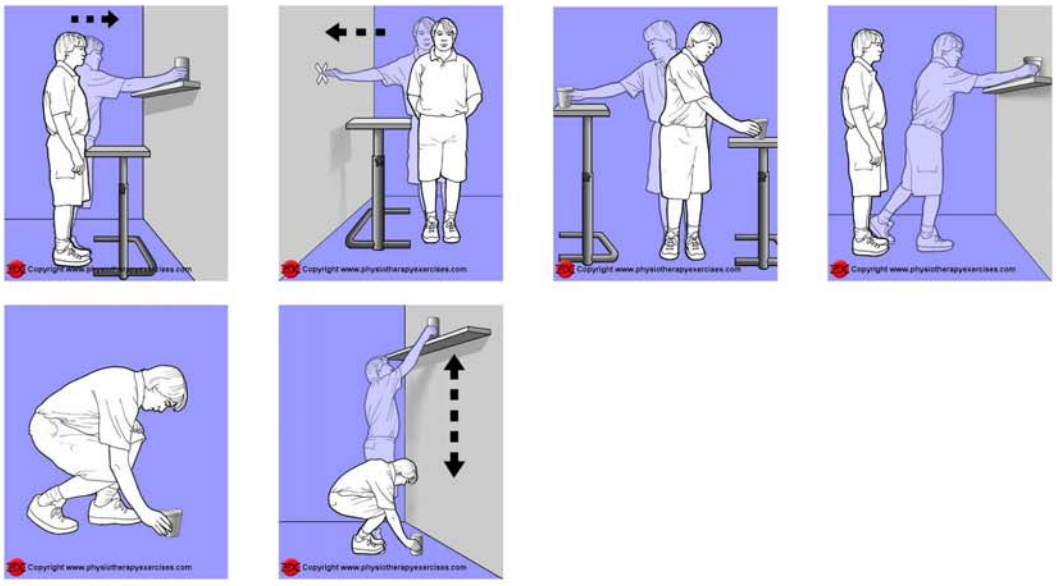
Making it easier:

- place a table beside the person for hand support
- give feedback to enable the task to be successfully completed (eg, keep your hips forward)
- structure the environment to enhance performance eg markers on floor to show foot position, an object to move hips towards

Tip. If you have a sway-meter, people may enjoy tracing different size "race track" paths with this.

To enhance co-ordination

- Minimise hand support
- Aim for as long as possible with out hand support



4. Stepping in different directions

Aims: enhance co-ordination

Prescription Principles:

Making it harder:

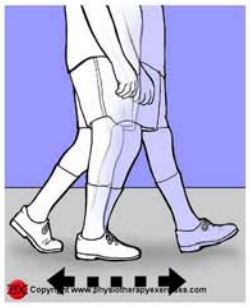
- Narrow foot position
- Longer steps
- Faster steps
- Step over objects
- Choice component eg step forward with left foot
- Incorporate pivoting on the non-stepping foot

Making it easier:

- place a table beside the person for hand support

To enhance co-ordination

- Minimise hand support
- Aim for as long as possible without hand support



5. Walking practice

Aims: enhance co-ordination and endurance

Prescription Principles:

Making it harder:

- Decrease base of support i.e. progress to tandem walk
- Increased step size
- Increase speed
- Change direction
- Walk on different surfaces
- Walk sideways, backwards
- Obstacles to step over and walk around

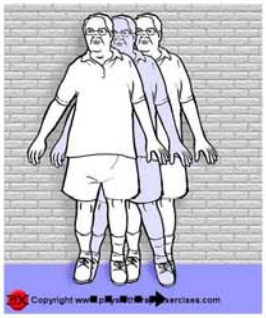
Making it easier:

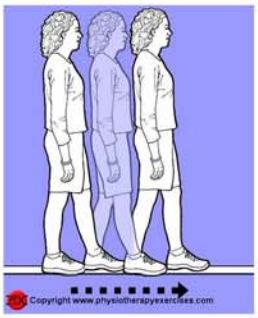
- Use a bar, wall or walking aid for hand support

To enhance co-ordination and endurance

- Minimise hand support
- Aim for as long as possible with out hand support



Strength and co-ordination exercises

6. Sit-to-stand

Aims: enhance co-ordination, strength and endurance

Prescription Principles:

Making it harder:

- lowering the height
- don't use hands to push off, cross arms across chest
- changing the nature of the surface (eg softer chair)
- ask the person to stand up with most weight on one leg- the other leg can be placed in front or on a stool to ensure this
- adding weight (either vest or belt)

Making it easier:

- place a table beside the person for hand support
- give feedback to enable the task to be successfully completed (eg feet back behind your knees, move your shoulders forward)
- structure the environment to assist performance eg markers on floor to show foot position

Tip. Height can be adjusted by using an electric plinth, using different chairs or stools and by placing large stable block/s under the feet.

To enhance co-ordination and endurance

- Aim for as many repetitions as possible, the height should be such that it is easy for the subject to complete multiple repetitions
- Minimise hand support
- Increase speed eg count repetitions done in one minute

To enhance strength

- Aim for a chair height and amount of weight added at which the person can do 2 sets of 10-15 repetitions




7. Heel raises

Aims: enhance co-ordination and muscle strength and endurance

Prescription Principles:

Making it harder:

- decrease hand support
- hold the raise for longer
- one leg at a time
- adding weight (either vest or belt)
- use a wedge to increase the range of motion

Making it easier:

- place a table on one or both sides of the person for hand support or use their walking aid

To enhance co-ordination and endurance

- Minimise hand support
- Do as many repetitions as possible

To enhance muscle strength

- Aim for an amount of weight added at which the person can do 2 sets of 10-15 repetitions




8. Lateral step-up

Aims: enhance co-ordination and strength

Prescription Principles:

Making it harder:

- increasing block height
- adding weight (either vest or belt)

Making it easier:

- place a table on one or both sides of the person for hand support or use their walking aid

Tip. Make sure the person doesn't push off by plantar flexing ankle of foot on floor instead of extending leg on block

To enhance co-ordination

- Aim for as many repetitions as possible, the height should be such that it is easy for the subject to complete multiple repetitions
- Minimise hand support

To enhance strength

- Aim for a block height and amount of weight added at which the person can do 2 sets of 10-15 repetitions

9. Forward step-up

Aims: enhance co-ordination and strength

Prescription Principles:

Making it harder:

- increasing step height
- adding weight (either vest or belt)
- decrease hand support
- step up and over block

Making it easier:

- place a table on one or both sides of the person for hand support or use their walking aid

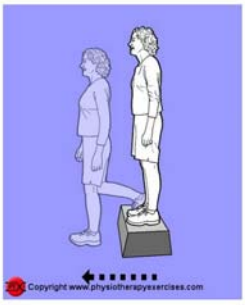
Tip. Make sure the person lowers the leg in a controlled manner when stepping over the block

To enhance co-ordination

- Aim for as many repetitions as possible, the height should be such that it is easy for the subject to complete multiple repetitions
- Minimise hand support

To enhance strength

- Aim for a block height and amount of weight added at which the person can do 2 sets of 10-15 repetitions



10. Half- squats sliding down a wall

Aims: enhance co-ordination and muscle endurance

Prescription Principles:

Making it harder:

- decrease hand support
- hold the squat for longer
- move a short distance away from the wall
- adding weight (either vest or belt)
- one leg at a time

Making it easier:

- place a table on one or both sides of the person for hand support or use their walking aid

To enhance co-ordination

- Minimise hand support

To enhance muscle endurance

- Aim to hold the position for as long as possible

FREEZING INFORMATION SHEET

"Freezing" is the word used to describe a sudden difficulty in starting or continuing a movement. People report feeling as though they are frozen, or that their feet are stuck to the ground.

Using cues is thought to help prevent freezing and to end a freezing episode. Cues are prompts that help people to move. They usually provide information about the

- timing (eg, stepping to metronome beat, counting) or
- size (eg, strip of tape on the floor to step over)

of the next movement.

Common times for freezing and some suggested strategies to overcome it are given below.

Taking the first step to start walking

- Shift your weight from side to side so you are rocking between your right and left leg.
- Count to yourself as you rock, and start walking on a particular number you have chosen.
- Use a metronome beat to rock with and then start walking on the beat.
- Step over a stripe or other object on the floor (if you regularly freeze in the same place, you could put a strip of tape on the floor there).
- Try to step into an uncrowded space.
- If shifting from side to side is not successful, try taking a step back or to the side, then step forwards.

Walking in a confined space (eg, doorway, between 2 chairs)

- Start counting to yourself a few steps before hand and keep stepping with your counting rhythm.
- If you feel you are beginning to freeze, then STOP. Use the strategies above to get started again.
- Take steps in time to a metronome to help you keep your rhythm.
- Step very deliberately or stamp your feet.
- Place strips of tape on the floor, step width apart, in places where you regularly freeze. Step over each strip of tape as you walk.
- Place a single strip of tape in doorways and focus on stepping over the tape.

Turning from a stationary start (eg, from kitchen bench) or in confined spaces

- Turn using a clock-like motion.
- Step around with high steps, keep feet apart, do not swivel.
- Count to yourself as you begin stepping on the spot, and maintain the stepping rhythm throughout the turn.
- Take steps in time with a metronome to help you keep your rhythm.

Turning when walking

- Turn in an arc using big steps.
- Start counting to yourself a few steps before the turn and keep stepping with your counting rhythm.
- Take steps in time to a metronome to help you keep your rhythm.
- Step very deliberately or stamp your feet as you turn.
- Place strips of tape on the floor, step width apart, in places where you regularly freeze when turning. Step over each strip of tape as you turn.

APPENDIX 4

The Parkinson's disease version of the Weight-bearing Exercise for Better Balance exercise program (PD-WEBB) –

Example of an exercise instruction and recording sheet

Name:_____ Month:_____

CO-ORDINATION EXERCISES

2. Standing with a decreased base

(d) Standing on one leg

Instructions

- Hold onto a stable object (eg, table). Stand on one leg. Once you feel balanced, let go of the object. Repeat on the other leg.

Additional Instructions:

Do this for up to 10 seconds
Repeat 15 times each leg

Please record your completed exercise here

Week Starting	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

APPENDIX 5

Authorship guidelines for submission to the journal

Movement Disorders

Form of Manuscripts

The text of the manuscript should be in the following sequence: (1) Title page, (2) Abstract, (3) Introduction, (4) Methods, (5) Results, (6) Discussion, (7) Acknowledgment, (8) Authors' Roles, (9) Financial Disclosures of all authors (for the preceding 12 months), (10) References, (11) Video Legend, (12) Figures, and (13) Tables. Pages should be numbered in succession, the title page being one.

Title: Titles should be short, specific, and clear. They should not exceed 100 characters. Do not use abbreviations in the title.

Title Page:The opening page of each manuscript should include only: (1) article title; (2) authors' names and affiliations (indicate the specific affiliation of each author by superscript, Arabic numerals); (3) name, address, and telephone and fax numbers of the person to whom proofs and reprint requests should be addressed; (4) word count; (5) any necessary footnotes to these items; (6) a running title not exceeding 45 letters and spaces; (7) Key words; (8) Financial Disclosure/Conflict of Interest concerning the research related to the manuscript: All information on support and financial issues from all authors relative to the research covered in the submitted manuscript must be disclosed regardless of date. Other financial information unrelated to the current research covering the past year will be documented at the end of the manuscript (see below). Note that submissions without this Financial Disclosure on the Title Page will be returned to the author. For clinical trials, a statement on ghost-writing is required (*Movement Disorders* 2005;20:1536).

Abstract:The page following the title page of Full-Length Articles should include a brief abstract of up to 250 words describing the background, methods, results, and conclusions of the study. We encourage authors to submit papers with structured

abstracts, especially for clinical trial papers. The page following the title page of a Brief Report should include a brief abstract of up to 100 words.

Key words: Up to six key words or terms should be provided following the abstract.

Introduction: Give a brief description of the background of the scientific contribution.

Methods:Informed consent: For experimental investigation of human or animal subjects, please state in this section that an appropriate institutional review board approved the project. For those investigators who do not have formal ethics review committees, the principles outlined in the "Declaration of Helsinki" should be followed. For investigations in human subjects, state in this section the manner in which informed consent was obtained from the subjects. A letter of consent must accompany all photographs, patient descriptions, and pedigrees in which a possibility of identification exists. The authors are responsible for proper anonymisation of their patients.

Results: No specific regulations.

Discussion: No specific regulations.

Acknowledgment: No specific regulations.

Author Roles: List all authors along with their specific roles in the project and preparation of the manuscript. These may include but are not restricted to: 1) Research project: A. Conception, B. Organization, C. Execution; 2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3) Manuscript: A. Writing of the first draft, B. Review and Critique.

Full Financial Disclosures of all Authors for the Past Year: Information concerning all sources of financial support and funding for the preceding twelve months, regardless

of relationship to current manuscript must be submitted with the following categories suggested. List sources or “none”.

Stock Ownership in medically-related fields	Intellectual Property Rights
Consultancies	Expert Testimony
Advisory Boards	Employment
Partnerships	Contracts
Honoraria	Royalties
Grants	Other

References: See “Details of Style” for the proper formatting of citations and References.

Video Legend: No specific regulations.

Tables and Figure Legends: Double-space legends of fewer than 40 words for tables and figures. For photomicrographs, include the type of specimen, original magnification, and stain type. Include internal scale-markers on photomicrographs. Where applicable, indicate the method used to digitally enhance images.

Tables: Tables should be typed neatly, each on a separate page, with a title above and any notes below. Explain all abbreviations. Do not repeat the same information in tables and figures or tables and text.

Figures and Illustrations: Adapt any figures to an appropriate size of art and letters to make them readable in the printed version. Illustrations in full color are accepted at additional charge from the publisher. Any illustration or figure from another publication

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Details of Style

No patient identifiers (e.g., patient initials) are to be included in the manuscript or video (e.g., case reports, tables, figures, etc.).

Units of measure: Conventional units of measure according to the *Systeme International* (SI) are preferred. The metric system is preferred for length, area, mass, and volume. Express temperature in degrees Celsius.

Drug Names: Use generic names only in referring to drugs, followed in parentheses after first mention by any commonly used generic variant.

Abbreviations: Follow the list of abbreviations given in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (see section on References). For additional abbreviations, consult the CBE Style Manual (available from the Council of Biology Editors, 9650 Rockville Pike, Bethesda, Maryland 20814, USA) or other standard sources.

Spelling: American spelling is used throughout the Journal.

References

Movement Disorders complies with the reference style given in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals". (See Annals of Internal Medicine 1982;96:766-771, or British Medical Journal 1982;284:1766-1770.)

References are to be cited in the text by number, and in the list of References they are to be numbered in the order in which they are cited. The reference section should be double-spaced at the end of the text, following the sample formats given below. Provide all authors' names when fewer than seven; when seven or more, list the first three and add et al. Provide article titles and inclusive pages. Accuracy of reference data is the responsibility of the author. For abbreviations of journal names, refer to List of Journals Indexed in Index Medicus (available from the Superintendent of Documents, U.S. Government Printing Office, Washington DC 20402, USA, DHEW Publication No. (NIH) 83-267; ISSN 0093-3821).

Sample References

- Journal article:

1. Horgan JH, O'Callaghan WG, Teo KK. Therapy of angina pectoris with low-dose perhexiline. J Cardiovasc Pharmacol 1981;3:566–572.

· Book:

2. Vanhoutte PM, Leusen I, editors. Vasodilatation. New York: Raven Press; 1981. 96 p.

· Chapter in a book:

3. Patrono C, Ciabattoni G, Pugliese F, et al. Effect of dietary variation in linoleic acid content on platelet aggregation and the major urinary metabolites of the E prostaglandins and (PGE-M) in infants. In: Hegyeli RJ, editor. Prostaglandins and cardiovascular disease. New York: Raven Press; 1981. p 111–122. (Atherosclerosis reviews; vol. 8).