OPEN ACCESS

Original research

Effect of long-term Tai Chi training on Parkinson's disease: a 3.5-year follow-up cohort study

Gen Li ,[1] Pei Huang,[1] Shishuang Cui,[1] Yachao He,[1] Yuyan Tan,[1] Shengdi Chen [1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2022-330967).

[1]Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China
[2]Lab for Translational Research of Neurodegenerative Diseases, Shanghai Institute for Advanced Immunochemical Studies (SIAIS), Shanghai Tech University, Shanghai, People's Republic of China

Correspondence to
Dr. Shengdi Chen, Dr. Yuyan Tan and Dr. Pei Huang, Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China; chensd@rjh.com.cn, tyy11672@rjh.com.cn, hp12585@rjh.com.cn

GL and PH contributed equally.

Received 30 December 2022
Accepted 5 September 2023

To cite: Li G, Huang P, Cui S, *et al*. *J Neurol Neurosurg Psychiatry* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jnnp-2022-330967

ABSTRACT

Background Tai Chi has shown beneficial effects on the motor and non-motor symptoms of Parkinson's disease (PD), but no study has reported the effect of long-term Tai Chi training.

Objective To examine whether long-term Tai Chi training can maintain improvement in patients with PD.

Methods Cohorts of patients with PD with Tai Chi training (n=143) and patients with PD without exercise as a control group (n=187) were built from January 2016. All subjects were assessed at baseline and in November 2019, October 2020 and June 2021. A logarithmic linear model was used to analyse rating scales for motor and non-motor symptoms. The need to increase antiparkinsonian therapies was presented as a Kaplan–Meier plot and as a box plot. The bootstrap method was used to resample for statistical estimation.

Results Tai Chi training reduced the annual changes in the deterioration of the Unified Parkinson's Disease Rating Scale and delayed the need for increasing antiparkinsonian therapies. The annual increase in the levodopa equivalent daily dosage was significantly lower in the Tai Chi group. Moreover, patients benefited from Tai Chi training in motor symptoms, non-motor symptoms and complications.

Conclusion Tai Chi training has a long-term beneficial effect on PD, with an improvement in motor and non-motor symptoms and reduced complications.

Trial registration number NCT05447975.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tai Chi has shown beneficial effects on the symptoms of Parkinson's disease (PD). However, the effect of long-term Tai Chi training is not known.

WHAT THIS STUDY ADDS

⇒ Following an average of 4.3 years of observation, Tai Chi training was found to have a long-term beneficial effect on PD, with improvement in motor and non-motor symptoms and a reduction in the prevalence of complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Tai Chi could be applied in the long-term management of PD. The long-term beneficial effect on PD could prolong the time during which patients are non-disabled, resulting in a higher quality of life, a lower caregiver burden and less drug usage.

INTRODUCTION

Parkinson's disease (PD) is a common debilitating and progressive neurodegenerative movement disorder characterised by bradykinesia, resting tremor and rigidity.[1] The pathological hallmarks of PD are the loss of dopaminergic neurons in the substantia nigra and the abnormal aggregation of α-synuclein.[2] It is estimated that, by 2030, the number of patients with PD in China will increase to 4.94 million, which will result in a huge burden to public health.[3] The treatment of PD consists mainly of drug therapy with levodopa and other antiparkinsonian drugs. Non-drug therapies such as physical exercise and rehabilitation also have an important role in the comprehensive management of patients with PD.[4]

A few studies have investigated whether some antiparkinsonian drugs with potential neuroprotection could serve as disease modifying therapy. However, none of them found definite effects on delaying the disease progression.[5] Drug therapy for PD is effective in improving the clinical symptoms, but long-term drug treatment can cause both motor and non-motor complications. Although monoamine oxidase B inhibitors such as rasagiline and selegiline may have potential disease modification effects,[5 6] there is no evidence to show that they delay disease progression.[7] Whether long-term exercise training could delay the disease progression of PD is of interest and worthy of investigation.

Previous studies focusing on exercise training have shown the effect of Tai Chi in improving the clinical symptoms of PD.[8–14] Li and colleagues found an improvement in maximal excursion, direction control, gait velocity and quality of life after 6 months of Tai Chi training for 1 hour twice a week.[9 10] Similarly, with the same exercise frequency, Hackney and colleagues found an improvement in balance and gait velocity in patients with PD after 13 weeks of Tai Chi training.[14] Similar results were observed by Zhang and colleagues in a 12-week randomised controlled trial.[13] Amano and colleagues found an improvement in gait performance and gait initiation after 16 weeks of Tai Chi training in a multicenter study.[8] In our previous study, the beneficial effect was observed after 1 year of Tai Chi training. With regard to non-motor symptoms, patients with PD showed an improvement in the executive function and the digit span backwards tests after Tai Chi training.[11 12] However, all of these studies only looked at the short-term (<1 year) effects after Tai Chi training and it is not known whether Tai Chi

can maintain the long-term beneficial effect in patients with PD. The effects of Tai Chi on motor complications and non-motor symptoms have not previously been reported.

Furthermore, Tai Chi is more economical than drug therapy. It is a traditional Chinese exercise widely accepted by the population and easy to be conducted anywhere. Thus, Tai Chi is a good choice to study as a long-term intervention for patients with PD. In this study we examine whether long-term Tai Chi training can maintain the beneficial effects on PD.

METHODS

Study population

Patients were recruited from our Movement Disorders Clinic in Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. PD was diagnosed by senior movement disorder specialists (SC, YT) based on diagnostic criteria from both the UK Brain Bank and the Movement Disorder Society.[15 16] When assessing patients with PD, those with secondary causes such as inflammatory, drug-induced, vascular and toxin-induced parkinsonism were excluded. Patients with PD with other neurodegenerative diseases such as progressive supranuclear palsy, multiple system atrophy, cortical basal ganglia degeneration or Wilson's disease were also excluded, as were those with other neurological diseases such as stroke. Hoehn–Yahr staging, familial history and other individual information was recorded. Patients with Hoehn–Yahr staging ≤2.5 were enrolled at baseline considering the safety during Tai Chi training. The control group was matched using propensity score matching with the ratio of 1:1.5. Patients with regular exercise of more than 50 min/week were excluded. Five Tai Chi classes were held successively from January 2016 (first class January 2016; second class November 2016; third class March 2017; fourth class September 2017; and fifth class January 2018). All classes were held without discontinuation until the last follow-up. All subjects were evaluated at baseline and re-evaluated in November–December 2019, October–November 2020 and June–July 2021 at "ON" state, respectively. The levodopa equivalent daily dosage (LEDD) was recorded. The medication remained stable unless it was necessary to change it due to disease progression. Attendance at the Tai Chi training group and the quality of the training were monitored as reported previously .[2]

Assessment rating scales

The following rating scales were used to assess the status of patients. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess the overall status of PD and the Timed Up and Go test (TUG) was used to assess the velocity of walking. To minimise errors we tested the TUG scale three times for each patient and then calculated the average time as the TUG time. The Berg Balance Scale (BBS) was used to assess balance function, the Mini-Mental State Examination – simplified Chinese version (MMSE) and the Parkinson's Disease Cognitive Rating Scale (PDCRS) were used to assess cognitive function, and the Hamilton Anxiety Rating Scale (HAMA) and Hamilton Depression Rating Scale (HAMD) were used to assess anxiety and depression. The Rapid Eye Movement Sleep Behaviour Disorder questionnaire – Hong Kong version (RBD-HK) was used to assess the status of probable rapid eye movement sleep behaviour disorder. The 39-item Parkinson's Disease Questionnaire (PDQ-39) was used to assess life quality of patients with PD, the Parkinson's Disease Sleep Scale (PDSS) was used to assess overall sleep status and the Epworth Sleepiness Scale (ESS) was used to assess excessive daytime sleepiness. The Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT) was used to assess autonomic function and the Non-Motor Symptoms Questionnaire (NMS-Quest) was used to assess non-motor symptoms of PD. All patients were assessed by well-trained doctors (PH, YH, GL, SC) who were blinded to the allocation of patients.

Exercise and quality control

The Tai Chi method taught by Sino Tai Chi, a professional Tai Chi organisation, was adopted for Tai Chi training, as previously reported.[2] The patients trained twice a week for 60 min each time. They were taught from segment to whole Tai Chi training. Coaches corrected inappropriate movements. Patients who discontinued Tai Chi training or those whose attendance rate was less than 75% were all regarded as giving up training.

In the control group, patients continued to use antiparkinsonian drugs and to keep their daily activity levels as usual. We did not restrict the daily activities that they had taken before being recruited into the study.

Outcomes

The study had three primary outcomes, all of which are related to the long-term beneficial effect:

- Rate of change in UPDRS total score per year.
- Rate of change in LEDD per year; the LEDD of patients who received deep brain stimulation (DBS) was not taken into account.
- Percentage of patients who increased antiparkinsonian therapy, including the need to increase the dose of antiparkinsonian drugs and DBS.

The following indicators were regarded as secondary outcomes:

- Evaluation of motor symptoms: UPDRS part III, TUG and BBS.
- Evaluation of non-motor symptoms: autonomic function, mood, sleep and cognition, assessed by rating scales.
- Quality of life evaluated by PDQ-39.
- Difference in the prevalence of complications (dyskinesia, wearing-off phenomenon, dystonia) and non-motor symptoms (including PD-MCI, hallucinations, restless leg syndrome).

Statistical methods

Analyses of the adjusted means of change from baseline to each follow-up in rating scales were performed and compared in the Tai Chi training group and the control group with a logarithmic linear model of covariance that included the following fixed effects: treatment group (Tai Chi=1, control group=0), age, gender, change in the amount of LEDD and baseline Hoehn–Yahr staging. Years of education were also included when analysing PDCRS. We calculated the p value with the bootstrap method for resampling 1000 times. The years of follow-up were calculated as months between follow-up/12. The results are presented as mean change with 95% CIs. The percentage need for increasing antiparkinsonian therapy was shown in a Kaplan–Meier plot and a bar plot and a Kaplan–Meier plot with a table of the number at risk was applied. Bonferroni correction was used for multiple corrections.

R (version 3.5.1) and RStudio (version 1.1463) were used to perform statistical analysis. Packages stats (version 3.5.1), base (version 3.5.1), spinds (version 2.2.0), plyr (version 1.8.5), survival (version 2.43–3) and survminer (version 0.4.3) were

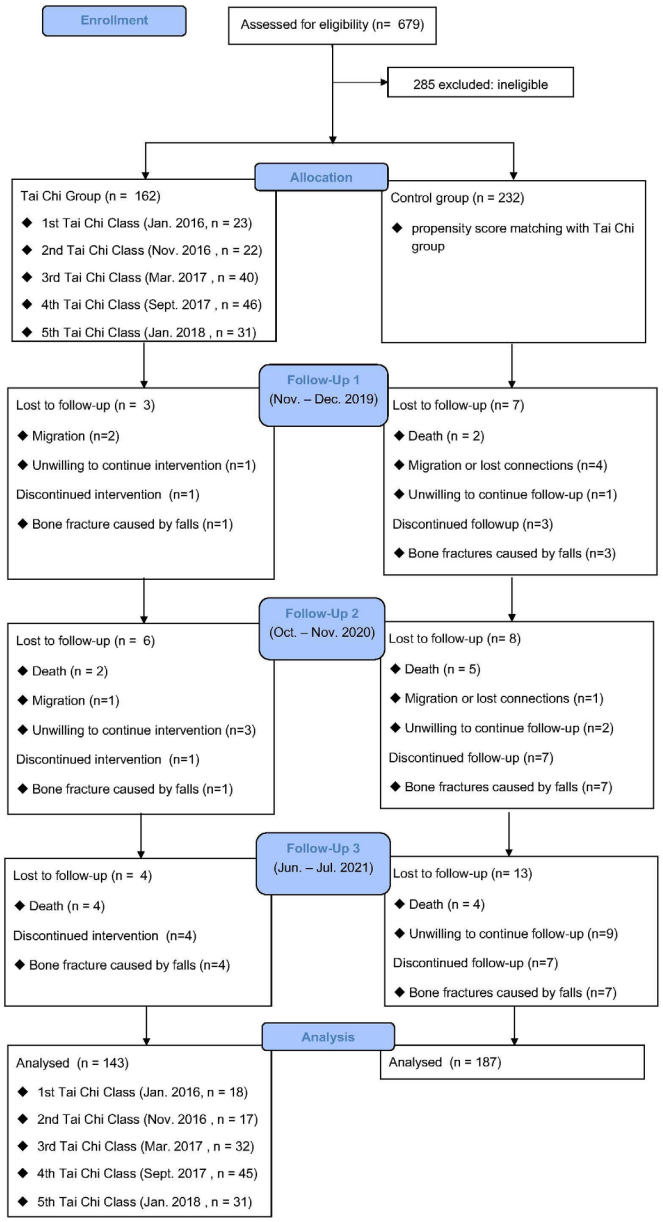

Figure 1 Flow chart of the study.

introduced into the statistical analysis. Figures were plotted in Prism 9 (version 9.3.1, San Diego, California, USA).

RESULTS

Demographic status

There was no significant difference in gender, age, education, disease duration, Hoehn–Yahr staging, amount of exercise per week, MMSE, HAMA, HAMD and LEDD at baseline between the patients undergoing Tai Chi training (n=143) and patients in the control group (n=187) (figure 1, table 1). In the Tai Chi group the dropout rate was 11.72% compared with 19.40% in the control group.

Effect of Tai Chi on long-term beneficial effect

The annual increase in the UPDRS total score was significantly higher in the control group than in the Tai Chi group in the follow-up of 2019, 2020 and 2021 (annual changes in UPDRS total score: Tai Chi group: 2.960±0.70 in 2019, 3.005±0.72 in 2020, 3.007±0.70 in 2021; control group: 4.907±0.93 in 2019, 4.975±0.93 in 2020, 4.975±0.94 in 2021; p<0.001) indicating faster progression of PD in the control group (figure 2A).

Table 1 Demographic data of study patients

	Tai Chi group (n=143)	Control group (n=187)	P value
Gender, female, N (%)	65 (45.45)	88 (47.06)	0.859
Age at baseline, mean (SD)	66.70 (9.02)	66.40 (8.13)	0.756
Education, years, mean (SD)	9.88 (2.45)	10.26 (2.99)	0.211
History of hypertension, N (%)	12 (8.39)	17 (9.09)	0.979
History of diabetes mellitus, N (%)	13 (9.09)	14 (7.49)	0.746
History of smoking, N (%)	18 (12.59)	26 (13.90)	0.853
Family history, N (%)	11 (7.69)	13 (6.95)	0.966
Tremor dominant, N (%)	89 (62.24)	118 (63.10)	0.963
Disease duration, mean (SD)	4.35 (2.01)	3.98 (1.85)	0.086
Amount of exercise at baseline, min/week, mean (SD)	25.47 (14.03)	23.12 (15.16)	0.147
MMSE at baseline, mean (SD)	27.80 (1.49)	27.96 (1.43)	0.315
UPDRS at baseline, mean (SD)	16.73 (3.37)	17.16 (3.75)	0.272
LEDD at baseline, mean (SD)	224.21 (91.51)	229.54 (85.38)	0.590
HAMD at baseline, mean (SD)	4.71 (1.65)	4.64 (1.72)	0.829
HAMA at baseline, mean (SD)	3.22 (1.02)	3.35 (1.37)	0.733

HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; LEDD, levodopa equivalent daily dosage; MMSE, Mini-Mental State Examination; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

Using a Kaplan–Meier plot, the greater need to increase antiparkinsonian therapy in the control group was also observed (figure 2D). The number of patients who needed to increase antiparkinsonian therapy in the control group was significantly higher than that in the Tai Chi group in the follow-up of 2019 and 2020. The percentage of patients who needed to increase antiparkinsonian therapy in the control group was 83.42% (year of 2019) and 96.26% (year of 2020), and the percentage of patients who needed to increase antiparkinsonian therapy in the Tai Chi group was 70.63% (year of 2019) and 87.41% (year of 2020) (figure 2C). Although all patients in the two groups increased antiparkinsonian therapy in the follow-up of 2021 (figure 2C), the annual increase in LEDD was higher in the control group in three follow-ups (Tai Chi group: 282.50±190.97 in 2019, 228.42±135.79 in 2020, 203.99±106.21 in 2021; control group: 410.20±247.71 in 2019, 434.10±151.11 in 2020, 436.80±99.37 in 2021; p<0.001) (figure 2B), which also reflected a faster progression of PD in the control group.

Effect of Tai Chi on motor and non-motor symptoms

Patients with PD benefited from Tai Chi training in motor symptoms assessed by UPDRS Part III, BBS and TUG. The Tai Chi group had slower deterioration in UPDRS III scores (annual changes of UPDRS III: Tai Chi group: 1.751±0.69 in 2019, 2.052±0.77 in 2020, 2.192±0.72 in 2021; control group: 3.482±1.03 in 2019, 3.989±1.00 in 2020, 4.135±0.99 in 2021; p<0.001, table 2). Continuous improvement in the BBS and TUG scales were also shown in the Tai Chi group (table 2).

For non-motor symptoms, autonomic symptoms were assessed by SCOPA-AUT, quality of life was assessed by PDQ39, sleep was assessed by PDSS and cognition was assessed by PDCRS and PDCRS frontal cortical score after Bonferroni correction. The Tai Chi group had slower deterioration in cognitive function (annual changes of PDCRS total score: Tai Chi group: –0.746±1.13 in 2019, –1.016±0.86 in 2020, –1.220±0.74 in 2021; control group: –3.266±0.75 in 2019, –2.758±0.57 in 2020, –2.630±0.50 in 2021, p<0.001; annual changes in

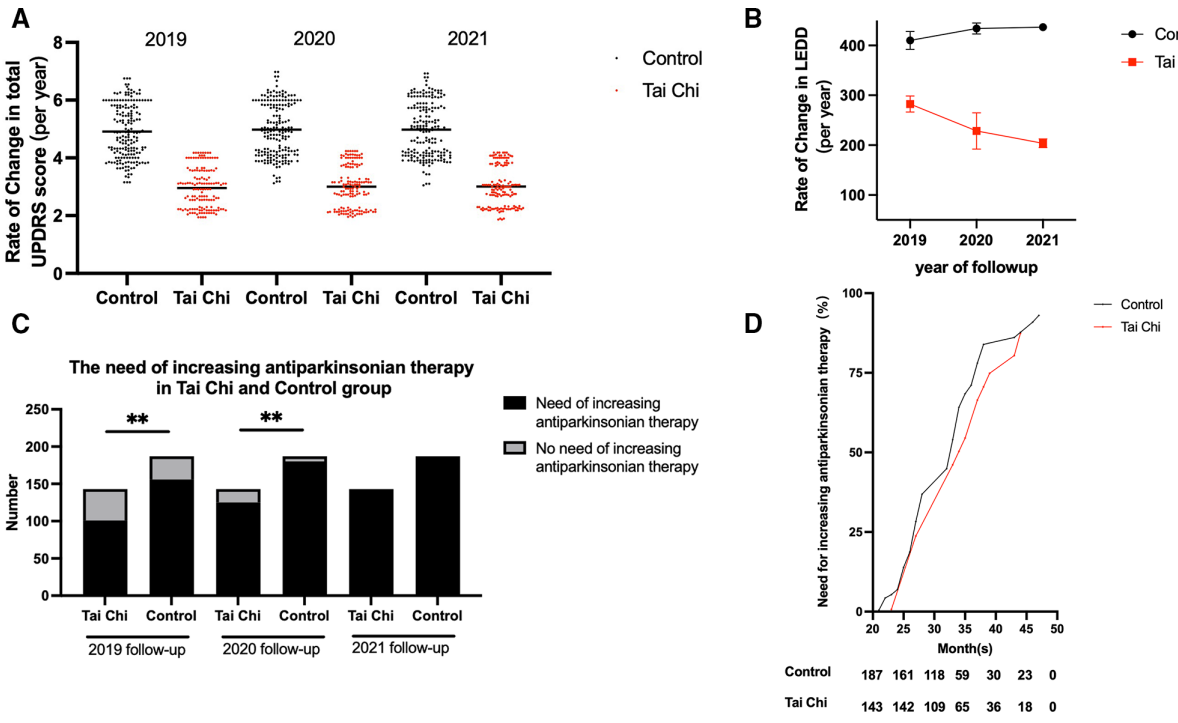

Figure 2 (A) Scatterplot showing the annual changes in Unified Parkinson's Disease Rating Scale (UPDRS) total score. There was no difference in the UPDRS total score at baseline. The rate shown for each year was calculated as (total score in that year – total score in baseline)/years of follow-up. Years of follow-up were calculated as months between follow-up/12. (B) Annual increases in levodopa equivalent daily dose (LEDD) showing a large difference between the control and Tai Chi groups. The bar is shown in SEM.(C) The need to increase antiparkinsonian therapy in the Tai Chi and control groups. In the follow-ups in 2019 and 2020, the need to increase antiparkinsonian therapy in the control group was significantly higher than that in the Tai Chi group. (D) Plot showing the need to increase antiparkinsonian therapy with a table of the number at risk. The need for antiparkinsonian therapy in the control group (black line) is significantly higher than that of the Tai Chi group (red line).

PDCRS frontal cortical score: Tai Chi group: –0.576±1.16 in 2019, –0.754±0.85 in 2020, –0.879±0.74 in 2021; control group: –2.682±0.49 in 2019, –2.219±0.42 in 2020, –2.067±0.39 in 2021, p=0.003; table 2). The Tai Chi group also showed improvements or slower deterioration in autonomic symptoms, sleep and quality of life (table 2).

Effect of Tai Chi on the prevalence of complications

We also calculated the prevalence of motor and non-motor complications and found that the prevalence of dyskinesia, wearing-off phenomenon, dystonia, hallucination, mild cognitive impairment (MCI) and restless legs syndrome in the Tai Chi group was significantly lower than in the control group. The percentage of motor complications was as follows: dyskinesia: Tai Chi group: 1.40%, control group: 7.49%; wearing-off phenomenon: Tai Chi group: 1.40%, control group: 6.42%; dystonia: Tai Chi group: 0%, control group: 1.60% and the percentage of non-motor symptoms was as follows: hallucinations: Tai Chi group: 0%, control group: 2.14%; PD-MCI: Tai Chi group: 2.80%, control group: 9.63%; restless legs syndrome: Tai Chi group: 6.99%, control group: 15.51% (p≤0.028) (figure 3)

Adverse events and serious adverse events

Falling, dizziness and back pain were the three types of adverse events in our study and occurred as follows: falling: 18 (11.11%) in the Tai Chi group and 39 (16.81%) in the control group (p=0.338); dizziness: 9 (5.56%) in the Tai Chi group and 17 (7.33%) in the control group (p=0.825); and back pain: 3 (1.85%) in the Tai Chi group and 15 (6.47%) in the control group (p=0.279).

Twenty-three cases of bone fractures were reported as serious adverse events. Six (3.70%) patients in the Tai Chi group and 17 (7.33%) in the control group had fractures caused by falls which occurred during daily life and not during training, which was the reason they discontinued the follow-up (p=0.208).

DISCUSSION

In our study, delayed progression in motor function (UPDRS-III, BBS) and continuous improvement in quality of life (PDQ39), sleep (ESS, PDSS) and cognition (PDCRS) were found in the Tai Chi group. The rate of UPDRS deterioration was much higher in the control group. The need to increase antiparkinsonian therapy and LEDD was also higher in the control group. The prevalence of complications (dyskinesia, wearing-off phenomenon, dystonia) and several non-motor symptoms (hallucinations, PD-MCI and restless legs syndrome) were lower in the Tai Chi group. Above all, Tai Chi was an effective treatment that could maintain the long-term beneficial effect on PD. To our knowledge, this is the first study to show Tai Chi can maintain its long-term beneficial effect on PD.

Drugs are currently the mainstay of PD treatment and show their effectiveness in many ways, but the management of PD is still challenging. First, from the motor symptom point of view, the response to antiparkinsonian drugs may decline during the course of the illness and the benefit of medications for gait and balance is limited.[17] Second, in contrast to the motor symptoms of PD for which treatment is available, non-motor symptoms are often more refractory and inadequately treated.[18] Third, current therapies for PD provide only symptomatic relief without intervening in the disease progression.[19] Although previous studies

Table 2 Primary and secondary outcomes in the Tai Chi and control groups

Measure	Tai Chi, mean (SD)	Control, mean (SD)	Between-group difference of annual rate in mean change from baseline		
			Tai Chi vs control	P value	Maximum P value*
UPDRS - total score (per year)					
Follow-up in 2019	2.960 (0.70)	4.907 (0.93)	−1.95 (−2.13 to −1.76)	<0.001	<0.001
Follow-up in 2020	3.005 (0.72)	4.975 (0.93)	−1.97 (−2.15 to −1.78)	<0.001	<0.001
Follow-up in 2021	3.007 (0.70)	4.975 (0.94)	−1.97 (−2.15 to −1.78)	<0.001	<0.001
UPDRS Part III (per year)					
Follow-up in 2019	1.751 (0.69)	3.482 (1.03)	−1.73 (−1.93 to −1.54)	<0.001	<0.001
Follow-up in 2020	2.052 (0.77)	3.989 (1.00)	−1.94 (−2.13 to −1.74)	<0.001	<0.001
Follow-up in 2021	2.192 (0.72)	4.135 (0.99)	−1.94 (−2.14 to −1.75)	<0.001	<0.001
TUG (second/year)					
Follow-up in 2019	0.521 (0.11)	0.856 (0.21)	−0.34 (−0.37 to −0.30)	<0.001	0.013†
Follow-up in 2020	0.546 (0.09)	0.810 (0.16)	−0.26 (−0.29 to −0.23)	<0.001	0.013†
Follow-up in 2021	0.552 (0.08)	0.777 (0.14)	−0.22 (−0.25 to −0.20)	<0.001	0.013†
BBS (per year)					
Follow-up in 2019	−0.551 (0.76)	−1.744 (0.57)	1.19 (1.05 to 1.34)	<0.001	<0.001
Follow-up in 2020	−0.570 (0.55)	−1.582 (0.44)	1.01 (0.90 to 1.12)	<0.001	<0.001
Follow-up in 2021	−0.597 (0.46)	−1.421 (0.39)	0.82 (0.73 to 0.92)	<0.001	<0.001
NMS-Quest (per year)					
Follow-up in 2019	0.796 (0.46)	1.459 (0.46)	−0.66 (−0.76 to −0.56)	<0.001	0.003
Follow-up in 2020	0.750 (0.37)	1.355 (0.42)	−0.61 (−0.69 to −0.52)	<0.001	0.003
Follow-up in 2021	0.730 (0.33)	1.248 (0.37)	−0.52 (−0.60 to −0.44)	<0.001	0.003
PDSS (per year)					
Follow-up in 2019	−1.676 (0.55)	−2.813 (0.84)	1.14 (0.98 to 1.30)	<0.001	<0.001
Follow-up in 2020	−1.512 (0.49)	−2.325 (0.63)	0.81 (0.69 to 0.94)	<0.001	<0.001
Follow-up in 2021	−1.490 (0.45)	−2.145 (0.52)	0.66 (0.55 to 0.76)	<0.001	<0.001
ESS (per year)					
Follow-up in 2019	0.559 (0.35)	0.959 (0.48)	−0.40 (−0.49 to −0.31)	<0.001	0.036†
Follow-up in 2020	0.561 (0.30)	0.848 (0.36)	−0.29 (−0.36 to −0.21)	<0.001	0.036†
Follow-up in 2021	0.575 (0.27)	0.820 (0.33)	−0.24 (−0.31 to −0.18)	<0.001	0.036†
HAMA (per year)					
Follow-up in 2019	0.749 (0.50)	1.180 (0.53)	−0.43 (−0.54 to −0.32)	0.001	0.050†
Follow-up in 2020	0.705 (0.40)	1.006 (0.42)	−0.30 (−0.39 to −0.21)	0.001	0.050†
Follow-up in 2021	0.715 (0.35)	0.961 (0.37)	−0.25 (−0.33 to −0.17)	0.001	0.050†
HAMD (per year)					
Follow-up in 2019	0.859 (0.38)	1.375 (0.41)	−0.52 (−0.60 to −0.43)	<0.001	0.006†
Follow-up in 2020	0.804 (0.29)	1.171 (0.32)	−0.37 (−0.43 to −0.30)	<0.001	0.006†
Follow-up in 2021	0.774 (0.26)	1.081 (0.30)	−0.31 (−0.37 to −0.24)	<0.001	0.006†
PDCRS total score (per year)					
Follow-up in 2019	−0.746 (1.13)	−3.266 (0.75)	2.52 (2.32 to 2.72)	<0.001	<0.001
Follow-up in 2020	−1.016 (0.86)	−2.758 (0.57)	1.74 (1.59 to 1.90)	<0.001	<0.001
Follow-up in 2021	−1.220 (0.74)	−2.630 (0.50)	1.41 (1.28 to 1.54)	<0.001	<0.001
PDCRS - frontal cortical score (per year)					
Follow-up in 2019	−0.576 (1.16)	−2.682 (0.49)	2.11 (1.92 to 2.29)	<0.001	<0.001
Follow-up in 2020	−0.754 (0.85)	−2.219 (0.42)	1.47 (1.33 to 1.61)	<0.001	<0.001
Follow-up in 2021	−0.879 (0.74)	−2.067 (0.39)	1.19 (1.06 to 1.31)	<0.001	<0.001
PDCRS - posterior cortical score (per year)					
Follow-up in 2019	−0.170 (0.25)	−0.584 (0.50)	0.41 (0.33 to 0.50)	0.002	0.041†
Follow-up in 2020	−0.262 (0.23)	−0.540 (0.37)	0.28 (0.21 to 0.35)	0.002	0.041†
Follow-up in 2021	−0.342 (0.23)	−0.563 (0.31)	0.22 (0.16 to 0.28)	0.002	0.041†
SCOPA-AUT (per year)					
Follow-up in 2019	0.940 (0.34)	1.735 (0.49)	−0.79 (−0.89 to −0.70)	<0.001	<0.001
Follow-up in 2020	0.806 (0.28)	1.369 (0.35)	−0.56 (−0.63 to −0.49)	<0.001	<0.001
Follow-up in 2021	0.789 (0.26)	1.250 (0.30)	−0.46 (−0.52 to −0.40)	<0.001	<0.001
PDQ39 (per year)					
Follow-up in 2019	3.439 (1.08)	5.769 (1.51)	−2.33 (−2.62 to −2.04)	<0.001	<0.001
Follow-up in 2020	2.895 (0.84)	4.558 (1.12)	−1.66 (−1.88 to −1.44)	<0.001	<0.001

Continued

Table 2 Continued

Measure	Tai Chi, mean (SD)	Control, mean (SD)	Between-group difference of annual rate in mean change from baseline		
			Tai Chi vs control	P value	Maximum P value*
Follow-up in 2021	2.596 (0.67)	3.987 (0.95)	−1.39 (−1.57 to −1.21)	<0.001	<0.001
LEDD (mg/ year)					
Follow-up in 2019	282.50 (190.97)	410.20 (247.71)	−127.73 (−176.70 to −78.76)	<0.001	<0.001
Follow-up in 2020	228.42 (135.79)	434.10 (151.11)	−205.65 (−237.15 to −174.15)	<0.001	<0.001
Follow-up in 2021	203.99 (106.21)	436.80 (99.37)	−232.85 (−255.14 to −210.56)	<0.001	<0.001

*This is the maximum p value after using the bootstrap method.
†The p value was not significant after Bonferroni correction.
BBS, Berg Balance scale; ESS, Epworth Sleepiness Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; LEDD, levodopa equivalent daily dosage; NMQuest, Non-Motor Symptoms Questionnaire; PDCRS, Parkinson's Disease Cognitive Rating Scale; PDQ-39, 39-item Parkinson's Disease Questionnaire; PDSS, Parkinson's Disease Sleep Scale; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire; TUG, Timed Up and Go test; UPDRS, Unified Parkinson's Disease Rating Scale.

have shown the effectiveness of Tai Chi treatment on PD, they mainly focused on motor symptoms over a short period of time (less than 6 months). It was not possible to conclude that there is a long-term beneficial effect from these previous studies. Based on this prospective cohort study, we found a long-term beneficial effect in both motor symptoms and non-motor symptoms in the Tai Chi group. We also demonstrated improvements in gait and imbalance, and improvements in sleep and cognition. PD is a progressive disabling neurodegenerative disorder with decreased motor function and worsened non-motor symptoms. A longer time without being disabled will give a higher quality of life, a lower burden for caregivers and less drug usage for patients with PD. Our results show that Tai Chi can prolong the improvements in motor and non-motor symptoms comprehensively, and those patients with PD who persevere with Tai Chi training could gain more benefits from exercise, indicating that continuing to exercise helps the control of symptoms. Thus, it is highly recommended that Tai Chi training is undertaken as early as possible.

Our study showed the long-term beneficial effect of Tai Chi on PD. Combined with the findings of our previous study, these results suggest that Tai Chi may have the potential to delay the progression of the disease.[2] Activated microglia and increased inflammation are involved in the pathogenesis of PD.

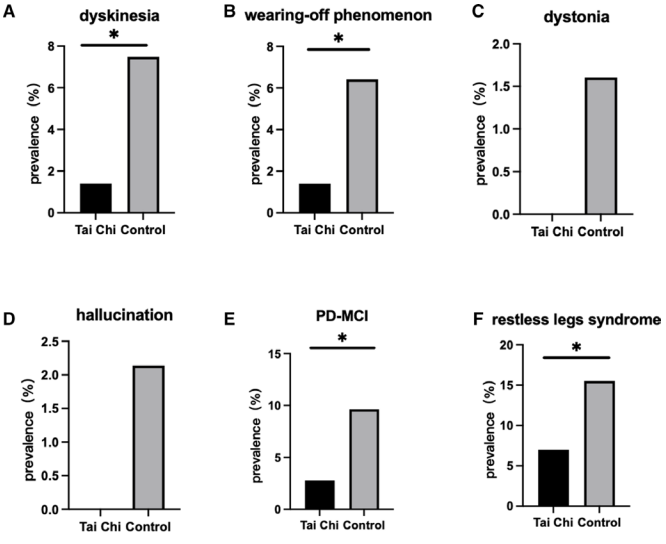

Figure 3 Prevalence of motor complications: (A) dyskinesia, (B) wearing-off phenomenon and (C) dystonia and non-motor complications: (D) hallucinations, (E) PD-mild cognitive impairment (PD-MCI) and (F) restless legs syndrome. All data are shown as bar plots.

Proinflammatory cytokines such as interleukin (IL)-17A and IL-6 are associated with the severity of the clinical symptoms.[20] It has been shown in mice that exercise lessens the inflammation including the microglia pathway in the brain.[21] After exercise, the levels of tumour necrosis factor-α and IL-1β are downregulated.[22] In our previous study we found that plasma cytokines IL-1β, IL-5, IL-7, IL-9, IL-13, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α and MIP-1β were relatively downregulated and granulocyte-macrophage colony stimulating factor (GM-CSF) levels were upregulated in patients after Tai Chi training.[2] Changes in IL-1β, IL-5, IL-9, IL-13, MIP-1α and GM-CSF were related to the clinical improvements. Arginine biosynthesis, the urea cycle, TCA cycle and beta oxidation of very long-chain fatty acids were involved in the improvement in PD symptoms by Tai Chi. Above all, the anti-inflammatory process involved the amelioration of PD symptoms found in our study. In addition to anti-inflammation, *HIP2* mRNA levels were also raised after Tai Chi training, indicating its role in enhancing the ubiquitin proteosome pathway which is associated with the degradation of abnormally folded proteins such as α-synuclein.[23] Our previous study used fMRI to investigate the neuroplasticity via functional connectivity[24] and found a significant association between changes in UPDRS and the switch in the default mode network, changes in BBS and the switch in the visual network, change in the somatomotor network and improvement of PDCRS and SCOPA-AUT. Other studies also showed that physical exercise could induce structural plasticity and enhance cognitive function, which is consistent with our results.[18]

Our study has shown that Tai Chi retains the long-term beneficial effect on PD, indicating the potential disease-modifying effects on both motor and non-motor symptoms, especially gait, balance, autonomic symptoms and cognition. PD can worsen motor function and non-motor symptoms progressively with time, resulting in disability and influencing the quality of life. The long-term beneficial effect on PD could prolong the time without disability, leading to a higher quality of life, a lower burden for caregivers and less drug usage.

Strengths and limitations

There are several strengths and interesting findings in our study. First, it is the first study to demonstrate the long-term effects of Tai Chi training with an average of 4.3 years of observation. Second, we observed that long-term Tai Chi training could maintain the beneficial effect on PD, while previous studies only observed a temporary improvement in motor symptoms. We have shown that exercise and other rehabilitation treatment might

achieve some form of neuroprotection and will be an important adjunct to drug treatments in the management of PD. Third, Tai Chi could ameliorate both motor and non-motor symptoms effectively and safely, which indicates that Tai Chi training combined with drug therapy could bring more comprehensive improvements and thus might delay the demand for increased drug therapy. In addition, Tai Chi is a safe physical exercise. The results of our study show that Tai Chi does not increase the risk of falls. Falls might be associated with postural instability due to disease progression. The lower rate of falls (11.11% in the Tai Chi group vs 16.81% in the control group) also indicated that Tai Chi might have a beneficial effect in improving postural instability.

Our study also has some limitations. First, the number of subjects is not sufficiently large and the patients were not randomised. Larger randomised long-term cohort studies are warranted. Second, we did not assess all symptoms and complications such as apathy. Third, there are several unmeasurable confounders, such as different motivations in pursuing health, different lifestyles, etc. We tried to minimise the impact of these confounders. Patients recruited as controls were mainly based on non-physical factors such as a long distance from home or time conflicts with their daily work/life rather than lack of motivation in practising Tai Chi. A balanced baseline also helped to minimise the potential influences, including LEDD, UPDRS, and mood assessments. However, these potential confounders might still exist.

CONCLUSION

Tai Chi training maintains the long-term beneficial effect on PD, improved motor and non-motor symptoms and reduced complications and could be used in the long-term management of PD.

Acknowledgements We thank all the subjects who participated in this study. We also thank all the coaches of Sino Taiji of Fuxing International for their Tai Chi training courses to PD patients.

Contributors GL: Assessed rating scales, performed statistical analysis and wrote the manuscript. PH: Assessed rating scales and wrote the manuscript. SC: Assessed rating scales. YH: Assessed rating scales. YT: Supervised the study, made the diagnosis of Parkinson's disease and revised the manuscript. SC: Designed and supervised the study, made the diagnosis of Parkinson's disease and revised the manuscript, and the guarantor of the overall content.

Funding This work was supported by grants from the National Natural Science Foundation of China (81430022, 81971187, 81771374, 82171401, 81801267, 81971183, 82371414), Shanghai Municipal Science and Technology Major Project (2018SHZDZX05) and Shanghai Municipal Education Commission (2017NKX001).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (ID number: 2014-096). Participants gave written informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

ORCID iDs
Gen Li http://orcid.org/0000-0002-7910-7980
Shengdi Chen http://orcid.org/0000-0002-6242-1025

REFERENCES

1 Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015;386:896–912.
2 Li G, Huang P, Cui S-S, *et al*. Mechanisms of motor symptom improvement by long-term Tai Chi training in Parkinson's disease patients. *Transl Neurodegener* 2022;11:6.
3 Li G, Ma J, Cui S, *et al*. Parkinson's disease in China: a forty-year growing track of bedside work. *Transl Neurodegener* 2019;8:22.
4 Lees AJ, Hardy J, Revesz T. Parkinson's disease. *Lancet* 2009;373:2055–66.
5 Lang AE, Espay AJ. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. *Mov Disord* 2018;33:660–77.
6 Kalia LV, Kalia SK, Lang AE. Disease-modifying strategies for Parkinson's disease. *Mov Disord* 2015;30:1442–50.
7 Rascol O, Fitzer-Attas CJ, Hauser R, *et al*. A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and post-hoc analyses of the need for additional therapies, changes in UPDRS scores, and non-motor outcomes. *Lancet Neurol* 2011;10:415–23.
8 Amano S, Nocera JR, Vallabhajosula S, *et al*. The effect of Tai Chi exercise on gait initiation and gait performance in persons with Parkinson's disease. *Parkinsonism Relat Disord* 2013;19:955–60.
9 Li F, Harmer P. Economic evaluation of a Tai Ji Quan intervention to reduce falls in people with Parkinson disease, Oregon, 2008-2011. *Prev Chronic Dis* 2015;12:E120.
10 Li F, Harmer P, Fitzgerald K, *et al*. Tai Chi and postural stability in patients with Parkinson's disease. *N Engl J Med* 2012;366:511–9.
11 Nocera JR, Amano S, Vallabhajosula S, *et al*. Tai Chi exercise to improve non-motor symptoms of Parkinson's disease. *J Yoga Phys Ther* 2013;3:10.4172/2157-7595.1000137.
12 Vergara-Diaz G, Osypiuk K, Hausdorff JM, *et al*. Tai Chi for reducing dual-task gait variability, a potential mediator of fall risk in Parkinson's disease: a pilot randomized controlled trial. *Glob Adv Health Med* 2018;7:2164956118775385.
13 Zhang T-Y, Hu Y, Nie Z-Y, *et al*. Effects of Tai Chi and multimodal exercise training on movement and balance function in mild to moderate idiopathic Parkinson disease. *Am J Phys Med Rehabil* 2015;94:921–9.
14 Hackney ME, Earhart GM. Tai Chi improves balance and mobility in people with Parkinson disease. *Gait Posture* 2008;28:456–60.
15 Hughes AJ, Daniel SE, Kilford L, *et al*. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4.
16 Postuma RB, Berg D, Stern M, *et al*. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord* 2015;30:1591–601.
17 Debû B, De Oliveira Godeiro C, Lino JC, *et al*. Managing gait, balance, and posture in Parkinson's disease. *Curr Neurol Neurosci Rep* 2018;18:23.
18 Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nat Rev Neurosci* 2017;18:509.
19 Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA* 2020;323:548–60.
20 Green HF, Khosousi S, Svenningsson P. Plasma IL-6 and IL-17A correlate with severity of motor and non-motor symptoms in Parkinson's disease. *J Parkinsons Dis* 2019;9:705–9.
21 Sung Y-H, Kim S-C, Hong H-P, *et al*. Treadmill exercise ameliorates dopaminergic neuronal loss through suppressing microglial activation in Parkinson's disease mice. *Life Sci* 2012;91:1309–16.
22 Jang Y, Koo J-H, Kwon I, *et al*. Neuroprotective effects of endurance exercise against neuroinflammation in MPTP-induced Parkinson's disease mice. *Brain Res* 2017;1655:186–93.
23 Stefanetti RJ, Lamon S, Wallace M, *et al*. Regulation of ubiquitin proteasome pathway molecular markers in response to endurance and resistance exercise and training. *Pflugers Arch* 2015;467:1523–37.
24 Rogge A-K, Röder B, Zech A, *et al*. Exercise-induced neuroplasticity: balance training increases cortical thickness in visual and vestibular cortical regions. *Neuroimage* 2018;179:471–9.