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Effect of customized Health Qigong exercise on freezing of gait and falls in Parkinson's disease: protocol for a single blind randomized controlled trial

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ABSTRACT

Introduction Parkinson's disease (PD) patients with freezing of gait (FOG) demonstrate a sudden inability to step forward or continue walking, resulting in falls or fall-related injury and independent activity loss. Many studies have shown that Health Qigong exercise is a safe, effective mind–body exercise to improve gait function and decrease fall risk. However, studies of the efficacy of customized Health Qigong on PD are rare. Our study will select twelve forms of Health Qigong exercise and investigate the effect of tailor-made Health Qigong exercise on gait function and fall reduction in PD patients.

Methods and analysis We propose a single-blind randomized control trial, recruiting 90 PD patients with FOG. They will randomly assigned to a Health Qigong exercise group, balance exercise group, and a control group by a computer-generated random-sequence table. The Health Qigong group will engage in customized Qigong exercise three times per week for one hour each session. The balance exercise group will focus on static and dynamic balance exercise. The control group will receive health education. The duration of this trial will be 12 weeks. All the participants will be assessed at baseline, 12 weeks (end of intervention), and 3 months follow-up. The primary outcomes will assess the gait parameter and occurrence of FOG. The secondary outcomes will assess the postural instability and walking disability, falls and fearing of fall, quality of life.

Ethics and dissemination This study has been approve by the ethics committee of Shanghai University of Sport. All the participants or their guardians signed informed consent prior to the study. The findings of the study will be submitted to peer-reviewed journals or academic conferences.

Trial registration China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on 6 June 2018.

Keywords Freezing of gait, Falls, Randomized control trial, Health Qigong, Parkinson's

disease

Strengths and limitations of this study

1.The customized Health Qigong exercise for gait improvement is targeted the mild to moderate Parkinson's disease by the research team of multidisciplinary professionals. In addition, it suits for Parkinson's disease patient to practice for a long time because of easy movement to practice as well as without site restriction.

2.The randomized controlled trial design reduces the factors of bias.

3.It is difficult to achieve a blinded intervention for this study because exercise as an intervention is open to the participants.

INTRODUCTION

Freezing of gait (FOG) is a paroxysmal syndrome in Parkinson's disease, and is characterized by sudden and brief episodes of an inability to produce effective forward progression. Freezing of gait occurs in the late stage of Parkinson's disease, which leads to increased risk of falls and loss of independent activities.[1] Although not all patients with PD develop FOG, between 21% and 27% of PD report FOG experience in early stages. However, the number of patients experiencing FOG increases up to 80% in all advanced PD patients.[2-4] Patients with FOG perform shuffling with small steps, tremble in place without forward movement, or experience total akinesia.[5] Patients often have difficulty in turning, transferring, walking across an obstacle, and have a sudden inability to start or continue walking, while their upper body continues its original trajectory. A freezing episode usually lasts 1–2 s, although some episodes exceed 30 s and a patient will fail to generate any steps long enough to provide useful ambulation.[6, 7]

With progression of the disease, patients with severe FOG have postural instability and gait dysfunction, causing difficultly in managing activities of daily life and frequently fall. The complex pathophysiology of the FOG remains poorly understood but is thought to be relative to degeneration of nigral-striatal dopaminergic neurons,[8] specifically an inhibitory striatal output nuclei projecting to the motor thalamus and brainstem locomotor regions.[5, 9] The prominent characteristics of frozen gait present a prolonged step initiation duration as a potential hallmark of impending freezing. This gait dysfunction can increase the risk of falling as it is often unexpected. Thus, intervention programs in the form of gait training may reduce the risk of falls in these patients.

Currently, wide application of multidisciplinary approaches combined with pharmacological and surgical treatment manage FOG. Current studies have verified the

effectiveness of non-pharmacological treatment for improving abnormal gait, including physiotherapy, physical exercise and occupational therapy. While advances have been made in holistic rehabilitation,[10] PD is an incurable and degenerative disease that affects functional activities and quality of life. An easily executed and low-cost therapeutic technique is necessary for PD patients to live independently. Previous studies have shown some inexpensive exercises without equipment, such as Tai Chi, dance, and yoga, demonstrating benefits in improving motor symptoms for PD patients.[11]

Traditional Chinese medicine is a unique therapeutic intervention applicable for disease prevention, treatment, or rehabilitation in chronic disease. Health Qigong exercise is one type of traditional Chinese exercise which incorporates meditative movements, breathing patterns, and mental regulation. The exercises are performed in a slow, relaxed manner which promote a sense of relaxation, improves balance and posture, and enhances physiological function of internal organs in an energy-efficient and comprehensive way.[12, 13] Most importantly, practicing Health Qigong is low cost and easy to learn, without equipment or site restrictions. Therefore, Health Qigong exercise has great therapeutic potential in chronic disease.

A growing number of studies have shown that Health Qigong exercise can improve muscle strength and balance in older adults. A systematic review and meta-analysis provided evidence that elderly people who practice Health Qigong exercise have enhanced equilibrium function and reduced fall risk.[14] Practicing Health Qigong requires slow movement, body control in space, and shifting body weight in different directions; thus; transfer of body posture can be beneficial to improving sense of balance and prevent falls.[12] In addition, Health Qigong exercise produces significant improvements in gait speed, stride length, and leg movement ability in PD patients.[15, 16]

Health Qigong consists of nine categories of exercise, including Baduanjin, Liuzijue,

Daoyin,12-step Dao Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Each exercise has its own characteristics and efficacy for a variety of diseases. Few studies have clarified the effect of combining different categories of Health Qigong on gait function and fall risk. Moreover, some studies concentrated on the efficacy of combined Tai Chi with Qigong,[13, 17] or one type of Qigong therapeutic effect on Parkinson's disease.

These two traditional Chinese exercises have similar theories and principles, but different movement patterns and treatment effects on disease. Qigong emphasizes the flow of qi harmony in the body and improves health via mind–body exercise, combined with coordinated rhythmic movements and regulated breathing.[18] Tai Chi is a martial art that highlights the maintenance of mental and body balance while neutralizing a rival's attack; the prominent motion is diagonal and requires slow movement in all planes via a constantly altering range.[19] They have differences in action routine, level of difficulty, and scale of activities. Therefore, we will select forms from nine categories to tailor Health Qigong exercise for PD patients to generate positive benefits for gait function.

The aim of this trial protocol is to explore a combination of different forms of Health Qigong and determine any improvement in freezing of gait and prevention of falls in patients with Parkinson's disease. We hypothesize that combining different forms of Health Qigong customized to the patient may ameliorate freezing of gait and thus lower the risk of falls in PD patients.

METHODS

Study design

The study design is a prospective, single-blind randomized controlled trial.

Design and procedures

We will recruit participants from Shanghai, China by means of the neurology department of the local hospital and TV programs during the same recruitment period. To reduce the potential expectation bias and confirm eligibility, a research assistant will make telephone contact with those referred by a neurologist and follow up with interested participants. Participants will be informed that the study will be conducted in three different groups, and will be randomly assigned to one group. The experimental group will perform Health Qigong exercise under instructor guidance, the balance exercise group will perform static and dynamic postural control training, and the control group will receive health education. The total intervention period will be 12 weeks, simultaneous for all patients. The primary and secondary outcomes will be assessed at baseline (pre-intervention), 12 weeks (end of intervention) and 3 months follow-up (see figure 1). Potential eligible participants who satisfy initial inclusion criteria will arrange a 2 hour to visit our research laboratory and register their personal information. The trial protocol has been approved by the ethics committee of Shanghai University of Sports. All participants who meet the inclusion and exclusion criteria will sign informed consent prior to the study. The protocol is registered as a China Clinical Trial (ID: ChiCTR1800016570).

Participants

Inclusion criteria

1) PD patients were diagnosed according to the clinical diagnostic criteria of UK; 2) age between 40 and 80 years old; 3) Hoehn & Yahr scale 1–3; 4) item three of the Freezing of Gait Questionnaire (FOGQ) scored M¸□5) Mini–Mental State Examination (MMSE) score >24; 6) ability to walk independently; and 7) have had a fall over the past year.

Exclusion criteria

1) Participation in Qigong exercise during the last year; 2) other diseases that could

interfere with conduct of the study protocol such as cardiopulmonary disease, liver and kidney disease, musculoskeletal dysfunction, or cancer; 3) severe cognitive, visual or auditory impairment; 4) unstable medication; 5) deep brain stimulation.

Sample size calculation

The power calculation is based on a pilot study of PD patients with similar characteristics to those of the patients in this trial, we estimated the effect size at least 35%, statistical sample size of 80% and alpha level of 0.05 calculated by G*Power 3.1.9.2 software (Franz Faul, Universitat Kiel, Germany). Considering a 10% attrition rate, the total sample size would be 90 participants, with 30 participants in each group.

Randomization and blinding

The study design will utilize a single blinded randomized controlled trial. Two trained assessors will be blinded to group allocation and will not participate in the intervention. Using computer generated random number sequencing (STATA 12.0, StataCorp LP, Texas, USA) in a ratio of 1:1:1, a random number will be put in a sealed envelope, and participants will be allocated randomly to a Qigong group, balance exercise group, or control group by extracting the envelope. Participants will reassessed for baseline measures on another day. This study is difficult to achieve the blinded to participants because exercise as an intervention is open to the participants.

Intervention

Health Qigong exercise group

The Health Qigong group will perform the exercise interventions in the sports science laboratory of Shanghai University of Sports. The Qigong protocol consist of twelve-forms of exercise, respectively selected movements from the Health Qigong

exercise guidelines organized and compiled by the China Qigong Management Center. The selection of movements will emphasize dynamic postural control and body weight shift stepping with lateral-medial and anterior-posterior, body symmetry pulling to upper-down and left-right, hand and eye coordination movement. The twelve forms of exercise are as follows:[20]

- *Form one*: Xu Exercise (Liu Zi Jue)
- *Form two*: CHUI Exercise (Liu Zi Jue)
- *Form three*: Raising the Tiger's Paws (Wu Qin Xi: Tiger Exercise)
- *Form four*: Holding the Hands High with Palms Up to Regulate the Internal Organs (Ba Duan Jin)
- *Form five*: Drawing a Bow (Mawangdui Daoyin Exercises)
- *Form six*: Posing as an Archer Shooting Both Left-and Right-Handed (Ba Duan Jin)
- *Form seven*: Pulling Nine Cows by Their Tails (Yi Jin Jing)
- *Form eight*: Rub Backbone (Da Wu)
- *Form nine*: Swaying Like a Bear (Wu Qin Xi: Bear exercise)
- *Form ten*: Picking Fruit (Wu Qin Xi: Money exercise)
- *Form eleven*: Golden Rooster Heralds the Dawn (12-Step Dao Yin Health Preservation Exercise)
- *Form twelve*: Flying Like a Bird (Wu Qin Xi: Bird Exercise)

Two instructors certified by the Chinese Health Qigong Association will instruct Qigong exercise. The beginning stage (i.e. the first 2 weeks) will emphasize learning the movement via practicing single forms with repetitions, while the later stages will concentrate on movement consistency and integrity of form. The instructors will correct the movements and participants will repeat the exercises in subsequent session to consolidate learning. A complete set of exercises will be performed in about 20 minutes. Participants will perform each exercise twice and rest with intervals of 5 minutes. Natural

breathing will be integrated into the Qigong movement routine. Each participant will receive Qigong exercise for 3 sessions per week for 12 consecutive weeks. Each session will consist of 10-minute warm-up, 40-minute Health Qigong exercise, and 10-minute cool-down. The heart rate of all the participants will be monitored by Polar-team^2 (Polar Electro, Finland) during training.

Balance exercise group

All balance exercises will be guided by two trained instructors. The participants in the balance exercise group will follow their regular medication scheme and perform balance exercise in their medication stage. They will engage in a 12-week intervention, with 3 sessions per week. Each training session will start with a 10 minute warm-up consist of breathing exercise, slow walking, and range-of-motion exercises. The 40-minute balance exercise includes a short resting time, and the training program consists of the following: 1) static balance exercise: standing on unstable surfaces to maintain postural control and progress to weight Shifting; 2) dynamic balance: postural control in standing position while adding upper limb and trunk movement; 3) balance strategy exercise: focus on hip strategy under maintain ankle strategy and stepping strategy under interference in different directions; 4) adaptation of varying base of support, standing in narrow space and uneven surface;[21] and 5) walk integrated balance training: walk a straight line, walk on soft blanket, and side walk. The end of training will include a 10-minute cool-down session of limb ROM movements, sustained stretching, and relaxing.

Control group

The control group will be instructed to maintain their formal lifestyle and not to engage in any other form of intensive training. They will receive health education every 4 weeks over the 12-week intervention period. The health education will involve information for Parkinson's disease related treatments and prevention such as modality of exercise,

regimen, preventing falls, and nutrition. Participants will receive a brochure of health education and will have follow-up by telephone twice per month.

All participants will maintain diaries to record their exercise and fall events every day throughout the trial, including both in the laboratory and at home. The participants in the Health Qigong exercise group and balance exercise group will perform the exercise at "on" stage in the morning.

Outcome measures

All measures will be performed at baseline, 12 weeks (end of intervention), and 3 months following the completion of the intervention. The measures will be conducted by two trained assessors and videotaped by a third assessor. All assessors will be blinded to the participant's group allocation and time of assessment.

Participants characteristics

Demographic and health characteristics of participants will be collected at baseline to describe the sample, compare conditions, and investigate characteristics associated with outcomes. It will include age, gender, education, age at onset and disease duration, health status, use of medication, resting blood pressure, body mass (kg/m^2), and height (cm). Blood pressure will be measured with the use of an automated device (Omron HealthCare). Body mass and height will be assessed with digital scales (Weighing scale & Meter)(see table 1).

Table 1 Demographic and clinical characteristics of the study participants*

	Health Qigong (N=)	Balance (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index[a]—kg/m^2			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
M□			
Age of onset—yr			
Duration of disease—yr			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status[b]—no. (%)			
Poor or fair			
Good			
Very good or excellent			
Falls in previous 6 months—no.			

* Mean values (standard deviation). The chi-square test is used for categorical variables, and one-way analysis of variance for continuous variables.

[a] The body-mass index is the weight in kilograms divided by the square of the height in meters

[b] Self-reported health status, included cardiovascular disease, lung disease, osteoporosis, arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions per participant ranged from 0 to 9.

Primary outcome assessment

Gait parameters were analyzed by a 10-camera Vicon Motion Analysis System (Vicon MX-13, Oxford Metrics, Oxford, UK) at 200 Hz, and reaction force at 1000 Hz will be recorded using force plates (models 9286AA, Kistler Instruments Corp., Winterthur, Switzerland), with Vicon Nexus 1.5.2 and Polygon 3.5.1 analysis software to process kinematic and kinetic parameters. According to the plug-in gait marker set, the trajectories of 45 reflective markers (14 mm in diameter) will be captured at different landmarks of the participants.[22, 23]

Freezing of Gait Questionnaire (FOG-Q) will measure the occurrence of FOG during the daily activity. It is constituted of three parts, part I (item 1, score is 0 or 1) detects the presence of FOG and distinguishes if patients are freezers or non-freezers if they have a FOG experience during the past month. Part II (items 2–6, score range 0 to 9) assesses the severity of FOG according to its duration and frequency in its common appearance. Item 2 was added to rate the overall frequency of FOG regardless of environment. Part III (items 7–9, score range from 0 to 9) assesses the influence of FOG on daily life, and the total score ranges from 0 to 28; higher scores reflects more severe FOG.[24]

Participants will asked to write the exercise diary to record their falls event. Data on fall will collected from the first day of intervention to the end of follow-up.

Secondary outcome assessment

Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults and Parkinson's disease, which has shown good reliability and validity in the clinic. It includes walking forward, backward, with eyes closed, stepping over obstacles, changing gait speeds, with different head turns, and with a narrow base of support. The FGA

includes 10 total items, with each item scored 0 to 3. A higher total score reflects better balance and walking ability, with a maximum score of 30.[25, 26]

Postural instability and gait disability will evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait, tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The modified Hoehn and Yahr scale was also used to evaluate disease severity.[27]

Falls and fear of fall were measured with the 14-item Modified Falls Efficacy Scale (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of daily living without falling. Each item was scored on a 10-point scale, with a minimum score of 0 indicating no confidence and a maximum score of 10 indicating full confidence (high falls efficacy) in performing the tasks without falling. The average score across all 14 items will be taken, with higher scores indicating greater falls efficacy.[28, 29]

The quality of life will be assessed using the 39-item Parkinson's Disease Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A summary index of eight domain scores ranges from 0 to 100, with higher scores representing worse health related quality of life (HRQoL).[30, 31]

The data collected are depicted in table 2.

305 **Table 2** Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up *	Mean difference at 12-weeks**	Mean difference at Follow-up**	*F(P Value)* Time Effect	*F(P Value)* Group Effect	*F(P Value)* Interaction Effect
Primary Outcome								
Stride length (cm)								
Health Qigong								
Balance								
Control								
Gait velocity (cm/sec)								
Health Qigong								
Balance								
Control								
NFOG								
Health Qigong								
Balance								
Control								
Total falls,								

no.								
Health Qigong								
Balance								
Control								
Secondary Outcome								
FGA								
Health Qigong								
Balance								
Control								
Health Qigong								
Part-III								
Balance								
Control								
MFES								
Health Qigong								
Balance								
Control								
PDQ-39								
Health Qigong								

Balance								
Control								

*Mean values (standard deviation).

**Mean difference (standard error).

Abbreviations: FGA, functional gait assessment; MDS-UPDRS Part-III, movement disorder society unified Parkinson's disease rating scale, motor subscale; MEFS, falls and fear of fall; PDQ-39, Parkinson's disease questionnaire.

Patient and Public involvement

Participants have not been involved in the study recruitment. The authors conceived the initial research questions and outcome measures, and modified according to the telephone interview with patients and their guardians by a research assistant. In order to assure the safety and feasibility of the intervention, we invited six patients with mild to moderate Parkinson's disease to learn and practice customized Health Qigong exercise before designing the RCT. The Health Qigong movements were revised base on the exercise performance and feedback provided by the participants. The burden of the intervention will assessed by patients and their advisors before signing informed consent. The findings of the study will be disseminated to the participants and their guardians.

Statistical Analysis

The statistical analysis will be performed using SPSS 22.0 software (Company city state). Baseline values of demographic differences in Qigong group and control group will be examined using Chi-squared tests. The analyses will be performed on an intention-to-treat based on original group assignment. The primary outcome and secondary outcome over time (i.e., baseline, 12 weeks, after 3 months follow-up) will be analyzed by mixed design repeated-measures analyses of variance (RM-ANOVA) for between- and within-group differences. Bonferroni's post hoc test will be applied to compare results where main effects are significant. Data will be expressed as the mean and standard deviation, and significance will be set at $p < 0.05$.

DISCUSSION

Medical treatment integrated with exercise therapy are still indispensable methods to manage the motor dysfunction for PD patients. Freezing of gait is common in PD patients which contributes to a protective postural response impairment and increases the risk of

falls. Nevertheless, this balance instability can be improved by extra training.[32] Qigong exercise can increase range of motion of joints, such as the shoulder, sacroiliac, and knee joints, and thus improve trunk flexibility and physical coordination.[33, 34]

Patients with Parkinson's disease exhibit difficulty in transitions from static to dynamic states. Transition activity is a vital component of physical activities, especially gait initiation, turning, and gait termination. Due to the deficiency in postural control, patients generate excessive trunk movement causing sway beyond the limits of stability and thus leading to falls.[35] Wuqingxi is a type of Qigong exercise that imitates the posture of five animals: the tiger, bear, crane, monkey, and deer. The bear swaying movement refers to changes in the center of gravity of the body, strength of the waist muscles and the sequence of the force-release transfer to lower limb muscles. Bear sway contributes to the ability to control the lower limbs and prevents unnecessary injuries in daily life. The monkey exercise requires practitioner to imitate a monkey climbing a tree to pick fruit, and involves stepping backward and forward while simultaneously extending the arm to pick fruit, and thus integrates eye-hand coordination.[36, 37] The Baduanjin movement "Posing as an Archer Shooting Both Left-and-Right-Handed" is akin to drawing the bow in a horse stance, with the chest puffed out and stretching of the shoulders back. This improves the tightness of muscles and joints and restores limb proprioception, strengthens the muscles and adjusts the breathing to promote a body that is more flexible, spiritual, and physically in harmony.[38] Xu Zi Jue and Chui Zi Jue can regulate breathing movements by diaphragmatic breathing and pursed lip breathing to expand lung capacity. These exercises have shown to improve walking endurance.[39, 40] Therefore, combining specific targeted Health Qigong movements based on the patient's specific gait dysfunction in PD can help regain walking ability and independent activities for mild to moderate PD patients.

Furthermore, Health Qigong is characterized by slow movement incorporated with

moderated breathing, as well as keeping the mind in a state of calm relaxation. The intensity of Health Qigong is around 1.5 to 2.6 metabolic equivalents (METs) and the average induced maximum heart rate ranges from 43% to 49% of the predicted maximum.[41] Thus, Health Qigong is a low-intensity physical exercise which has lower risk of muscle strain and overfatigue and is suitable for PD patients as a long-term physical exercise program.

For a variety of features of gait pattern, whatever muscle stiffness or abnormal postural control, we may consider the global or specific efficacy of Health Qigong on gait function in PD.[42] We expect that a 12-week customized Health Qigong exercise can improve muscle stiffness, postural stability, and joint flexibility in PD patients. This could enhance balance function and locomotion during walking. However, gait deficiency in PD patients is a complex syndrome and is associated with neural control regulated by different areas of the brain, particularly the prefrontal lobe and related circuits.[43] In future studies, we will explore the mechanism of the different forms of Qigong on brain activities, combining imaging with functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS),[44] to determine if the Health Qigong exercise is beneficial to restore brain function or prevent brain degeneration. We still consider that environmental changes influence gait performance, and therefore tailor-made Qigong movements are necessary to PD patient adapt to various contexts. We hope this trial will demonstrate that the tailored Health Qigong exercise possesses positive effects on recovery of gait function and prevention of falls for mild and moderate PD patients. This will provide a supplemental therapy that can be applied to improve physical dysfunction, improve quality of life, and increase longevity.

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Competing interests None declared.

Contributors Zhenlan Li, Jie Zhuang and Zheng Wang conceived the conception and design of the trial, and to drafting the manuscript. Guiping Xiao and Kuncheng Jie participated in trail registration, communication, and monitoring. Yan Jiang and Tian Wang carried out the statistical calculation. All authors participated in revision of the manuscript and approved the final version.

Patient consent Obtained.

Ethics approval This work was approved by the ethics committee of science research of Shanghai University of Sport(protocol number: 2018031).

Provenance and peer review Not commissioned;externally peer reviewed

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Figure Legend

Figure 1 Flow diagram of study design.

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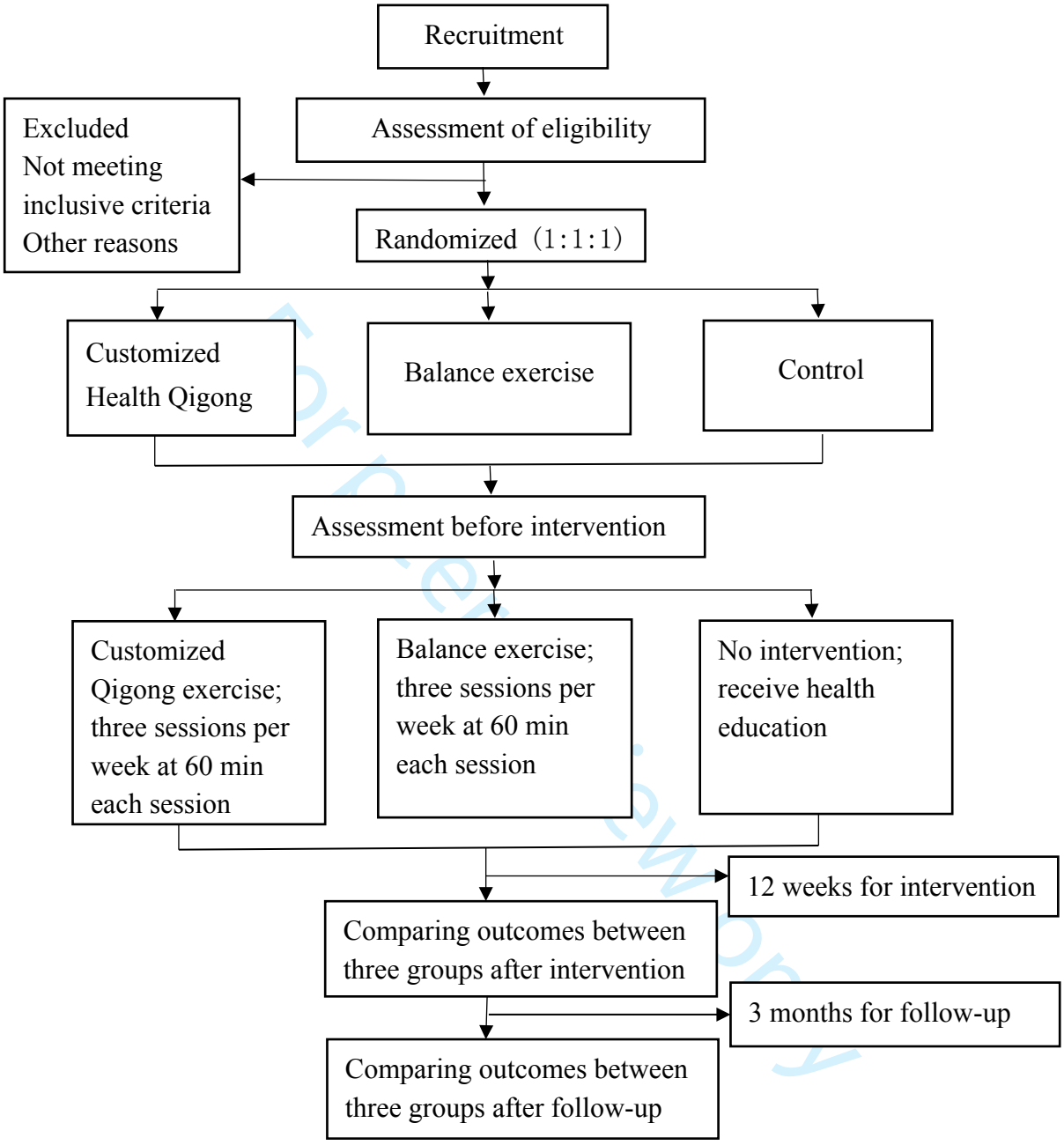

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title(P1)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P17)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P17-18)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale(P3)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses

Trial design**(P9)**	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting**(P9)**	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria**(P8-9)**	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions **(P9-12)**	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes **(P12-14)**	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline**(Figure1)**	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size**(P9)**	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment**(P8)**	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation**(P9)**	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism **(P9)**	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation **(P8)**	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) **(P12)**	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods**(P14)**	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management **(P14)**	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods**(P14)**	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring **(n/a)**	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms **(n/a)**	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing **(n/a)**	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval **(P8)**	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments **(n/a)**	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent **(P8)**	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality **(see informed consent)**	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests **(n/a)**	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data **(n/a)**	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care **(n/a)**	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy **(n/a)**	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials **(see informed consent)**	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens **(n/a)**	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Study protocol for a single-blind, randomized controlled trial evaluating clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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Keywords:	gait interruption, exercise, neurodegenerative disease, movement disorder

Study protocol for a single-blind, randomized controlled trial evaluating clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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ABSTRACT

Introduction

Qigong exercise offers a potentially safe, low-cost, and effective mind–body rehabilitative intervention for mitigating the problem of gait interruption among Parkinson's disease (PD) patients who have frequent freezing of gait (FOG) episodes. However, its clinical effects have not been established. This paper describes the trial protocol of evaluating the clinical efficacy of a newly developed Integrated Qigong in improving gait among PD patients with FOG.

Methods and analysis

A single-blind, randomized, controlled trial comparing Integrated Qigong and balance training, relative to an attention control. Participants will be mild to moderate PD patients who experience FOG and recruited from local communities in the city of Shanghai, China. Participants will be randomly allocated to one of the three arms: Integrated Qigong, a balance exercise intervention, or an attention control group. The total number of participants will be 126, and masked assessments will be administered at baseline, 12 weeks (end of intervention), and 12-week follow-up. Both Integrated Qigong and balance training groups receive a group-based exercise intervention that meets three times per week, 60 minutes in duration, for 12 weeks. The control group receives a 60-minute group session per week and monthly health education. The primary outcome measures are gait (stride length, gait velocity, stride time variability) and occurrence of FOG. The secondary outcomes are postural instability and walking disability, falls, fearing of falling, and quality of life.

Ethics and dissemination This study has been approved by the ethics committee of Shanghai University of Sport and registered at China Clinical Trial Registry (ChiCTR1800016570). Participants will sign informed consent prior to the participation of the trial. The findings of the study will be published in peer-reviewed academic journals

and disseminated to PD support groups, medical community, and media.

Trial registration China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on 6 June 2018.

Keywords gait interruption, exercise, neurodegenerative disease, movement disorder

Strengths and limitations of this study

1. The first study that combines commonly practiced Qigong exercises into a single rehabilitative intervention aimed at improving gait outcome for PD patients with FOG.
2. The findings of the study will inform patients and healthcare providers of an alternative, potentially low-cost and safe, effective, and easily implementable exercise intervention for treating and managing gait interruption in patients with PD.
3. The study patients will come from one geographic area that limits the generalizability.

INTRODUCTION

Freezing of gait (FOG) is characterized by a sudden and brief episodic absence or marked reduction of forward progression. The syndrome is most common among patients with Parkinson's disease(PD).[1] It is estimated that between 21% and 27% of early stage patients report FOG episode with number increasing up 80% among those in advanced stages.[2-4] Patients with FOG often show difficulty in turning, transferring, walking, and experience and inability to start or continue walking. As the disease progresses, patients with severe FOG develop postural instability and gait dysfunction, causing difficulty in managing activates of daily living and frequent falls and, consequently, impact negatively on quality of life.[5, 6]

There are multidisciplinary approaches, including pharmacological and surgical based treatment for managing FOG among people with PD. Current research evidence has shown, however, effectiveness of non-pharmacological and rehabilitation based intervention, including physiotherapy, physical exercise, and occupational therapy, for improving abnormal gait in patients with FOG.[7, 8] Increasing evidence also suggests the effectiveness of various alternative exercise interventions to ameliorate motor symptoms and improve gait. Theses include low-cost, non-equipment dependent exercises such as Tai Chi, dance, and yoga.[9]

In this study, we focus on Health Qigong exercise which is one of traditional Chinese exercises that incorporates meditative movements, breathing patterns, and mental regulation. The exercises are performed in a slow, rhythmic, relaxed manner; features that are conducive to organs.[10,11] Growing evidence supports the health benefits of Health Qigong. A systematic review and meta-analysis indicates that older adults who practice Health Qigong show an improved balance and postural control and reduced fall risk among individuals with PD.[12] Health Qigong has also been shown to improve gait speed, stride length, and leg movement ability.[13,14]

Qigong consists of various types, including Baduanjin, Liuzijue, Daoyin, 12-step Dao Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Although each of them has its own training characteristics, they nevertheless share some common features. In general, Qigong integrates both static and dynamic exercises with a great emphasis on regulating breath, and exercising intrinsic control and mental intent.[15] Exercise of Qigong is characterized by trunk rotation, bending and extending at waist and movement of limbs both medial-laterally and anterior-posteriorly, all driven by the core of the body.[14,16] Like other techniques such as Tai Ji Quan, Qigong exercise also involves dynamic movements that involves intermittent stepping and turning. As such, exercise involves postural demanding movements such as single leg standing and chirographic and manipulative moving postures.[17,18] Furthermore, Qigong exercise requires regulating breathing by engaging in diaphragmatic to expand lung capacity and control upright posture.[19,20]

To date, there has been little effort made to evaluate the therapeutic effect of combing different types of Qigong exercise on gait in individuals with PD. This paper describes the trial protocol of a newly developed Integrated Qigong intervention that combines seven types of commonly exercised Qigong into a single rehabilitation program for mild to moderate PD patients with FOG. Specifically, we aim to determine the therapeutic effect of the Integrated Qigong intervention on gait. We hypothesize that, relative to an attention control group, both Integrated Qigong and a conventional balance training intervention will be clinically more effective in improving the primary outcome of gait.

METHODS

Study design

The study design is a prospective, single-blind randomized controlled trial.

Design and procedures

We will recruit participants from Shanghai, China by means of the neurology department of the local hospital and TV programs during the same recruitment period. To reduce potential expectation bias and confirm eligibility, a research assistant will make telephone contact with those referred by a neurologist and follow up with interested participants. Participants will be informed that they will be randomly assigned to three different groups. The integrated Qigong exercise group will engage in training program that combines seven types of commonly exercised Qigong, the balance training group will perform static and dynamic postural control training, the two intervention groups will receive the guidance of instructor, and the control group will receive group session per week and monthly health education. The total intervention period will be 12 weeks, and will occur simultaneously for all participants. The primary and secondary outcomes will be assessed at baseline (pre-intervention), 12 weeks (end of intervention) and 12-week follow-up (see figure 1). Potential eligible participants who satisfy initial inclusion criteria will arrange a two-hour visit at our research laboratory and register their personal information. The trial protocol has been approved by the ethics committee of Shanghai University of Sport. All participants who meet the inclusion and exclusion criteria will sign informed consent prior to the study. The protocol is registered as a China Clinical Trial (ID: ChiCTR1800016570).

Participants

Inclusion criteria

(1) PD patients were diagnosed according to the clinical diagnostic of UK Brain Bank

criteria; (2) age between 40 and 80 years old; (3) Hoehn & Yahr scale of 1–3; (4) item three of the New Freezing of Gait Questionnaire (NFOGQ) scored ≥1; (5) Mini–Mental State Examination (MMSE) score >24; (6) ability to walk independently; and (7) have experienced a fall over the past six months.

Exclusion criteria

(1) Participation in Qigong exercise during the last year; (2) other diseases that could interfere with conduct of the study protocol such as cardiopulmonary disease, liver and kidney disease, musculoskeletal dysfunction, or cancer; (3) severe cognitive, visual or auditory impairment; (4) unstable medication; and (5) deep brain stimulation.

Sample size calculation

A statistical analysis was conducted for sample size estimation using G*power 3.1 (Franz Faul, Universita Kiel, Germany). The study was powered to detect a between-group difference in primary gait outcome measures between Qigong exercise and Balance training groups relative to the attention control groups. Because there was no a priori hypothesis formulated between the two active interventions (Qigong exercise and Balance Training), the study was not powered on these two conditions. Due to the lack of informed preliminary data and empirical evidence on the effects of Qigong exercise, we approximated the effect size in our power calculations using estimated from the published studies that compared Qigong exercise with a control condition on gait (i.e., gait speed, freezing of gait, and mobility).[13,14] In general, these studies, with an intervention length ranging from 10 weeks to 24 weeks, have shown a weak intervention effect, with effect sizes ranging from no effect to small-to-moderate effects. On the basis of these observations , a conservative approach was taken. Specially, we used a small effect size (η^2=0.01) based on the partial eta squared estimate within the ANOVA framework.[21]

Our initial power estimates indicated that, in a mixed-effect repeated measures design with a between-subject factor (Integrated Qigong, Balance training, Control), and a within-subject factor (baseline, 12 weeks) and a correlation of 0.08 on the repeated measures, a sample size of 99 subjects would be required to achieve an 80% power at an 0.05 error rate. To be more conservative, we estimated the sample sizes based on a range of small sizes (f=0.08, f=0.10, f=0.12). The sample sizes generated from these calculations were averaged to arrive at a total of 107 subjects. With an anticipated 15% attrition rate, a final enrollment number of 126 (42 in each group) was set for the study to detect a difference in gait outcomes between Integrated Qigong and Balance Training relative to the attention control group.

Randomization and blinding

The study design will utilize a single blinded randomized controlled trial. Two trained assessors will be blinded to group allocation and will not participate in the intervention. We will apply the stratified random sampling method by stage of the disease (H&Y Stage). Using computer generated random number sequencing (STATA 12.0, StataCorp LP, Texas, USA) in a ratio of 1:1:1, a random number will be placed in a sealed envelope, and participants will be allocated randomly to a Qigong group, balance training group, or control group by extracting the random number from the envelope. Participants will be reassessed for baseline measurements on another day. This study is not amenable to blinding to participants of their designated experimental groups because the interventional exercises they perform will reveal their group allocation.

Intervention

The participants in all groups will follow their regular medication scheme during the study

period. Both integrated Qigong and balance training groups will receive group-based exercise intervention at the sports science laboratory of Shanghai University of Sport. The group size is 10-15 people in order to provide sufficient instructional attention to each participant, one trained instructor will guide the participants to perform the exercises. The two interventional groups will perform three weekly sessions of 60 minutes per session for 12 consecutive weeks. Each session will consist of 10 minutes of warm-up, 40 minutes of core exercises, 5 minutes of break intervals, and 5 minutes of cool-down. The heart rates of the participants will be monitored by Polar-team^2 (Polar Electro, Finland) during training. Participants in the interventional groups will be required to not perform any additional in-home exercises throughout the 12 weeks of training.

Integrated Qigong exercise group

The Integrated Qigong protocol will consist of twelve-forms of exercise, with selected movements from the Health Qigong exercise guidelines organized and compiled by the China Qigong Management Center. The integrated Qigong exercise will emphasize dynamic postural control and body weight shift stepping with lateral-medial and anterior-posterior movements, body symmetry pulling across up-down and left-right axes, hand-eye coordination movement. The twelve forms of exercise have been seen previously documented[22] and can be seen in Figure 2.

During initial 2-3 weeks, training will mainly emphasize learning and practicing two or three forms through multiple repetitions along with review of previously learned movements. The practice in each session concentrate on upper and lower limbs in place, trunk rotation, as well as stepping in different directions (i.e., forward, backward, sideways, diagonal). Participants will be requested to perform personalized movement requirements based on functional level. The range of motion of each movement will be reduced for participates with rigidity. The pace of movement will be decreased for

participate with bradykinesia. For participates with freezing, they will be instructed to perform transferring and stepping while maintaining postural stability. The intensity, difficulty of movement, time, and frequency will be adjusted to demands of each participant. The later weeks concentrate on improving balance, locomotion, and action consistency, participants will practice each movement with six repetitions, and natural breathing will be incorporated into the movement routine. Participants will be guided to perform the entire range of movement in which they fell safe.

Balance training group

Each training session will start with a 10 minute warm-up consist of breathing exercise, slow walking, and range-of-motion exercises. The 40-minute balance training will include a short resting time, and the training program will consist of the following: 1) static balance training: standing on unstable surfaces to maintain postural control and progression to weight shifting; 2) dynamic balance training: postural control in standing position while adding upper limb and trunk movements; 3) balance strategy exercise: focus on hip strategy while maintaining ankle strategy and stepping strategy under interference in different directions; 4) adaptation of varying base of support, and standing in a narrow space and on uneven surface;[23] and 5) walk integrated balance training: walk in a straight line, walk on a soft blanket, and sideways. The training will progress from simple to complex, static to dynamic, low to high the center of gravity, wide to narrow the base of support, and will continue to raise challenges in regard to flexibility, stability and range of movement. The end of training will include a 5-minute cool-down session of limb ROM movements, sustained stretching, and relaxing.

Control group

The control group will be instructed to maintain their formal lifestyle and not to engage in

any other form of intensive training. The participant in control group will join one 60-min group session per week, which will consist of a 30-min lecture, 20-min discussion, and will be followed by a 10-min question and answer session. Participants in control group will receive health education every four weeks over the 12-week interventional period. The health education will involve information for PD-related treatments and prevention such as modalities of exercise, regimens, fall prevention, and nutrition. Participants will receive a brochure of health education and will have follow-up by telephone twice per month, which will involve discussion of physical activity, progression of disease, health status, and psychological status.

All participants will maintain diaries to record their exercise and fall events every day throughout the trial, including both in the laboratory and at home. The participants in the Health Qigong exercise group and balance training group will perform the exercises at the "on" stage in the morning.

Outcome measures

All measurements will be performed at baseline, 12 weeks (end of intervention), and 12 weeks following the completion of the intervention. The measurements will be conducted by two trained assessors and will be videotaped by a third assessor. All assessors will be blinded to the participant's group allocation and time of assessment.

Participants characteristics

Demographic and health characteristics of participants will be collected at baseline to describe the sample, compare conditions, and investigate characteristics associated with outcomes. These characteristics will include age, gender, education, age at disease onset, disease duration, health status, use of medication, resting blood pressure, body mass (kg/m^2), height (cm), family situation and physical performance. Blood pressure will be measured with the use of an automated device (Omron HealthCare). Body mass and height

will be assessed with digital scales (Weighing scale & Meter) Physical performance will be measured by the scores from self-reported habitual physical activity scale. (See Table 1)

Table 1 Demographic and clinical characteristics of the study participants*

	Integrated Qigong (N=)	Balance Training (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index[a]—kg/m^2			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
≥3			
Age of onset—yr			
Duration of disease—yr			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status[b]—no. (%)			
Poor or fair			
Good			
Very good or excellent			
Family situation-no. (%)			
Living along			
Living with husband/wife			
Living with husband/wife and children			
Score for Self-reported habitual physical activity[c]			
Falls in previous 6 months—no.			

* Mean values (standard deviation). The chi-square test is used for categorical variables, and one-way analysis of variance for continuous variables.

[a] The body-mass index is the weight in kilograms divided by the square of the height in meters

[b] Self-reported health status, included cardiovascular disease, lung disease, osteoporosis, arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions per participant ranged from 0 to 9.

[c] This is measured by the Physical Activity Scale for the Elderly,[24] with higher scores indicating higher levels of habitual physical activity

Primary outcome assessment

Gait will be analyzed using a 7-m-long instrumented computerized walkway (GAIRite, CIR, System Inc., Franklin, NJ), and will include gait velocity, stride length, and stride time variability. Gait velocity is crucial parameter for walking coordination and can be used as basic factor for the assessment of normal and pathological gait. [25] Gait variability is a valuable indicator of whole-gait performance and can reflect gait disorder. Stride length and stride time variability are sensitive measures that related to fall risk in older people. [26, 27]

New freezing of gait questionnaire (NFOG-Q) is a reliable tool to detect and assess the influence and severity of FOG. It consists of the following three parts: (1) part I (item 1, score is 0 or 1) detects the presence of FOG and distinguishes if patients are freezers or non-freezers if they have had a FOG experience during the past month; (2) part II (items 2–6, score range from 0-9) assesses the severity of FOG according to its duration and frequency and its common appearance. Item 2 was added to rate the overall frequency of FOG regardless of the environment; (3)part III (items 7–9, score range from 0-9) assesses the influence of FOG on daily life, and the total score ranges from 0-28; higher scores reflects more severe FOG.[28]

Secondary outcome assessment

Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults and individuals with PD and has shown good reliability and validity in the clinic. FGA includes under following conditions: forward, backward, with eyes closed, stepping over obstacles, changing gait speeds, with different head turns, and with a narrow base of support. The FGA includes 10 total items, with each item scored from 0-3. A higher total score reflects better balance and walking ability, with a maximum score of 30. [29, 30]

Postural instability and gait disability will be evaluated by the Unified Parkinson's

Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait, tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The modified Hoehn and Yahr scale has also been used to evaluate disease severity.[31]

Falls frequency will be reported at the baseline test, during the 12-week training period, and at 12-week of follow-up. A blind assessor will record fall event based on the following definition of falling: "a person unintentionally coming to rest on the ground or other lower level, not occurring as a result of a major intrinsic overwhelming hazard."[32] The following approaches will be used to ascertain the fall event: (1) monthly collection of fall diary, (2) monthly phone interview, and (3) self-report from each assessment.

Falls and fear of falling will measured with the 14-item Modified Falls Efficacy Scale (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of daily living without falling. Each item is scored on a 10-point scale, with a minimum score of 0 indicating no confidence and a maximum score of 10 indicating full confidence (high falls efficacy) in performing the tasks without falling. The average score across all 14 items will be taken, with higher scores indicating greater falls efficacy.[33, 34]

The quality of life will be assessed using the 39-item Parkinson's Disease Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A summary index of eight domain scores ranges from 0 to 100, with higher scores representing worse health related quality of life (HRQoL).[35, 36]

The data collected are depicted in Table 2.

Table 2 Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up*	Mean difference at 12-weeks**	Mean difference at Follow-up**	*F(P Value)* Time Effect	*F(P Value)* Group Effect	*F(P Value)* Interaction Effect
Primary Outcome								
Stride length (cm)								
Integrated Qigong								
Balance training								
Control								
Gait velocity (cm/sec)								
Integrated Qigong								
Balance training								
Control								
Stride time Vabililty(CV)								
Integrated Qigong								

Balance training								
Control								
NFOG								
Integrated Qigong								
Balance training								
Control								
Secondary Outcome								
FGA								
Integrated Qigong								
Balance training								
Control								
MDS-UPDRS Part-III								
Integrated Qigong								
Balance training								
Control								
Total falls,								

no.								
Integrated Qigong								
Balance training								
Control								
MFES								
Integrated Qigong								
Balance training								
Control								
PDQ-39								
Integrated Qigong								
Balance training								
Control								

*Mean values (standard deviation).

**Mean difference (standard error).

Abbreviations: CV, coefficient variation; NFOG, new freezing of gait questionnaire; FGA, functional gait assessment; MDS-UPDRS Part-III, movement disorder society unified Parkinson's disease rating scale, motor subscale; MEFS, falls and fear of fall; PDQ-39, the 39-item Parkinson's disease questionnaire.

Patient and Public involvement

Participants will not been involved in the study recruitment. The authors conceived the initial research questions and outcome measures, and modified according to the telephone interview with patients and their guardians by a research assistant. In order to assure the safety and feasibility of the intervention, we invited six patients with mild to moderate Parkinson's disease to learn and practice Integrated Qigong exercise before designing the RCT. The Integrated Qigong movements were revised based on the exercise performance and feedback provided by the participants. The burden of the intervention will assessed by patients and their advisors through face-to-face interview before signing informed consent. The findings of the study will be disseminated to the participants and their guardians.

Statistical Analysis

The statistical analysis will be performed using SPSS 22.0 software(IBM Corp, Armonk, New York). Baseline values of demographic differences in intervention groups and control group will be examined using Chi-squared tests. The primary outcome and secondary outcome over time (i.e., baseline, 12 weeks, after 12-week follow-up) will be analyzed by mixed design repeated-measures analyses of variance (RM-ANOVA) for between- and within-group differences. Bonferroni's post hoc test will be applied to compare results where main effects are significant. Data will be expressed as the mean and standard deviation or standard error, and significance will be set at $p < 0.05$. An intention-to-treat analysis will be adopted to deal with missing data, including all participants in the analysis based on the initial group allocation.

DISCUSSION

Medical treatment integrated with exercise therapy is still an indispensable method to

manage the motor dysfunction for PD. FOG is common in people with PD which contributes to a protective postural response impairment and increases the risk of falls. Nevertheless, this balance instability can be improved by extra training.[37] Qigong exercise synthesizes training in balance, flexibility, neuromuscular coordination, and cognition, it consists of body consciousness, attention, imagination, multiple activities and goal-oriented training which may benefit to the improvement of improve gait and postural control, beyond conventional single-mode exercise.[38]

Patients with PD exhibit difficulty in transitions from static to dynamic states. Transitional activity is a vital component of physical activities, especially gait initiation, turning, and gait termination. Due to the deficiency in postural control, patients generate excessive trunk movement that causes swaying beyond the limits of stability and, thus, lead to falling. [39] Qigong practice requires the center of gravity moves and changes accompany with the movement of the upper limb, slow movement, body control in space, and shifting body weight in different directions. Thus, Qigong practice can be beneficial to improve the ability to focus on the base of support and postural stability. Moreover, Qigong exercise can enhance core muscle to stress weight-bearing joints and to increase proprioception input of trunk and lower limb joint. Most Qigong movements involve closed-chain exercise of the lower limbs, and contribute to rectifying deficiencies of heel stride and knee extension on gait cycle. [14, 38] In addition, the meditative movement in Qigong exercise can relieve psychological load and consumption, which may benefit for practitioner to reduce muscle tension, and alleviate effect of freezing on stepping forward. [40]

Furthermore, Qigong is characterized by slow movement incorporated with moderated breathing, as well as keeping the mind in a state of calm relaxation. The intensity of Qigong is around 1.5 to 2.6 metabolic equivalents (METs) and the average induced maximum heart rate ranges from 43% to 49% of the predicted maximum.[13]

Thus, Qigong is a low-intensity physical exercise that has lower risk of muscle strain and overfatigue and is suitable for individuals with PD as a long-term physical exercise program.

For a variety of features of gait pattern, whatever muscle stiffness or abnormal postural control, we may consider the global or specific efficacy of Qigong on gait function in PD.[41] We expect that a 12-week Integrated Qigong exercise can create positive therapeutic effects on PD patients with FOG. However, gait deficiency in individuals with PD is a complex syndrome and is associated with neural control regulated by different areas of the brain, particularly the prefrontal lobe and related circuits.[42] In future studies, we might focus on the mechanism of the different forms of Qigong on the relationship between brain activities and FOG, and explore whether Qigong exercise is conducive to restoring brain function and/or preventing brain degeneration. We hope that this trial will demonstrate that the Integrated Qigong exercise promote the recovery of gait function and prevention of falls for people with mild and moderate PD. The results of this study may furnish evidence to support the beneficial effects of Qigong exercise on improvement of walking ability and reduction of fall risk in people with PD. The findings of this study will provide evidence for a supplemental therapy to manage gait disorder for clinicians and physical therapist.

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Competing interests None declared.

Contributors Zhenlan Li, Jie Zhuang and Zheng Wang conceived the conception and design of the trial, and drafted the manuscript. Guiping Xiao, Kuncheng Jie and Wenhan Yin participated in trial registration, communication, and monitoring. Yan Jiang and Tian Wang carried out statistical calculations. Yu Zhang provided medical clearance and Parkinson's disease stage diagnoses for the participating patients. All authors participated in revision of the manuscript and approved the final version.

Patient consent Obtained.

Ethics approval This work was approved by the ethics committee of science research of Shanghai University of Sport(protocol number: 2018031).

Provenance and peer review Not commissioned;externally peer reviewed

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Figure Legend

Figure 1 Flow diagram of study design.

Figure 2 Twelve forms of Integrated Qigong exercise.

A: Form one: Xu Exercise

B: Form two: Chui Exercise

C: Form three: Raising the Tiger's Paws

D: Form four: Holding the Hands High with Palms Up to Regulate the Internal Organ

E: Form five: Drawing a Bow

F: Form six: Posing as an Archer Shooting Both Left-and Right-Handed

G: Form seven: Pulling Nine Cows by Their Tails

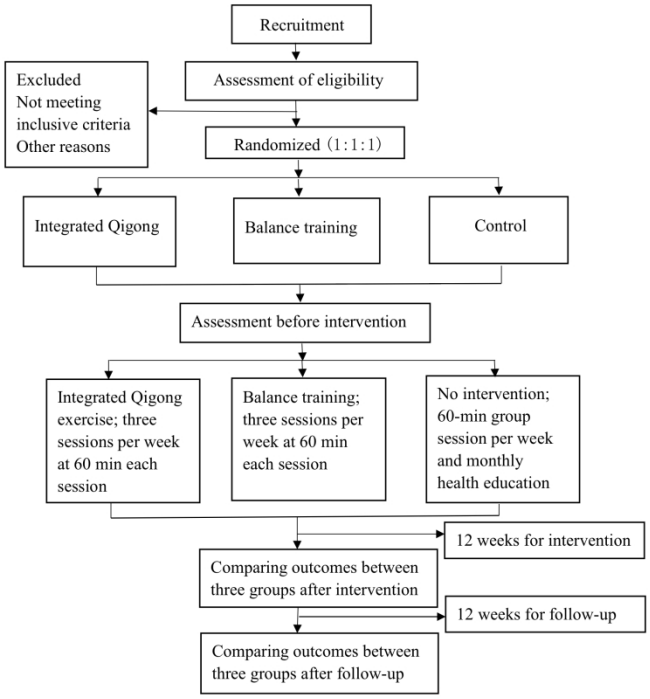
H: Form eight: Rub Backbone

I: Form nine: Swaying Like a Bear

J: Form ten: Picking Fruit

K: Form eleven: Golden Rooster Heralds the Dawn

L: Form twelve: Flying Like a Bird



Flow diagram of study design.

209x297mm (300 x 300 DPI)

Twelve forms of Integrated Qigong exercise.

90x90mm (600 x 600 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title(P0)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P21)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P22)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale(P3)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives(P3)	7	Specific objectives or hypotheses

Trial design**(P5)**	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting**(P8)**	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria**(P6)**	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions **(P8-10)**	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes **(P10-15)**	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline**(Figure1)**	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size**(P6-7)**	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment**(P5)**	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation**(P7)**	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism **(P7)**	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation **(P7)**	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) **(P7)**	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods**(P10)**	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management **(P19)**	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods**(P19)**	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring **(n/a)**	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms **(n/a)**	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing **(n/a)**	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval **(P5)**	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments **(n/a)**	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent **(P5)**	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality **(see informed consent)**	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests **(n/a)**	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data **(n/a)**	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care **(n/a)**	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy **(n/a)**	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials **(see informed consent)**	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens **(n/a)**	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A study protocol for a single-blind, randomized controlled trial to evaluate clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Geriatric medicine, Rehabilitation medicine
Keywords:	gait interruption, exercise, neurodegenerative disease, movement disorder

A study protocol for a single-blind, randomized controlled trial to evaluate clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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ABSTRACT

Introduction

Qigong exercise offers a potentially safe, low-cost, and effective mind–body rehabilitative intervention for mitigating the problem of gait interruption among Parkinson's disease (PD) patients who have frequent freezing of gait (FOG) episodes. However, its clinical effects have not been established. This paper describes the trial protocol of evaluating the clinical efficacy of a newly developed Integrated Qigong in improving gait among PD patients with FOG.

Methods and analysis

A single-blind, randomized, controlled trial is designed to compare Integrated Qigong and balance training with an attention control. Participants will be mild to moderate PD patients who experience FOG and are recruited from local communities in Shanghai, China. Participants will be randomly allocated to one of the three groups: Integrated Qigong group, a balance exercise intervention group, or control group. The total number of participants will be 126, and masked assessments will be made at baseline, 12 weeks (end of intervention), and 12-week follow-up. Both Integrated Qigong group and balance training group will receive a group-based exercise intervention that meets three times per week, 60 minutes in duration, for 12 weeks. The control group will receive a 60-minute weekly group session and monthly health education. The primary outcome are gait parameters (stride length, gait velocity, stride time variability) and occurrence of FOG. The secondary outcomes are postural instability, walking disability, falling, fear of falling, and quality of life.

Ethics and dissemination This study has been approved by the ethics committee of Shanghai University of Sport and registered at China Clinical Trial Registry (ChiCTR1800016570). Participants will sign informed consent prior to the participation of the trial. The findings of the study will be published in peer-reviewed academic journals

and disseminated to PD support groups, medical community, and media.

Trial registration China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on 6 June 2018.

Keywords gait interruption, exercise, neurodegenerative disease, movement disorder

Strengths and limitations of this study

1. The first study that combines commonly practiced Qigong exercises into a single rehabilitative intervention aims at improving gait outcomes for PD patients with FOG.
2. The findings of the study will inform patients and healthcare providers of an alternative, potentially low-cost and safe, effective, and easily implementable exercise intervention for treating and managing gait interruption in patients with PD.
3. The patients will come from one geographic area which limits the generalizability.

INTRODUCTION

Freezing of gait (FOG) is characterized by a sudden and brief episodic absence or marked reduction of forward progression. The syndrome is most common in patients with Parkinson's disease(PD).[1] It is estimated that between 21% and 27% of early stage patients report FOG episode with number increasing up 80% among those in advanced stages.[2-4] Patients with FOG often show difficulty in turning, transferring, walking, and experience and inability to start or continue walking. As the disease progresses, patients with severe FOG develop postural instability and gait dysfunction, causing difficulty in managing daily life and frequent falls, which consequently impact on the quality of life.[5, 6]

There are multidisciplinary approaches, including pharmacological and surgical based treatment for managing FOG among people with PD. Current research evidence has shown, however, effectiveness of non-pharmacological and rehabilitation based intervention, including physiotherapy, physical exercise, and occupational therapy, for improving abnormal gait in patients with FOG.[7, 8] More researches suggest that various alternative exercise interventions can ameliorate motor symptoms and improve gait. Theses interventions include low-cost, non-equipment dependent exercises such as Tai Chi, dance, and yoga.[9]

In this study, we focus on Health Qigong exercise which is one of traditional Chinese exercises that incorporates meditative movements, breathing patterns, and mental regulation. The exercises are performed in a slow, rhythmic, relaxed manner; features that are conducive to organs.[10,11] Growing evidence supports the health benefits of Health Qigong. A systematic review and meta-analysis indicates that older adults who practice Health Qigong improves balance and postural control and reduces fall risk among individuals with PD.[12] Health Qigong also improves gait speed, stride length, and leg movement ability.[13,14]

Qigong consists of various types, including Baduanjin, Liuzijue, Daoyin, 12-step Dao Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Although each of them has its own training characteristics, they nevertheless share some common features. In general, Qigong integrates both static and dynamic exercises with a great emphasis on regulating breath, and exercising intrinsic control and mental intent.[15] Exercise of Qigong is characterized by trunk rotation, bending and extending at waist and movement of limbs both medial-laterally and anterior-posteriorly, all driven by the core of the body.[14,16] Like other techniques such as Tai Ji Quan, Qigong exercise also involves dynamic movements with intermittent stepping and turning. Besides, exercise involves postural demanding movements such as single leg standing and chirographic and manipulative moving postures.[17,18] Furthermore, Qigong exercise requires regulating breathing by engaging in diaphragmatic to expand lung capacity and control upright posture.[19,20]

To date, there has been little effort to evaluate the therapeutic effect of combing different types of Qigong exercise on gait in individuals with PD. This paper describes the trial protocol of a newly developed Integrated Qigong intervention that combines seven types of commonly exercised Qigong into a single rehabilitation program for mild to moderate PD patients with FOG. Specifically, we aim to determine the therapeutic effect of the Integrated Qigong intervention on gait. We hypothesize that, compared to control group, both Integrated Qigong and conventional balance training intervention will be clinically more effective in improving the primary outcomes of gait.

METHODS

Study design

The study is designed as a prospective, single-blind randomized controlled trial.

Design and procedures

We will recruit participants from Shanghai, China by means of the neurology department of the local hospital and TV programs during the same recruitment period. To reduce potential expectation bias and confirm eligibility, a research assistant will make telephone contact with those referred by a neurologist and follow up with interested participants. Participants will be informed that they will be randomly assigned to three groups. The integrated Qigong exercise group will engage in training program that combines seven types of commonly exercised Qigong. The balance training group will perform static and dynamic postural control training. The two intervention groups will receive the guidance of instructor, and the control group will receive weekly group session and monthly health education. The total intervention period will be 12 weeks, and will occur simultaneously for all participants. The primary and secondary outcomes will be assessed at baseline (pre-intervention), 12 weeks (end of intervention) and 12-week follow-up (see figure 1). Potential eligible participants who satisfy initial inclusion criteria will arrange a two-hour visit at our research laboratory and register their personal information. The trial protocol has been approved by the ethics committee of Shanghai University of Sport. All participants who meet the inclusion and exclusion criteria need to sign informed consent prior to the study. The protocol is registered as a China Clinical Trial (ID: ChiCTR1800016570).

Participants

Inclusion criteria

(1) PD patients diagnosed according to the clinical diagnostic of UK Brain Bank criteria; (2) age between 40 and 80 years old; (3) Hoehn & Yahr scale of 1–3; (4) item three of the New Freezing of Gait Questionnaire (NFOGQ) scored ≥1; (5) Mini–Mental State Examination (MMSE) score >24; (6) ability to walk independently.

Exclusion criteria

(1) Participation in Qigong exercise during the last year; (2) other diseases that could interfere with conduct of the study protocol such as cardiopulmonary disease, liver and kidney disease, musculoskeletal dysfunction, or cancer; (3) severe cognitive, visual or auditory impairment; (4) unstable medication; (5) deep brain stimulation.

Sample size calculation

A statistical analysis was conducted for sample size estimation using G*power 3.1 (Franz Faul, Universita Kiel, Germany). The study was powered to detect a between-group difference in primary gait outcome measures between Qigong exercise group and balance training group relative to the attention control group. Because there was no a priori hypothesis formulated between the two active interventions (Qigong exercise and balance training), the study was not powered on these two conditions. Due to the lack of informed preliminary data and empirical evidence on the effects of Qigong exercise, we approximated the effect size in our power calculations using estimated from the published studies that compared Qigong exercise with a control condition on gait (i.e., gait speed, freezing of gait, and mobility).[13,14] In general, these studies, with an intervention length ranging from 10 weeks to 24 weeks, have shown a weak intervention effect, with effect sizes ranging from no effect to small-to-moderate effects. On the basis of these observations, a conservative approach was taken. Specially, we used a small effect size (η^2=0.01) based on the partial eta squared estimate within the ANOVA framework.[21] Our initial power estimates indicated that, in a mixed-effect repeated measures design with a between-subject factor (Integrated Qigong, balance training, control), and a within-subject factor (baseline, 12 weeks) and a correlation of 0.08 on the repeated measures, a sample size of 99 subjects would be required to achieve an 80% power at an 0.05 error rate.

To be more conservative, we estimated the sample sizes based on a range of small sizes (f=0.08, f=0.10, f=0.12). The sample sizes generated from these calculations were averaged to arrive at a total of 107 subjects. With an anticipated 15% attrition rate, a final enrollment number of 126 (42 in each group) was set for the study to detect a difference in gait outcomes between Integrated Qigong and balance training relative to the attention control group.

Randomization and blinding

The study design will utilize a single blinded randomized controlled trial. Two trained assessors will be blinded to group allocation and will not participate in the intervention. We will apply the stratified random sampling method by stage of the disease (H&Y Stage). Using computer generated random number sequencing (STATA 12.0, StataCorp LP, Texas, USA) in a ratio of 1:1:1, a random number will be placed in a sealed envelope, and participants will be allocated randomly to Integrated Qigong group, balance training group, or control group by extracting the random number from the envelope. Participants will be reassessed for baseline measurements on another day. This study is not amenable to blinding to participants of their designated experimental groups because the interventional exercises they perform will reveal their group allocation.

Intervention

The participants in all groups will follow their regular medication scheme during the study period. Both Integrated Qigong group and balance training group will receive group-based exercise intervention at the sports science laboratory of Shanghai University of Sport. The group size is 10 to15 people in order to provide sufficient instructional attention to each participant. Two trained instructors will guide the participants to perform the exercises of

their own group. The two interventional groups will perform three weekly sessions of 60 minutes per session for 12 consecutive weeks. Each session will consist of 10 minutes of warm-up, 40 minutes of core exercises, 5 minutes of break intervals, and 5 minutes of cool-down. The heart rates of the participants will be monitored by Polar-team^2 (Polar Electro, Finland) during training in order to progressively control the intensity. Participants in the interventional groups will be required to not perform any additional in-home exercises throughout the 12 weeks of training.

Integrated Qigong exercise group

The Integrated Qigong protocol will consist of twelve-forms of exercise, with selected movements from the Health Qigong exercise guidelines organized and compiled by the China Qigong Management Center. The Integrated Qigong exercise will emphasize dynamic postural control and body weight shift stepping with lateral-medial and anterior-posterior movements, body symmetry pulling across up-down and left-right axes, hand-eye coordination movement. The twelve forms of exercise have been previously documented [22] and can be seen in Figure 2.

During the initial 2to 3 weeks, training will mainly emphasize learning and practicing two or three forms through multiple repetitions along with review of previously learned movements. The practice in each session concentrate on upper and lower limbs in place, trunk rotation, as well as stepping in different directions (i.e., forward, backward, sideways, diagonal). Participants will be requested to perform personalized movement requirements based on functional level. The range of motion of each movement will be reduced for participants with rigidity. The pace of movement will be decreased for participants with bradykinesia. For participants experiencing FOG episode during training, they will be instructed to perform transferring and stepping while maintaining postural stability. The intensity, difficulty of movement, time, and frequency

will be adjusted to the demands of each participant. The later weeks will concentrate on improving balance, locomotion, and action consistency. Participants will practice each movement with six repetitions, and natural breathing will be incorporated into the movement routine. Participants will be guided to perform the entire range of movement in which they feel safe.

Balance training group

Each training session will start with a 10 minutes warm-up consisting of breathing exercise, slow walking, and range-of-motion exercises. The 40-minute balance training will include a short resting time, and the training program will consist of the following: 1) static balance training: standing on unstable surfaces to maintain postural control and progression to weight shifting; 2) dynamic balance training: postural control in standing position while adding upper limb and trunk movements; 3) balance strategy exercise: focus on hip strategy while maintaining ankle strategy and stepping strategy under interference in different directions; 4) adaptation of varying base of support, and standing in a narrow space and on uneven surface; [23] and 5) walk integrated balance training: walk in a straight line, walk on a soft blanket, and sideways. The training will progress from simple to complex, static to dynamic, low to high center of gravity, wide to narrow the base of support, and will continue to raise challenges in regard to flexibility, stability and range of movement. The end of training will include a 5-minute cool-down session of limb ROM movements, sustained stretching, and relaxing.

Control group

The control group will be instructed to maintain their formal lifestyle and not to engage in any other form of intensive training. The participants in the control group will join one 60-min group session per week, which will consist of a 30-min lecture, 20-min discussion, and

will be followed by a 10-min question and answer session. Participants in the control group will receive health education every four weeks over the 12-week interventional period. The health education will involve information for PD-related treatments and prevention such as modalities of exercise, regimens, fall prevention, and nutrition. Participants will receive a brochure of health education and will have follow-up by telephone twice per month, which will involve discussion of physical activity, progression of disease, health status, and psychological status.

All participants will maintain diaries to record their exercise and fall events every day throughout the trial, including both in the laboratory and at home. The participants in the Integrated Qigong exercise group and balance training group will perform the exercises at the "on" stage in the morning.

Outcome measures

All measurements will be performed at baseline, 12 weeks (end of intervention), and 12 weeks following the completion of the intervention. The measurements will be conducted by two trained assessors and will be videotaped by a third assessor. All assessors will be blinded to the participant's group allocation and time of assessment.

Participants characteristics

Demographic and health characteristics of participants will be collected at baseline to describe the sample, compare conditions, and investigate characteristics associated with outcomes. These characteristics will include age, gender, education, age at disease onset, disease duration, cognition ability, health status, medication dose, resting blood pressure, body mass (kg/m^2), height (cm), family situation and physical performance. Blood pressure will be measured with the use of an automated device (Omron HealthCare). Body mass and height will be assessed with digital scales (Weighing scale & Meter) Physical performance will be measured by the scores from self-reported habitual physical activity

scale. (See Table 1)

Table 1 Demographic and clinical characteristics of the study participants*

	Integrated Qigong (N=)	Balance Training (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index[a]—kg/m^2			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
≥3			
Age of onset—yr			
Duration of disease—yr			
Score of MoCA(/30)[b]			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status[c]—no. (%)			
Poor or fair			
Good			
Very good or excellent			
Family situation-no. (%)			
Living along			
Living with husband/wife			
Living with husband/wife and children			
Score for Self-reported habitual physical activity[d]			
Falls in previous 6 months—no.			

* Mean values (standard deviation). The chi-square test is used for categorical variables, and one-way analysis of variance for continuous variables.

[a] The body-mass index is the weight in kilograms divided by the square of the height in

meters.

[b] MoCA, Montreal Cognitive Assessment.

[c] Self-reported health status, included cardiovascular disease, lung disease, osteoporosis, arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions per participant ranged from 0 to 9.

[d] This is measured by the Physical Activity Scale for the Elderly, [24] with higher scores indicating higher levels of habitual physical activity.

Primary outcome assessment

Gait will be analyzed using a 7-m-long instrumented computerized walkway (GAIRite, CIR, System Inc., Franklin, NJ), and will include gait velocity, stride length, and stride time variability. Gait velocity is crucial parameter for walking coordination and can be used as basic factor for the assessment of normal and pathological gait. [25] Gait variability is a valuable indicator of whole-gait performance and can reflect gait disorders. Stride length and stride time variability are sensitive measures that relate to fall risk in older people. [26, 27]

New freezing of gait questionnaire (NFOG-Q) is a reliable tool to detect and assess the influence and severity of FOG. It consists of the following three parts: (1) part I (item 1, score is 0 or 1) detects the presence of FOG and distinguishes if patients are freezers or non-freezers if they have had a FOG experience during the past month; (2) part II (items 2–6, score range from 0-9) assesses the severity of FOG according to its duration and frequency and its common appearance. Item 2 was added to rate the overall frequency of FOG regardless of the environment; (3)part III (items 7–9, score range from 0-9) assesses the influence of FOG on daily life, and the total score ranges from 0-28; higher scores reflect more severe FOG.[28]

Secondary outcome assessment

Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults and individuals with PD and has shown good reliability and validity in the clinic. FGA includes under following conditions: forward, backward, with eyes closed, stepping over obstacles, changing gait speeds, with different head turns, and a narrow base of support. The FGA includes 10 total items, with each item scored from 0-3. A higher total score reflects better balance and walking ability, with a maximum score of 30. [29, 30]

Postural instability and gait disability will be evaluated by the Unified Parkinson's

Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait, tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The modified Hoehn and Yahr scale has also been used to evaluate disease severity.[31]

The balance performance will be measured by Mini-Balance Evaluation Systems Test (Mini-BESTest), consisting of 14 items from 4 different balance control systems: anticipatory postural adjustments, reactive postural control, sensory orientation, and dynamic gait. Each item is evaluated on a 3-point scale from 0 to 2 and the total score ranges from 0 to 28, with a higher score indicating better balance performance.[32,33]

Falling frequency will be reported at the baseline test, during the 12-week training period, and at a 12-week follow-up. A blind assessor will record fall event based on the following definition of falling: "a person unintentionally coming to rest on the ground or other lower level, not occurring as a result of a major intrinsic overwhelming hazard."[34] The following approaches will be used to ascertain the fall event: (1) monthly collection of fall diary, (2) monthly phone interview, and (3) self-report from each assessment.

Falls and fear of falling will measured with the 14-item Modified Falls Efficacy Scale (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of daily living without falling. Each item is scored on a 10-point scale, with a minimum score of 0 indicating no confidence and a maximum score of 10 indicating full confidence (high falls efficacy) in performing the tasks without falling. The average score across all 14 items will be taken, with higher scores indicating greater falls efficacy.[35,36]

The quality of life will be assessed using the 39-item Parkinson's Disease Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A summary index of eight domain scores ranges from 0 to 100, with higher scores

representing worse health related quality of life (HRQoL).[37,38]

The data collected are depicted in Table 2.

328 **Table 2** Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up*	Mean difference at 12-weeks**	Mean difference at Follow-up**	*F(P Value)* Time Effect	*F(P Value)* Group Effect	*F(P Value)* Interaction Effect
Primary Outcome								
Stride length (cm)								
Integrated Qigong								
Balance training								
Control								
Gait velocity (cm/sec)								
Integrated Qigong								
Balance training								
Control								
Stride time Variability (CV)								
Integrated Qigong								
Balance training								
Control								
NFOG								
Integrated Qigong								
Balance training								
Control								
Secondary								

Outcome								
FGA								
Integrated Qigong								
Balance training								
Control								
MDS-UPDRS Part-III								
Integrated Qigong								
Balance training								
Control								
Mini-BESTest								
Integrated Qigong								
Balance training								
Control								
Total falls, no.								
Integrated Qigong								
Balance training								
Control								
MFES								
Integrated Qigong								
Balance training								
Control								
PDQ-39								
Integrated Qigong								

Balance training								
Control								

*Mean values (standard deviation).

**Mean difference (standard error).

Abbreviations: CV, coefficient variation; NFOG, new freezing of gait questionnaire; FGA, functional gait assessment; MDS-UPDRS Part-III, movement disorder society unified Parkinson's disease rating scale, motor subscale; Mini-BESTest, Mini-Balance Evaluation Systems Test; MEFS, falls and fear of fall; PDQ-39, the 39-item Parkinson's disease questionnaire.

Patient and Public involvement

Participants will not been involved in the study recruitment. The authors conceived the initial research questions and outcome measures, and modified according to the telephone interviews with patients and their guardians by a research assistant. In order to assure the safety and feasibility of the intervention, we invited six patients with mild to moderate PD to learn and practice Integrated Qigong exercise before designing the RCT. Integrated Qigong movements were revised based on the exercise performance and feedback provided by the participants. The burden of the intervention will assessed by patients and their advisors through face-to-face interviews before signing informed consent. The findings of the study will be disseminated to the participants and their guardians.

Statistical Analysis

The statistical analysis will be performed using SPSS 22.0 software (IBM Corp, Armonk, New York). Baseline values of demographic differences in interventional groups and the control group will be examined using Chi-squared tests. The primary outcomes and secondary outcomes over time (i.e., baseline, 12 weeks, after 12-week

follow-up) will be analyzed by mixed design repeated-measures analyses of variance (RM-ANOVA) for between- and within-group differences. Bonferroni's post hoc test will be applied to compare results where main effects are significant. Data will be expressed as the mean and standard deviation or standard error, and significance will be set at $p < 0.05$. An intention-to-treat analysis will be adopted to deal with missing data, including all participants in the analysis based on the initial group allocation. A linear mixed model approach (a direct likelihood estimation method) will be applied to analyze all continuous as value is missing at random. All analysis will include H&Y and MoCA as covariates, as these variables may differ significantly between groups.

DISCUSSION

Medical treatment integrated with exercise therapy is still an indispensable method to manage the motor dysfunction for PD. FOG is common in people with PD which contributes to a protective postural response impairment and increases the risk of falls. Nevertheless, this balance instability can be improved by extra training.[39] Qigong exercise synthesizes training in balance, flexibility, neuromuscular coordination, and cognition, it consists of body consciousness, attention, imagination, multiple activities and goal-oriented training which may benefit the improvement of gait and postural control, beyond conventional single-mode exercise.[40]

Patients with PD exhibit difficulty in transitions from static to dynamic states. Transitional activity is a vital component of physical activities, especially gait initiation, turning, and gait termination. Due to the deficiency in postural control, patients generate excessive trunk movement that causes swaying beyond the limits of stability. [41] Moreover, people with PD often manifest impaired protective postural response and postural adjustment in preparation for stepping, thus, increasing the risk of fall.[42,43] Qigong practice requires that the center of gravity moves and changes to accompany with

the movement of the upper limb, slow movement, body control in space, and shifting body weight in different directions. Hence, Qigong practice can be beneficial to improve the ability to focus on the base of support and postural stability, as well as enhance core muscle to stress weight-bearing joints and to increase proprioception input of trunk and lower limb joints.

Most Qigong movements involve closed-chain exercise of the lower limbs, and contribute to rectifying deficiencies of heel stride and knee extension on gait cycle. [14, 40] In addition, the meditative movement in Qigong exercise can relieve psychological load and consumption, which may benefit for practitioner to reduce muscle tension, and alleviate effect of freezing on stepping forward. [44] Furthermore, Qigong is characterized by slow movement incorporated with moderated breathing, as well as keeping the mind in a state of calm relaxation. The intensity of Qigong is around 1.5 to 2.6 metabolic equivalents (METs) and the average induced maximum heart rate ranges from 43% to 49% of the predicted maximum.[13] Therefore, Qigong is a low-intensity physical exercise that has lower risk of muscle strain and overfatigue and is suitable for individuals with PD as a long-term physical exercise program.

There are several limitations in this study. First, it is difficult to achieve a blinded intervention for this study because exercise served as an intervention is widely open to the participants. Second, participants are limited to people with mild-to-moderate PD. Therefore, it is unclear whether the results would be valid for people with advanced PD. Third, the study patients will come from the same geographic area which limits the generalizability and so that it is not a multicenter trial.

For a variety of features of gait pattern, whatever muscle stiffness or abnormal postural control, we may consider the global or specific efficacy of Qigong on gait function in PD.[45] We expect that a 12-week Integrated Qigong exercise can establish positive therapeutic effects on PD patients with FOG. However, gait deficiency in individuals with

PD is a complex syndrome and is associated with neural control regulated by different areas of the brain, particularly the prefrontal lobe and related circuits.[46] In future studies, we might focus on the mechanism of the different forms of Qigong on the relationship between brain activities and FOG, and explore whether Qigong exercise is conducive to restoring brain function and/or preventing brain degeneration. We hope that this trial will demonstrate that the Integrated Qigong exercise promote the recovery of gait function and prevention of falls for people with mild and moderate PD. The results of this study may furnish evidence to support the beneficial effects of Qigong exercise on improvement of walking ability and reduction of fall risk in people with PD. The findings of this study will provide evidence for a supplemental therapy to manage gait disorder for clinicians and physical therapist.

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Competing interests None declared.

Contributors Zhenlan Li, Jie Zhuang and Zheng Wang conceived the conception and design of the trial, and drafted the manuscript. Guiping Xiao, Kuncheng Jie and Wenhan Yin participated in trial registration, communication, and monitoring. Yan Jiang and Tian

Wang carried out statistical calculations. Yu Zhang provided medical clearance and Parkinson's disease stage diagnoses for the participating patients. All authors participated in revision of the manuscript and approved the final version.

Patient consent Obtained.

Ethics approval This work was approved by the ethics committee of science research of Shanghai University of Sport (protocol number: 2018031).

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Figure Legend

Figure 1 Flow diagram of study design.

Figure 2 Twelve forms of Integrated Qigong exercise.

A: Form one: Xu Exercise

B: Form two: Chui Exercise

C: Form three: Raising the Tiger's Paws

D: Form four: Holding the Hands High with Palms Up to Regulate the Internal Organ

E: Form five: Drawing a Bow

F: Form six: Posing as an Archer Shooting Both Left-and Right-Handed

G: Form seven: Pulling Nine Cows by Their Tails

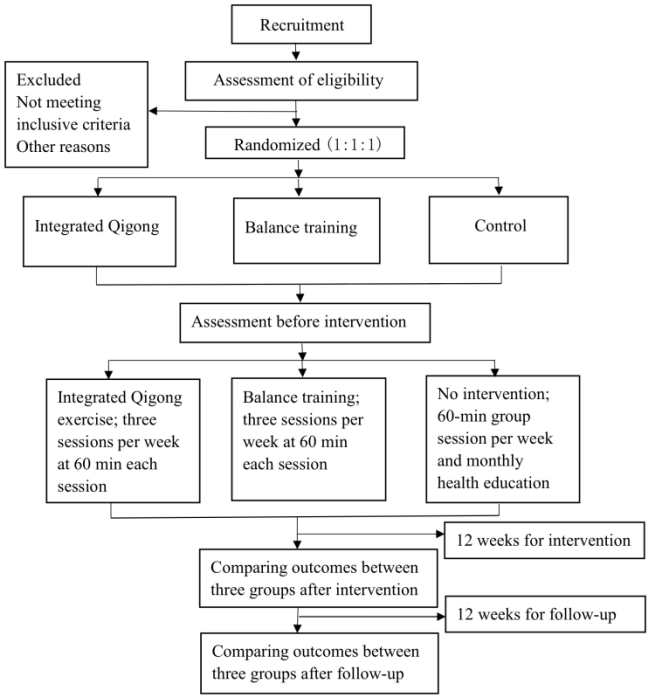
H: Form eight: Rub Backbone

I: Form nine: Swaying Like a Bear

J: Form ten: Picking Fruit

K: Form eleven: Golden Rooster Heralds the Dawn

L: Form twelve: Flying Like a Bird



Flow diagram of study design.

209x297mm (300 x 300 DPI)

Twelve forms of Integrated Qigong exercise.

90x90mm (600 x 600 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title(P0)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P21)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P21-22)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale(P3)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses

Trial design**(P5)**	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting**(P7)**	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria**(P5-6)**	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions **(P7-10)**	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes **(P10-15)**	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline**(Figure1)**	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size**(P6-7)**	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment**(P5)**	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation**(P7)**	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism **(P7)**	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation **(P7)**	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) **(P7)**	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods**(P10)**	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management **(P19-20)**	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods**(P19-20)**	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring **(n/a)**	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms **(n/a)**	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing **(n/a)**	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval **(P5)**	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments **(n/a)**	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent **(P5)**	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality **(see informed consent)**	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests **(n/a)**	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data **(n/a)**	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care **(n/a)**	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy **(n/a)**	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials **(see informed consent)**	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens **(n/a)**	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A study protocol for a single-blind, randomized controlled trial to evaluate clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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A study protocol for a single-blind, randomized controlled trial to evaluate clinical effects of an Integrated Qigong exercise intervention on freezing of gait in Parkinson's disease

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ABSTRACT

Introduction

Qigong exercise offers a potentially safe, low-cost, and effective mind–body rehabilitative intervention for mitigating the problem of gait interruption among Parkinson's disease (PD) patients who have frequent freezing of gait (FOG) episodes. However, its clinical effects have not been established. This paper describes the trial protocol of evaluating the clinical efficacy of a newly developed Integrated Qigong in improving gait among PD patients with FOG.

Methods and analysis

A single-blind, randomized, controlled trial is designed to compare Integrated Qigong and balance training with an attention control. Participants will be mild to moderate PD patients who experience FOG and are recruited from local communities in Shanghai, China. Participants will be randomly allocated to one of the three groups: Integrated Qigong group, a balance exercise intervention group, or control group. The total number of participants will be 126, and masked assessments will be made at baseline, 12 weeks (end of intervention), and 12-week follow-up. Both Integrated Qigong group and balance training group will receive a group-based exercise intervention that meets three times per week, 60 minutes in duration, for 12 weeks. The control group will receive a 60-minute weekly group session and monthly health education. The primary outcome are gait parameters (stride length, gait velocity, stride time variability) and occurrence of FOG. The secondary outcomes are postural instability, walking disability, falling, fear of falling, and quality of life.

Ethics and dissemination This study has been approved by the ethics committee of Shanghai University of Sport and registered at China Clinical Trial Registry (ChiCTR1800016570). Participants will sign informed consent prior to the participation of the trial. The findings of the study will be published in peer-reviewed academic journals

and disseminated to PD support groups, medical community, and media.

Trial registration China Clinical Trial Registry, ID: ChiCTR1800016570. Registered on 6 June 2018.

Keywords gait interruption, exercise, neurodegenerative disease, movement disorder

Strengths and limitations of this study

1. The first study that combines commonly practiced Qigong exercises into a single rehabilitative intervention aims at improving gait outcomes for PD patients with FOG.
2. The findings of the study will inform patients and healthcare providers of an alternative, potentially low-cost and safe, effective, and easily implementable exercise intervention for treating and managing gait interruption in patients with PD.
3. The patients will come from one geographic area which limits the generalizability.

INTRODUCTION

Freezing of gait (FOG) is characterized by a sudden and brief episodic absence or marked reduction of forward progression. The syndrome is most common in patients with Parkinson's disease(PD).[1] It is estimated that between 21% and 27% of early stage patients report FOG episode with number increasing up 80% among those in advanced stages.[2-4] Patients with FOG often show difficulty in turning, transferring, walking, and experience and inability to start or continue walking. As the disease progresses, patients with severe FOG develop postural instability and gait dysfunction, causing difficulty in managing daily life and frequent falls, which consequently impact on the quality of life.[5, 6]

There are multidisciplinary approaches, including pharmacological and surgical based treatment for managing FOG among people with PD. Current research evidence has shown, however, effectiveness of non-pharmacological and rehabilitation based intervention, including physiotherapy, physical exercise, and occupational therapy, for improving abnormal gait in patients with FOG.[7, 8] More researches suggest that various alternative exercise interventions can ameliorate motor symptoms and improve gait. Theses interventions include low-cost, non-equipment dependent exercises such as Tai Chi, dance, and yoga.[9]

In this study, we focus on Health Qigong exercise which is one of traditional Chinese exercises that incorporates meditative movements, breathing patterns, and mental regulation. The exercises are performed in a slow, rhythmic, relaxed manner; features that are conducive to organs.[10,11] Growing evidence supports the health benefits of Health Qigong. A systematic review and meta-analysis indicates that older adults who practice Health Qigong improves balance and postural control and reduces fall risk among individuals with PD.[12] Health Qigong also improves gait speed, stride length, and leg movement ability.[13,14]

Qigong consists of various types, including Baduanjin, Liuzijue, Daoyin, 12-step Dao Yin Health Preservation Exercise, Yijinjing, and Wuqinxi. Although each of them has its own training characteristics, they nevertheless share some common features. In general, Qigong integrates both static and dynamic exercises with a great emphasis on regulating breath, and exercising intrinsic control and mental intent.[15] Exercise of Qigong is characterized by trunk rotation, bending and extending at waist and movement of limbs both medial-laterally and anterior-posteriorly, all driven by the core of the body.[14,16] Like other techniques such as Tai Ji Quan, Qigong exercise also involves dynamic movements with intermittent stepping and turning. Besides, exercise involves postural demanding movements such as single leg standing and chirographic and manipulative moving postures.[17,18] Furthermore, Qigong exercise requires regulating breathing by engaging in diaphragmatic to expand lung capacity and control upright posture.[19,20]

To date, there has been little effort to evaluate the therapeutic effect of combing different types of Qigong exercise on gait in individuals with PD. This paper describes the trial protocol of a newly developed Integrated Qigong intervention that combines seven types of commonly exercised Qigong into a single rehabilitation program for mild to moderate PD patients with FOG. Specifically, we aim to determine the therapeutic effect of the Integrated Qigong intervention on gait. We hypothesize that, compared to control group, both Integrated Qigong and conventional balance training intervention will be clinically more effective in improving the primary outcomes of gait.

METHODS

Study design

The study is designed as a prospective, single-blind randomized controlled trial.

Design and procedures

We will recruit participants from Shanghai, China by means of the neurology department of the local hospital and TV programs during the same recruitment period. To reduce potential expectation bias and confirm eligibility, a research assistant will make telephone contact with those referred by a neurologist and follow up with interested participants. Participants will be informed that they will be randomly assigned to three groups. The integrated Qigong exercise group will engage in training program that combines seven types of commonly exercised Qigong. The balance training group will perform static and dynamic postural control training. The two intervention groups will receive the guidance of instructor, and the control group will receive weekly group session and monthly health education. The total intervention period will be 12 weeks, and will occur simultaneously for all participants. The primary and secondary outcomes will be assessed at baseline (pre-intervention), 12 weeks (end of intervention) and 12-week follow-up (see figure 1). Potential eligible participants who satisfy initial inclusion criteria will arrange a two-hour visit at our research laboratory and register their personal information. The trial protocol has been approved by the ethics committee of Shanghai University of Sport. All participants who meet the inclusion and exclusion criteria need to sign informed consent prior to the study. The protocol is registered as a China Clinical Trial (ID: ChiCTR1800016570).

Participants

Inclusion criteria

(1) PD patients diagnosed according to the clinical diagnostic of UK Brain Bank criteria; (2) age between 40 and 80 years old; (3) Hoehn & Yahr scale of 1–3; (4) item three of the New Freezing of Gait Questionnaire (NFOGQ) scored ≥1; (5) Mini–Mental State Examination (MMSE) score >24; (6) ability to walk independently; and (7) have

experienced a fall over the past six months.

Exclusion criteria

(1) Participation in Qigong exercise during the last year; (2) other diseases that could interfere with conduct of the study protocol such as cardiopulmonary disease, liver and kidney disease, musculoskeletal dysfunction, or cancer; (3) severe cognitive, visual or auditory impairment; (4) unstable medication; (5) unstable deep brain stimulation.

Sample size calculation

A statistical analysis was conducted for sample size estimation using G*power 3.1 (Franz Faul, Universita Kiel, Germany). The study was powered to detect a between-group difference in primary gait outcome measures between Qigong exercise group and balance training group relative to the attention control group. Because there was no a priori hypothesis formulated between the two active interventions (Qigong exercise and balance training), the study was not powered on these two conditions. Due to the lack of informed preliminary data and empirical evidence on the effects of Qigong exercise, we approximated the effect size in our power calculations using estimated from the published studies that compared Qigong exercise with a control condition on gait (i.e., gait speed, freezing of gait, and mobility).[13,14] In general, these studies, with an intervention length ranging from 10 weeks to 24 weeks, have shown a weak intervention effect, with effect sizes ranging from no effect to small-to-moderate effects. On the basis of these observations, a conservative approach was taken. Specially, we used a small effect size (η^2=0.01) based on the partial eta squared estimate within the ANOVA framework.[21] Our initial power estimates indicated that, in a mixed-effect repeated measures design with a between-subject factor (Integrated Qigong, balance training, control), and a within-subject factor (baseline, 12 weeks) and a correlation of 0.08 on the repeated measures, a

sample size of 99 subjects would be required to achieve an 80% power at an 0.05 error rate. To be more conservative, we estimated the sample sizes based on a range of small sizes (f=0.08, f=0.10, f=0.12). The sample sizes generated from these calculations were averaged to arrive at a total of 107 subjects. With an anticipated 15% attrition rate, a final enrollment number of 126 (42 in each group) was set for the study to detect a difference in gait outcomes between Integrated Qigong and balance training relative to the attention control group.

Randomization and blinding

The study design will utilize a single blinded randomized controlled trial. Two trained assessors will be blinded to group allocation and will not participate in the intervention. We will apply the stratified random sampling method by stage of the disease (H&Y Stage). Using computer generated random number sequencing (STATA 12.0, StataCorp LP, Texas, USA) in a ratio of 1:1:1, a random number will be placed in a sealed envelope, and participants will be allocated randomly to Integrated Qigong group, balance training group, or control group by extracting the random number from the envelope. Participants will be reassessed for baseline measurements on another day. This study is not amenable to blinding to participants of their designated experimental groups because the interventional exercises they perform will reveal their group allocation.

Intervention

The participants in all groups will follow their regular medication scheme during the study period. Both Integrated Qigong group and balance training group will receive group-based exercise intervention at the sports science laboratory of Shanghai University of Sport. The group size is 5 to 7 people in order to provide sufficient instructional attention to each participant. Two trained instructors will guide the participants to perform the exercises of

their own group. The two interventional groups will perform three weekly sessions of 60 minutes per session for 12 consecutive weeks. Each session will consist of 10 minutes of warm-up, 40 minutes of core exercises, 5 minutes of break intervals, and 5 minutes of cool-down. The heart rates of the participants will be monitored by Polar-team[2] (Polar Electro, Finland) during training in order to progressively control the intensity. Participants in the interventional groups will be required to not perform any additional in-home exercises throughout the 12 weeks of training.

Integrated Qigong exercise group

The Integrated Qigong protocol will consist of twelve-forms of exercise, with selected movements from the Health Qigong exercise guidelines organized and compiled by the China Qigong Management Center. The Integrated Qigong exercise will emphasize dynamic postural control and body weight shift stepping with lateral-medial and anterior-posterior movements, body symmetry pulling across up-down and left-right axes, hand-eye coordination movement. The twelve forms of exercise have been previously documented [22] and can be seen in Figure 2.

During the initial 2 to 3 weeks, training will mainly emphasize learning and practicing two or three forms through multiple repetitions along with review of previously learned movements. The practice in each session concentrate on upper and lower limbs in place, trunk rotation, as well as stepping in different directions (i.e., forward, backward, sideways, diagonal). Participants will be requested to perform personalized movement requirements based on functional level. The range of motion of each movement will be reduced for participants with rigidity. The pace of movement will be decreased for participants with bradykinesia. For participants experiencing FOG episode during training, they will be instructed to perform transferring and stepping while maintaining postural stability. The intensity, difficulty of movement, time, and frequency will be adjusted to the demands of each participant. The later weeks will concentrate on

improving balance, locomotion, and action consistency. Participants will practice each movement with six repetitions, and natural breathing will be incorporated into the movement routine. Participants will be guided to perform the entire range of movement in which they feel safe.

Balance training group

Each training session will start with a 10 minutes warm-up consisting of breathing exercise, slow walking, and range-of-motion exercises. The 40-minute balance training will include a short resting time, and the training program will consist of the following: 1) static balance training: standing on unstable surfaces to maintain postural control and progression to weight shifting; 2) dynamic balance training: postural control in standing position while adding upper limb and trunk movements; 3) balance strategy exercise: focus on hip strategy while maintaining ankle strategy and stepping strategy under interference in different directions; 4) adaptation of varying base of support, and standing in a narrow space and on uneven surface; [23] and 5) walk integrated balance training: walk in a straight line, walk on a soft blanket, and sideways. The training will progress from simple to complex, static to dynamic, low to high center of gravity, wide to narrow the base of support, and will continue to raise challenges in regard to flexibility, stability and range of movement. The end of training will include a 5-minute cool-down session of limb ROM movements, sustained stretching, and relaxing.

Control group

The control group will be instructed to maintain their formal lifestyle and not to engage in any other form of intensive training. The participants in the control group will join one 60-min group session per week, which will consist of a 30-min lecture, 20-min discussion, and will be followed by a 10-min question and answer session. Participants in the control group will receive health education every four weeks over the 12-week interventional period. The

health education will involve information for PD-related treatments and prevention such as modalities of exercise, regimens, fall prevention, and nutrition. Participants will receive a brochure of health education and will have follow-up by telephone twice per month, which will involve discussion of physical activity, progression of disease, health status, and psychological status.

All participants will maintain diaries to record their exercise and fall events every day throughout the trial, including both in the laboratory and at home. The participants in the Integrated Qigong exercise group and balance training group will perform the exercises at the "on" stage in the morning.

Outcome measures

All measurements will be performed at baseline, 12 weeks (end of intervention), and 12 weeks following the completion of the intervention. The measurements will be conducted by two trained assessors and will be videotaped by a third assessor. All assessors will be blinded to the participant's group allocation and time of assessment.

Participants characteristics

Demographic and health characteristics of participants will be collected at baseline to describe the sample, compare conditions, and investigate characteristics associated with outcomes. These characteristics will include age, gender, education, age at disease onset, disease duration, cognition ability, health status, medication dose, resting blood pressure, body mass (kg/m^2), height (cm), family situation and physical performance. Blood pressure will be measured with the use of an automated device (Omron HealthCare). Body mass and height will be assessed with digital scales (Weighing scale & Meter) Physical performance will be measured by the scores from self-reported habitual physical activity scale. (See Table 1)

Table 1 Demographic and clinical characteristics of the study participants*

	Integrated Qigong (N=)	Balance Training (N=)	Control (N=)
Age—yr			
Gender—(male% : female%)			
Body-mass index[a]—kg/m^2			
Height—cm			
Hoehn and Yahr stage—no. (%)			
1-1.5			
2-2.5			
≥3			
Age of onset—yr			
Duration of disease—yr			
Score of MoCA(/30)[b]			
Antiparkinsonian medications taken—no.			
Levodopa or carbidopa			
Pramipexole or ropinirole			
Other			
Self-reported health status[c]—no. (%)			
Poor or fair			
Good			
Very good or excellent			
Family situation-no. (%)			
Living along			
Living with husband/wife			
Living with husband/wife and children			
Score for Self-reported habitual physical activity[d]			
Falls in previous 6 months—no.			

* Mean values (standard deviation). The chi-square test is used for categorical variables, and one-way analysis of variance for continuous variables.

[a] The body-mass index is the weight in kilograms divided by the square of the height in

meters.

[b] MoCA, Montreal Cognitive Assessment.

[c] Self-reported health status, included cardiovascular disease, lung disease, osteoporosis, arthritis, liver and kidney disease, low back pain, and cancer; the number of conditions per participant ranged from 0 to 9.

[d] This is measured by the Physical Activity Scale for the Elderly, [24] with higher scores indicating higher levels of habitual physical activity.

Primary outcome assessment

Spatiotemporal kinematic parameters is one approach to characterize FOG, particular the increased cadence, decreased stride before FOG episode.[25] Hence, we will describe spatiotemporal characteristics to better understand the relationship between gait and FOG. Gait parameters will be analyzed using a 7-m-long instrumented computerized walkway (GAIRite, CIR, System Inc., Franklin, NJ), and will include stride length, gait velocity, cadence, and stride time variability. Gait velocity is crucial parameter for walking coordination and can be used as basic factor for the assessment of normal and pathological gait. [26] Gait variability is a valuable indicator of whole-gait performance and can reflect gait disorders. Stride length and stride time variability are sensitive measures that relate to fall risk in older people. [27,28]

New freezing of gait questionnaire (NFOG-Q) is a reliable tool to detect freezing behavior and assess effectiveness of intervention. It consists of the following three parts: (1) part I (item 1, score is 0 or 1) detects the presence of FOG and distinguishes if patients are freezers or non-freezers if they have had a FOG experience during the past month; (2) part II (items 2–6, score range from 0-9) assesses the severity of FOG according to its duration and frequency and its common appearance. Item 2 was added to rate the overall frequency of FOG regardless of the environment; (3)part III (items 7–9, score range from 0-9) assesses the influence of FOG on daily life, and the total score ranges from 0-28; higher scores reflect more severe FOG.[29]

Secondary outcome assessment

Functional Gait Assessment (FGA) is a measure of walking balance ability in older adults and individuals with PD and has shown good reliability and validity in the clinic. FGA includes under following conditions: forward, backward, with eyes closed, stepping over obstacles, changing gait speeds, with different head turns, and a narrow base of support.

The FGA includes 10 total items, with each item scored from 0-3. A higher total score reflects better balance and walking ability, with a maximum score of 30. [30,31]

Postural instability and gait disability will be evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) Part III evaluation. It consists of rigidity measures, gait, tremor, hand/arm and leg movements (bradykinesia), speech, and facial expressions. The modified Hoehn and Yahr scale has also been used to evaluate disease severity.[32]

The balance performance will be measured by Mini-Balance Evaluation Systems Test (Mini-BESTest), consisting of 14 items from 4 different balance control systems: anticipatory postural adjustments, reactive postural control, sensory orientation, and dynamic gait. Each item is evaluated on a 3-point scale from 0 to 2 and the total score ranges from 0 to 28, with a higher score indicating better balance performance.[33, 34]

Falling frequency will be reported at the baseline test, during the 12-week training period, and at a 12-week follow-up. A blind assessor will record fall event based on the following definition of falling: "a person unintentionally coming to rest on the ground or other lower level, not occurring as a result of a major intrinsic overwhelming hazard."[35] The following approaches will be used to ascertain the fall event: (1) monthly collection of fall diary, (2) monthly phone interview, and (3) self-report from each assessment.

Falls and fear of falling will measured with the 14-item Modified Falls Efficacy Scale (MFES) questionnaire, which reflects self-perceived confidence to engage in activities of daily living without falling. Each item is scored on a 10-point scale, with a minimum score of 0 indicating no confidence and a maximum score of 10 indicating full confidence (high falls efficacy) in performing the tasks without falling. The average score across all 14 items will be taken, with higher scores indicating greater falls efficacy.[36,37]

The quality of life will be assessed using the 39-item Parkinson's Disease Questionnaire (PDQ39). It is composed of 39 items grouped in eight domains: mobility,

activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Each item ranges from 0 (never) to 4 (always). A summary index of eight domain scores ranges from 0 to 100, with higher scores representing worse health related quality of life (HRQoL).[38,39] The data collected are depicted in Table 2.

329 **Table 2** Changes over time within and between control and experimental groups

Group	Baseline*	12-weeks*	Follow-up*	Mean difference at 12-weeks**	Mean difference at Follow-up**	*F(P Value)* Time Effect	*F(P Value)* Group Effect	*F(P Value)* Interaction Effect
Primary Outcome								
Stride length (cm)								
Integrated Qigong								
Balance training								
Control								
Gait velocity (cm/sec)								
Integrated Qigong								
Balance training								
Control								
Cadence (steps/min)								
Integrated Qigong								
Balance training								
Control								
Stride time Variability (CV)								
Integrated Qigong								
Balance training								
Control								

NFOG								
Integrated Qigong								
Balance training								
Control								
Secondary Outcome								
FGA								
Integrated Qigong								
Balance training								
Control								
MDS-UPDRS Part-III								
Integrated Qigong								
Balance training								
Control								
Mini-BESTest								
Integrated Qigong								
Balance training								
Control								
Total falls, no.								
Integrated Qigong								
Balance training								
Control								
MFES								
Integrated Qigong								
Balance training								

Control								
PDQ-39								
Integrated Qigong								
Balance training								
Control								

*Mean values (standard deviation).

**Mean difference (standard error).

Abbreviations: CV, coefficient variation; NFOG, new freezing of gait questionnaire; FGA, functional gait assessment; MDS-UPDRS Part-III, movement disorder society unified Parkinson's disease rating scale, motor subscale; Mini-BESTest, Mini-Balance Evaluation Systems Test; MEFS, falls and fear of fall; PDQ-39, the 39-item Parkinson's disease questionnaire.

Patient and Public involvement

Participants will not been involved in the study recruitment. The authors conceived the initial research questions and outcome measures, and modified according to the telephone interviews with patients and their guardians by a research assistant. In order to assure the safety and feasibility of the intervention, we invited six patients with mild to moderate PD to learn and practice Integrated Qigong exercise before designing the RCT. Integrated Qigong movements were revised based on the exercise performance and feedback provided by the participants. The burden of the intervention will assessed by patients and their advisors through face-to-face interviews before signing informed consent. The findings of

the study will be disseminated to the participants and their guardians.

Statistical Analysis

The statistical analysis will be performed using SPSS 22.0 software (IBM Corp, Armonk, New York). Baseline values of demographic differences in interventional groups and the control group will be examined using Chi-squared tests. The primary outcomes and secondary outcomes over time (i.e., baseline, 12 weeks, after 12-week follow-up) will be analyzed by mixed design repeated-measures analyses of variance (RM-ANOVA) for between- and within-group differences. Bonferroni's post hoc test will be applied to compare results where main effects are significant. Data will be expressed as the mean and standard deviation or standard error, and significance will be set at $p < 0.05$. An intention-to-treat analysis will be adopted to deal with missing data, including all participants in the analysis based on the initial group allocation. A linear mixed model approach (a direct likelihood estimation method) will be applied to analyze all continuous as value is missing at random. All analysis will include H&Y and MoCA as covariates, as these variables may differ significantly between groups.

DISCUSSION

Medical treatment integrated with exercise therapy is still an indispensable method to manage the motor dysfunction for PD. FOG is common in people with PD which contributes to a protective postural response impairment and increases the risk of falls. Nevertheless, this balance instability can be improved by extra training.[40] Qigong exercise synthesizes training in balance, flexibility, neuromuscular coordination, and cognition, it consists of body consciousness, attention, imagination, multiple activities and goal-oriented training which may benefit the improvement of gait and postural control, beyond conventional single-mode exercise.[41]

Patients with PD exhibit difficulty in transitions from static to dynamic states.

Transitional activity is a vital component of physical activities, especially gait initiation, turning, and gait termination. Due to the deficiency in postural control, patients generate excessive trunk movement that causes swaying beyond the limits of stability. [42] Moreover, people with PD often manifest impaired protective postural response and postural adjustment in preparation for stepping, thus, increasing the risk of fall.[43,44] Qigong practice requires that the center of gravity moves and changes to accompany with the movement of the upper limb, slow movement, body control in space, and shifting body weight in different directions. Hence, Qigong practice can be beneficial to improve the ability to focus on the base of support and postural stability, as well as enhance core muscle to stress weight-bearing joints and to increase proprioception input of trunk and lower limb joints.

Most Qigong movements involve closed-chain exercise of the lower limbs, and contribute to rectifying deficiencies of heel stride and knee extension on gait cycle. [14, 41] In addition, the meditative movement in Qigong exercise can relieve psychological load and consumption, which may benefit for practitioner to reduce muscle tension, and alleviate effect of freezing on stepping forward. [45] Furthermore, Qigong is characterized by slow movement incorporated with moderated breathing, as well as keeping the mind in a state of calm relaxation. The intensity of Qigong is around 1.5 to 2.6 metabolic equivalents (METs) and the average induced maximum heart rate ranges from 43% to 49% of the predicted maximum.[13] Therefore, Qigong is a low-intensity physical exercise that has lower risk of muscle strain and overfatigue and is suitable for individuals with PD as a long-term physical exercise program.

There are several limitations in this study. First, it is difficult to achieve a blinded intervention for this study because exercise served as an intervention is widely open to the participants. Second, the control group will have much less contact than training groups, this may induce bias to the study. Future, the impact of attention/social interaction for each participant would be controlled to ensure the equal dosage of

training and attention in different interventions. Third, participants are limited to people with mild-to-moderate PD. Therefore, it is unclear whether the results would be valid for people with advanced PD. Forth, the study patients will come from the same geographic area which limits the generalizability and so that it is not a multicenter trial.

For a variety of features of gait pattern, whatever muscle stiffness or abnormal postural control, we may consider the global or specific efficacy of Qigong on gait function in PD.[46] We expect that a 12-week Integrated Qigong exercise can establish positive therapeutic effects on PD patients with FOG. However, gait deficiency in individuals with PD is a complex syndrome and is associated with neural control regulated by different areas of the brain, particularly the prefrontal lobe and related circuits.[47] In future studies, we might focus on the mechanism of the different forms of Qigong on the relationship between brain activities and FOG, and explore whether Qigong exercise is conducive to restoring brain function and/or preventing brain degeneration. We hope that this trial will demonstrate that the Integrated Qigong exercise promote the recovery of gait function and prevention of falls for people with mild and moderate PD. The results of this study may furnish evidence to support the beneficial effects of Qigong exercise on improvement of walking ability and reduction of fall risk in people with PD. The findings of this study will provide evidence for a supplemental therapy to manage gait disorder for clinicians and physical therapist.

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Competing interests None declared.

Contributors Zhenlan Li, Jie Zhuang and Zheng Wang conceived the conception and design of the trial, and drafted the manuscript. Guiping Xiao, Kuncheng Jie and Wenhan Yin participated in trial registration, communication, and monitoring. Yan Jiang and Tian Wang carried out statistical calculations. Yu Zhang provided medical clearance and Parkinson's disease stage diagnoses for the participating patients. All authors participated in revision of the manuscript and approved the final version.

Patient consent Obtained.

Ethics approval This work was approved by the ethics committee of science research of Shanghai University of Sport (protocol number: 2018031).

Provenance and peer review Not commissioned;externally peer reviewed

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Figure Legend

Figure 1 Flow diagram of study design

Figure 2 Twelve forms of Integrated Qigong exercise.

A: Form one: Xu Exercise

B: Form two: Chui Exercise

C: Form three: Raising the Tiger's Paws

D: Form four: Holding the Hands High with Palms Up to Regulate the Internal Organ

E: Form five: Drawing a Bow

F: Form six: Posing as an Archer Shooting Both Left-and Right-Handed

G: Form seven: Pulling Nine Cows by Their Tails

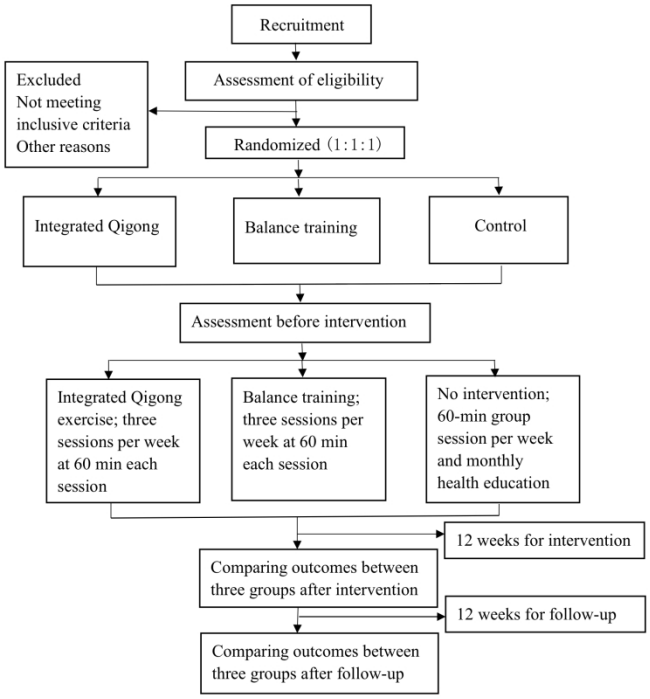
H: Form eight: Rub Backbone

I: Form nine: Swaying Like a Bear

J: Form ten: Picking Fruit

K: Form eleven: Golden Rooster Heralds the Dawn

L: Form twelve: Flying Like a Bird



Flow diagram of study design.

209x297mm (300 x 300 DPI)

Twelve forms of Integrated Qigong exercise.

90x90mm (600 x 600 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title(P0)	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration(P2)	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding(P21)	4	Sources and types of financial, material, and other support
Roles and responsibilities (P21-22)	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale(P3)	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives(P4)	7	Specific objectives or hypotheses

Trial design**(P5)**	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting**(P7)**	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria**(P5-6)**	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions **(P7-10)**	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes **(P10-15)**	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline**(Figure1)**	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size**(P6-7)**	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment**(P5)**	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation**(P7)**	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism **(P7)**	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation **(P7)**	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking) **(P7)**	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods**(P10)**	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management **(P19-20)**	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods**(P19-20)**	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring **(n/a)**	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms **(n/a)**	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing **(n/a)**	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval **(P5)**	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments **(n/a)**	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent **(P5)**	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality **(see informed consent)**	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests **(n/a)**	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data **(n/a)**	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care **(n/a)**	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy **(n/a)**	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials **(see informed consent)**	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens **(n/a)**	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.