

Research paper

Promoting independence in Lewy body dementia through exercise (PRIDE) study: Protocol for a pilot study



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ABSTRACT

Background: Lewy Body dementia (LBD) is the second most prevalent neurodegenerative dementia. This form of dementia is notable for an aggressive disease course consisting of a combination of cognitive, Parkinsonian, affective, and physiological symptoms that significantly increase morbidity and mortality, and decrease life expectancy in this population compared to more common dementias. Additionally, those diagnosed with LBD are often excluded from trials evaluating exercise in similar diseases such as Alzheimer's disease or Parkinson's disease due to the complexity and concurrency of motor and cognitive symptoms. Consequently, there is scarce research evaluating the effect of exercise on individuals with LBD.

Methods: The PRomoting Independence in Lewy Body Dementia through Exercise (PRIDE) trial is a novel non-randomised, crossover pilot study consisting of an 8-week wait-list usual care period, followed by an 8-week exercise intervention targeting progressive resistance and balance training. The trial aim is to evaluate the effect of exercise on the primary outcome of functional independence and secondary outcomes including cognitive, physical, psychosocial and quality of life measures in people living with LBD and their caregivers. The intervention involves 3 supervised 1-h sessions per week (24 sessions in total) administered by an Accredited Exercise Physiologist in a clinical facility at the University of Sydney in Lidcombe, Australia.

Discussion: The PRIDE study is the first controlled trial to evaluate a robust exercise intervention within a LBD cohort and will provide crucial information required to inform robust future clinical trials.

Trial registration: Australia and New Zealand Trial Register (ANZCTR): ACTRN12616000466448; Key words: Lewy body; dementia; exercise; anabolic; functional independence.

1. Introduction

Lewy body dementia (LBD) is an umbrella term for the diseases of dementia with Lewy bodies (DLB), and Parkinson's disease dementia (PDD) which share common pathology, and have a variable estimated prevalence of up to 24% of all dementia diagnosis [1]. LBD has complex, fluctuating symptomatology, including parkinsonism, psychosis, autonomic and cognitive impairments; with afflicted individuals progressing more rapidly to residential care and death following diagnosis [2]. The prevalence of frailty in early LBD (37%) is double that of Alzheimer's disease (AD) or Parkinson's disease (PD) [3,4], and strongly associated with neuropsychiatric disturbances, poorer prognosis, lower quality of

life and ultimately a reduction in functional independence [2]. Importantly, the rapid development of frailty in LBD is only minimally attributable to disease pathophysiology itself [5], with a greater involvement stemming from potentially treatable and highly prevalent risk factors in LBD including malnutrition, sarcopenia, delirium, infection, polypharmacy, injurious falls and behavioural disturbances [6–11]. However, current treatments for LBD are predominantly pharmacological with significant risk of adverse outcomes, and do not effectively address the development of these risk factors or frailty in this cohort [12,13].

Conversely, non-pharmacological treatments such as exercise, which may offer a low-risk treatment option for improving frailty in LBD are

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inadequately researched [14] and sub-optimally utilised. Guidelines for managing frailty in older adults recommend robust anabolic exercise such as progressive resistance training (PRT) to target the weakness, mobility impairment and sarcopenia at the core of the frailty phenotype [15]. However, the efficacy of any exercise, including PRT, is unknown in LBD, therefore can only be inferred from the substantial body of literature on exercise that exists in the two diseases sharing some features of LBD: PD (for motor symptoms) and AD (for cognitive symptoms). Currently, anabolic exercise is increasingly recognised as an effective means to treat the cognitive and physical components of frailty in these two cohorts [16,17].

In PD for example, PRT significantly improves strength, physical function and balance, with higher training intensities and integration of challenging balance exercise further augmenting these improvements [18]. Cognition is also improved with resistance training over a two-year period [19], in contrast to the typical decline in cognition of 3.9% per year observed in this cohort [20]. Likewise, in frail dementia cohorts, PRT significantly improves cognition along with physical function, strength, and gait speed [21,22]. Furthermore, rapid improvement in muscle power (~30%), muscle volume (3–6%), and physical function (all of which contribute to frailty), are achievable in relatively short training programs of less than 3 months in both PD and dementia cohorts [23,24]. Thus, there is a compelling rationale to suggest that an anabolic exercise intervention may be effective in the treatment of frailty in LBD, yet no published evidence of its utility or feasibility to our knowledge. Therefore, we designed the first trial evaluating robust exercise in this cohort; The *PRomoting Independence in Lewy body Dementia through Exercise (PRIDE)* Study. This trial will provide preliminary insight into the feasibility of anabolic exercise as a novel treatment for frailty and functional independence in LBD.

1.1. Objectives and hypothesis

The primary aims of the PRIDE study are to:

1. Identify determinants of functional independence and quality of life (QoL) in individuals living with LBD that may be amenable to a targeted exercise intervention
2. Assess the feasibility, including adoption and adherence, adverse events, and preliminary efficacy of this evidence-based exercise program on important clinical outcomes in individuals with LBD, as well as QoL and stress in their caregivers

The primary hypotheses of the PRIDE study are:

1. Low muscle strength and balance will be associated with impaired performance-based tests of function and functional dependency in LBD at baseline.
2. A robust, progressive exercise intervention targeting strength and balance will improve functional independence in LBD, mediated in part by improvements in physiological capacity and performance-based tests of function.

2. Materials and methods

2.1. Study design

The PRIDE study involves participants from both community and aged care residential settings, and is a non-randomised, unblinded, crossover trial. A crossover design was chosen due to the anticipated small number of patients with LBD in the local area available for recruitment. Randomisation to order of control vs. intervention period is not possible in this exercise intervention as it is anticipated to result in physiological adaptations with no predictable persistence of effect after exposure. Blinding of the interventionist and the participant is not possible due to the nature of the intervention compared to usual care.

The assessor will not be blinded due to limited study resources.

The study design consists of a baseline assessment, followed by an 8-week wait-list usual care period, then a crossover to an 8-week intervention of anabolic exercise (Fig. 1). All assessment timepoints involve two separate assessment visits separated by one week and performed within the participant's residence (baseline) or the clinical facility at Cumberland campus, University of Sydney in Lidcombe, Australia (Fig. 1). All outcomes are measured at baseline, before and after the intervention. Intervention length was chosen based on literature in PD and AD cohorts to be sufficient to demonstrate improvement in outcome measures [22,25]. The trial was prospectively registered prior to commencement of recruitment on 08/04/2016 (ANZCTR Reg. ACTRN12616000466448) [26].

2.2. Ethics

Ethical approval was obtained from the University of Sydney Human Research Ethics (HREC 2: 2016/209). Consent is gained from caregivers for all participants, and written and/or verbal consent is gained from all participants where possible. The study adheres to the CONSORT guidelines for pilot trials [27] in the relevant sections.

2.2.1. Participants recruitment

Recruitment began in April 2016. Individuals with a diagnosis with LBD (either dementia with Lewy bodies or Parkinson's disease dementia) are recruited via geriatricians, neurologists, GPs, dementia and PD support groups and networks in the Sydney metropolitan area. Written informed consent of both the individual and caregiver is obtained.

Inclusionary criteria include:

- Diagnosis of LBD by a medical specialist which is confirmed by general practitioner
- Age over 55
- Ambulatory with/without assistance
- Ability to follow rudimentary instructions
- Ability to tolerate functional testing
- Ability to travel to gym facility (with caregiver) and complete 3 sessions/week for 8 weeks of exercise

Exclusionary criteria include:

- Inability to communicate in English
- Major musculoskeletal, cardiovascular or other neurological conditions precluding exercise as determined by study geriatrician
- Inability to follow simple commands or mimic movements by the assessor/interventionist-

2.2.2. Screening procedure

Participants and/or their caregivers are screened over the telephone via a 1-h screening questionnaire to determine eligibility for the PRIDE trial and are read the participant information statement. Questions relating to demographics (inclusive of caregiver), study eligibility, physical activity, current health status, prior and current injury and illness, prescribed medications, and medical professionals associated with care of the participant are asked. Medical information is sought from participant's GP or specialists after obtaining consent to further clarify eligibility as required. Additionally, comprehensive assessment of each participant is performed by the study geriatrician prior to commencing baseline one-repetition maximum (1RM) strength testing and exercise intervention.

2.2.3. Estimated sample size

Based upon similar cross-sectional studies in PD, to be able to show moderate correlations ($r = 0.5$) with $\beta = 0.20$ and $\alpha = 0.05$ for the baseline cross-sectional analysis, we calculate a minimum of 30 participants would be needed, taking into consideration a 20% expected

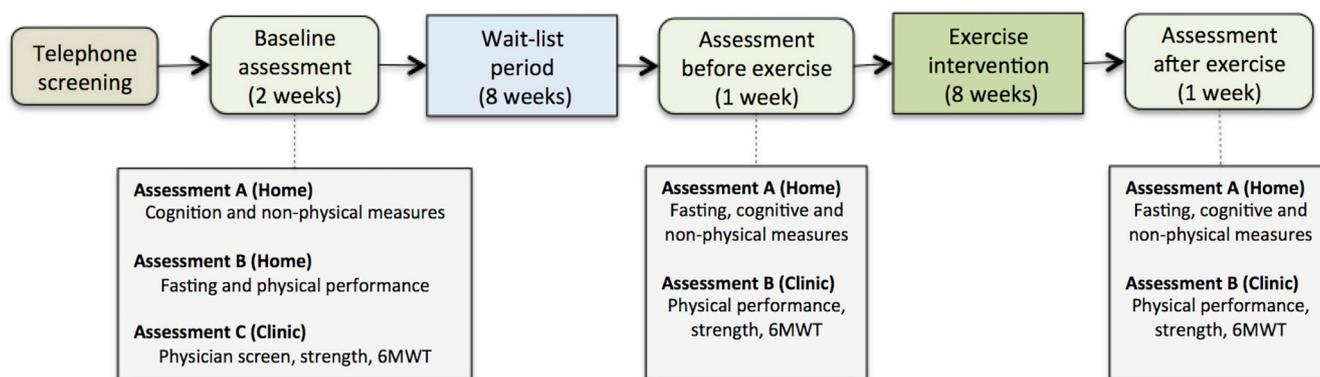


Fig. 1. Study design flow chart .

attrition rate. The power calculation for the fixed period crossover trial requires a minimum of 24 participants to demonstrate significance for an effect size of 0.61 (with $\beta = 0.20$ and $\alpha = 0.05$). These calculations are based upon results described in Rose and colleagues [25], who trained a cohort of individuals with moderate to severe PD for 8 weeks with the same primary functional independence outcome measure (MDS-UPDRS) we propose for PRIDE, but using an aerobic intervention.

2.2.4. Assessment procedures

The study coordinator, an accredited exercise physiologist (AEP), performs all assessment and intervention procedures with participants with the exception of the physician screen performed by the study geriatrician. The assessor is experienced in neuropsychiatric assessment, exercise training and assessment, and has completed required accreditation for administration of the MDS-UPDRS and FIM measures. There are two 4-h assessment sessions at baseline, before intervention and after intervention (Fig. 1) with an additional 3-h assessment session at baseline at the clinic, which includes the physician screen prior to 6-min walk test, and 1RM strength testing.

2.3. Intervention

2.3.1. Wait-listed usual care period

The wait-list usual care period involves the participant and caregiver continuing normal daily activities and routines. The study coordinator calls the caregiver weekly to monitor the status of the participant, and record any adverse events or changes in medications prescribed by the participant's health care providers.

2.3.2. Exercise intervention

Exercise training is conducted in the medically supervised clinic at the University of Sydney Cumberland campus (Lidcombe, Australia). Training sessions are conducted 3 day/week and have a maximum duration of 60 min each session. An AEP supervises the sessions that are conducted one-on-one with the participant and with the aid of the caregiver when required. The training sessions are divided into four training sections; *static balance*, *dynamic balance*, *functional practice*, and *progressive resistive exercise* (detailed in Fig. 2). Balance tasks and functional practice are performed prior to resistance exercise in order to avoid fatigue in the participant. The participant and caregiver are provided with a small snack following the sessions that contains approximately 13 g of protein and 1100 kJ of energy. The study coordinator calls the caregiver weekly to monitor the status of the participant and response to exercise, as well as record any adverse events or changes in medications. Details of each intervention component are described below, and in Fig. 2.

2.3.2.1. Static balance. Static balance is performed for a maximum of 10 min of the total session duration inside a custom-built apparatus

(Fig. 3). The participant stands in a position that challenges their postural stability, which is determined by choosing the most challenging balance position (e.g., narrow stance, tandem, etc.) that the participant had been able to hold for 15 s during the assessment before intervention. The participant interacts with the apparatus, a network of magnetic whiteboards positioned on a semi-immersive frame, by moving coloured button magnets in various tasks requiring manual dexterity, visuospatial and executive function, and reaching outside of the centre of gravity. The tasks progress with increasing cognitive and physical difficulty until performance plateaus, after which the stance position is progressed to a more unstable/difficult stance. The apparatus was purposely constructed to provide a safe area for the participant to stand with the assessor providing support if needed and direction from behind the participant. The dual-task activities are designed to promote natural, random movements outside of the centre of gravity and balance recovery manoeuvres performed under challenging cognitive conditions, which have been shown to improve balance and reduce falls risk in older adults [28,29].

2.3.2.2. Dynamic balance. Dynamic balance is performed by instructing the participant to walk in tandem for 5 m along a red tape line. The participant walks in tandem along the length, around a cone and returns the length in tandem while performing a physical dual-task (plate holding), with the addition of a cognitive task as the difficulty progresses. The assessor closely follows the participant for safety, and provides performance prompts and imagery such as walking with 'light feet on squeaky floorboards' to encourage fast moving feet and smooth movements. Prompting the participant to concurrently walk in tandem as fast as possible with minimal errors, and simultaneously perform the cognitive task to their best ability creates the challenging conditions necessary to improve performance in complex daily conditions in PD cohorts [28,29].

2.3.2.3. Functional training. Specific functional deficits identified during baseline assessment are practised during the session for a total of 5 min. Safe technique for daily tasks such as chair stands or descents and walking are practised under the supervision of the EP. Specific items practiced include correctly shifting gravity forward to rise from a chair with minimal assistance, locating the armrest of the chair before descending, and practising smooth walking in a controlled environment with no walking aids, under contact guard.

2.3.2.4. Progressive resistance exercise. The machine-based exercises (Fig. 2) are performed using K400 Keiser pneumatic machines (Keiser Sports Health Equipment, Ltd, Fresno, CA, USA) and are prescribed to participants to appropriately target muscle groups associated with maintaining independence, reducing falls risk, and aiding in posture in older adults [30,31]. The volume for each exercise consists of 2 sets of 6 repetitions at the target load for the session, and is chosen to provide

1. Static balance (10 minutes)		
Exercise	Volume	Intensity progression
Challenging balance exercises are performed on custom apparatus (A) with physical and cognitive dual-task. Conditions require reaching outside of centre of gravity in all planes, performing manual dexterity tasks and completing cognitive challenges such as mirroring and Stroop inhibition at fast processing speeds. Tasks are performed by moving coloured button magnets on magnetic whiteboards with gridlines.	5 attempts for a given position per side (~10 mins)	The balance position is initially set at the most challenging position successfully held in testing for 15 seconds. Simple physical dual-tasks (such as picking and placing) added initially, and progressed to cognitive dual tasks when improvements in speed of completion and errors plateau for two consecutive sessions. Cognitive dual-tasks include pattern replication, pattern mirroring and opposite colour pattern mirroring.
2. Dynamic balance (5 minutes)		
Exercise	Volume	Intensity progression
Heel-to-toe (tandem) walking (B) performed along a 5-m red line with a cone for turning. The participant tandem walks along the line, around the cone and back to the start as fast as possible while trying to make as few errors with feet placement as possible. A physical dual task (holding a plate and cup) and cognitive dual-task (category naming, arithmetic) is added for complexity and both tasks are coached simultaneously	5 attempts of 10-m course at maximal performance (~5 mins)	Initial intensity is set at fast tandem walk with no dual-task. Task is progressed when errors and time improvements plateau for two consecutive sessions. Physical dual-task with plate holding is initially added, and cognitive dual-task is added in addition to physical dual-task when similar criteria are met
3. Functional practice (5 minutes)		
Identified functional deficits with each participant are practised each session with technique instructed. For example, appropriate weight shifting for a chair stand (C), or supervised walking without a cane are practised in a controlled space		
4. High Intensity progressive resistance training (40 minutes)		
Exercise	Volume	Notes on technique & Intensity progression
Bilateral Leg Press (D) Knee Extension (E) Triceps Pushdown (F) Standing Hip Abduction (G) Standing Cable Row (H)	2 sets of 6 repetitions + warm up sets	Repetitions are performed with fast concentric phase prompted by somatosensory cueing (lobby bell, tapping muscle, verbal cues) and slow eccentric phase. Session 1 intensity is 70% of 1RM, and progresses to 80% 1RM by Session 4. Further progression each session is made when objective modified RPE score is < 8/10*

Exercises performed within the 60 minute session 3 days/week

Fig. 2. Exercise prescription - The four exercise components are combined sequentially in a 60-min session. The order of completion for each of the exercise components follows the order in the table, and is adjusted as tolerated by the participants.

sufficient dose [32] in the limited, 40-min duration allocated to PRT. The initial intensity is set at 70% of the testing 1RM and progresses to 80% 1RM by the 2nd week as previously described in PRT in older adults [33]. The intensity is progressed for a given exercise when the participant or assessor rating of perceived exertion (RPE) on the OMNI-Res scale [34] falls below 8/10, indicating that training adaptation has occurred for a given load. The concentric phase of each exercise is executed fast to target muscle power, with power training at higher

loads appropriate for older adults and those with parkinsonism due to a greater contribution of load rather than speed to peak power [35,36]. The eccentric phase is executed slowly to enhance metabolic benefit and hypertrophy [24]. The target tempo is 1 s concentric, no pause, and 3 s eccentric (1-0-3). Auditory (lobby bell, verbal encouragement) and somatosensory (tapping target muscle) cueing are engaged to promote fast movement initiation and sustain high intensity [35,37].



Fig. 3. Static balance dual-task apparatus - The custom-made apparatus, affectionately named 'Humphre' - consists of coloured button magnets, and magnetic whiteboards laterally, in front, and above the participant to allow completion of physical and cognitive dual-task. A grab bar in front of the participant provides additional support during the movement.

2.3.3. Adverse events

Monitoring of adverse events and all changes in health status and medical care/interventions is carried out via weekly telephone questionnaires with the caregiver and interview within sessions. Additional information is gathered from medical and nurse care teams if appropriate for participants residing within aged care facilities. Adverse events are defined *a priori* and include any exacerbation of underlying disease, or new onset musculoskeletal, cardiovascular or metabolic abnormalities. The study geriatrician and ethics committee evaluate all adverse events to ascertain if there is any relation to the study exercise or assessment protocols or need to change the study protocol.

2.3.4. Following trial completion

Following completion of the trial, participants are invited to continue exercising within the medically supervised clinic at no additional cost under the supervision of the clinic staff and students. There is no obligation to continue exercise beyond the study nor is there a limit on the total duration of participation beyond the trial.

2.4. Measures

The assessment battery (Table 1) was selected to evaluate the potential contributions of a wide range of factors to functional independence and quality of life in individuals with LBD.

2.4.1. Primary outcomes

2.4.1.1. Functional independence. Functional independence is measured via the total and sub-scores of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [38], which is an effective tool for evaluating disease severity, disability and independence in Parkinsonian disorders including LBD [39]. The original and current version of scale has been used to track changes in disease status previously in PD cohorts after exercise interventions [40,41], and is correlated with quality of life and independence [42,43].

Table 1
Primary and secondary outcome measures.

Domain	Description
Measure	
Primary outcome measures	
Functional independence	
Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) – sub scores and total score	A clinical rating scale validated in Parkinsonian cohorts involving four parts: Non-motor experiences of daily living, motor experiences of daily living, motor examination, motor complications. Total score (/272) and sub-scores used to capture change in disease-related function and independence, with higher scores indicating greater disease related disability and symptom burden [38].
Secondary outcome measures	
Functional independence	
Bayer-instrumental Activities of Daily Living (B-ADL)	The B-ADL is a 25-item informant or questionnaire sensitive to changes over time developed for pharmaceutical trials in dementia, and a valid indicator of functional impairments attributed to cognitive deficits. An averaged score between 1.00 and 10.00 is generated, whereby lower scores indicate less impairment in daily tasks [44].
Functional Independence Measure (FIM)	A scale used to track changes in patient disability comprising of 18 items grouped into motor and cognition parts. Scale applied in outpatient setting using caregiver reports and objective testing to summate functional independence. Scored between 18 and 128 with a higher score indicating greater levels of independence [45].
Cognitive	
Mini-mental State Exam (MMSE)	Well-validated, brief screening measure of cognitive function with sensitivity to changes over time. Scores range from 0 to 30, with higher scores indicating better function. Scores <24 suggestive of moderate or greater cognitive impairment [46].
Parkinson's Disease Cognitive Rating Scale (PD-CRS)	A comprehensive 9-part cognitive assessment specific to deficits typically observed in Parkinsonian disorders (executive function, visuospatial dysfunction) and very sensitive and specific to LBD. A higher score indicates better cognitive function, up until a maximum score of 134 [47].
Trail-making (TMT) A & B	Trials A & B evaluate speed of attention, sequencing, visual search and include a motor component. Trails B also assesses executive function [48]. This domain is known to be impaired in LBD [49]. Higher scores (time) taken to complete each tasks indicates greater impairment.
Benton Visual Retention Test (BVRT)	A visual memory and reconstruction test that evaluates visuospatial memory from simple designs and motor function. Sensitive to impairments specific to LBD [49]. Scored using an 'all-or-nothing' system whereby each of the 10 attempts are given '0' for incorrect image or '1' for correct image for a maximum of 10 points, where Higher scores indicate better function [50].
Psychiatric	
Geriatric Depression Score – 15 item (GDS-15)	A screening test used to assess level of depression in older adults with simple yes/no responses validated against structured clinical interview with good sensitivity and specificity. Designed to focus on non-somatic symptoms of

(continued on next page)

Table 1 (continued)

Domain	Description
Measure	
Neuropsychiatric Inventory (NPI)	depression to avoid overlap with physical illnesses in older adults. Higher scores indicate increasing depressive symptoms. A score of >5/15 is suggestive of depression, with higher scores indicating more depressive symptoms [51]. A comprehensive clinician-administered tool designed for proxy-reporting, involving 10 scored domains of behavioural disturbance occurring in dementia, and two additional domains involving sleep disturbances and eating behavior which do not form part of the final score. Presence of symptom, frequency, severity and caregiver distress rated for each relevant item. A symptom score (/12) and caregiver distress score (/5) is generated for each domain with higher scores indicating greater symptom impact and distress respectively [52].
Quality of life Dementia Quality of Life Scale & Proxy version (DEMqOL, DEMqOL - Proxy)	DEMqOL is a 28-part questionnaire administered to person with dementia asking questions relating to quality of life items potentially affected by symptoms of dementia. DEMqOL-PROXY is a 31-items questionnaire administered to the caregiver of the person with dementia asking about the perceived quality of life of the care recipient. Higher scores for both measures indicate better quality of life for the participants, with a Likert scale from '1' – all the time, to '4' not at all, being used to rate the frequency of each concern [53].
Satisfaction with Life Scale (SWLS)	A global 5-item scale rating overall life satisfaction. Rated on a 7-point scale from strongly disagree to strongly agree. Scored between 5 and 35, with higher scores indicating greater relative satisfaction with life, and 20/35 considered a neutral point between dissatisfaction and satisfaction with life [54].
University of Alabama Study of Ageing – Life Space Assessment (LSA)	The LSA provides insight into the mobility and travel patterns of the person within home and community ranging from in bedroom to unrestricted travel zones outside of community. The LSA is associated with quality of life and disability. Scored from 0 to 120 with a higher score indicating a greater life-space [55].
Physiological capacity Muscle strength	Maximal dynamic lower and upper extremity strength obtained using the digital K400 Keiser pneumatic machines (Keiser Corp, Fresno, CA, USA). Isometric strength assessed using the Chatillon CSD200 force dynamometer (Ametek Inc., Largo, FL USA) at all timepoints. Muscle groups assessed included hip and knee extensors, hop abductors, and triceps extension.
Isometric handgrip strength	Isometric strength of dominant and non-dominant hand assessed using JAMAR handgrip dynamometer (Sammons Preston, Bolingbrook, IL). Highest result of 3 trials in each hand used for analysis. A grip strength of <27 kg is a cut off point for sarcopenia [56].

Table 1 (continued)

Domain	Description
Measure	
6-min walk distance (6MWD)	Widely used test of walking endurance, which is a proxy for overall cardiovascular endurance in elderly adults with comprehensive normative data [57]. Total distance walked within 6 min recorded along with stoppages
Static balance	Assessed for 15 s in six different conditions (wide, narrow, semi-tandem and tandem stance, and on one leg without and with eyes closed). 2nd, 3rd and 4th position used in SPPB score calculation with 10s cut off.
Tandem walk	A heel-to-toe walk over 3 m performed at maximal pace with as minimal errors as possible. Two trials performed and fastest time used for analysis.
Physical performance Gait speed – Habitual and maximal	Habitual measured over a 3-m course with a stopwatch as specified in SPPB protocol [58], then measured along with maximal gait speed over 2-m distance from a dynamic start with an Ultra-timer (Raymar, Oxfordshire, UK). Average of times ultra-timer times used for analysis. A habitual walking speed of 0.8 m/s or less is a cut off for sarcopenia [56].
Chair stand	A proxy for lower extremity power, or the ability to generate high forces rapidly. Primarily, participants used hip and knee extensors muscles. Time taken to complete 5 stands recorded and used in the SPPB score calculation. A time of more than 15 s for the 5 stands is a cut off for sarcopenia [56].
Short Physical Performance Battery (SPPB)	Performance-based testing of functional mobility generating a score up to 4 points for three domains (gait speed, static balance, chair stand) for a total of 12 points. Higher score is indicative of better function and strongly predictive of mortality and nursing home placement [58]. A score of 8 or less is a cut-off for sarcopenia [56].
Cardiovascular Orthostatic blood pressure (BP) and heart rate (HR)	Measurement of orthostatic hypotension and HR in fasting state with rest (>5 min) in supine position, and then in standing position at 1 and 3 min. A drop in systolic of 20 mmHg and/or diastolic of 10 mmHg is indicative of orthostatic hypotension. HR response can also be suggestive of cause [59].
Body composition Anthropometry	Stretch stature height (BL only), weight (kg), and waist circumference (cm) are obtained in triplicate after overnight fast. BMI calculated (weight kg/height m ²).
Bioelectrical Impedence Analysis (BIA)	Whole body skeletal muscle mass (kg), fat free mass (kg) and skeletal muscle index calculated** using average resistance and reactance values measured in supine, fasted state with BIA analyser (RLJ Prizum, S/N B10875E, Mode BIA-101s)
Mini Nutritional Assessment –Short Form (MNA-SF)	A short clinician rated form to assess risk of malnutrition in elderly patients based on risk factors for reduced dietary intake. Score out of 14, with a score less than 8 considered malnourished [60].
Health status Medical history	Comprehensive physician screen performed by study Geriatrician

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Table 1 (continued)

Domain	Description
Measure	
Habitual physical activity	involving past medical history, review of systems examination Habitual physical activity, sedentary time and sleep patterns will be recorded using activity monitors (AX3, Axivity, Newcastle upon Tyne, UK) worn on lumbar spine.
Clinical Dementia Rating (CDR)	Commonly used dementia assessment tool for the assessment of dementia severity. Completed by clinician in conjunction with cognitive testing, and informant reports. Domain ratings range from 0 (no impairment) to 3 (severe impairment) and an algorithm using the total sum of domain scores (/18) is used to produce a summary score from 0 to 3 [61].
Adverse events	Any adverse events that occur during the study period will be detailed and adjudication from study geriatrician and ethics committee will inform whether related or unrelated to intervention.
Caregiver psychiatric and quality of life	
Geriatric Depression Scale (GDS-15)	See secondary outcomes – psychiatric section in table for description.
Satisfaction With Life Scale (SWLS)	See secondary outcomes – quality of life section in table for description.
Positive and Negative Affect Scale (PANAS)	A scale consisting of 10 positive items and 10 negative items to measure affect. Rated from not feeling a particular emotion [1] to feeling the emotion extremely [5] over a period of a few hours. A score range between 10 and 50 is generated separately for both positive affect items and negative affect items. In the positive items a higher score indicates more positive affect, and lower scores on the negative items indicate less negative affect [62].
Quality of Life Scale (QOLS)	A 5-domain scale consisting of 16 items evaluating quality of life in the caregiver. Total score summated. Scored between 16 and 112 with a higher score indicating greater overall quality of life [63].
Zarit Burden interview-22 item	A 22-item scale measuring levels of caregiver burden relating to the care of a person with dementia and correlated with behavioural problems in care recipient and depression in caregiver. Rated from 0 to 88, a higher score indicates increased caregiver burden [64].

** *Skeletal muscle mass (SMM) = 0.401(height in cm²/resistance in ohms)+3.825 (sex: male = 1; female = 0)+age in years(-0.071) + 5.102 [65]. Fat-free mass (FFM) = -4.03 + 0.734 (height in cm²/resistance in ohms) +0.116 (body weight in kg) + 0.096 (reactance in ohms) +0.984 (sex: male = 1; female = 0) [66].

2.4.2. Secondary outcomes

A range of secondary outcomes including *cognition, psychosocial, quality of life, cardiovascular, body composition, health status, physical performance, exercise capacity and additional function independence* measures are assessed. Additionally, *caregiver burden and psychosocial outcomes* are assessed. Table 1 details the total list of assessments performed.

2.5. Statistical analysis

All data will be evaluated visually and statistically for normality of distribution, and transformed prior to use in parametric statistics as

required. Descriptive measures will be generated from the baseline cross-sectional data, including means (standard deviations), medians (ranges) or frequencies, as appropriate. Associations between variables of interest will be evaluated through simple linear regression for normally distributed data; otherwise Spearman's correlation will be used. Primary intention-to-treat (ITT) analysis for all primary and secondary outcomes will be conducted using repeated-measures mixed models across all three time points: Baseline (T₁), prior to exercise (T₂), and after exercise (T₃). A secondary all-available data (AAD) analysis will be conducted using repeated measures analysis of variance (ANOVA). Statistical significance will be defined as $\alpha < 0.05$. When the main effect of TIME is significant in mixed models or ANOVAs, all pairwise comparisons will be analysed via *post-hoc* Bonferroni *post-hoc* t tests to investigate differences across the wait-list, intervention, and total trial periods. Additionally, Cohen's d effect sizes (ESs) will be calculated for primary and secondary outcomes during the exercise intervention period using the formula:

$$T_3 - T_2 / SD_{T_2}$$

Interpretation of these ESs will conform to standard definitions of small (0.2-<0.5), medium (0.5–0.8), and large (>0.8). Feasibility will be assessed via adoption & adherence rates; reported as percentage completion and compared with reported adherence from similar cohorts. Safety will be monitored via tabulation of adverse events ascertained from a variety of sources as described in Section 2.3.3. Statistical analysis will be performed using SPSS software (Version 26, SPSS, Inc, Chicago).

3. Discussion

The primary aim of this study is to evaluate the determinants of functional independence in LBD and the effect of a targeted exercise intervention. LBD is a disease with complex, rapid progressing and fluctuating symptoms, which warrants the assessment of a comprehensive range of clinically meaningful outcomes including physical function, strength, cognition, quality of life, psychiatric, and nutritional outcomes. Unfortunately, individuals with LBD are often excluded from trials of exercise in PD and other dementias due to this complex combination of motor and cognitive symptoms, which are perceived as potentially compromising to the homogeneity of cohort characteristics and adaptations(14). Additionally, the fluctuating nature of the disease course and difficulty with recruitment is a major barrier to conducting exercise research in this cohort, just as it is for the conduct of pharmaceutical trials in LBD(2). As a result, the literature pertaining to exercise and LBD is scarce, and consists of only a few case reports and fragments of trial data evaluating non-anabolic, motor interventions such as low intensity recumbent cycling, skill, and gait training.

The PRIDE study is the first empirical trial evaluating the feasibility of an exercise intervention in LBD, and will provide much needed data to contribute to the under-researched field of non-pharmacological therapies in LBD. As such, the trial responds to recommendations from the international *Forth Consensus Report of the DLB Consortium* to develop and evaluate non-pharmacological therapies in this disease [67]. The data collected from this pilot study will provide valuable information on ESs for the major outcomes, and thus refine estimates of samples sizes requirements for adequately powered future trials. In addition, the feasibility of assessment tools and training techniques in this population will be evaluated. Importantly, the PRIDE Study will provide an opportunity for those individuals typically excluded from clinical trials to participate in an intervention specifically designed for their needs while advancing knowledge in this field.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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