Research Article

Evaluation of Effecting Factors About Exercise Motivation in Patients with Parkinson’s Disease

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Abstract

AIM: The aim of this study was to explore the factors that affect exercise motivation in patients with Parkinson’s disease.

METHODS: Data collected in Taiwan from March 2016 to January 2017. Using convenience sampling, a total of 49 participants were recruited, and participants who usually regularly exercise ≥ 150 minutes per week. Using the 8-item Parkinson’s Disease Questionnaire (PDQ-8), Geriatric Depression Scale (GDS), Unified Parkinson’s Disease Rating Scale part II & III (UPDRS part II & III), Fatigue Severity Scale (FSS), Pittsburg Sleep Quality Index (PSQI), and Hospital Anxiety Scale (HAS). Descriptive statistics, Pearson correlation analysis, and multiple linear regression analysis were adopted for data analysis.

RESULTS: Pearson correlation analysis showed L-Dopa dosage, UPDRS part II & III, FSS, PSQI, GDS-15, Hospital Anxiety Scale, and PDQ-8 were significantly correlated with exercise motivation. Fatigue was the strongest factor related to exercise motivation and explained 42.52% of the total variances; moreover, motor ability and activity of daily living explained 24.8% and 12.0% of the total variances, respectively.

CONCLUSION: Motor ability, the activity of daily living and fatigue were related factors of Parkinson’s disease patients’ exercise motivation.

Keywords: Activity of daily living, exercise motivation, fatigue, motor ability, Parkinson’s Disease

Introduction

Parkinson’s disease (PD) is a common long-term neurodegenerative disorder and the incidence of the disease rises considerably with age. According to the estimate, the overall prevalence of PD among those aged ≥45 years to be 572 per 100,000 that there were 680,000 individuals in the United States aged ≥45 years with PD in 2010, and that the number will rise to approximately 930,000 in 2020 and 1,238,000 in 2030 (Marras et al., 2018). PD prevalence is increasing steadily with age and affects approximately 1% of the population above 60 years (Hirsch et al., 2016; Tysnes & Storstein, 2017), and it is regarded as a movement disorder with motor symptoms (MS) and non-motor symptoms (NMS). The movement disorder with motor features, such as tremor, rigidity, bradykinesia, and postural instability (Mu et al., 2017), NMS includes fatigue, sleep problem, depression, and anxiety mood that affect health-related quality of life (HRQOL) (Kadastik-Eerme et al., 2015; Rosqvist et al., 2021). Regular exercise can reduce the risk of chronic progressive and improve MS and NMS in PD patients (Amara & Memon, 2018). Exercises are beneficial for patients with PD, also can improve their fatigue, sleep quality, depression, anxiety, and quality of life (Wu et al., 2017). According to the American College of Sport Medicine (ACSM) and American Heart Association (AHA) guidelines, it is recommended that adults need moderate-intensity aerobic (60-90% maximum heart rate) physical activity for a minimum of 30 min for 5 days each week or can be gradually accumulated with each exercise for 10 min, continuously and multiple shorter times (at least 10 min) are acceptable, to accumulate the amount of daily exercise required (Garber et al., 2011; Haskell et al., 2007).

Several factors have been reported to be associated with exercise motivation in PD patients. The most significant determinants affecting exercise motivation are disease severity, motor complications, bodily pain, postural instability, and gait disorder among MS (Allen et al., 2015). In addition, some studies revealed the most significant determinants of exercise motivation that are depression, anxiety, fatigue, lower quality of life, lack of time to exercise, and fear of falling (Afshari et al., 2017; Ellis et al., 2011, 2013). Several NMS appears to be associated with fatigue and negatively impact the quality of life. Fatigue is reflected in the patient’s physical energy, which in turn affects the underlying psychological dimension (Ribas et al., 2017). Studies reported among PD patients that high-exercisers were more likely to start exercising after being diagnosed, whereas low-exercisers were more likely to reduce their amount of exercise (Ellis et al., 2013). Low-exercisers required more motivating factors and reported twice as many barriers as high-exercisers. Barriers that were significantly more common in low-exercisers were: lacking someone to motivate them, fatigue, and depression.
Parkinson’s disease is a progressive neurodegenerative disease that causes a variety of MS and NMS, and usually has a life-changing impact on people with this disease, as well as for their family and caregivers. Nurses can have a major impact on the lives of people affected by PD, whether in acute settings, community settings, or nursing homes. Nurses have a role in clinical monitoring, medicine management, and providing support and information to PD patients and their families or caregivers (Cotterell, 2018; Lennaerts et al., 2017).

Although there is evidence that exercise is effective on MS and NMS in PD patients, however, due to the disease symptoms or some individual factors, patients are lower motivated or less willing to perform the exercise, barriers lead to disease progression and deterioration. However, few studies have investigated the exercise-related factors that affect motivation and willingness to exercise in patients with PD in Taiwan. In this study, the participants’ exercise type combined stretching exercise, aerobic exercise, and resistance exercise for more than 150 min/week. The main contribution of this study was that by understanding exercise motivation, medical staff can design appropriate exercise prescriptions for PD patients based on the results of this study; with proper exercise, PD patients can maintain the activity of daily living (ADL) and improve MS, NMS, and quality of life. This study aims to explore the related factors (MS and NMS) that affect exercise motivation in PD patients.

Research Question
1. What factors affect the exercise motivation of PD patients?

Methods

Study Design
The study was a descriptive and correlational design.

Sample
Data collection was from March 2016 to January 2017. This study was recruited in a convenience sampling and a total of 49 participants were enrolled. All participants with PD diagnosis confirmed by neurologists were included. Inclusion criteria were (1) be diagnosed PD with Hoehn and Yahr stages I and II, (2) under stable medication use for at least 3 months’ treatment, (3) >60 years old, (4) usual physical activity or exercise accumulated ≥150 min/week, (5) moderate-intensity exercise, and (6) continue to exercise for >3 months (Afshari et al., 2017). Exclusion criteria were (1) exercise <150 min/week and (2) unstable medical status.

Data Collection Tools

Demographic Questionnaire and Clinical Data
The tools used in this study included a demographic questionnaire and clinical data. The demographic data (e.g., age, gender, and exercise hours per week) and clinical data (disease duration, clinical stage of PD, levodopa equivalent daily dose, chronic illness, and pain scores) were recorded from the medical record or self-report during data collection. Additionally, the patients’ clinical stage of PD was assessed using the Hoehn and Yahr scale (HY) (Hoehn & Yahr, 1967).

Movement Disorder Society—Unified Parkinson’s Disease Rating Scale Parts II and III
In 2008, the Movement Disorder Society (MDS) adopted a new, validated version of the Movement Disorder Society—Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), which included several significant updates in comparison with the previous version, including the new NMS of PD. MDS-UPDRS includes four parts: Part I (Non-Motor Experiences of Daily Living), Part II (Motor Experiences of Daily Living), Part III (Motor Examination), and Part IV (Motor Complications). The MDS-UPDRS Part II regards the motor experiences ADL living as assessed by the patient or caregiver; Part III assesses MS (motor ability) based on an objective neurological examination. In this study, we used MDS-UPDRS Part II & III to examine participants’ ADL and motor ability. The MDS-UPDRS showed high internal consistency (Cronbach’s alpha =.79–.93 across parts) (Goetz et al., 2008). The Cronbach’s alpha of UPDRS Parts II & III in this study was .79 and .83, respectively. Parts II & III are scored on a 0–4 rating scale, the higher the scores, the higher the severity (Goetz et al., 2008).

Fatigue Severity Scale
This scale (FSS) was used to assess the severity of fatigue. A total of nine questions on the scale and each item is scored on a 7-point scale to indicate the severity of fatigue symptoms, from 1 = strongly disagree to 7 = strongly agree. These scores are the average of nine statements. An average score ≥4.0 indicates the level of clinically significant characteristics of fatigue, and a total score ≥36 indicates fatigue. The original Cronbach’s alpha of FSS was .81–.89 (Krupp et al., 1989); the Cronbach’s alpha of FSS in this study was .94.

Pittsburg Sleep Quality Index
The Pittsburg Sleep Quality Index (PSQI) was widely used by many studies to measure the overall sleep quality of an individual in the past month. The PSQI content 19 questions include seven aspects: subjective sleep quality, time to fall asleep, sleep hours, sleep efficiency, sleep disturbance, sleep deprivation, use of sedation, and daytime dysfunction. Each item is scored from 0 to 3 points, from “never” to “more than three times a week,” and the total score ranges from 0 to 21 points. A total score >5 indicates insufficient sleep quality, a total score ≤5 indicates good sleep, while a total score >5 indicates poor sleep (Duncan et al., 2014). The Chinese version of the PSQI is translated by Tsai et al. (2005) and has good internal consistency reliability (Cronbach’s alpha is .83). The Cronbach’s alpha of PSQI in this study was .70.

Geriatric Depression Scale
The Geriatric Depression Scale short form (GDS-SF, 15 items) was used to measure the depressive symptoms, the total score was 15, score ≥7–9 indicates depression symptoms, and ≥10 was depression. The Cronbach’s alpha was .94, suggesting a high degree of internal consistency for the GDS (Yesavage et al., 1983). The Cronbach’s alpha of GDS-15 in this study was .85.

Hospital Anxiety Scale
There are seven items in the Hospital Anxiety Scale (HAS). A four-point scoring is adopted to evaluate the respondent’s anxiety with four levels of “never,” “rarely,” “sometimes,” and
“often,” respectively. A score ≥8 indicates anxiety mood. The scoring of the scale adopts a 0–3 point; total scores were the sum of each item. The higher the score indicates that the degree of anxiety is higher. Cronbach’s alpha for HAS varied from .68 to .93 (Bjelland et al., 2006), the Cronbach’s alpha of HAS in this study was .90.

**Parkinson’s Disease Questionnaire**
The Parkinson’s Disease Questionnaire (PDQ-39) assesses how often people suffering from PD encounter difficulties in eight dimensions of daily life (including interpersonal relationships, social status, and communication). A validated, disease-specific quality of life instrument was used to assess the HRQOL, it is a self-administered questionnaire (Jenkinson et al., 1997). The Parkinson’s Disease Questionnaire-8 is a short-form version, derived from the PDQ-39. The higher the PDQ-8 index score, the lower the patient’s perception of quality of life (Jenkinson & Fitzpatrick, 2007). A Chinese version of the PDQ-8 has been shown as a reliable instrument and internal consistency (Cronbach’s alpha α is .87) (Tan et al., 2007); the Cronbach’s alpha of PDQ-8 in this study was .70.

**Data Collection**
The data for this study were collected from March 2016 to January 2017 in Taiwan. Participants came from the neurology department of two medical centers in central Taiwan. After screening, those who meet the criteria were included in this study. After the explanation of the study procedure, the participants filled out an informed consent form, and then the researchers asked the participants to fill out the questionnaire in the outpatient department. The whole process took about 30–60 min.

**Statistical Analysis**
Statistical analysis used SPSS version 20.0 software (IBM Corporation, Armonk, NY, USA). Demographic data was based on descriptive statistics (percentage and mean). Pearson’s correlation coefficients were used to assess the associations between variables. Correlation coefficients were interpreted as very weak ($r = 0.19$), weak ($r = 0.39$), moderate ($r = 0.59$), strong ($r = 0.79$), or very strong ($r = 1.00$) (Akoglu, 2018). A multiple linear regression analysis was performed to determine factors that contribute to predicting exercise motivation of PD patients. The statistical significance level was set at $p < .05$.

**Ethics Considerations**
The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Changhua Christian Hospital and Taichung Veterans General Hospital (IRB TCVGH No: CG15272A & CCH IRB N: 151223). After a briefing introduction of the purpose and procedure of the study, the informed consent of all participants was obtained. Participants were informed that they could withdraw from the study at any time without losing any rights. All data of participants were kept confidential and anonymous by means of using research codes; the research data was securely locked in a drawer and locking. All participants signed an informed consent form approved by the IRB.

**Table 1.**
Demographic Data and Disease Characteristics (N=49)

| Baseline Characteristics      | n  | %   | Mean | SD  |
|-------------------------------|----|-----|------|-----|
| Age (years)                   | 63.65 | 6.02 |
| Gender                       |     |     |      |     |
| Male                          | 26  | 53.1|
| Female                       | 23  | 46.9|
| Exercise hours/week           | 49  | 174.64 | 100.45 |
| Duration of disease           | 4.97 | 3.91 |
| Disease (H&Y stage)           |     |     |      |     |
| I                             | 31  | 63.3|
| II (unilateral)               | 18  | 36.7|
| L-Dopa dosage (mg)            | 580.48 | 425.50 |
| Chronic Illness               |     |     |      |     |
| Non                           | 33  | 67.3|
| Yes                           | 16  | 32.7|
| Pain                          |     |     |      |     |
| Non                           | 27  | 55.1|
| Yes                           | 22  | 44.9|
| Pain score                    | 1.90 | 2.58 |
| MDS-UPDRS                     |     |     |      |     |
| Part-II (ADL)                 | 5.08 | 3.49 |
| Part-III (motor ability)      | 7.61 | 4.09 |
| FSS                           | 31.88 | 14.42 |
| PSQI                          | 8.69 | 3.72 |
| GDS-15                        | 5.20 | 3.76 |
| HAS                           | 3.84 | 4.01 |
| PDQ-8                         | 27.23 | 14.18 |

**Results**

**Participant Characteristics**
Demographic and clinical characteristics of the study population are given in Table 1: Mean age was 63.65 years ($SD = 6.02$), male and female ($n = 26, 53.10\%$ and $n = 23, 46.90\%$, respectively), mean exercise hours were 174.64 hours/week ($SD = 100.45$), can be diagnosed as PD for 4.97 years ($SD = 3.91$), daily dose of L-Dopa was 580.48 mg ($SD = 425.50$), the VAS 1-10 for pain score was 1.90 ($SD = 2.58$), HY stage I and II ($n = 31, 63.30\%$ and $n = 18, 36.70\%$, respectively), without the other chronic illness ($n = 33, 67.30\%$), and without pain ($n = 27, 55.10\%$). The scores of the scale were MDS-UPDRS part II & III, respectively, 5.08 ($SD = 3.49$) and 7.61 ($SD = 4.09$), FFS was 31.88 ($SD = 14.42$), PSQI was 8.69 ($SD = 3.72$), GDS-15 was 5.20 ($SD = 3.76$), HAS was 3.84 ($SD = 4.01$), and the PDQ-8 was 27.23 ($SD = 14.18$) (Table 1).
Correlation Between all Variables and Exercise Hours

Table 2 shows the exercise hours was a significant negative correlation with a daily dose of L-Dopa dosage ($r = -0.326; p = .025$), MDS-UPDRS part II ($r = -0.348; p = .014$) and III ($r = -0.454; p = .001$). In addition, the exercise hours were significant negative correlation with NMS, including FSS ($r = -0.511; p = 0.000$), PSQI ($r = -0.290; p = 0.043$), GDS-15 ($r = -0.493; p = .000$), HAS ($r = -0.364; p = .010$), and PDQ-8 ($r = -0.471; p = .001$).

Factors Affecting Exercise Motivation in PD Patients

The multiple linear regression model was used to predict the related factors on exercise motivation of PD patients, it was an important analysis to predict the affecting factors. Potential predictors were determined based on the previous correlation analysis. In the regression model, age, duration of disease, and pain scores were not correlated with exercise hours, therefore, they were excluded from further analyses (Table 2). The FFS was the strongest factor related to exercise motivation and explained 42.52% of the total variances; moreover, MDS-UPDRS part II & UPDRS part III explained 12.0% and 24.6% of the total variances, respectively (Table 3). Fatigue was the most significant predictor of exercise motivation.

Discussion

The purpose of this study was to investigate the related factors on exercise motivation in patients with PD. Previous studies have shown that physical activity or exercise was beneficial to PD patients and can maintain their physical function, therefore, exercise motivation is very important for PD patients (Wu et al., 2017). In this study found the main clinical predictor of exercise motivation was fatigue; in addition, motor ability and ADL were also predictors of exercise motivation.

The natural disease progression and course of the PD will increase every 5 years of the PD, that is, the disease stage will continue to progress over time, and this progressing is significant during the first 15 years of the disease (Skorvanek et al., 2017). As the disease progresses, functional status and ADL restriction in PD patients often lead them to the loss of independence in self-care, they have the lower motor ability and physical functions. Additionally, the literature pointed out that PD patients are unwilling to exercise, due to reasons such as disease progression, symptoms, or falls, which leads to weakness of the lower limbs, lack of strength, and inability to stand for a long time, thus reducing the motivation of exercise (Landers et al., 2017). Ellis et al. (2011, 2013) also pointed out that the reasons of fewer motivations or barriers to exercise include patients who are unaware of the benefits of exercise, have lack of time, and have a fear of falling. The duration of the disease, the severity of the pain, a thought that self-health is in a good condition or the sense of well-being, and a thought that exercises are very time-consuming (Allen et al., 2015) and lack motivation, as well as fatigue and depression (Ellis et al., 2011), all these factors will limit the patient’s physical activity and leading barriers to exercise, thereby affecting the motivation for exercise, the results of the above factors are consistent with this study. In this study, participants self-report that due to disease symptoms and motor disability, they have reduced their motivation to exercise and are less willing to do exercise, though they know that exercise is good for physical and mental health. However, it is worth noting that the more the exercise, the more fatigue they feel, the more energy consumption, more unable to bear the load, and do not want to put too much effort on exercise. Moreover, the participants in this study also mentioned that with the progression of the disease, physical discomfort, and MS due to disease also decrease their exercise motivations.

Fatigue often occurs in the early stages, it is a common NMS and is an independent existence NMS that persists throughout the course of the disease in patients with PD (Ongre et al., 2017). A meta-analysis showed a 50% prevalence of fatigue in patients

Table 2.

| Variable                  | Coefficient | p-value |
|---------------------------|-------------|---------|
| Age                       | .142        | .331    |
| Duration of Disease       | .061        | .679    |
| L-Dopa Dosage             | -.326       | .025    |
| Pain Scores               | -.088       | .547    |
| MDS-UPDRS (part-II)       | -.348       | .014    |
| MDS-UPDRS (part-III)      | -.454       | .001    |
| FSS                       | -.511       | .000    |
| PSQI                      | -.290       | .043    |
| GDS-15                    | -.493       | .000    |
| HAS                       | -.364       | .010    |
| PDQ-8                     | -.471       | .001    |

Note: MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale; FSS = Fatigue Severity Scale; PSQI = Pittsburg Sleep Quality Index; GDS-15 = Geriatric Depression Scale short form; HAS = Hospital Anxiety Scale; PDQ-8 = The 8 Item Parkinson’s Disease Questionnaire.

Table 3.

| Variable          | Unstandardized Coefficients | Adjusted R² | p value |
|-------------------|----------------------------|-------------|---------|
| L-Dopa dosage     | -.030                      | .033        | .0086   | .373 |
| MDS-UPDRS part II | 9.525                      | 4.669       | .159    | .120 | .045 |
| MDS-UPDRS part III| -11.980                    | 4.569       | .295    | .246 | .009 |
| FSS               | -3.600                     | .998        | .475    | .425 | .000 |
| PSQI              | .414                       | 3.305       | .475    | .411 | .901 |
| GDS-15            | .533                       | 6.605       | .476    | .397 | .533 |
| HAD               | .589                       | 3.576       | .476    | .381 | .589 |
| PDQ-8             | .238                       | 1.862       | .495    | .388 | .238 |

Note: MDS-UPDRS = Movement Disorder Society Unified Parkinson’s Disease Rating Scale; FSS = Fatigue Severity Scale; PSQI = Pittsburg Sleep Quality Index; GDS-15 = Geriatric Depression Scale short form; HAS = Hospital Anxiety Scale; PDQ-8 = The 8 Item Parkinson’s Disease Questionnaire.
with PD; fatigue in PD patients is associated with age, duration of the disease, equivalent daily dose, higher UPDRS-III scores and H&Y stage, and the risk of comorbid depression, and is also associated with anxiety, sleep disturbance and poorer quality of life (Siciliano et al., 2018). The relevant factors mentioned in the literature are consistent with this study. Fatigue makes PD patients feel energy-consuming and exhausted, and it is difficult to maintain physical and mental functions (Siciliano et al., 2018); therefore, patients are lack motivated and are reluctant to exercise.

Participants in this study also understand that exercise is good for fatigue, but they need a balance between rest and exercise, and they need enough rest and energy recovery to exercise. However, balance disorder, unsteady gait, and limb stiffness in patients with PD cannot be recovered by drug treatment; Although non-pharmacological approaches cannot effectively improve the main symptoms of PD, they can help maintain the stability of patients. Physical activity and exercise are known to improve gait, balance, motivation, and motor ability in daily activities in PD patients through stretching, muscle strength, and balance training, thereby improving fatigue, depression, anxiety, and quality of life (Chen et al., 2020).

Study Limitations
There were several limitations in this study. First, due to various reasons, PD patients are less willing/reject to exercise, it is difficult for us to recruit eligibility participants, 49 participants were recruited, which was a relatively small sample size. Second, we used self-reports to record exercise hours and asked participants to recall the 1-min pulse rate during exercise to determine exercise intensity. Self-reporting affects accurate results, and we recommend that electronic monitoring tools can be implemented to measure the data.

Conclusion and Recommendations
L-Dopa dose, ADL, motor ability, fatigue, sleep quality, depression, anxiety, and health-related quality of life were correlated with exercise motivation. Fatigue was the strongest factor related to exercise motivation. This study advises patients to stay safe (e.g., avoid falls), provide emotional support, encourage exercise, and recommend 3–5 days per week of physical or moderate-intensity exercise for a cumulative 150 minutes per week.

Although there is evidence that exercise is effective for patients with PD, patients are less willing to perform exercise due to disease symptoms and MS, which leads to disease progression and deterioration. The results of this study showed that MS and NMS can affect the exercise motivation of PD patients, and fatigue was the strongest predictor of patients’ motivation to exercise. Therefore, ADL and motor ability may require concern, and we believe that fatigue should be treated appropriately. Both MS and NMS were associated with exercise motivation and compliance/adherence, there is currently insufficient evidence to support any pharmacological treatment or non-pharmacological interventions are effective on fatigue for PD patients.

Considering MS and NMS, as well as the potential complications that PD patients may encounter, it is important to comprehensively evaluate and identify PD-related issues. Nurses are necessary to ensure that medicines are taken as prescribed and on time. Deterioration of symptoms should be considered and appropriate interventions are undertaken. Identifying motor fluctuations is important to ensure that patients remain mobile. As the condition changes over time, nurses can provide advice on strategies to adapt to any changes and to maintain safety, such as fall avoidance (Cotterell, 2018). Therefore, in addition to appropriate pharmacological treatment, non-pharmacological intervention is also needed, such as physical activity or exercise which may delay the progress of the disease and emotional support to help the patients reduce depression and anxiety, so as to maintain a good quality of life. We investigated the barriers to exercise and want to arouse the attention of patients and their families to exercise. Encourage patients to participate in moderate exercises, such as free-moving sports, teach them how to start lifting from a chair by placing their hands on the arms of the chair, and individual mental support for patients can minimize distress (Lennarts et al., 2017). According to the adjusted FITT (frequency, intensity, type, and time) guidelines of ACSM, we also recommend that PD patients take 3–5 days of physical activity or exercise, accumulating to 150 min of moderate-intensity exercise per week (Burnet et al., 2020; Bushman, 2018).

Although certain exercise motivations were a barrier to exercise, we still encourage patients to do exercise. Factors related to the exercise motivation of these patients need to be explored for a long time, and we suggest that longitudinal studies are needed in the future. Furthermore, we recommend that further intervention research designs of exercise plans should be designed to improve the exercise motivation of PD patients. Further research is required to find better interventions on fatigue, MS, and NMS; we suggest that researchers explore and design the appropriate exercise program or better exercise prescriptions to improve exercise compliance and motivation for PD patients in the future.

Parkinson’s disease is a common chronic movement disorder in the elderly. Its symptoms include MS and NMS, which have a negative impact on the quality of life. The main finding of this study was that motor ability, ADL, and fatigue were related factors that affect the exercise motivation of PD patients. With the deterioration of the disease and the influence of progressive symptoms, the irreversible physical dysfunction, and the lack of self-care ability, the patient gradually encounters difficulties in daily life, we suggest and encourage PD patients to do exercise accumulated to 150 min/week. This study provides information to nurses and healthcare workers in diverse areas of neuroscience care. The result and information of this study are applicable to professionals working in the aspect of clinical, research, and education.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Changhua Christian Hospital (Approval date: April 07, 2016, Protocol no: 151223) and Taichung Veterans General Hospital (Approval date: December 14, 2015, Protocol no: CG15272A).
Wu and Ho. Exercise Motivation in Parkinson’s Disease

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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