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Effects of Qigong on Chronic Fatigue Syndrome

Qigong Exercise Alleviates Fatigue, Anxiety, and Depressive Symptoms, Improves Sleep Quality, and Shortens Sleep Latency in Persons with Chronic Fatigue Syndrome-Like Illness

Objectives. To evaluate the effectiveness of Baduanjin Qigong exercise on sleep, fatigue, anxiety, and depressive symptoms in chronic fatigue syndrome- (CFS-) like illness and to determine the dose-response relationship. *Methods*. One hundred fifty participants with CFS-like illness (mean age = 39.0, SD = 7.9) were randomly assigned to Qigong and waitlist. Sixteen 1.5-hour Qigong lessons were arranged over 9 consecutive weeks. Pittsburgh Sleep Quality Index (PSQI), Chalder Fatigue Scale (ChFS), and Hospital Anxiety and Depression Scale (HADS) were assessed at baseline, immediate posttreatment, and 3-month posttreatment. The amount of Qigong self-practice was assessed by self-report. *Results*. Repeated measures analyses of covariance showed a marginally nonsignificant (P = 0.064) group by time interaction in the PSQI total score, but it was significant for the "subjective sleep quality" and "sleep latency" items, favoring Qigong exercise. Improvement in "subjective sleep quality" was maintained at 3-month posttreatment. Significant group by time interaction was also detected for the ChFS and HADS anxiety and depression scores. The number of Qigong lessons attended and the amount of Qigong self-practice were significantly associated with sleep, fatigue, anxiety, and depressive symptom improvement. *Conclusion*. Baduanjin Qigong was an efficacious and acceptable treatment for sleep disturbance in CFS-like illness. This trial is registered with Hong Kong Clinical Trial Register: HKCTR-1380.

1. Introduction

CFS is a complex, medically unexplained, and debilitating condition, which is characterized by persistent fatigue of at least 6 months. Estimated prevalence of CFS ranged between 0.007% and 2.8% of the general adult population [1]. Sleep disturbance presenting as unrefreshing or nonrestorative sleep is one of the diagnostic criteria of CFS and is very common in the patients with CFS [2]. Up to 87–95% of patients with CFS have nonrestorative sleep and the associated daytime dysfunction [3]. Subjective sleep quality was significantly worse in CFS patients compared with healthy controls [4]. Psychiatric comorbidity is also common in chronic fatigue and CFS; over 80% of patients with chronic fatigue and CFS had a lifetime history of psychiatric disorders such as depression or generalized anxiety disorder [5, 6]. People with CFS are likely undertreated for their psychiatric illnesses [7]. A large part of the patients with CFS remains unrecognized by general practitioners in the community [8]. CFS-like illness is defined based on self-reported fatigue characteristics, associated symptoms, and medical history using the similar criteria for CFS but without confirmation by medical examination [9–11]. Thus, CFS-like illness may include chronic fatigue and CFS.

To date, no curative treatment is available for CFS [12] and the treatment is often symptom based [1]. Only cognitive behavior therapy and graded exercise therapy have been shown to be effective in treating fatigue and the associated symptoms of CFS [1, 12]. Pharmacotherapy is commonly used for sleep disturbance and psychiatric symptoms in CFS [13]; however, psychotropic medications, especially hypnotics, have limited clinical benefits and significant side effects and are not recommended for long-term use [14]. Various nonpharmacological therapies have been proposed, and the use of complementary and alternative medicine (CAM) is growing for the treatment of CFS [15]. Various CAM modalities including mind-body intervention [16], exercise therapy [17, 18], and Qigong exercise [15, 19] have demonstrated positive effects in relieving insomnia, chronic fatigue, anxiety, and depressive symptoms. Qigong is an ancient Chinese self-healing mind-body exercise and it contains meditation, breathing, body posture, and gentle movement. According to the traditional Chinese medicine theory, Qigong aims to promote the circulation of vital energy "Qi" in the meridian system (Qi vital energy channel) and to improve the balance of Qi through the regulation of body, mind, and breathing [20].

Our prior study has demonstrated that Qigong exercise not only reduces fatigue and depressive symptoms, but also improves mental functioning and increases telomerase activity in patients with CFS-like illness [21, 22]; however, the effects on sleep remain unclear. A number of studies have reported that aerobic exercise has positive effect on sleep quality in patients with chronic insomnia [23, 24] and obstructive sleep apnea [25]; and several studies have shown that Qigong exercise improves sleep quality in patients with fibromyalgia [26, 27], perimenopausal women [28], and community-dwelling older adults [29]. However, to our knowledge, no study has examined whether Qigong exercise can improve sleep quality in patients with CFS-like illness or assessed the dose-response relationship between Qigong exercise and symptom improvement. In addition, recent systematic reviews on CAM therapies for CFS, insomnia, depression, and anxiety have highlighted that limited scientific evidence is available and more rigorous randomized controlled trials (RCTs) with adequate sample size and appropriate controls are warranted [15, 19, 30]. Thus, the primary objective of this large-scale RCT was to evaluate the effectiveness of Baduanjin Qigong exercise on sleep, fatigue, anxiety, and depressive symptoms in patients with CFS-like illness. Baduanjin (also called Eight-Section Brocades, 八段錦) is one of the most common forms of Chinese health Qigong exercise, characterized by its simple, slow, and relaxing movements. The exercise involves 8 simple movements, according to the traditional Chinese medicine theory, each of which can enhance the function of certain organs or parts of the body [31]. As Baduanjin Qigong is very easy to learn and less physically or cognitively demanding, it is popular in the Chinese population as a safe Qigong exercise to promote health [31]. The secondary objective was to investigate the dose-response relationship between Qigong exercise and symptom improvement.

2. Methods

2.1. Study Design. This was a randomized, waitlist-controlled, parallel-group study. Major assessments were at baseline (T0), immediate postintervention (T1), and 3-month postintervention (T2). Participants were randomly assigned to either Qigong exercise or waitlist. Randomization was done using computer-generated random numbers. Blinding of the participants was not possible due to the nature of intervention. Sample size was calculated based on changes in Chalder Fatigue Scale (ChFS) score. According to our prior study [21], we expected a between-group difference of 6.5 points on the ChFS, equivalent to an effect size of 0.64. A sample size of 51 in each group would have a power of 80% to detect the 6.5-point between-group difference in total ChFS score at a significance level of 0.05. Allowing a 30% dropout, we estimated that this study would require a sample size of 75 in each group. Ethics approval was obtained from the local institutional review board. The study was registered in the Hong Kong Clinical Trial Register (number HKCTR-1380). We followed the CONSORT recommendations in designing and reported the controlled trial [32].

2.2. Participants. After the study was advertised in the media, a total of 3848 Chinese adults from the local community were interested in the study and completed an online screening questionnaire. The questionnaire was set according to the US Centers for Disease Control and Prevention (CDC) diagnostic criteria for CFS [33]. Participants were diagnosed as having CFS-like illness if they had unexplained, persistent fatigue of new onset (not lifelong) for 6 or more months, accompanied by 4 or more of the following 8 symptoms: unrefreshing sleep, new headaches, impaired memory or concentration, postexertional malaise, muscle pain, multijoint pain, sore throat, and tender lymph nodes, and did not report any history of cancer, hypothyroidism, sleep apnea, narcolepsy, hepatitis B or C virus infection, severe obesity, and mental disorders, including major depressive disorder, schizophrenia, and bipolar disorder, and alcohol or other substances abuse based on a medical history checklist [33]. To minimize the impact of other undiagnosed chronic illnesses, we excluded people older than 50 years who were more likely to have chronic illnesses presenting with chronic fatigue than younger participants. We also excluded people who had participated in Qigong practice in the past 6 months.

The participants were firstly screened through online questionnaires. If there was any uncertainty concerning eligibility, the online questionnaires were reviewed by 2 investigators and any discrepancies were resolved by discussion. A computer-generated list of random numbers was used for allocation of the participants. We randomly selected from among 1409 eligible subjects and contacted them by phone until the target sample size was met. The randomization procedure was done prior to phone contact with the potential subjects. Figure 1 presents the participant flowchart.

2.3. Procedure. All participants gave written informed consent prior to further assessment and intervention. At T0, T1, and T2, participants completed a set of questionnaires on sleep, fatigue, anxiety, and depression. Participants were advised to sign an attendance record prior to each class. Daily self-practice of Qigong and other exercises and any adverse events were recorded on a standard log sheet, which were collected weekly during the intervention period and monthly after intervention. However, a majority of the participants did not return their log sheet after intervention; hence, we only analyzed the Qigong self-practice data during the intervention period. No subjects were paid any monetary rewards for participation. However, the Qigong class was provided free of charge and those who completed all assessments and had an attendance rate ≥ 80% would be given a brief health report based on their own data and a DVD on Baduanjin Qigong exercise.

2.4. Intervention. Baduanjin Qigong, comprising 8 standardized movements, has been endorsed by the Sports and Culture Commission of the People's Republic of China (PRC). Sixteen sessions of Baduanjin Qigong group training were provided over nine consecutive weeks. Each session lasted 1.5 hours and was conducted by an experienced Qigong master with more than 20 years of experience in teaching and 7-8 assistant Qigong teachers who had 3–5 years of experience in Qigong practice and were certified in teaching Qigong. The session began with body stretching and relaxation (15 minutes), followed by introduction and demonstration of each movement, explanation of the precautions in Qigong exercise, and answering of the questions raised by the participants (25 minutes), then a group Qigong training involving 75 participants (20 minutes) and lastly a small group Qigong practice involving 15 participants with individual guidance by the assistant Qigong teacher who helped to correct the movement of the participants, and the experienced Qigong master oversaw all small groups and provided additional advice (30 min). Participants in the intervention group were advised to practice Qigong for at least 30 minutes every day. Participants in the waitlist group were advised to keep their lifestyle as usual and refrain from joining any Qigong class.

2.5. Measures

2.5.1. Screening Measures and Demographics. The online screening questionnaire includes (1) the CDC diagnostic checklist for CFS [33]; (2) a list of medical illnesses based on the CDC exclusion criteria for CFS; (3) sociodemographics, including age, gender, employment status, educational level, marital status, number of children, religious affiliation, and monthly income; (4) lifestyle variables, including exercise habit, smoking, and alcohol drinking; and (5) weight and height.

2.5.2. Pittsburgh Sleep Quality Index (PSQI). The PSQI is a widely used 19-item self-administered instrument to assess sleep quality and disturbances over a 1-month period [34]. It contains 7 components, subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction. The total score ranges from 0 to 21 and a higher score indicates poorer sleep quality. The Chinese version of PSQI has been shown to have adequate psychometric properties [35, 36].

2.5.3. Chalder Fatigue Scale (ChFS). The ChFS is a 14-item self-rating scale on the severity of physical fatigue (8 items) and mental fatigue symptoms (6 items) [37]. A higher score is suggestive of greater severity of fatigue. The Chinese version of the ChFS has been shown to be valid and reliable in Chinese adults [38].

2.5.4. Hospital Anxiety and Depression Scale (HADS). The HADS is a 14-item self-assessment scale on anxiety (7 items) and depressive symptoms (7 items) [39]. Each item can be scored on a 0–3 scale and a higher score denotes a higher level of anxiety or depressive symptoms. The Chinese version of the HADS has satisfactory psychometric properties [40].

2.5.5. Global Assessment, Satisfaction, and Adverse Events. Participants were asked to compare their condition before and after joining the Qigong lessons as very marked improvement, marked improvement, same as before, marked deterioration, and very marked deterioration and whether they were satisfied with the lessons, from very satisfied to very dissatisfied. Participants reported any adverse events by free text in the log sheet.

2.6. Data Analysis. All analyses were conducted with Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc., Chicago, IL). Continuous data were presented by mean and standard deviation (SD). Categorical data were presented by frequency (percentage). Between-group differences at baseline were assessed by chi-squared test for categorical data and independent t-test for continuous data. Repeated measures analyses of covariance (ANCOVA) were performed to assess the interaction effect of group and time for each outcome measure, adjusting for gender, due to a significant between-group difference in gender ratio. The within-group changes were assessed by paired t-test and the between-group differences were evaluated by independent t-test. Effect size was calculated by Cohen's d statistics. The data analysis was conducted based on intention-to-treat principle. The missing values were substituted by the last observed values. The dose-response relationship was assessed using correlation analysis between symptom change scores and the number of Qigong classes attended and the average self-reported Qigong practice per week in minutes.

3. Results

3.1. Baseline Characteristics of the Participants. Table 1 describes the sociodemographic and lifestyle variables. The mean age was 39.1 years (SD = 7.8) in the Qigong group and 38.9 years (SD = 8.1) in the waitlist group. The participants were predominantly female, employed full time, highly educated, and married. The most often reported duration of fatigue was 1-2 years (n = 61, 40.7%), followed by 2–5 years (n = 56, 37.3%) and more than 5 years (n = 33, 22.0%).

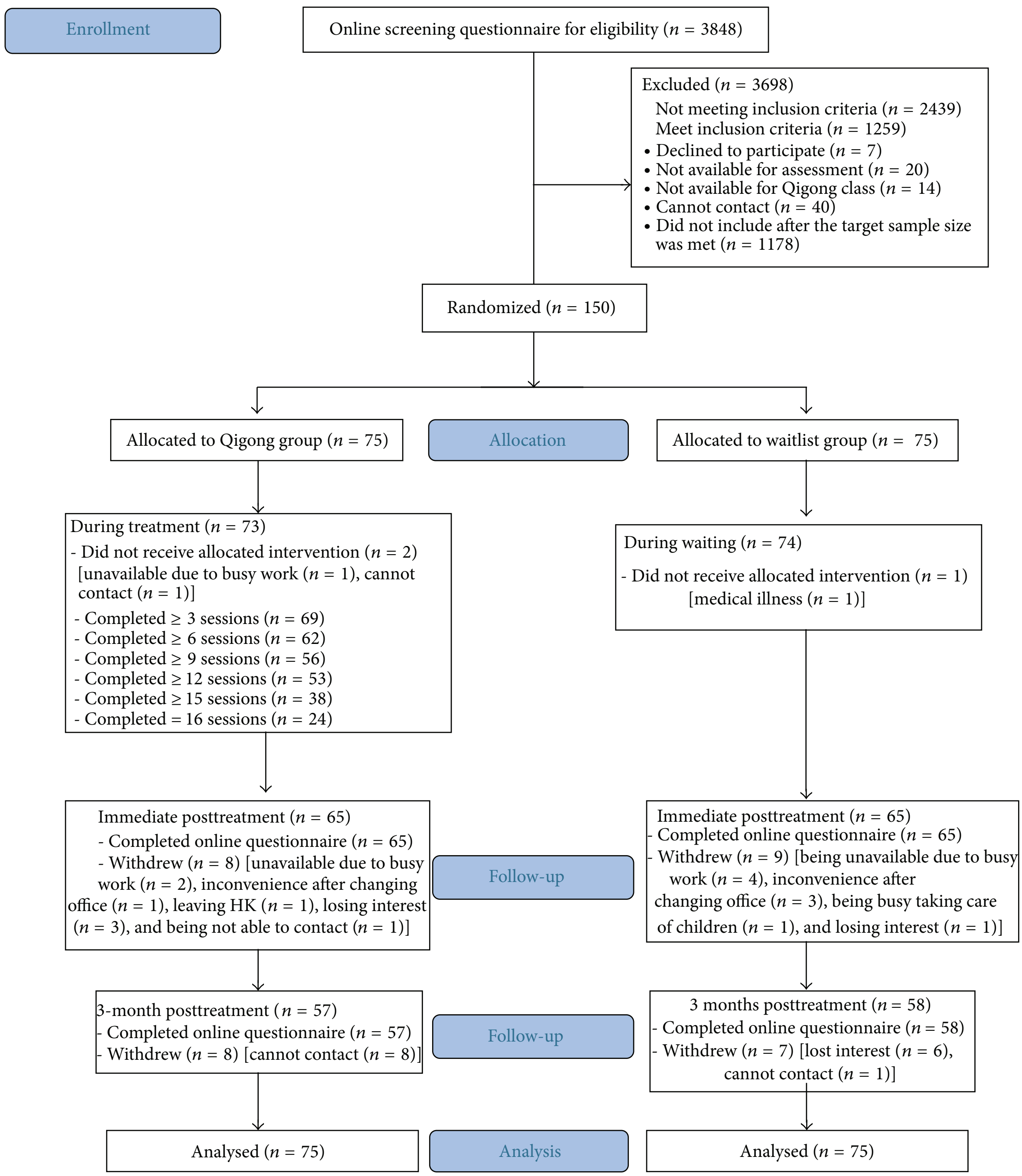

Figure 1: Recruitment flowchart.

The most frequent associated complaint was sleep problems ($n = 144$, 96.0%), followed by muscle pain ($n = 143$, 95.3%), impaired memory or concentration ($n = 132$, 88.0%), postexertional malaise ($n = 106$, 70.7%), arthralgia ($n = 84$, 56.0%), headache ($n = 82$, 54.7%), tender cervical or axillary lymph nodes ($n = 62$, 41.3%), and recurrent sore throat ($n = 55$, 36.7%). A majority of the participants had neither seen any doctors for their fatigue problem ($n = 117$, 78.0%) nor used any medications as treatment ($n = 138$, 92.0%). Except for gender distribution, there were no statistically significant differences in sociodemographic and lifestyle variables between the two groups.

Two participants in the Qigong group dropped out prior to intervention and 8 participants dropped out at immediate posttreatment; in the waitlist group, there was 1 participant who dropped out prior to intervention and 9 dropped out at immediate posttreatment (chi-square test, $P > 0.05$). None of the participants in the Qigong group dropped out due to adverse event (Figure 1).

Table 1: Demographic characteristics and lifestyles variables ($n = 150$).

Variables	Qigong ($n = 75$)		Waitlist ($n = 75$)		P value
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Age (years)	39.1 (7.8)		38.9 (8.1)		0.853
Gender					
Female		46 (61.3%)		62 (82.7%)	0.004
Employment					
Full time		67 (89.3%)		68 (90.7%)	
Part time		1 (1.3%)		3 (4.0%)	0.401
Housewife/unemployed/retired		7 (9.3%)		4 (5.3%)	
Education					
Secondary or below		29 (38.7%)		27 (36.0%)	
Tertiary or undergraduate		36 (48.0%)		30 (40.0%)	0.234
Master or above		10 (13.3%)		18 (24.0%)	
Marital status					
Single		29 (38.7%)		26 (34.7%)	
Married/cohabiting		45 (60.0%)		44 (58.7%)	0.242
Divorced/separated		1 (1.3%)		5 (6.7%)	
Number of children					
0		43 (57.3%)		45 (60.0%)	
1		11 (14.7%)		12 (16.0%)	0.707
2		18 (24.0%)		13 (17.3%)	
3 or more		3 (4.0%)		8 (5.3%)	
Has religious affiliation		33 (44.0%)		29 (38.7%)	0.507
Household monthly income (HK$)					
<10,000		10 (13.3%)		11 (14.7%)	
10,000–19,999		22 (29.3%)		22 (29.3%)	
20,000–29,999		19 (25.3%)		10 (13.3%)	0.378
≥30,000		10 (13.3%)		18 (24.0%)	
No income		4 (5.3%)		3 (4.0%)	
Refused to answer		10 (13.3%)		11 (14.7%)	
Lifestyle variables					
Regular exercise		30 (40.0%)		27 (36.0%)	0.614
Daily smoking		3 (4.0%)		3 (4.0%)	1.000
Alcohol drinking ≥2/week		2 (2.7%)		3 (4.0%)	1.000
Body mass index	22.3 (4.9)		21.6 (3.4)		0.360

As shown in Table 2, at baseline, the mean PSQI score was 10.0 and 10.2, while the mean ChFS total score was 37.4 for the Qigong group and 36.4 for the waitlist group, respectively. All clinical measures were balanced between the two groups at baseline.

3.2. Efficacy

3.2.1. Sleep. The PSQI total score in the Qigong group was significantly lower at T1 and T2, compared to T0 ($d = -0.51$ and -0.48, resp., all P values < 0.001) (Table 2). In the waitlist group, the PSQI total score was also significantly improved at T1 and T2, compared to T0 ($d = -0.19$ and -0.25, $P = 0.024$ and 0.042, resp.). The improvement in the PSQI total score in the Qigong group was significantly greater than that in the waitlist group at T1 ($P = 0.019$) but not at T2 ($P = 0.149$). The group by time interaction in the PSQI total score was marginally nonsignificant ($F(2, 284) = 2.777$, $P = 0.064$).

However, there was significant group by time interaction in the "subjective sleep quality" ($F(2, 288) = 6.364$, $P = 0.002$) and "sleep latency" ($F(2, 294) = 3.168$, $P = 0.044$) items of the PSQI, while the "sleep disturbance" item was marginally nonsignificant ($F(2, 294) = 2.802$, $P = 0.062$). The "subjective sleep quality" in the Qigong group was significantly improved at T1 and T2 compared with the waitlist group ($P = 0.003$ and 0.004, resp.). The improvement in "sleep latency" in the Qigong group was only significant at T1 ($P = 0.019$) but not at T2 ($P = 0.264$), compared with the waitlist group (Table 2).

3.2.2. Fatigue. As shown in Table 2, compared with baseline values, the ChFS total score ($d = -1.19$), ChFS physical score

Table 2: Sleep, fatigue, anxiety, and depressive symptoms at baseline, immediate postintervention, and 3-month postintervention.

	Within-group effects					Between-group effects			
	T0 Mean (SD)	T1[a] Mean (SD)	Effect size Cohen's d	T2[a] Mean (SD)	Effect size Cohen's d	T1 − T0[b] Mean (SD)	T2 − T0[b] Mean (SD)	Time × group[c] F	 P value
PSQI total									
Qigong (n = 73)	10.0 (3.7)	8.2 (3.4)***	−0.51	8.3 (3.4)***	−0.48	−1.9 (3.4)*	−1.7 (3.4)	2.777	0.064
Waitlist (n = 72)	10.2 (3.8)	9.5 (3.7)*	−0.19	9.3 (3.5)*	−0.25	−0.7 (2.6)	−0.9 (3.5)		
Subjective sleep quality									
Qigong (n = 74)	1.93 (0.71)	1.42 (0.74)***	−0.70	1.49 (0.73)***	−0.61	−0.51 (0.71)**	−0.45 (0.7)**	6.364	0.002
Waitlist (n = 73)	1.86 (0.71)	1.68 (0.69)*	−0.26	1.75 (0.70)	−0.16	−0.18 (0.67)	−0.11 (0.72)		
Sleep latency									
Qigong (n = 75)	1.63 (1.06)	1.23 (0.99)***	−0.39	1.28 (1.02)***	−0.34	−0.40 (0.75)*	−0.35 (0.81)	3.168	0.044
Waitlist (n = 75)	1.69 (0.97)	1.57 (0.92)	−0.13	1.49 (0.95)*	−0.21	−0.12 (0.70)	−0.20 (0.79)		
Sleep duration									
Qigong (n = 75)	1.67 (0.91)	1.44 (0.83)*	−0.26	1.40 (0.81)**	−0.31	−0.23 (0.80)*	−0.27 (0.72)	1.905	0.151
Waitlist (n = 75)	1.75 (0.84)	1.79 (0.89)	−0.05	1.61 (0.85)	−0.17	0.04 (0.81)	−0.13 (0.83)		
Sleep efficiency									
Qigong (n = 75)	0.87 (1.16)	0.72 (1.09)	−0.13	0.96 (1.26)	0.07	−0.15 (1.32)	0.09 (1.29)	0.651	0.522
Waitlist (n = 75)	1.09 (1.12)	0.79 (1.15)	−0.26	1.05 (1.26)	−0.03	−0.31 (0.97)	−0.04 (1.41)		
Sleep disturbance									
Qigong (n = 75)	1.64 (0.69)	1.40 (0.62)***	−0.37	1.36 (0.63)***	−0.42	−0.24 (0.52)	−0.28 (0.48)	2.802	0.062
Waitlist (n = 75)	1.73 (0.68)	1.63 (0.65)	−0.15	1.63 (0.61)	−0.15	−0.11 (0.61)	−0.11 (0.63)		
Use of sleep medication									
Qigong (n = 74)	0.31 (0.78)	0.28 (0.77)	−0.04	0.30 (0.75)	−0.01	−0.03 (0.83)	−0.01 (0.80)	0.220	0.803
Waitlist (n = 73)	0.26 (0.60)	0.32 (0.72)	0.09	0.34 (0.79)	0.11	0.05 (0.72)	0.08 (0.89)		
Daytime dysfunction									
Qigong (n = 73)	1.90 (0.82)	1.59 (0.94)	−0.35	1.52 (0.96)	−0.43	−0.32 (0.86)	−0.38 (0.92)	1.381	0.253
Waitlist (n = 73)	1.77 (0.77)	1.64 (0.75)	−0.17	1.53 (0.73)	−0.32	−0.12 (0.76)	−0.23 (0.83)		
ChFS total									
Qigong (n = 75)	37.4 (6.2)	25.6 (12.6)***	−1.19	25.2 (12.7)***	−1.22	−11.8 (11.4)***	−12.2 (11.9)***	16.650	<0.001
Waitlist (n = 75)	36.4 (8.3)	32.3 (9.7)***	−0.45	31.1 (10.9)***	−0.55	−4.1 (6.5)	−5.3 (7.8)		
ChFS physical									
Qigong (n = 75)	24.2 (4.0)	16.7 (8.0)***	−1.19	16.2 (8.1)***	−1.25	−7.5 (7.3)***	−8.0 (7.5)***	18.527	<0.001
Waitlist (n = 75)	23.0 (5.0)	20.6 (5.9)***	−0.44	20.0 (6.7)***	−0.51	−2.4 (4.1)	−3.1 (5.0)		
ChFS mental									
Qigong (n = 75)	13.2 (3.6)	9.0 (5.4)***	−0.92	9.0 (5.3)***	−0.93	−4.3 (4.9)***	−4.3 (5.0)**	9.290	<0.001
Waitlist (n = 75)	13.3 (4.5)	11.7 (4.6)***	−0.35	11.2 (4.9)***	−0.45	−1.7 (3.4)	−2.2 (3.7)		
HADS Anxiety									
Qigong (n = 75)	10.9 (3.7)	8.5 (4.0)***	−0.62	8.8 (4.4)***	−0.52	−2.3 (3.2)**	−2.1 (3.7)*	4.172	0.016
Waitlist (n = 75)	11.2 (3.6)	10.4 (4.0)*	−0.21	10.2 (4.0)*	−0.26	−0.8 (3.3)	−1.0 (3.3)		
HADS depression									
Qigong (n = 75)	9.4 (3.5)	6.6 (3.7)***	−0.78	7.2 (4.1)***	−0.58	−2.7 (3.5)***	−2.1 (3.9)	10.262	<0.001
Waitlist (n = 75)	9.5 (3.4)	8.8 (3.9)*	−0.19	8.5 (4.0)**	−0.27	−0.7 (2.9)	−1.0 (3.0)		

PSQI: Pittsburgh Sleep Quality Index; ChFS: Chalder Fatigue Scale; HADS: Hospital Anxiety and Depression Scale; SD: standard deviation; T0: baseline; T1: immediate postintervention; T2: 3-month postintervention.

[a]Compared with baseline using paired t-test; [b]compared the change score between groups using independent t-test; [c]repeated measures ANCOVA adjusting for between-group difference in gender ratio. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$.

(d = −1.19), and ChFS mental score (d = −0.92) were significantly improved in the Qigong group immediately after intervention (T1) (all P values < 0.001), and the improvements were maintained at T2 (all P values < 0.001). In the waitlist group, the total fatigue score (d = −0.45, P < 0.001), physical fatigue score (d = −0.44, P < 0.001), and mental fatigue score (d = −0.35, P < 0.001) were also significantly improved at T1 and T2 (all P values < 0.001), but the magnitudes of improvement were much smaller. Compared with the waitlist group, the Qigong group had significantly greater

Table 3: Correlations between Pittsburgh Sleep Quality Index (PSQI), Chalder Fatigue Scale (ChFS), and Hospital Anxiety and Depression Scale (HADS) change scores with number of Qigong sessions attended and weekly duration of Qigong practice.

	Attendance frequency (n = 75)		Self-practice (min./week) (n = 64)			
Mean (SD)	11.9 (5.1)		145.4 (77.2)			
Median	15.0		151.7			
Interquartile	(8.0–16.0)		(105.8–185.9)			
T1 − T0	R	P	R	P	R^a	P^a
Change in PSQI	−0.288	0.013	−0.093	0.474	−0.101	0.439
Change in PSQI-subjective sleep quality	−0.422	0.001	−0.300	0.017	−0.315	0.013
Change in PSQI-sleep latency	−0.321	0.005	−0.205	0.104	−0.189	0.137
Change in PSQI-sleep duration	−0.089	0.445	0.107	0.401	0.115	0.371
Change in PSQI-sleep efficiency	−0.055	0.638	0.122	0.338	0.110	0.389
Change in PSQI-sleep disturbance	−0.266	0.021	−0.318	0.010	−0.303	0.018
Change in PSQI-use of sleep medication	0.039	0.743	0.007	0.956	−0.030	0.816
Change in PSQI-daytime dysfunction	−0.213	0.070	−0.083	0.520	−0.081	0.536
Change in total fatigue	−0.587	<0.001	−0.418	0.001	−0.398	0.001
Change in HADS-anxiety	−0.328	0.004	−0.269	0.031	−0.253	0.045
Change in HADS-depression	−0.420	<0.001	−0.397	0.001	−0.388	0.002
T2 − T0	R	P	R	P	R^a	P^a
Change in PSQI	−0.254	0.030	−0.099	0.442	−0.127	0.330
Change in PSQI-subjective sleep quality	−0.377	0.001	−0.272	0.031	−0.311	0.014
Change in PSQI-sleep latency	−0.255	0.027	−0.205	0.105	−0.222	0.080
Change in PSQI-sleep duration	−0.147	0.209	0.020	0.874	0.001	0.991
Change in PSQI-sleep efficiency	−0.071	0.548	0.126	0.322	0.110	0.393
Change in PSQI-sleep disturbance	−0.336	0.003	−0.235	0.062	−0.228	0.072
Change in PSQI-use of sleep medication	0.027	0.822	0.040	0.754	0.012	0.927
Change in PSQI-daytime dysfunction	−0.256	0.029	−0.157	0.222	−0.159	0.222
Change in total fatigue	−0.611	<0.001	−0.403	0.001	−0.360	0.004
Change in HADS-anxiety	−0.274	0.018	−0.313	0.012	−0.297	0.018
Change in HADS-depression	−0.286	0.013	−0.299	0.016	−0.292	0.020

T0: baseline; T1: immediate postintervention; T2: 3-month postintervention.
[a]Partial correlation controlling the amount of other exercises.

improvements in ChFS fatigue score ($F(2, 294) = 16.650$, $P < 0.001$), ChFS physical score ($F(2, 294) = 18.527$, $P < 0.001$), and ChFS mental score ($F(2, 294) = 9.290$, $P < 0.001$).

3.2.3. Anxiety and Depression. As shown in Table 2, there are significant group by time interactions in the HADS anxiety and depression scores. The reduction in anxiety and depressive symptoms was significantly greater in the Qigong group, compared to the waitlist group (HADS anxiety: $F(2, 294) = 4.172$, $P = 0.016$; HDAS depression: $F(2, 294) = 10.262$, $P < 0.001$).

3.3. Dose-Response Relationship. Two participants never came to Qigong lessons. Sixty-two of the 75 participants (82.7%) attended at least 6 of the 16 lessons and 56 participants (74.7%) attended at least 9 lessons (Figure 1). The average number of Qigong sessions attended was 11.9 (SD = 5.1, range = 0–16). There was significant relationship between the number of Qigong sessions attended and the reduction in PSQI, ChFS, and HADS scores from T0 to T1 and from T0 to T2 (Table 3).

Only 64 of the 75 participants returned their log sheet on Qigong self-practice for at least 2 weeks and their self-practice data were included in the analysis. The mean duration of Qigong self-practice was 145.4 minutes per week (SD = 77.2). The amount of Qigong self-practice was significantly associated with the ChFS and HADS change scores from T0 to T1 and from T0 to T2. However, only the "subjective sleep quality" and "sleep disturbance" items of the PSQI from T0 to T1 and the "subjective sleep quality" item from T0 to T2 had significant dose-response relationships with the amount of Qigong self-practice during the intervention period. The dose-response relationship between symptom improvement and the amount of Qigong self-practice remained unchanged after controlling the amount of time spent on other exercises (Table 3).

3.4. Global Assessment, Satisfaction, and Adverse Events. Only 53 of the 75 participants in the intervention group returned their questionnaire on global assessment and satisfaction. Thirty-six of the 53 participants (67.9%) felt they had marked or very marked improvement after the Qigong lessons, while the others reported being the same as before. Forty-seven of the 53 participants (88.7%) were satisfied or very satisfied and the rest was neutral. The most common adverse event was muscle ache ($n = 24$), followed by palpitation ($n = 4$), giddiness ($n = 3$), knee pain ($n = 2$), backache ($n = 2$), fatigue ($n = 2$), nervousness ($n = 2$), Qi movement inside body ($n = 2$), dizziness ($n = 2$), shoulder pain ($n = 1$), chest tightness ($n = 1$), shortness of breath ($n = 1$), and increased dreaming ($n = 1$).

4. Discussion

To the best of our knowledge, this is the first large scale RCT to investigate the effect of Qigong exercise on sleep quality in persons with CFS-like illness and the dose-response relationship of Qigong. The results indicated that Baduanjin Qigong exercise was more efficacious than waitlist control in relieving sleep, fatigue, anxiety, and depressive symptoms in CFS-like illness. Although the group by time interaction was marginally nonsignificant ($P = 0.062$) for PSQI total score, it was significant for the "subjective sleep quality" and "sleep latency" items of the PSQI. The significant improvement in "subjective sleep quality" was maintained at 3-month postintervention, suggesting that Baduanjin Qigong exercise had at least short-term effect. Most of the participants were satisfied with Qigong exercise and felt they had greatly benefited from the intervention. Three-quarters of the participants attended more than half of the Qigong lessons arranged. Except muscle ache, adverse events were uncommon. Our findings are in line with the growing evidence on the benefits of Qigong for CFS-like illness [21, 22]. In light of the efficacy, acceptability, low cost, and accessibility of Qigong exercise, it should be tested in future studies as an entry-level treatment in a stepped care model for insomnia [41].

Compared with waitlist group, participants receiving Baduanjin Qigong exercise had better sleep quality, shorter sleep latency, and longer sleep duration at immediate postintervention; however, only the improvement in sleep quality was maintained at 3-month postintervention. It was likely that after the lessons participants had not continued to practice Qigong themselves; hence, the early improvement would not be maintained. However, due to the missing data on Qigong self-practice after the intervention period, future studies are needed to confirm our hypothesis. The beneficial effects of Baduanjin Qigong exercise on sleep quality have been shown in previous studies of smaller sample size and on perimenopausal women [28], patients with fibromyalgia [26, 27], and community-dwelling older adults [29]. Our results suggested that Qigong exercise was efficacious in the treatment of sleep disturbance in CFS-like illness. In line with previous studies [27, 28], there was a direct relationship between symptom improvement and the amount of Qigong practice.

We showed that Baduanjin Qigong exercise significantly reduced fatigue, anxiety, and depressive symptoms in patients with CFS-like illness, replicating part of the results in our previous studies that examined another Qigong exercise, named Wu Xing Ping Heng Gong. In our previous studies, Wu Xing Ping Heng Gong improved fatigue and depressive symptoms [21, 22] but not anxiety symptoms. The longer duration of intervention probably accounted for the effectiveness of Qigong for anxiety in this study. There were only 10 sessions of Qigong exercise in 5 weeks in our previous studies instead of 16 sessions in 9 weeks in this study. Another possible reason was that in this study we strongly advised the participants to have daily Qigong self-practice for at least 30 minutes and to keep a personal log sheet. The advice on self-practice and self-monitoring might have encouraged the self-practice of Qigong and enhanced its effectiveness. Our finding of the positive effect of Qigong exercise on anxiety was in line with the conclusion of a recent systematic review [42].

Although the findings of our study were promising, there were several notable limitations. First, our participants were recruited from the community solely based on self-report and they did not receive a thorough physical and mental state examination; hence, it was possible that some of them may not fully meet the CDC criteria for CFS. However, through online questionnaires and exclusion of people older than 50 years, the chance that the chronic fatigue is caused by medical and psychiatric conditions was reduced. Due to the unknown etiology and lack of effective treatment for CFS, a large proportion of CFS patients remains unrecognized and undertreated in the community [7, 8]; it is very difficult to recruit participants with diagnosed CFS. Another limitation was that participants were not blind to the intervention and therefore might have high expectations in the effectiveness of treatment, which could inflate the response; however, improvements were maintained at 3-month postintervention, suggesting that the beneficial effects of Qigong cannot be due to expectancy alone. Our sample was limited to adults younger than 50 years; hence, the results could not be generalized to the older population. We have not assessed the daytime functioning or used more sophisticated methods, such as sleep diary, actigraphy, and polysomnography, in the assessment of sleep disturbance. Our sample size was estimated based on fatigue scale, and hence the sample size might not be sufficient to detect between-group difference in sleep variables. The amount of Qigong self-practice was assessed by self-report and there were missing data; hence, the results should be treated as preliminary. There still existed other nonspecific factors, such as stretch exercise, didactic teaching from Qigong masters, personal attention, and social support among participants, which may contribute to the improved outcomes. Future studies using a control intervention with all the nonspecific factors included can help to understand the specific therapeutic components of Qigong exercise. Despite these limitations, the present study was the first large-scale RCT that showed the beneficial effects of Qigong exercise on sleep disturbance in CFS-like illness.

In conclusion, we found that 16 sessions of Baduanjin Qigong exercise were an efficacious and acceptable treatment for sleep disturbance, fatigue, anxiety, and depressive symptoms in people with CFS-like illness. Future studies should examine the effectiveness of Qigong exercise in a mixed group of insomnia and insomnia in other comorbid conditions. Strategies to enhance participation in Qigong lesson and regular practice are needed.

Conflict of Interests

The authors have no conflict of interests to disclose. The funding sources had no further role in the study design, the collection, analysis, and interpretation of data and in writing report of this work.

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A Randomized Controlled Trial of Qigong Exercise on Fatigue Symptoms, Functioning, and Telomerase Activity in Persons with Chronic Fatigue or Chronic Fatigue Syndrome

Abstract

Background Chronic fatigue is common in the general population. Complementary therapies are often used by patients with chronic fatigue or chronic fatigue syndrome to manage their symptoms.

Purpose This study aimed to assess the effect of a 4-month qigong intervention program among patients with chronic fatigue or chronic fatigue syndrome.

Methods Sixty-four participants were randomly assigned to either an intervention group or a wait list control group. Outcome measures included fatigue symptoms, physical functioning, mental functioning, and telomerase activity.

Results Fatigue symptoms and mental functioning were significantly improved in the qigong group compared to controls. Telomerase activity increased in the qigong group from 0.102 to 0.178 arbitrary units ($p<0.05$). The change was statistically significant when compared to the control group ($p<0.05$).

Conclusion Qigong exercise may be used as an alternative and complementary therapy or rehabilitative program for chronic fatigue and chronic fatigue syndrome.

Keywords Qigong · Exercise · Chronic fatigue · Telomerase · Randomized controlled trial

Introduction

Chronic fatigue is a common complaint in both primary care settings and in the general population. According to criteria established in the USA [1] and Canada [2], chronic fatigue is severe fatigue that persists or relapses for at least 6 months, while chronic fatigue syndrome, which is distinguished from chronic fatigue by severity and chronicity [3], is defined as “medically unexplained” fatigue lasting for six or more months. In recent years, researchers have paid increasing attention to chronic fatigue and chronic fatigue syndrome. The reported rates of chronic fatigue have ranged from 0.037 to 18.3 % in the general adult population [3–6]. The reported rates of chronic fatigue syndrome, however, have ranged between 0.007 and 2.8 % of the general adult population and between 0.006 and 3 % of patients seeking medical care [4, 7–9]. A population-based study in Hong Kong reported a point prevalence of chronic fatigue among adults as 10.7 % [3], while chronic fatigue syndrome was identified in 3 % of the local adult patients [10]. Chronic fatigue symptoms were reported as particularly common in women [6]. Given the unfavorable mental and physical outcomes of chronic fatigue and chronic fatigue syndrome that affect daily functioning, the burden of these conditions on healthcare and the economy should not be underestimated.

Though the etiopathogenesis of chronic fatigue syndrome is not yet well understood, the multifactorial disease pathways and the biopsychosocial model have been widely accepted as explanations for its complex symptoms and underlying mechanisms [11–13]. The inflammatory, immune, oxidative, and nitrosative pathways were suggested to induce a series of immunological and biological consequences that further impair physical and psychological functioning. According to this model, chronic fatigue symptoms develop through a developmental and cumulative process that involves different psychobiological factors contributing to triggering, predisposing, and maintaining stages. Among those factors, stress has been increasingly recognized as playing an important role in both the etiology and pathophysiology of chronic fatigue and chronic fatigue syndrome [14–16]. Clinically, psychiatric disorders are common among patients with chronic fatigue or chronic fatigue syndrome [3]. Research has demonstrated that both the occurrence of recent stressful life events and chronic stress levels appear to be increased in patients with chronic fatigue or chronic fatigue syndrome [17–20].

Because the pathophysiology of chronic fatigue and chronic fatigue syndrome remains inchoate, current treatment modalities mainly seek to alleviate symptoms [14]. To date, there are controversies regarding appropriate strategies for the treatment or management of chronic fatigue and chronic fatigue syndrome. Because western treatments and medications are often associated with limited clinical benefits [21] and possible undesirable side effects [22], complementary and alternative therapies are often used by individuals with chronic fatigue or chronic fatigue syndrome to manage their symptoms [23, 24]. From the perspective of traditional Chinese medicine, chronic fatigue and chronic fatigue syndrome are caused by blood stasis due to *qi* (vital energy) deficiency and/or emotional constrain; therefore, stimulation of the blood and *qi* circulation (Xing Qi Huo Xue, 行氣活血) is the core treatment strategy for chronic fatigue and chronic fatigue syndrome [22, 25].

Qigong, a mind–body exercise within the paradigm of traditional Chinese medicine, is practiced by a large number of people in Chinese communities. It aims to achieve a harmonious flow of energy (*qi*) in the body through gentle movements that integrate body, mind, and spirit, to improve physical fitness, overall well-being, and longevity. Several randomized controlled trials of qigong exercise have demonstrated health benefits for patients with chronic neck pain [26, 27], knee osteoarthritis [28], fibromyalgia [29], chronic obstructive pulmonary disease [30], or cancer [31]. Qigong exercise has also been applied in two pilot studies for the treatment of chronic fatigue and chronic fatigue syndrome [32, 33], and desirable effects on symptoms and physical and mental functioning have been suggested in these studies. The beneficial effects of qigong exercise for chronic fatigue and chronic fatigue syndrome should be further tested in large-scale randomized controlled trials.

To date, little is known about the effects of qigong exercise on telomeres and telomerase. Telomeres are protective DNA sequences at the ends of linear chromosomes that ensure chromosomal stability. They shorten with each cell division or under conditions of oxidative stress [34, 35]. Telomere length has been used as a "psychobiomarker" linking stress and disease [36]. Shortened telomere in humans is emerging as a marker of disease risk and progression, and premature mortality [37–39]. Telomere shortening can be counteracted by the cellular enzyme telomerase. Telomerase activity plays an essential role in cell survival by extending telomere length and protecting the chromosomes, which promotes cell growth and longevity. Previous studies have suggested that detectable changes in telomere length cannot be detected over a short period of time and at least 1 year may be needed [40]. Thus, testing telomerase activity is an optimal alternative and has been used in some studies. Previous studies have shown that both shortened telomere and lower telomerase activity are associated with chronic psychological distress such as chronic fatigue syndrome [40–43]. Recent findings suggest that telomerase activity may be improved by intensive meditation training [44], yogic meditation [45], physical exercise [46, 47], or comprehensive lifestyle changes [40]. However, little is known about whether telomerase activity can be improved by other forms of mind–body intervention, such as qigong exercise, which is considered a holistic health practice promoting physical and mental well-being as well as longevity.

Thus, the primary aim of this randomized controlled trial is to evaluate the effects of qigong exercise on fatigue-related symptoms and physical and mental functioning in patients with chronic fatigue or chronic fatigue syndrome. The secondary aim of this trial is to evaluate the effect of qigong exercise on telomerase activity, drawing on its potential impact on stress-related damage at the cellular level. We hypothesized that qigong exercise would lead to positive improvements in fatigue-related symptoms and functioning in persons with chronic fatigue or chronic fatigue syndrome and would result in increased telomerase activity.

Methods

Participants

Participants in this study were recruited from communities through advertising online and in local newspapers, as it is generally rare for patients with chronic fatigue or chronic fatigue syndrome alone to stay in public hospitals, and there is no register of or self-help organization for patients with chronic fatigue syndrome in Hong Kong. Eligible participants were adults aged 18 to 55 years (those older than 55 years were excluded due to high possibility of chronic illness) who were available at all testing points, were receptive to random allocation, and met the United States Centers for Disease Control (CDC) inclusion criteria for chronic fatigue syndrome [1], which are the most widely used in the field. According to these criteria, individuals with chronic fatigue or chronic fatigue syndrome are those with fatigue that has persisted or relapsed for six or more months and is accompanied by four or more of the following eight distinctive symptoms: impaired memory or concentration capacity, post-exertional malaise, sleep problems, muscle pain, arthralgia, headache, recurrent sore throat, and tender cervical or axillary lymph nodes. To minimize the impact of chronic illnesses as much as possible, those with any diagnosed medical conditions that might explain the presence of chronic fatigue were excluded. Examples of these conditions included cancer, hypothyroidism, sleep apnea, narcolepsy, hepatitis B or C virus infection, substance abuse, and mental disorders (e.g., major depressive disorder, bipolar affective disorders, schizophrenia), and severe obesity. We also excluded persons who had participated in qigong training within the previous 6 months and those with serious medical conditions that might limit their participation. All participants provided written informed consent. Ethical approval was obtained from the Institutional Review Board of the University of Hong Kong/Queen Mary Hospital/Hong Kong Hospital Authority West Cluster.

The study was advertised in the media, and 1,441 adults volunteered to fill in an online screening questionnaire. Two hundred and thirty-six subjects met the inclusion criterion, of which 82 subjects were excluded because they could not be contacted or were unavailable for the qigong training. Of the 154 subjects who were willing to take part in the study, 84 were excluded because they were unavailable for the blood sample collection at the baseline measurement (there was no significant difference in demographic characteristics and reported fatigue symptoms between this group of subjects and those included). Consequently, 70 subjects were included in this study, but 6 dropped out before qigong training (2 in the intervention group and 4 in the control group). Thus, the analyses were based on a final sample of 64 participants (33 in the intervention group and 31 in the control group). The recruitment target of 30 participants per group was calculated on the basis of a similar number of referred subjects in two previous studies on chronic fatigue syndrome [48, 49]. A trial with 60 participants would provide a power of 80 % to detect a 0.72 standardized difference at a two-sided significance level of 5 %. The flow chart of the selection of participants is presented in Fig. 1.

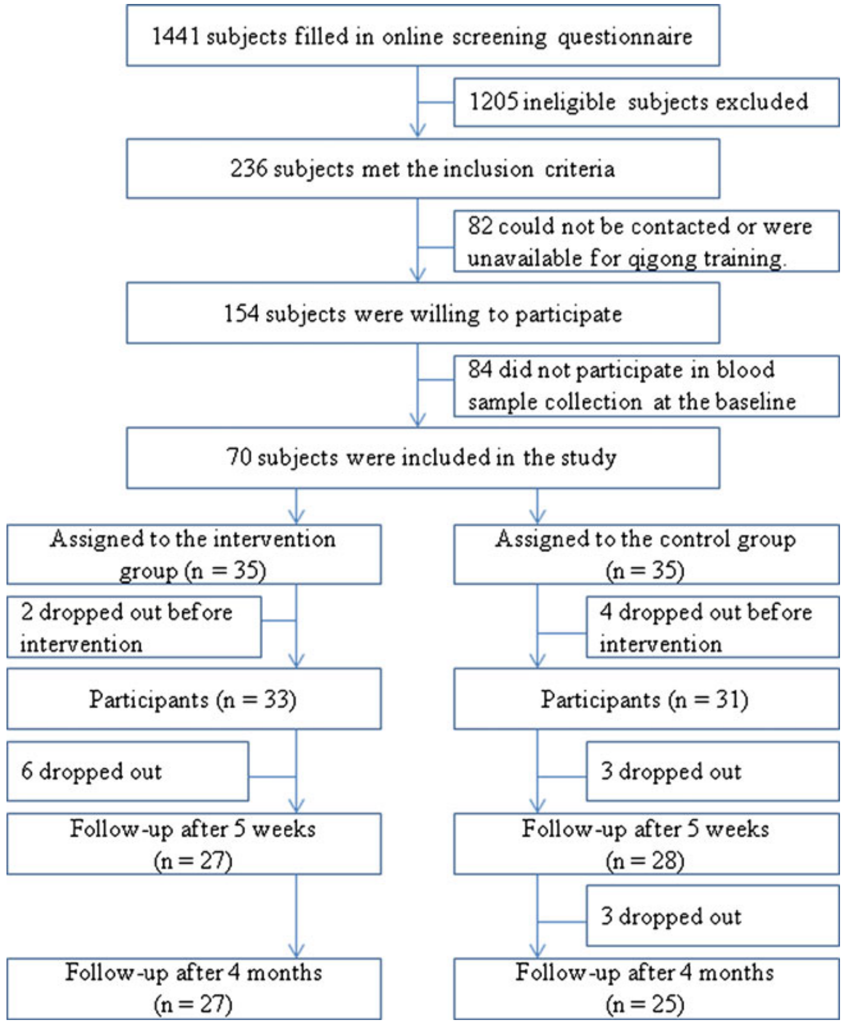
Study Design and Procedure

This study was a randomized controlled clinical trial with repeated measures, which was conducted between October 2010 and March 2011. Each potential participant was required to complete an online screening questionnaire and was evaluated for eligibility by a pair of investigators with any discrepancies being resolved by discussion. Eligible participants were required to complete an additional questionnaire to measure the severity of their chronic fatigue symptoms and physical and mental functioning before intervention and at follow-ups. Following the online screening, the participants completed the baseline measures and gave a blood sample after having signed the written informed consent form. Each participant was assigned an order number before the baseline assessment. They were then randomly assigned to either the intervention group or a wait list control group according to the order numbers. For allocation of the participants, a computer-generated list of random numbers was used. Blinding the participants to the allocation was not possible due to the nature of intervention. The intervention program lasted 4 months, with group qigong training for 5 weeks followed by home-based qigong exercise for 12 weeks in the intervention group. Primary outcomes were self-perceived fatigue symptoms severity and physical and mental functioning, while secondary outcome was telomerase activity in peripheral blood mononuclear cells. Data for the subjective outcome measures were collected from both the intervention group and control group at three time points: pre-intervention (T0, baseline), post-training (T1, 5 weeks after), and post-intervention (T2, 4 months after). Blood samples from the participants were collected at two time points: pre-intervention (T0) and post-intervention (T2).

Intervention

Participants assigned to the intervention group received group qigong exercise training (Wu Xing Ping Heng Gong, 五行平衡功) twice a week for five consecutive weeks, followed by home-based qigong exercise for 12 weeks. Each session of qigong exercise training lasted 2 h, with a brief introduction to the basic theories of traditional Chinese medicine or educational session on the physiology of mind–body connections (30–40 min), followed by mindful meditation for relaxation and mind concentration and then gentle movement or body stretching in standing postures to facilitate a harmonious flow of *qi* along the energy channels (20 min). Lastly, a 1-h session of qigong exercise training was delivered by an experienced Daoist qigong master (Yuen L.P.) with more than 20 years of experience in qigong practice as well as a background in traditional Chinese

Fig. 1 Flow chart of the selection of participants in the study



medicine. During the 4-month intervention program, all participants in the intervention group were required to engage in qigong exercise 30 min every day at home. To assess home exercise, they were required to report the frequency and duration as well as adverse effects of the self-practice at home at the end of the program. No adverse effects were reported. Participants assigned to the control group were advised to undertake normal activities but were asked to refrain from joining any outside qigong training class. No participants in the control group joined an outside qigong class as qigong exercise training was provided to them after the final outcome measurement.

Measures

Screening Measures

Each potential participant was required to complete an online screening questionnaire that elicited the following: (1) demographic information consisting of age, gender, employment status, education level, marital status, religion, and the number of family members living together with the participant; (2) an item to indicate whether or not fatigue symptoms persisted or relapsed for six or more months, and a list of the eight distinctive chronic fatigue symptoms recommended in the CDC inclusion criteria for chronic fatigue syndrome [1]; (3) a checklist of medical history based on the CDC exclusion criteria for chronic fatigue syndrome [1]; and (4) reported lifestyle in the previous 6 months, including details on exercise, smoking, and alcohol consumption.

Chalder's Fatigue Scale

The severity of chronic fatigue was assessed by using Chalder's Fatigue Scale [50], which was developed to measure the severity of fatigue over the previous 6 months. The scale consists of 14 items for evaluating two dimensions of chronic fatigue: physical fatigue (8 items) and mental fatigue (6 items) on a five-point Likert scale (none, better than usual, no more than usual, worse than usual, much worse than usual). The five responses are scored from 0–4. The subscale scores are equal to the summed scores for the physical fatigue and mental fatigue items. The total fatigue score is obtained by summing all of the items [50]. The scale was found to be both reliable (r=0.86 for physical fatigue, and r=0.85 for mental fatigue) and valid (Cronbach's α=0.89). A recent study of the Chinese version of Chalder’s Fatigue Scale also supported the notion of a two-factor structure in the community sample, and the internal consistency of the Chinese version was good (α=0.863) [51].

Medical Outcomes Study 12-Item Short-Form Health Survey

Physical functioning and mental functioning were assessed by the Chinese version of the Medical Outcomes Study 12-Item Short-Form Health Survey [52, 53]. The 12 items are classified into two subscales to measure the two dimensions of health: physical functioning (6 items) and mental functioning (6 items). Accordingly, two summary scores are yielded. Each subscale is scored on a 0–100 scale in which 100 indicates the best possible score and 0 indicates the worst.

Measurement of Telomerase Activity

For each participant, 3 ml of peripheral blood was collected in heparinized tubes. The peripheral blood mononuclear cells were isolated from each blood sample using Ficoll-Paque PLUS (GE Healthcare). In brief, 1 ml of blood sample was layered on 750 μl of Ficoll-Paque, and subsequently centrifuged at 400×*g* for 20 min at room temperature. The upper plasma layer was then removed, and the monocyte layer was collected immediately following centrifugation. The extracts were stored at −80 °C until further processing. Telomerase activity was tested by a commercially available kit TeloTAGGG telomerase PCR ELISA (Roche) according to the protocol. In brief, 10 μl of mononuclear cells isolated were lysed in 200 μl of lysis buffer, and 3 μl of the obtained protein extract was used for the subsequent telomerase-catalyzed primer elongation and PCR reaction. Biotin-labeled primers were used in the PCR reaction, then 5 μl of the PCR product was denatured, hybridized to digoxigenin-labeled probes, and immobilized to streptavidin-coated wells. Finally, the digoxigenin-labeled products were visualized by a peroxidase-conjugated anti-digoxigenin antibody and tetramethyl benzidine acting as a peroxidase substrate. The level of telomerase activity is in proportion to the colorimetric measures. The values were normalized to the positive control provided in the ELISA kit, which is in a relative manner. For each participant, telomerase activity in the peripheral blood mononuclear cells was assayed at pre-intervention and at the end of the 4-month intervention. The blood samples were collected in an identical manner, at the same time of day, and at the same location, and were treated identically at all steps. The group allocation was blinded for laboratory technicians.

Statistical Analysis

Continuous data were summarized by means and standard deviations, and categorical data were summarized by frequency. Differences at baseline for the demographic information, lifestyles, and reported fatigue symptoms between the two groups were compared using a chi-squared test for categorical data and a *t* test or pairwise *t* test for continuous data. The intragroup differences between different time points for each outcome measure were compared using a pairwise *t* test. Cohen’s *d* statistic was also calculated to determine effect size for each outcome. Repeated measures analyses of covariance (ANCOVA) were then performed to test the interaction effect of time and group for each outcome, adjusting for two fatigue symptoms (muscle pain, and tender cervical or axillary lymph nodes). Effects were evaluated on an intention-to-treat basis, and the missing values were substituted by way of mean imputation for each outcome measure [54]. All data analysis was conducted with SPSS (version 18.0, SPSS Inc., Chicago, IL). A p value less than 0.05 was considered as statistically significant.

Results

Demographic Characteristics and Lifestyles at Baseline

Table 1 shows the baseline data for the demographic characteristics, lifestyles, and self-reported chronic fatigue symptoms of the intervention group and the control group. The mean ages were 42.1 years (range 23–52) in the intervention group and 42.5 years (range 29–51) in the control group, respectively. More than three quarters of participants were female (75.8 and 83.9 % in the two groups, respectively). As shown in the table, baseline characteristics were reasonably well balanced between the two groups. There were no significant differences in lifestyles and the number of chronic fatigue symptoms between the two groups, apart from a just significant intergroup difference in the two types of fatigue symptoms (muscle pain, and tender cervical or axillary lymph nodes, $p<0.05$).

Twenty-seven participants (81.8 %) in the intervention group and 25 (80.6 %) in the control group completed the 4-month program. Six participants in each group withdrew from the study (Fig. 1). Three additional participants in the intervention group and one additional participant in the control group did not fill in the questionnaire but provided a blood sample for telomerase activity testing at the end of the intervention program.

Table 1 Baseline characteristics, lifestyles, and chronic symptoms

Demographic	Intervention (n=33)		Control (n=31)		p^{a}
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Age (years)	42.1 (7.3)		42.5 (5.5)		0.849
Gender					
Female		25 (75.8 %)		26 (83.9 %)	0.420
Education					0.326
Secondary or high school		13 (39.4 %)		16 (51.6 %)	
College or above		20 (60.6 %)		15 (48.4 %)	
Marital status					0.756
Unmarried		9 (27.3 %)		11 (35.5 %)	
Married/cohabited		21 (63.6 %)		17 (54.8 %)	
Divorced/separated		3 (9.1 %)		3 (9.7 %)	
Employment					0.374
Full time		27 (81.8 %)		24 (77.4 %)	
Part time		2 (6.1 %)		0	
Housewife		3 (9.1 %)		6 (19.4 %)	
Unemployed		1 (3.0 %)		1 (3.2 %)	
Religion involvement					
Yes		8 (24.2 %)		12 (38.7 %)	0.212
Number of family members living together					0.610
None		4 (12.1 %)		3 (9.7 %)	
1–2		14 (42.4 %)		17 (54.8 %)	
3 or more		15 (45.5 %)		11 (35.5 %)	
Lifestyles					
Doing exercise regularly		9 (27.3 %)		3 (9.7 %)	0.071
Smoking		1 (3.0 %)		2 (6.5 %)	0.518
Alcohol drinking		12 (36.4 %)		11 (35.5 %)	0.942
Fatigue symptoms (at least 6 months)					
Impaired memory or concentration capacity		31 (93.9 %)		29 (93.5 %)	1.000
Post-exertional malaise		29 (87.9 %)		29 (93.5 %)	0.673
Sleep problems		32 (97.0 %)		30 (96.8 %)	1.000
Muscle pain		27 (81.8 %)		31 (100 %)	0.025
Arthralgia		24 (72.7 %)		23 (74.2 %)	0.894
Headache		21 (63.6 %)		23 (74.2 %)	0.362
Recurrent sore throat		18 (54.5 %)		17 (54.8 %)	0.981
Tender cervical or axillary lymph nodes		19 (57.6 %)		26 (83.9 %)	0.021
Average number of reported fatigue symptoms	6.1 (1.4)		6.7 (1.3)		0.072

[a] Chi-squared test for categorical variables and t test for continuous variables

The Efficacy of Intervention

Table 2 shows the intragroup and intergroup differences of the subjective outcome measures, including the total fatigue score, physical fatigue score, mental fatigue score, physical functioning score, and mental functioning score. Compared to baseline values, the total fatigue score (p<0.001, d=−1.5), physical fatigue score (p<0.001, d=−1.9), mental fatigue score (p=0.001, d=−0.9), and mental functioning score (p<0.001, d=1.3) were significantly improved in the intervention group at 5 weeks, and the improvement was maintained at 4 months. Only the physical functioning score was not significantly changed in the intervention group. In the control group, the total fatigue score, physical fatigue score, and mental fatigue score were also significantly improved at 5 weeks (p=0.003, d=−0.7; p=0.001, d=−0.6; and p=0.031, d=−0.6 respectively) and at the end of the 4-month program (p=0.001, d=−1.0; p=0.001, d=−0.9; and p<0.001, d=−0.9 respectively). The physical functioning score

Table 2 Intragroup and intergroup comparisons for subjective outcomes using repeated measures ANCOVA adjusting for fatigue symptoms (muscle pain, tender cervical or axillary lymph nodes) at baseline

	Baseline (T0)	5 weeks after (T1)[a]		4 months after (T2)[a]		Time×group effect	
	Mean (SD)	Mean (SD)	Effect size (*d*)	Mean (SD)	Effect size (*d*)	*F*	*p*
Total fatigue score							
Intervention group	39.9 (6.3)	26.3 (10.9)***	−1.5	21.6 (10.4)***	−2.1	12.93	0.000
Control group	39.7 (6.1)	34.8 (8.0)**	−0.7	32.1 (8.8)***	−1.0		
Physical fatigue score							
Intervention group	25.0 (3.7)	15.2 (6.5)***	−1.9	12.9 (6.1)***	−2.4	20.09	0.000
Control group	24.7 (4.1)	21.8 (5.1)**	−0.6	20.3 (5.7)***	−0.9		
Mental fatigue score							
Intervention group	14.9 (3.6)	11.1 (5.1)**	−0.9	8.8 (4.6)***	−1.5	4.60	0.012
Control group	15.0 (3.2)	13.0 (3.9)*	−0.6	11.9 (3.8)**	−0.9		
Physical functioning score							
Intervention group	36.9 (7.2)	38.4 (6.1)	0.2	40.1 (6.9)	0.5	0.69	0.484
Control group	35.7 (7.1)	37.5 (8.1)	0.2	37.8 (5.6)	0.3		
Mental functioning score							
Intervention group	32.5 (10.7)	43.8 (6.9)**	1.3	42.7 (7.2)**	1.1	7.60	0.001
Control group	33.5 (9.6)	34.6 (9.6)	0.1	35.7 (9.5)	0.2		

*$p<0.05$; **$p<0.01$; ***$p<.0.001$

[a] Compared with baseline values

and the mental functioning score were not significantly improved in the control group compared to baseline values.

As shown in Table 2, the difference in the change of each outcome measure was examined with the time and group interaction effect. Compared to the control group, the improvement in the total fatigue score [$F(2, 120)=12.93$, $p<0.05$], physical fatigue score [$F(2, 120)=20.09$, $p<0.01$], mental fatigue score [$F(2, 120)=4.60$, $p<0.05$], and mental functioning score [$F(2, 120)=7.60$, $p=0.001$] was significant in the intervention group, whereas the changes in the physical functioning score in the intervention group were not significant [$F(2, 120)=0.69$, $p>0.05$].

In Table 3, the telomerase activity at baseline and at the end of the 4-month intervention program was compared within and between the two groups. Compared to baseline values, telomerase activity was significantly improved at the end of the program in the intervention group ($p=0.033$, $d=0.52$), but was not improved in the control group. The change of telomerase activity in the intervention group was statistically significant when compared to the control group, as indicated by the interaction effect of time and group [$F(2, 120)=5.03$, $p<0.05$].

Discussion

The results of the current study suggested that qigong exercise improved fatigue symptoms for patients with chronic fatigue or chronic fatigue syndrome, as indicated by the significant change in the total fatigue score. This result confirms the findings of an uncontrolled pilot study [32] and a small-scale randomized controlled trial of qigong exercise among patients with chronic fatigue syndrome [33]. Our results further indicated that qigong exercise improved physical fatigue symptoms more significantly than mental fatigue symptoms. Given the nature of chronic fatigue syndrome, these effects are understandable. Clinically, chronic fatigue syndrome is also named myalgic encephalomyelitis.

Table 3 Intragroup and intergroup comparisons for telomerase activity using repeated measures ANCOVA adjusting for fatigue symptoms (muscle pain, tender cervical, or axillary lymph nodes) at baseline

Telomerase activity (arbitrary unit)	Baseline (T0)	4 months after (T2)		Time×group effect	
	Mean (SD)	Mean (SD)	Effect size (*d*)	*F*	*p*
Intervention group	0.102 (0.051)	0.178 (0.201)*	0.52	5.03	0.029
Control group	0.089 (0.036)	0.104 (0.059)	0.31		

*$p<0.05$

Diagnosed chronic fatigue syndrome is actually a neurological disorder, rather than a physical or mental problem alone. Patients with chronic fatigue syndrome may be subject to cognitive deterioration or impairment [55]. The mental fatigue subscale of the Chalder's Fatigue Scale includes items to measure such dimensions as memory, concentration, problem thinking, and difficulty finding correct words. These dimensions are generally related to cognitive functioning. Generally, it is more difficult to improve cognitive function than psychological well-being or mental health, including such dimensions as energy and fatigue, body pain, and psychological wellness as measured by the SF-12.

In the current study, the mental functioning score in the qigong group was significantly improved compared to controls. In a prior pilot randomized controlled trial on chronic fatigue syndrome [33], bodily pain and mental health as measured by SF-36 were significantly improved in the qigong group compared to the baseline values, but the difference in changes between the qigong group and the control group was not significant, possibly due to the study's small sample size (n=31). Our study indicated that physical functioning measured by the physical health subscale of SF-12 was not significantly improved in the qigong group when compared to the controls. These results are inconsistent with previous findings in an uncontrolled study of qigong over 6 months among patients with chronic fatigue syndrome [32], in which both physical functioning and mental health as measured by the 116-item RAND Medical Outcomes Study questionnaire were significantly improved. Our results suggest that short-term qigong exercise may improve fatigue symptoms but is not as effective in improving physical functioning for patients with chronic fatigue or chronic fatigue syndrome. The improvement in physical functioning may instead require long-term qigong exercise.

The current study is the first randomized controlled clinical trial to measure the effect of qigong exercise on telomerase activity for individuals with chronic fatigue or chronic fatigue syndrome. Findings from this study indicated that telomerase activity was significantly improved among patients with chronic fatigue or chronic fatigue syndrome who received qigong exercise intervention over a 4-month period, and the change in telomerase activity in the qigong group was statistically significant when compared to the control group. This result confirms the findings in previous studies on intensive meditative training [44], yogic meditation [45], and comprehensive lifestyle changes [40]. In a pilot study among 30 adult patients with prostate cancer, Ornish et al. [40] reported that 3 months of intensive lifestyle changes increased telomerase activity in peripheral blood mononuclear cells; however, there was not a usual care control group in the study. In a recent randomized controlled trial [44] of intensive meditation training among 60 healthy subjects, 46 (20 meditation retreat participants and 26 controls) participated in telomerase activity assessment and the results suggested greater telomerase activity in the retreat participants than in the control group after 3 months of intensive meditation training, but there was no baseline measure of telomerase activity in the study. Therefore, generalization of the findings from these two studies is limited. Most recently, Lavretsky and colleagues [45] conducted a pilot randomized controlled trial to examine the effect of 8 weeks of brief daily yogic meditation on immune cell telomerase activity in family dementia caregivers with mild depressive symptoms, and the results indicated a marginally significant difference (p=0.05) in the change of telomerase activity between the meditation group (n=23) and the relaxation control group (n=16), probably due to small size in the study. In the current randomized trial on the basis of a justified sample of patients with chronic fatigue or chronic fatigue syndrome, we examined the effect by comparing the intervention group with the control group and adjusting for the baseline values. The result suggested a statistically significant association between qigong exercise and cellular telomerase activity.

As mentioned before, chronic fatigue and chronic fatigue syndrome are often associated with a high level of perceived stress and psychiatric disorders including depression, which are common among patients with chronic fatigue or chronic fatigue syndrome. Although a recent study [56] has suggested increased telomerase activity in major depression, explanations of the finding remain speculative and a number of studies have suggested low telomerase activity in response to psychological and oxidative stress as experienced by patients with chronic fatigue or chronic fatigue syndrome [43, 57, 58]. It is suggested that low telomerase activity could result in shortened telomeres by limiting the replenishment of impaired telomeres [59]. The underlying mechanism for the beneficial effects of qigong exercise as a mind–body intervention on telomerase activity in the current study may be explained in terms of two major components of qigong exercise. During qigong exercise, mindfulness, a key component of intensive meditative training, is often effectively cultivated. Thus, qigong exercise is often used as a stress management strategy and is potentially effective in enhancing cellular telomerase activity for patients with chronic fatigue or chronic fatigue syndrome through the reduction of the oxidative stress level [43, 60] and regulating immune response [43, 44]. The hypothalamic–pituitary–adrenal axis is an important pathway for these effects [61]. Another underlying mechanism may be that qigong exercise as a low-impact physical activity may increase serum concentrations of insulin-like growth factor (IGF) 1, which enhances telomerase activity and delays cellular aging [46]. Even though a retrospective study [62] among 69 healthy adults aged 50–70 years did not observe a significant association between physical activity level and telomerase activity, a study in mice indicated that short-term physical exercise (21 days) upregulated telomerase activity to more than twice that of sedentary controls [46]. Another study also indicated that physical exercise increased telomerase activity and neurogenesis in a mouse model of schizophrenia [47].

Although the results of this study are promising, the study has some limitations. One of major limitations is that participants did not receive a medical examination from a physician at the beginning of the study, so some of them might have not fully met the CDC criteria for chronic fatigue syndrome. Thus, the effects on telomerase activity and subjective outcomes might have been confounded by possible chronic disorders. Further studies should strictly adhere to the CDC diagnostic criteria for chronic fatigue syndrome. Another limitation is that the current study was neither double blind nor included a control group that did something equivalent to the controls, such as health education class. Thus, the effects might be due to demand characteristics, the Hawthorn effect, or possible placebo effect of being in a group. Moreover, telomerase activity was not tested during post-training; thus, attributing increased telomerase activity to qigong may be challenged given the unknown reaction time for changing telomerase activity after intervention. Furthermore, it is possible that other factors besides qigong exercise such as meditation, physical activity, body weight and life style change including diet, and inflammation or infections [40, 43–47] might have contributed to the increase in telomerase activity over a period of 4 months. These confounders should be strictly controlled in future studies. Finally, participants' stress levels were not measured before and after the invention, so the mediating effect of decreased psychological stress in the link between qigong exercise and the change in telomerase activity could not be examined. Due to aforementioned limitations, interpretation and generalization of the association between qigong exercise and telomerase activity observed in this study should be cautious. This finding needs to be replicated in further carefully designed randomized controlled trails, but it does raise the possibility of the involvement of telomerase as an important biomarker for mind–body interventions.

Conclusion

In conclusion, the results of the present study indicate that qigong exercise may improve chronic fatigue symptoms and mental functioning and result in increased telomerase activity for patients with chronic fatigue or chronic fatigue syndrome. The improvement in telomerase activity may be an alternative pathway of the potential health benefits of qigong exercise as a mind–body intervention. The results suggest that qigong exercise as a modality of mind–body therapy may be used as an alternative and complementary therapy or rehabilitation program for chronic fatigue and chronic fatigue syndrome.

Effects of Qigong Exercise on Fatigue, Anxiety, and Depressive Symptoms of Patients with Chronic Fatigue Syndrome-Like Illness: A Randomized Controlled Trial

Background. Anxiety/depressive symptoms are common in patients with chronic fatigue syndrome- (CFS-) like illness. Qigong as a modality of complementary and alternative therapy has been increasingly applied by patients with chronic illnesses, but little is known about the effect of Qigong on anxiety/depressive symptoms of the patients with CFS-like illness. *Purpose*. To investigate the effects of Qigong on fatigue, anxiety, and depressive symptoms in patients with CFS-illness. *Methods*. One hundred and thirty-seven participants who met the diagnostic criteria for CFS-like illness were randomly assigned to either an intervention group or a waitlist control group. Participants in the intervention group received 10 sessions of Qigong training twice a week for 5 consecutive weeks, followed by home-based practice for 12 weeks. Fatigue, anxiety, and depressive symptoms were assessed at baseline and postintervention. *Results*. Total fatigue score [$F(1, 135) = 13.888$, $P < 0.001$], physical fatigue score [$F(1, 135) = 20.852$, $P < 0.001$] and depression score [$F(1, 135) = 9.918$, $P = 0.002$] were significantly improved and mental fatigue score [$F(1, 135) = 3.902$, $P = 0.050$] was marginally significantly improved in the Qigong group compared to controls. The anxiety score was not significantly improved in the Qigong group. *Conclusion*. Qigong may not only reduce the fatigue symptoms, but also has antidepressive effect for patients with CFS-like illness. Trial registration HKCTR-1200.

1. Introduction

CFS is characterized by unexplained persistent fatigue of at least 6 months with no definite effective treatment yet [1]. As a large part of the patients with CFS in the community remain unrecognized by general practitioners [2], CFS-like illness is defined based on self-reported fatigue symptoms and medical history with similar criteria for CFS, but no confirmed clinical examination [3–5]. Current and lifetime psychiatric disorders were common among the patients with CFS-like illness [6–9], with particularly strong association between unexplained fatigue and depression [10, 11]. A study with a multinational primary care sample from 14 countries suggested that over 80% of patients with CFS-like illness had a lifetime psychiatric disorder such as depression or generalized anxiety disorder [7, 12]. Most of the patients with CFS-like illness are undertreated for psychiatric illness [6]. Unexplained chronic fatigue is also a common disabling condition in the general population and is strongly associated with psychiatric morbidity [13]. In Hong Kong, the lifetime prevalence of anxiety and depressive disorders was 54% among the primary care patients with chronic fatigue (CF) [14]. The patients with CFS-like illness reported poorer mental health (higher levels of anxiety and depression) than their non-CFS-like illness counterparts [15].

To date, no curative treatment that is effective exists for the patients with CFS-like illness [16]. The use of complementary and alternative medicine (CAM) is increasing among the patients with CFS-like illness. A recent systematic review of 26 randomized clinical trials (RCTs) has suggested beneficial effects of CAM including Qigong, massage, and tuina for patients with CFS [17]. Qigong is an ancient self-healing mind-body exercise, which includes meditation, breathing, body posture, and gentle movement. It focuses to promote the circulation of vital energy, which is called "Qi" in the meridian system (Qi vital energy channel) of the human body to facilitate the harmony of the mind, body, and breathing [18].

A number of empirical studies reported that Qigong had beneficial effects on fatigue symptoms [19, 20] and other outcomes related with CFS such as sleep, pain, mental attitude, and general mobility [21]. Our prior study demonstrated that Qigong exercise was effective in reducing the severity of fatigue symptoms, improving health-related quality of life [22], and increasing telomerase activity for the patients with CFS-like illness [23]. RCTs of Qigong exercise also suggested a beneficial effect of Qigong for older people with depressive symptoms secondary to chronic illnesses [24, 25]. However, a recent systematic review and meta-analysis of the effect of Qigong exercise on depressive and anxiety symptoms suggested that scientific evidence in the field was still limited, and that further rigorously designed RCTs were warranted [26]. To date, to our knowledge, no study has examined the effect of Qigong exercise on depressive and anxiety symptoms in patients with CFS-like illness. Thus, the purpose of this large-scale study was to investigate the effectiveness of Qigong exercise as a modality of complementary and alternative therapy in reducing fatigue, anxiety, and depressive symptoms of patients with CFS-like illness.

2. Methods

2.1. Study Participants. One thousand four hundred and forty-one Chinese adults who claimed to have fatigue symptoms volunteered to fill in an online questionnaire after the study was advertised in the media. The screening questionnaire was set according to the US Centers for Disease Control and Prevention (CDC) Diagnosis criteria for CFS [1], which is widely used in the field. As it was rare that patients with persistent fatigue symptoms alone stayed in public hospitals, the participants were recruited from local community.

The diagnosis of CFS-like illness [3–5] was made based on subjective chronic symptoms and their medical history self-reported in the online questionnaire without further clinical confirmation by medical examination. A participant was diagnosed as having CFS-like illness if he or she had unexplained, persistent fatigue over 6 months which was of new onset (not lifelong) with presence of four or more of the following eight symptoms: impaired memory or concentration, postexertion malaise, unrefreshing sleep, muscle pain, multijoint pain, new headaches, sore throat, and tender lymph nodes [1]. To minimize the impact of other chronic illness as much as possible, those with any medical conditions that may explain the presence of chronic fatigue were excluded.

Two hundred and thirty-six participants met the inclusion criteria, of which 82 participants were excluded because they could not be contacted or were unavailable for the Qigong training. One hundred and fifty-four participants with CFS-like illness were recruited into the study and were randomly assigned to the intervention group ($n = 77$) and control group ($n = 77$), respectively. Among these 154 participants, 5 subjects in the intervention group and 12 subjects in the control group dropped out before the Qigong class. Only 137 subjects (72 for intervention group and 65 for control group) were included as the final sample for the data analysis. A flow chart of the selection of participants is presented in Figure 1.

2.2. Study Design and Procedure. This was a prospective randomized wait list-controlled trial. Each potential participant was required to complete an online screening questionnaire and was evaluated for eligibility by a pair of investigators with any discrepancies being resolved by discussion. Eligible participants were required to complete an additional questionnaire to measure the severity of their chronic fatigue symptoms and depressive and anxiety symptoms before intervention (T0) after having signed the written informed consent form. They were then randomly assigned to either an intervention group or a waitlist control group. Randomization was done using computer-generated random numbers. Blinding the participants to the allocation was not possible due to the nature of intervention. The intervention program lasted 4 months, with group Qigong training for 5 weeks followed by home-based Qigong exercise for 12 weeks in the intervention group. The primary outcome was fatigue symptoms and the secondary outcomes were anxiety and depressive symptoms. Data for the outcome measures were also collected at postintervention (T1) from each subject in the intervention group and control group. Ethical approval was obtained from the local review board.

Sample size was calculated according to power and estimated effect size. In order to achieve statistical power of 80% at a significance level of 0.05 (assuming treatment effect = 3 and standard deviation = 5 according to a previous local study on CFS [27]), 53 participants were required in each group. Assuming 30% dropout rate, at least 76 subjects were required in each group (the intervention group and the waitlist control group).

2.3. Intervention. Participants in the intervention group attended 10 sessions of Qigong exercise training (Wu Xing Ping Heng Gong, 五行平衡功) twice a week for 5 consecutive weeks, followed by home-based Qigong self-practice for 12 weeks. Each session of Qigong exercise training lasted 2 hours, with a brief introduction of the basic theories of traditional Chinese medicine (such as the concepts of Qi, yin-yang, five elements, and meridian system) or the precautions in doing Qigong exercise including answering any questions or concerns raised by the participants about Qigong practice (45 min), followed by mindful meditation for relaxation and then gentle movement or body stretching in standing postures to facilitate a harmonious flow of Qi along the energy channels (15 min) and a 1 h session of Qigong exercise training, which was delivered by an experienced Taoist Qigong master (Yuen L. P.) with more than 20 years

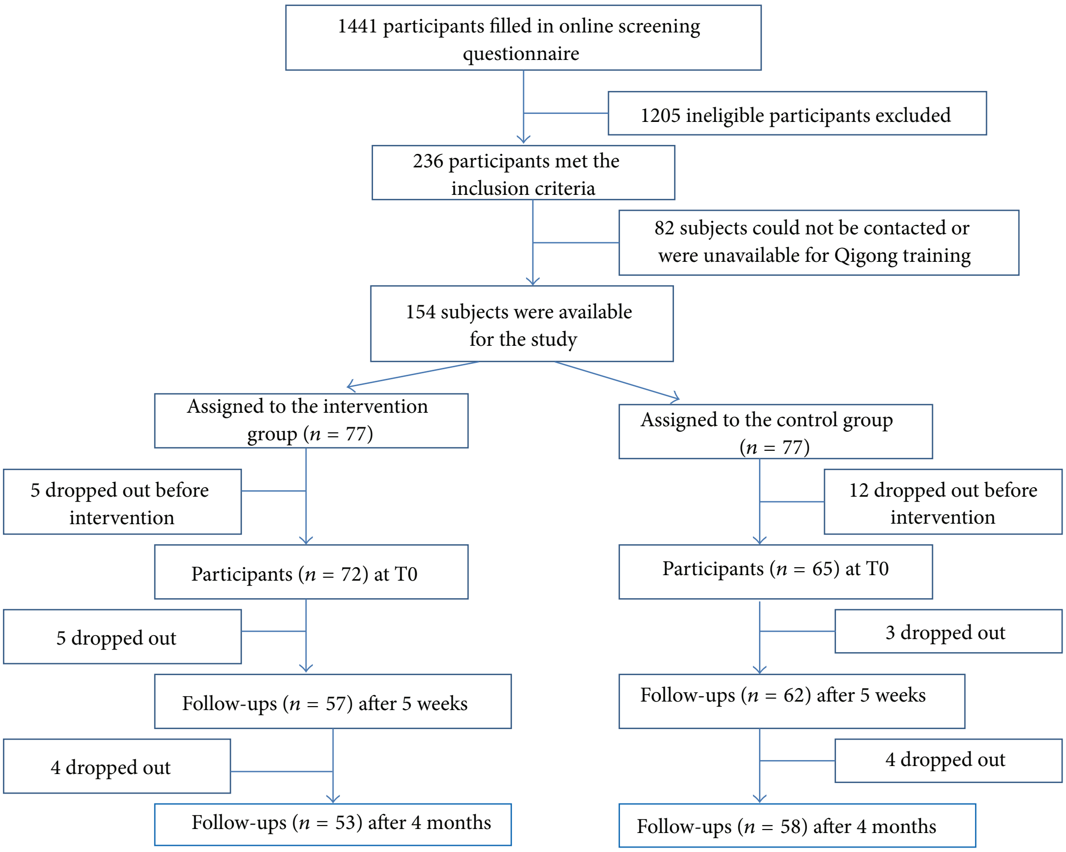


Figure 1: Flow chart of the selection of participants in the study.

of experience in Qigong practice and also a background in traditional Chinese Medicine.

Apart from mindful meditation, rhythmic breathing and concentrated relaxation, Xu Xing Ping Heng Gong, was applied in this study including 10 forms of movement which aims at enhancing the smooth flow of Qi along the various meridians of the body and meditation for relaxation and mind concentration. The movements involve stretching of arms and legs, turning of torso, relaxing, and deep breathing with the objectives of fostering harmonious energy flow of Qi along the various meridians of the body. A description of the Xu Xing Ping Heng Gong is presented in Appendix.

All participants in the intervention group were also required to do Qigong self-practice for at least 30 minutes every day at home during the 4-month intervention period. To assess home exercise, they were required to report the frequency and duration as well as adverse effects of the self-practice at home at the end of the program. The participants in control group were advised to keep their lifestyle as usual and to refrain from joining any outside Qigong exercise class during the study period. No participants in the control group joined any outside Qigong class as they were provided the Qigong training after the final outcome measurements were collected.

2.4. Measurements

2.4.1. Screening Measures. The potential participants were screened by online questionnaire including (1) whether or not the fatigue symptoms persisted or relapsed for six or more months; (2) a list of eight chronic fatigue symptoms of CDC diagnostic inclusion criteria for CFS [1]; (3) a list of medical diseases based on the CDC diagnostic exclusion criteria for CFS [1] according to their self-reported medical history without further medical examination; (4) basic demographic data such as age, gender, employment status, education level, marital status, religion, and monthly income; (5) lifestyle including exercise habits, smoking, alcohol drinking, and sleep time.

2.4.2. Chalder Fatigue Scale. The severity of fatigue symptoms was measured by the Chalder Fatigue Scale, which is a 14-item self-rating scale to measure the severity of both physical fatigue symptoms (8 items) and mental fatigue symptoms (6 items). The response pattern for each item is a five-point Likert scale (none, better than usual, no more than usual, worse than usual, much worse than usual), which is scored from 0 to 4. The subscale scores are equal to the summed scores of all items in the subscale and the total fatigue score was obtained by adding up all of the 14 items (the higher, the worse) [28]. The Chinese version of the Chalder Fatigue Scale has shown acceptable psychometric properties [29].

2.4.3. Hospital Anxiety and Depression Scale (HADS). Depressive and anxiety symptoms were measured by the HADS [30], which is a 14-item instrument with two subscales measuring anxiety symptoms (7 items) and depressive symptoms (7 items) separately. Each item is scored on a 0–3 scale and the total score of each subscale is scored on a 0–21 scale, with a higher score indicating a higher level of anxiety and depressive symptoms. Internal consistency for HADS Chinese version was revealed to be satisfactory, with Cronbach's alpha coefficients of 0.77 for anxiety subscale and 0.82 for depression subscale, respectively [31, 32].

2.5. Statistical Analyses. Means and standard deviations were used to summarize continuous data and frequency was used to summarize categorical data. Differences at baseline for the demographic information, lifestyles, and reported fatigue, anxiety, and depressive symptoms between the two groups were compared using a t-test for continuous data and a Chi-squared test for categorical data. The within group effects of outcome measures were compared between pre- and postintervention using pairwise t-test for each group. The effect size was determined by Cohen's d statistics for each outcome. The repeated measures analyses of variance (ANOVA) were then conducted to assess the interaction effect of group and time for each outcome. Intention to treat analysis was applied in this study and the missing data were substituted by the last observed values. The correlation analysis of the changes in all outcomes between pre- and postintervention and the linear regression analysis using the change of depression score as a dependent variable and changes of other outcomes as independent variables were also conducted. All data analysis was conducted with Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc., Chicago, IL, USA). A P value of less than 0.05 was considered as statistically significant.

3. Results

3.1. The Demographic Characteristics and Lifestyles at Baseline. The data on demographic characteristics and lifestyles of the two groups are shown in Table 1. The mean ages were 42.4 (SD = 6.7) in the intervention group and 42.5 (SD = 6.4) in the control group, respectively. More than 70% of the participants were female (72% and 82% in the intervention and control groups, resp.). As shown in the table, baseline characteristics were well balanced between the two groups. The average number of reported fatigue symptoms was 6.3 (SD = 1.4) in both groups. Among eight chronic fatigue symptoms (last at least 6 months), the most common symptoms ($n = 129, 94.2\%$) was sleep disturbance followed by muscle pain ($n = 128, 93.4\%$) and impaired memory/concentration ($n = 126, 92.0\%$). There was no significant difference in fatigue symptoms between the two groups. Overall, the participants had a moderate level of anxiety symptoms (mean scores for the anxiety subscale were 11.0 for the intervention group and 10.9 for the control group resp.) and a mild level of depressive symptoms (mean scores for the depression subscale were 9.1 and 9.4 for the intervention and control groups resp.) at baseline.

3.2. The Efficacy of Intervention. Table 2 shows the within-group and between-group differences of fatigue symptoms as measured by the Chalder Fatigue Scale and anxiety and depressive symptoms as measured by the HADS for the two groups. At baseline (T0), two groups were comparable in terms of total fatigue score, physical fatigue score, mental fatigue score, anxiety score, and depression score ($P > 0.05$ for all variables). Compared with baseline values, the total fatigue score ($d = -1.2$, $P < 0.001$), physical fatigue score ($d = -1.4$, $P < 0.001$), mental fatigue score ($d = -0.9$, $P < 0.001$), anxiety score ($d = -1.1$, $P < 0.001$), and depression score ($d = -0.5$, $P < 0.001$) were significantly improved in the intervention group after 4 months of Qigong intervention, while the total fatigue score, physical fatigue score, mental fatigue score and anxiety score in the control group were also significantly improved 4 months after ($d = -0.8$, $P < 0.001$; $d = -0.8$, $P < 0.001$; $d = -0.6$, $P < 0.001$; $d = -0.6$, $P = 0.006$, resp.). However, the change of the depression score in the control group was not significant ($d = 0.1$, $P = 0.365$).

The between-group difference in the change of each outcome measure was then examined by interaction effect of time and group. Compared with controls, the total fatigue score [$F(1, 135) = 13.888$, $P < 0.001$], physical fatigue score [$F(1, 135) = 20.852$, $P < 0.001$], and depression score [$F(1, 135) = 9.918$, $P = 0.002$] were significantly improved, and the mental fatigue score [$F(1, 135) = 3.902$, $P = 0.050$] was marginally significantly improved in the intervention group, whereas the change in the anxiety score in the intervention group was not significant after adjusting for control [$F(1, 135) = 0.302$, $P = 0.584$]. No adverse effects were reported in both groups during the implementation of intervention and self-practice at home throughout the study.

3.3. Predictors of Changes in Depressive Symptoms. In correlation analysis, change in the depression score was significantly correlated with changes in the total fatigue score ($r = 0.331$, $P < 0.001$) and anxiety score ($r = 0.579$, $P < 0.001$). Linear regression analysis further revealed that the change in the total fatigue score ($\beta = 0.182$, $P = 0.013$) and anxiety score ($\beta = 0.528$, $P < 0.001$) significantly explained the change in the level of depressive symptoms (adjusted $R^2 = 0.356$).

4. Discussion

To the best of our knowledge, this study is the first large-scale randomized control trial to investigate the anti-depressive effect of Qigong exercise for the patients with CFS-like illness. The findings of this study showed that Qigong exercise could improve depressive symptoms and fatigue symptoms among the patients with CFS-like illness, which provided additional evidence to support the conclusive statement of a recent systematic review [26] that Qigong exercise may have beneficial effect on depressive symptoms. An earlier study [33] showed that depressive symptoms were not significantly improved after Qigong intervention in elderly with chronic illnesses, probably due to the small sample size ($n = 50$) and short intervention period (12 weeks). The current study with a larger sample suggested that Qigong exercise could reduce depressive symptoms for persons with CFS-like illness. Our

Table 1: Patients' demographic information and lifestyles at baseline (n = 137).

Demographic	Intervention (n = 72)		Control (n = 65)		P^*
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Age (years)	42.4 (6.7)		42.5 (6.4)		.979
Gender					.198
Female		52 (72.2%)		53 (81.5%)	
Employment					.629
Full-time		55 (76.4%)		52 (80.0%)	
Part-time		3 (4.2%)		1 (1.5%)	
Housewife		9 (12.5%)		10 (15.4%)	
Unemployed		4 (5.6%)		1 (1.5%)	
Other		1 (1.4%)		1 (1.5%)	
Education					.366
Secondary school		31 (43.1%)		33 (50.8%)	
Tertiary or above		41 (56.9%)		32 (49.2%)	
Marital status					.738
Single		21 (29.2%)		23 (35.4%)	
Married/cohabiting		46 (63.9%)		38 (58.5%)	
Divorced/separated/widowed		5 (6.9%)		4 (6.2%)	
Have religion					.334
Yes		21 (29.2%)		24 (36.9%)	
Monthly income					.824
<10,000		11 (15.3%)		6 (9.2%)	
10,000–19,999		20 (27.8%)		18 (27.7%)	
20,000–29,999		9 (12.5%)		8 (12.3%)	
≥30,000		9 (12.5%)		10 (15.4%)	
No income/not available		10 (13.9%)		7 (10.8%)	
Not want to answer		13 (18.1%)		16 (24.6%)	
Lifestyles					
Do exercise regularly		19 (26.4%)		17 (26.2%)	.975
Smoking		6 (8.3%)		2 (3.1%)	.190
Alcohol drinking		31 (43.1%)		22 (33.8%)	.269
Sleep time (hours)	5.0 (1.8)		4.7 (2.2)		.434
Average number of reported fatigue symptoms	6.3 (1.4)		6.3 (1.4)		.864

*Chi-squared test for categorical variable and t-test for continuous variable.

findings coincided with the results reported in other studies that Qigong exercise might have a beneficial effect on depressive symptoms in depressed elderly with chronic illness [24, 25], mild essential hypertension [34], subhealth [35], and female college students [36].

In this study, participants' anxiety symptoms were significantly improved in both groups compared with baseline values, but there was no significant difference in the change of anxiety symptoms between the intervention group and the control group. To date, only a very few studies [34–37] have examined the effect of Qigong exercise on anxiety symptoms but the findings were inconsistent, probably due to diversity of participants or sample size, variability in the severity of comorbidities or anxiety symptoms, and heterogeneity in outcome measures. Our results supported the conclusive statement of a recent systematic review that the limited existing evidence did not support the effect of Qigong exercise on anxiety symptoms [26]. Further well-designed RCTs were still warranted to test the effect of Qigong on anxiety disorders.

Interestingly, we found that the total fatigue, physical fatigue, mental fatigue, and anxiety symptoms in the waitlist control group were also significantly improved four months after. These results may be explained by two schools of mechanism. The first one may be that the results were due to the effects of self-care or other self-applied treatments. Generally, efforts to manage their symptoms are always under way for patients with chronic illnesses. In our study, most participants reported that they had tried other numerous therapies to manage their symptoms or treat their illnesses before joining this study, even though those therapies were ineffective. The second possible reason may be related to a beneficial effect of hope on physical health and psychological or emotional wellbeing [38]. In our study, all participants in the control group were told that they could join the Qigong training after completing the study, so they might have

Table 2: Within-group and between-group comparisons for Chalder Fatigue Scale, anxiety, and depression at T0 and T1 ($n = 137$) using repeated measures ANOVA.

	Within-group effects				Between-group effects		
	Baseline (T0)[a]	Post-intervention (T1)[b]			T1-T0	Time × group	
	Mean (SD)	Mean (SD)	P^b	Effect Size (d)	Mean (SD)	$F(1, 135)$	P
Total fatigue score						13.888	.000
Intervention group ($n = 72$)	39.7 (6.6)	26.6 (13.6)	<0.001	−1.2	−13.1 (11.7)		
Control group ($n = 65$)	39.8 (6.3)	33.2 (9.6)	<0.001	−0.8	−6.6 (8.3)		
Physical fatigue score						20.852	.000
Intervention group ($n = 72$)	24.7 (4.0)	15.9 (8.0)	<0.001	−1.4	−8.8 (7.3)		
Control group ($n = 65$)	24.6 (3.7)	20.8 (5.7)	<0.001	−0.8	−3.8 (5.0)		
Mental fatigue score						3.902	.050
Intervention group ($n = 72$)	15.0 (3.8)	10.6 (6.1)	<0.001	−0.9	−4.3 (5.3)		
Control group ($n = 65$)	15.2 (3.9)	12.4 (4.9)	<0.001	−0.6	−2.7 (3.9)		
Anxiety score						0.302	.584
Intervention group ($n = 72$)	11.0 (2.1)	8.7 (3.2)	<0.001	−1.1	−2.3 (3.9)		
Control group ($n = 65$)	10.9 (2.4)	9.0 (4.0)	0.006	−0.6	−1.9 (5.4)		
Depression score						9.918	.002
Intervention group ($n = 72$)	9.1 (2.0)	7.7 (3.2)	<0.001	−0.5	−1.3 (2.7)		
Control group ($n = 65$)	9.4 (2.2)	9.8 (4.1)	0.365	0.1	0.4 (3.7)		

[a]Compared with control group using independent t-test, [b]Compared with baseline using pairwise t-test.

a desirable expectation that might exert a beneficial effect on their psychological wellbeing and physical symptoms. Previous studies have shown that hope is inversely associated with total fatigue, mental fatigue and level of anxiety and depression [39–41].

Our study also showed a significant correlation between alleviation of depression and fatigue reduction, as well as reduced anxiety following Qigong exercise. Regression analyses further revealed that the improvements of fatigue and anxiety symptoms significantly predicted the alleviation of depressive symptoms after Qigong intervention. The results confirmed an established association between fatigue symptoms and psychiatric disorders [8, 9, 11].

Qigong as a mind-body integrative exercise is distinguished from conventional forms of exercise [42]. The underlying physiological mechanism of mind-body intervention may be of interest. Tsang and Fung [43] have hypothesized three possible neurobiological pathways of the antidepressive effect of Qigong exercise including monoamine neurotransmitters in the brain, the hypothalamic-pituitary-adrenal (HPA) axis, and the brain-derived neurotropic factors (BDNF), but these hypotheses need to be further tested.

Although the results of our study are promising, some limitations of this study should be noted. First, the participants with CFS-like illness were recruited from local community, who did not receive medical examinations conducted by clinicians. Thus, some of them may not fully meet the CDC criteria for CFS. Although around three-quarters of the participants were female, it is similar to the proportion of females with CFS in other earlier studies [16]. Second, this study was a waitlist controlled trial, so social interaction effects might have been existed in the intervention group. It is recommended that active controls should be applied in future studies to avoid possible placebo effect. Third, the dosage and quality of home-based Qigong exercise were not adjusted for in our data analysis. Given that some studies have suggested a relationship between amount of Qigong practice and health outcomes [44], it should be measured and taken into account in data analysis in future studies. Finally, some other factors such as diet, physical activities, social interaction, body weight, and comorbidities may affect the outcomes, which should be adjusted in further trials. Despite these limitations, this study was the first RCT to examine the effect of Qigong exercise on anxiety and depressive symptoms among patients with CFS-like illness, which may provide complementary evidence to the body of knowledge in this field.

5. Conclusion

In conclusion, the results of this study show that Qigong exercise may be effective in reducing fatigue symptoms and alleviating depressive symptoms for patients with CFS-like illness and that the improvement of fatigue symptoms may predict the alleviation of depressive symptoms after Qigong intervention. The findings suggest that Qigong exercise may be used as an alternative and complementary therapy or rehabilitation program for patients with CFS-like illness.

Appendix

Description of the Movements in Wu Xing Ping Heng Gong

Warm-up Movement. Swinging of arms by turning the torso with relaxed shoulders (preferably to be practiced in a relaxing outdoor space with trees).

Movement 1. Standing on toes with hand movements to the front and to the side.
Movement 2. Circular movements of hands, wrists, hips; stretching by arching backwards of neck and torso.
Movement 3. Movement of fingers, wrists, elbow and shoulders; stretching of arms.
Movement 4. Movement of wrists; stretching shoulder muscles; twisting movements of shoulders.
Movement 5. Massage of ears.
Movement 6. Swinging of hands to gently hit the chest and back; standing on one foot and hitting back of the standing foot's calf by the dorsum of other foot.
Movement 7. Stretching of trunk and hip joints by stepping forward and backward.
Movement 8. Swinging movements of lower body; squatting and bending forward to stretch the back of the torso.
Movement 9. Movement of legs with hands in cupping pose; turning of torso in kneeling position.
Sitting meditation. Sitting meditation with deep breathing can be conducted for 20–30 minutes after the movement exercises if possible. If not, move directly to the concluding movement. Sitting meditation is recommended in the evening, before going to bed.
Concluding movement. Hands in cupping pose in front of the lower abdomen for about 20 seconds; rub hands and then use palms to massage face (upward movement like washing face), followed by the use of fingertips to massage the scalp in combing movement.