

## Adiponectin Potentially Contributes to the Antidepressive Effects of Baduanjin Qigong Exercise in Women With Chronic Fatigue Syndrome-Like Illness

Jessie S. M. Chan,<sup>\*†1</sup> Ang Li,<sup>‡§¶</sup> Siu-man Ng,<sup>†</sup> Rainbow T. H. Ho,<sup>\*†</sup> Aimin Xu,<sup>#\*\*††</sup>  
Tzy-jyun Yao,<sup>‡‡</sup> Xiao-Min Wang,<sup>\*</sup> Kwok-Fai So,<sup>‡§¶</sup> and Cecilia L. W. Chan<sup>\*†</sup>

<sup>\*</sup>Department of Social Work and Social Administration, Faculty of Social Science,  
The University of Hong Kong, Hong Kong Special Administration Region (Hong Kong SAR), P.R. China

<sup>†</sup>Centre on Behavioral Health, Faculty of Social Science, The University of Hong Kong,  
Hong Kong SAR, P.R. China

<sup>‡</sup>Guangdong–Hong Kong–Macau Institute of CNS Regeneration, Guangdong Key Laboratory  
of Brain Function and Diseases, Jinan University, Guangzhou, P.R. China

<sup>§</sup>Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong,  
Hong Kong SAR, P.R. China

<sup>¶</sup>State Key Laboratory of Brain and Cognitive Sciences, Li Ka Shing Faculty of Medicine,  
The University of Hong Kong, Hong Kong SAR, P.R. China

<sup>#</sup>Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong,  
Hong Kong SAR, P.R. China

<sup>\*\*</sup>Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine,  
The University of Hong Kong, Hong Kong SAR, P.R. China

<sup>††</sup>State Key Laboratory of Pharmaceutical Biotechnology, Li Ka Shing Faculty of Medicine,  
The University of Hong Kong, Hong Kong SAR, P.R. China

<sup>‡‡</sup>Department of Biostatistics, Harvard C.H. Chan School of Public Health, Cambridge, MA, USA

Our recent study demonstrates that adiponectin signaling plays a significant role in mediating physical exercise-exerted effects on hippocampal neurogenesis and antidepression in mice. Whether the findings can be translated to humans remains unknown. This study aimed to investigate the effects of Baduanjin Qigong exercise on adiponectin and to evaluate whether adiponectin is involved in the antidepressive effects of Qigong exercise on chronic fatigue syndrome (CFS)-like illness. This is a randomized, waitlist-controlled trial. One hundred eight female participants were randomly assigned to either Qigong exercise or waitlist groups. Sixteen 1.5-h Qigong lessons were conducted. Outcome measures were taken at three time points. Baseline adiponectin levels were negatively associated with body weight, body mass index, waist circumference, hip circumference, and waist/hip ratio in women with CFS-like illness. Compared with the waitlist control, Qigong exercise significantly reduced anxiety and depression symptoms and significantly raised plasma adiponectin levels (median=0.8 vs. -0.1,  $p < 0.05$ ). More interestingly, increases in adiponectin levels following Qigong exercise were associated with decreases in depression scores for the Qigong group ( $r = -0.38$ ,  $p = 0.04$ ). Moreover, adjusted linear regression analysis further identified Qigong exercise and change in adiponectin levels as the significant factors accounting for reduction of depression symptoms. Baduanjin Qigong significantly increased adiponectin levels in females with CFS-like illness. Decreases in depression symptoms were associated with increases in adiponectin levels following Qigong exercise, indicating that the potential contribution of adiponectin to Qigong exercise elicited antidepressive effects in human subjects.

**Key words: Adiponectin; Baduanjin Qigong exercise; Chronic fatigue syndrome (CFS); Depression; Female**

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<sup>†</sup>These authors provided equal contribution to this work.

Address correspondence to Professor Cecilia L. W. Chan, Department of Social Work and Social Administration, The University of Hong Kong, 5/F Jockey Club Tower, The Centennial Campus, Pokfulam, Hong Kong SAR, P.R. China. Tel: 852-3917-2093; Fax: 852-2858-7604; E-mail: [cecichan@hku.hk](mailto:cecichan@hku.hk) or Kwok-Fai So, Department of Ophthalmology, Room 410, 5 Sassoon Rd, Pokfulam, Hong Kong SAR, P.R. China. E-mail: [hmaskf@hku.hk](mailto:hmaskf@hku.hk)

## INTRODUCTION

Adiponectin, an adipocyte-secreted hormone, possesses an antidepressant-like function when directly injected into the brain of an animal model of depression<sup>1</sup>. Our latest study not only confirmed this mood-altering property but also demonstrated that adiponectin alleviates depression-like behaviors through promoting hippocampal neurogenesis in mice<sup>2</sup>. Several prior studies reported that adiponectin levels were reduced in depressed patients<sup>1,3-5</sup>, which could be reversed following antidepressant therapy<sup>6</sup>. Thus, adiponectin has been proposed as an emerging depression biomarker<sup>7</sup> for non-pharmacological antidepressive interventions<sup>8</sup>.

Chronic fatigue syndrome (CFS) is a complex, unexplained, and persistent fatigue lasting for at least 6 months. So far, there has been no treatment that was found to be definitively effective<sup>9</sup>. A review showed that the prevalence of CFS in women was two to three times higher than in men, and around three-quarters of CFS patients were female<sup>10</sup>. Depression and anxiety symptoms (80%) are very common in CFS<sup>11,12</sup>. Compared with men, more women with CFS suffer from depression. Because of the unknown etiology and lack of effective remedies for CFS, a large number of patients with CFS remain unrecognized or undertreated in the community<sup>13,14</sup>. A CFS-like illness, defined based on the self-reported fatigue characteristics, associated symptoms, and medical history, is identical to those symptoms observed in CFS, except that the latter has a confirmed medical diagnosis<sup>15-17</sup>. Unfortunately, these comorbid mood symptoms are often neglected or insufficiently treated in people with CFS-like illness<sup>14</sup>.

Physical exercise has been advocated as an alternative and effective therapy for depression<sup>18</sup>. However, the underlying mechanism mediating the antidepressive action of exercise is largely unknown. Previous studies have suggested that hippocampal neurogenesis plays an indispensable role in mediating the antidepressive effects of antidepressants<sup>19</sup>. Our latest animal study first reported that adiponectin may be an essential factor that mediates the effects of exercise on hippocampal neurogenesis and antidepressive<sup>2</sup>. Nonetheless, the potential application of adiponectin to predict the outcome of exercise for depression is impeded by the conflicting results from different clinical studies. Some studies reported that physical activity raised adiponectin levels in inactive, abdominally obese men<sup>20</sup> and breast cancer survivors<sup>21</sup>, whereas another study showed that exercise did not affect the adiponectin levels of breast cancer survivors<sup>22</sup>. In addition, although an association between adiponectin and some healthful factors such as reduction of oxidative stress, anti-inflammation, and antivascularization<sup>23</sup> has been suggested, the relationship between adiponectin and other psychological parameters remains underreported.

Similar to Taichi<sup>24,25</sup>, Baduanjin Qigong exercise (abbreviated as Qigong here) is a mind/body exercise that focuses on promoting the circulation of vital energy (also called Qi) in the meridian system (Qi vital energy channel) to regulate the body, mind, and breathing<sup>26</sup>. The Sports and Culture Commission of the People's Republic of China (PRC) endorses Baduanjin Qigong, which is composed of eight standardized movements. Our prior studies demonstrated that Qigong exercise has antidepressive<sup>27,28</sup> and antiaging effects<sup>29</sup> on CFS-like illness. So far, there has been no published report on its effects on adiponectin levels in patients with CFS-like illness. Given that we have demonstrated that adiponectin may mediate exercise-induced effects on enhancing hippocampal neurogenesis and mitigating depression in animal models<sup>2</sup>, here we tested whether such a conclusion can be applied to humans by investigating the impacts of Qigong exercise on adiponectin in women with CFS-like illness and the associations between adiponectin and various clinical parameters.

## MATERIALS AND METHODS

### *Study Design*

This was a randomized, waitlist-controlled, parallel-group study. This trial is registered with Hong Kong Clinical Trial Register: HKCRT-1380. The details of the study design, procedure, and intervention were previously published<sup>27</sup>. One hundred eight female participants were randomly assigned to either the Qigong exercise group or the waitlist group, and major assessments were conducted for a total of three times: at baseline (T0), immediately postintervention (T1), and 3 months postintervention (T2).

### *Participants*

Chinese adults [mean age=39.0, standard deviation (SD)=7.9] in the local community were screened through an online questionnaire in Chinese that was structured according to the US Centers for Disease Control and Prevention (CDC) diagnostic criteria for CFS<sup>30</sup>. CFS-like illness was identified if the participants had unexplained, persistent fatigue of new onset (not lifelong) for at least 6 months, accompanied by four or more of the following eight symptoms: nonrefreshing sleep, impaired memory or concentration, new headaches, muscle pain, multi-joint pain, sore throat, postexertional malaise, and tender lymph nodes. Meanwhile, these patients with CFS-like illness did not have any history of cancer, sleep apnea, narcolepsy, hypothyroidism, hepatitis B or C virus infection, severe obesity, or mental disorders including major depressive disorder, schizophrenia, bipolar disorder, and alcohol or other forms of substance abuse based on a medical history checklist<sup>30</sup>. To minimize the impact of

other undiagnosed chronic illnesses, we excluded people older than 50 years, who were more likely to have chronic illnesses present with chronic fatigue than were younger participants. Most studies have shown that the mean age at onset of CFS is between 29 and 35 years, and the mean course of illness ranges from 3 to 9 years<sup>31</sup>. We also excluded those who had practiced Qigong in the past 6 months.

As the gender ratio between the Qigong group and the control group (female/male=46:29 for the Qigong group and 62:13 for the control group;  $p=0.004$ ) was unbalanced and the adiponectin level in females was significantly higher ( $12.94 \pm 7.32$  mg/L vs.  $7.83 \pm 3.57$  mg/L;  $p < 0.001$ ), in order to ensure homogeneity in terms of adiponectin levels between the Qigong group and the control group, a small number of male participants ( $n=42$ ) were also excluded, and only female participants were included in this study.

#### *Procedure and Intervention*

All participants provided written informed consent prior to further assessment and intervention. At the three designated time points, participants completed a series of questionnaires on anxiety and depression, and 5-ml whole-blood samples were collected. Sixteen sessions of Baduanjin Qigong group training were provided over 9 consecutive weeks. Each session lasted 1.5 h and was guided by an experienced Qigong master and seven or eight assistant Qigong teachers. Participants in the Qigong exercise group were advised to practice Qigong for at least 30 min every day, while those in the waitlist group were advised to keep their usual lifestyle and refrain from participating in any active exercise.

#### *Measures*

*Screening Measures and Demographics.* The online screening questionnaire includes (1) the CDC diagnostic checklist for CFS<sup>30</sup>; (2) a list of medical illnesses based on the CDC exclusion criteria for CFS; (3) demographics, including age, gender, employment status, educational level, marital status, and religious affiliation; and (4) lifestyle variables, including exercise habit, smoking, and alcohol consumption. In addition, anthropometric variables, including weight, height, blood pressure, waist circumference, and hip circumference, were also measured at baseline (T0).

*Hospital Anxiety and Depression Scale (HADS).* The HADS is a 14-item self-rating scale on anxiety (seven items) and depression symptoms (seven items)<sup>32</sup>. Each item can be scored on a scale from zero to three, with a higher score indicating a higher level of anxiety or depression. The Chinese version of the HADS was validated and was found to have satisfactory psychometric properties<sup>33</sup>.

*Measurement of Plasma Adiponectin Levels.* Whole-blood samples obtained from participants were placed into ethylenediaminetetraacetic acid (EDTA)-containing tubes (BD Vacutainer PLUS Blood Collection Tubes; Becton Dickinson, Franklin Lakes, NJ, USA), followed by centrifugation ( $1,000 \times g$ ) at  $4^\circ\text{C}$  for 15 min. The supernatants were transferred into new tubes and stored at  $-80^\circ\text{C}$ . Plasma levels of adiponectin were measured using a human adiponectin enzyme-linked immunosorbent assay (ELISA) kit (Antibody and Immunoassay Services, The University of Hong Kong, Hong Kong) following the manufacturer's instructions, as previously described<sup>34</sup>.

#### *Data Analysis*

Categorical data were summarized by frequencies (percentages). Continuous data were summarized by the median and interquartile range. As the sample size was small and there were some missing data at T1 and T2, between-group differences were assessed by the Mann-Whitney *U*-test for continuous data and by chi-square tests for categorical data. Pearson's correlation was used to assess the association between adiponectin levels and demographic variables and the anxiety and depression symptoms scale. General linear regressions were conducted to identify the significant factors in reducing depression symptoms using the change in depression symptoms (T1 - T0) as the dependent variable and group (Qigong or waitlist), change in adiponectin (T1 - T0), baseline adiponectin (T0), and the interaction of group and change in adiponectin [group  $\times$  change in adiponectin (T1 - T0)] as the independent variables with/without controlling for age, lifestyle factors, body mass index (BMI), and waist circumference as the covariates. All analyses were conducted with Statistical Package for the Social Sciences (SPSS version 24.0; IBM, Armonk, NY, USA).

## RESULTS

#### *Demographic Characteristics of the Participants*

Table 1 describes the sociodemographic, lifestyle, and anthropometric variables of the participants. The median age of the participants was 39.5 years in the Qigong group and 42.0 years in the waitlist group. The participants were predominantly employed full time (86.1%), highly educated (58.3%), and married/cohabiting (58.3%). There were no statistically significant differences in sociodemographic, lifestyle, and anthropometric variables between the two groups.

#### *Plasma Adiponectin Levels at Baseline*

The smokers had marginally lower adiponectin levels than the nonsmokers [smoker: 7.4 (4.8-10.1) mg/L,

**Table 1.** Demographic Characteristics, Lifestyles, and Anthropometric Variables ( $N=108$ )

	Qigong group ( $n=46$ )		Waitlist group ( $n=62$ )		$p$ Value
	Median (Interquartile)	$n$ (%)	Median (Interquartile)	$n$ (%)	
Age (years)	39.5 (33.5–45.3)		42.0 (32.5–47.0)		0.573
Employment					0.365
Full time		38 (82.6%)		55 (88.7%)	
Others		8 (17.4%)		7 (11.3%)	
Education					0.742
Secondary or below		20 (43.5%)		25 (40.3%)	
Tertiary/undergraduate or above		26 (56.5%)		37 (59.7%)	
Marital status					0.645
Single/divorced/separated		18 (39.1%)		27 (43.5%)	
Married/cohabiting		28 (60.9%)		35 (56.5%)	
Religious affiliation		21 (45.7%)		23 (37.1%)	0.371
Lifestyle variables					
Regular exercise		15 (32.6%)		22 (35.5%)	0.756
Daily smoking		1 (2.2%)		2 (3.2%)	1.000
Alcohol drinking $\geq 2$ /week		1 (2.2%)		2 (3.2%)	1.000
Body weight (kg)	54.0 (46.0–60.3)		[2] 52.3 (49.0–59.9)		0.896
Body mass index	20.8 (18.0–23.7)		[2] 20.1 (19.1–22.9)		0.992
Blood pressure (mmHg)					
Systolic	114.5 (100.0–124.8)		[2] 112.0 (105.0–126.0)		0.916
Diastolic	74.0 (64.8–79.3)		[2] 74.0 (68.0–81.5)		0.210
Waist circumference (cm)	28.3 (26.0–31.6)		[2] 29.0 (27.1–31.7)		0.448
Hip circumference (cm)	37.0 (35.0–39.6)		[2] 37.4 (35.6–39.4)		0.855
Waist/hip ratio	0.77 (0.74–0.79)		[2] 0.78 (0.75–0.82)		0.148

[Number of missing data], Mann–Whitney test for continuous data and chi-square test for categorical data.

nonsmoker: 11.6 (8.5–14.6) mg/L;  $p=0.072$ ]. However, alcohol consumption (twice or more per week) did not seem to affect this parameter [drinker: 11.6 (8.1–13.9) mg/L, nondrinker: 11.1 (8.4–14.6) mg/L;  $p=0.969$ ]. Likewise, no significant difference in adiponectin levels was observed between the participants who participated in regular exercise and those who did not [exerciser: 12.1 (8.2–17.3) mg/L, nonexerciser: 10.8 (8.4–13.6) mg/L;  $p=0.596$ ].

#### Association Between Adiponectin and Other Factors at Baseline

As shown in Table 2, the baseline plasma level of adiponectin was negatively associated with body weight ( $r=-0.287$ ,  $p=0.003$ ), BMI ( $r=-0.327$ ,  $p=0.001$ ), waist circumference ( $r=-0.345$ ,  $p<0.001$ ), hip circumference ( $r=-0.263$ ,  $p=0.007$ ), and waist/hip ratio ( $r=-0.310$ ,  $p=0.001$ ). No significant association was found between the adiponectin level and blood pressure, anxiety, and depression (all  $p>0.05$ ).

#### Unadjusted Effects of Qigong Exercise

As displayed in Table 3, at baseline (T0), all outcome measures were balanced between the two groups. The median adiponectin levels were 11.5 and 11.1 mg/L, and the median depression scores were 9.5 and 9.0 for the Qigong group and the waitlist group, respectively.

Compared with the waitlist group, the median adiponectin level of the Qigong group significantly increased following Qigong, from baseline to immediately post-intervention (T1 – T0) (median = 0.8 mg/L for the Qigong group vs. –0.1 mg/L for the waitlist group;  $p<0.05$ ). The median score for anxiety symptoms in the intervention group following Qigong exercise (T1) was significantly

**Table 2.** Correlation Analysis of Plasma Adiponectin Levels With Other Factors at Baseline (T0)

	Plasma Adiponectin (T0)	
	Correlation Coefficient ( $r$ )	$p$ Value
Age	0.012	0.899
Body weight	<b>–0.287</b>	<b>0.003</b>
BMI	<b>–0.327</b>	<b>0.001</b>
Waist circumference	<b>–0.345</b>	<b>&lt;0.001</b>
Hip circumference	<b>–0.263</b>	<b>0.007</b>
Waist/hip ratio	<b>–0.310</b>	<b>0.001</b>
Systolic blood pressure	–0.064	0.519
Diastolic blood pressure	–0.127	0.198
HADS		
Anxiety	0.005	0.610
Depression	0.011	0.914

BMI, body mass index; HADS, Hospital Anxiety and Depression Scale.

**Table 3.** Changes in Plasma Adiponectin, Anxiety, and Depressive Symptoms at Different Time Points Following Qigong Exercise

	Baseline (T0)		Immediate Postintervention (T1) <sup>a</sup>		3-Month Postintervention (T2) <sup>a</sup>		T1-T0 <sup>a</sup>		T2-T0 <sup>a</sup>	
	Median	(Interquartile)	Median	(Interquartile)	Median	(Interquartile)	Median	(Interquartile)	Median	(Interquartile)
Plasma adiponectin (mg/L)										
Qigong (n=46)	[2] 11.5	(7.7-17.2)	[14] 11.6	(7.6-17.1)	[19] 10.5	(7.4-19.1)	[16] 0.8	(-0.7-2.7)*	[21] 0.3	(-3.0-2.4)
Waitlist (n=62)	[1] 11.1	(9.0-14.1)	[16] 10.1	(7.8-14.5)	[23] 12.1	(9.4-15.7)	[16] -0.1	(-2.3-0.9)	[23] 0.4	(-1.6-3.2)
HADS anxiety										
Qigong (n=46)	10.0	(8.0-13.0)	[13] 7.0	(5.5-10.0)*	[19] 8.0	(6.0-11.0)	[13] -3.0	(-5.0--0.5)	[19] -3.0	(-5.0-1.0)
Waitlist (n=62)	11.0	(8.0-14.0)	[12] 10.0	(6.8-12.3)	[15] 9.0	(7.0-12.0)	[12] -1.0	(-3.3-1.0)	[15] -1.0	(-3.0-0.0)
HADS depression										
Qigong (n=46)	9.5	(7.0-11.0)	[13] 5.0	(3.0-8.0)*	[19] 6.0	(3.0-11.0)	[13] -4.0	(-7.0--1.5)**	[19] -1.0	(-5.0-0.0)
Waitlist (n=62)	9.0	(6.8-11.0)	[12] 7.0	(5.0-10.0)	[15] 7.0	(5.0-9.0)	[12] -1.0	(-3.0-0.0)	[15] -2.0	(-3.0-0.0)

HADS, Hospital Anxiety and Depression Scale. <sup>a</sup>Compare two groups by Mann-Whitney test. \* $p < 0.05$ , \*\* $p < 0.001$ ; [number of missing data].

lower compared with the waitlist group (median=7.0 vs. 10.0;  $p < 0.05$ ). The same holds true for depression symptoms (median=5.0 vs. 7.0;  $p < 0.05$ ). The reduction in depression symptoms immediately postintervention (T1-T0) was also significantly greater in the Qigong group (median=-4.0 vs. -1.0;  $p < 0.001$ ). However, no significant differences in the adiponectin levels, anxiety, or depression symptoms between the Qigong and the waitlist groups were found at T2 (3 months postintervention).

#### Predictors of Changes in Depressive Symptoms Following Qigong Exercise

The linear regression analysis revealed that Qigong (regression coefficient,  $B = -3.316$ ,  $p < 0.001$ ) and changes in adiponectin levels (T1-T0) ( $B = -0.446$ ,  $p = 0.033$ ) were the significant factors for the reduction of depression symptoms following Qigong exercise at T1 (adjusted  $R^2 = 0.245$ ), while baseline adiponectin ( $B = 0.001$ ,  $p = 0.978$ ) and interaction of group and change in adiponectin ( $B = 0.217$ ,  $p = 0.064$ ) were not the significant factors. After controlling for the covariates age, alcohol drinking, daily smoking, regular exercise, BMI, and waist circumference, Qigong exercise ( $B = -3.443$ ,  $p < 0.001$ ) and change in adiponectin ( $B = -0.449$ ,  $p = 0.030$ ) were still significant factors in the regression model (adjusted  $R^2 = 0.289$ ). The details for all factors in the regression model are shown in Table 4. We also found that baseline adiponectin was negatively associated with the change in the adiponectin levels ( $R = -0.342$ ,  $p < 0.001$  at T1 and  $R = -0.579$ ,  $p < 0.001$  at T2), but not for changes in the depression symptoms.

In the Qigong group, changes in the adiponectin levels immediately after Qigong intervention (i.e., T1-T0) were negatively associated with changes in depression severity ( $r = -0.382$ ,  $p = 0.041$ ), but not for anxiety ( $r = -0.280$ ,  $p = 0.141$ ) (Table 5). No significant association was detected between the changes in adiponectin levels and the changes in anxiety and depression outcomes measured at T2 (i.e., T2-T0). For the waitlist group, there were no significant associations between the changes in adiponectin levels and the changes in anxiety and depression outcome measures at T1 and T2.

## DISCUSSION

This is the first study to investigate the effects of Baduanjin Qigong exercise on adiponectin levels of females with CFS-like illness. Consistent with our previous reports<sup>28</sup> using another Qigong exercise (Wu Xing Ping Heng Gong), Baduanjin Qigong exercise showed antidepressive effects in females with CFS-like illness. Interestingly, we found that 16 sessions of Baduanjin Qigong exercise significantly increased adiponectin levels in female participants. Notably, the increase in the adiponectin levels was associated with decreases

**Table 4.** Linear Regression to Predict the Change in Depression (T1 – T0) After Qigong Exercise

Variables	Regression Coefficient (B)	Standard Error (B)	95% CI	$\beta$	p Value
<b>Qigong group</b>	<b>-3.316</b>	<b>0.731</b>	<b>-4.774–-1.859</b>	<b>-0.466</b>	<b>&lt;0.001</b>
<b>Change in adiponectin (T1 – T0)</b>	<b>-0.446</b>	<b>0.205</b>	<b>-0.854–-0.037</b>	<b>-0.858</b>	<b>0.033</b>
Adiponectin at T0	0.001	0.048	-0.095–0.097	0.003	0.978
Group $\times$ difference in adiponectin (T1 – T0)	0.217	0.115	-0.013–0.447	0.732	0.064
Controlling for covariates: age, alcohol drink, smoke status, regular exercise, BMI, and waist circumference					
<b>Qigong group</b>	<b>-3.443</b>	<b>0.718</b>	<b>-4.879–-2.008</b>	<b>-0.484</b>	<b>&lt;0.001</b>
<b>Change in adiponectin (T1 – T0)</b>	<b>-0.449</b>	<b>0.203</b>	<b>-0.855–-0.044</b>	<b>-0.865</b>	<b>0.030</b>
Adiponectin at T0	-0.035	0.055	-0.145–0.076	-0.080	0.533
Group $\times$ difference in adiponectin (T1 – T0)	0.200	0.115	-0.029–0.429	0.675	0.086
Age	-0.057	0.064	-0.178–0.065	-0.115	0.355
Alcohol drinking ( $\geq 2$ /week)	-1.289	0.755	-2.797–0.220	-0.183	0.093
Daily smoking	-2.643	2.277	-7.193–1.908	-0.123	0.250
Regular exercise	-0.186	0.732	-1.649–1.276	-0.026	0.800
BMI	-0.264	0.209	-0.682–0.153	-0.222	0.210
Waist circumference	0.032	0.171	-0.309–0.374	0.031	0.850

B, regression coefficient;  $\beta$ , standardized coefficient; CI, confidence interval; BMI, body mass index.

in depression scores for female participants following Qigong exercise, which was in line with prior studies that showed depressed patients had reduced adiponectin levels<sup>1,3-5</sup>. After adjusting for covariates (age, alcohol drinking, daily smoking, regular exercise, BMI, and waist circumference), the linear regression analysis further predicted Qigong exercise and change in adiponectin following Qigong exercise to be the significant factors for ameliorating depression symptoms immediately after intervention.

This trial was in line with our latest research on animals<sup>2</sup>, which showed that adiponectin deficiency diminished the beneficial effects of exercise on depression-like behaviors, together suggesting that adiponectin may play an important role in mediating the beneficial effects of Qigong exercise on depression. This finding was also consistent with some previous studies that showed physical activity raised the adiponectin levels in inactive,

abdominally obese men<sup>20</sup> and in breast cancer survivors<sup>21</sup>. However, another study reported that a 16-week mixed strength and aerobic intervention failed to increase the adiponectin levels of sedentary overweight breast cancer survivors<sup>22</sup>. In the present study, our data suggested that the increase of adiponectin by exercise might be related to the baseline adiponectin level, although no association was found between the baseline adiponectin level and the baseline depression score, as well as the decrease of depression score following Qigong exercise. The role of baseline adiponectin in the antidepressive effects of exercise warrants further exploration in future studies.

The view that dynamic changes in adiponectin levels following intervention may be a better biomarker for antidepressive treatment was also supported by our results, which showed that Qigong exercise significantly improved adiponectin levels in females, although the baseline adiponectin level was not associated with the severity of

**Table 5.** Correlation Analysis of Adiponectin With Other Outcome Variables After Qigong Exercise

	Qigong Group		Control Group	
	Correlation Coefficient (R)	p	Correlation Coefficient (R)	p
<b>(T1 – T0)</b>				
Change in adiponectin (T1 – T0)				
Change in HADS-anxiety	-0.280	0.141	0.207	0.171
Change in HADS-depression	<b>-0.382</b>	<b>0.041</b>	-0.033	0.829
<b>(T2 – T0)</b>				
Change in adiponectin (T2 – T0)				
Change in HADS-anxiety	-0.139	0.517	0.256	0.116
Change in HADS-depression	-0.224	0.293	-0.019	0.910

HADS, Hospital Anxiety and Depression Scale.

depression symptoms. Interestingly, a recent meta-analysis indicated that depressed patients of European origin had lower adiponectin levels compared with their healthy counterparts<sup>3</sup>, whereas similar studies on the Asian population showed opposite results<sup>35-37</sup>. The ethnic differences between Asians and Caucasians may contribute to these conflicting conclusions<sup>35</sup>.

On the other hand, consistent with reports from two other groups<sup>38,39</sup>, smokers had marginally lower adiponectin levels compared with nonsmokers. The present study demonstrated that plasma adiponectin concentrations were negatively associated with body weight, BMI, waist circumference, hip circumference, and waist/hip ratio for females, all of which were in accordance with prior publications<sup>35,40-42</sup>. Likewise, age did not affect adiponectin levels in the current study, similar to previously reported findings<sup>42</sup>.

Besides that, we found that benefits of Qigong exercise were not maintained 3 months postintervention, which may be related to lower levels of motivation and less self-Qigong practice 3 months after the initial Qigong intervention compared with the levels during the intervention. Strategies to reduce the dropout with missing data and enhance participation in regular Qigong practice after the initial intervention are needed in future studies.

There were several notable limitations in this study. First, the participants with CFS-like illness were exclusively younger than 50 years; hence, the results may not be applicable to other populations. Second, the sample size between the intervention group and the control group was unbalanced; the sample size of the intervention group was relatively smaller. Third, our Qigong intervention was of moderate intensity; hence, the conclusions can only be generalized to other exercise modes with similar properties. Despite the above limitations, this is a large-scale randomized controlled trial showing the influence of Qigong exercise on adiponectin, as well as the potential contribution of adiponectin to Qigong exercise-elicited antidepressive effects in human subjects.

## CONCLUSIONS

To the best of our knowledge, this is the first study demonstrating that Baduanjin Qigong exercise significantly improves adiponectin levels in females with CFS-like illness. It also demonstrated that increase in plasma adiponectin levels following Qigong exercise was associated with the decrease in depression scores in females suffering from CFS-like illness. These findings suggest that adiponectin might contribute, at least in part, to the antidepressive effects of exercise. The data echoed our latest findings in mice that showed adiponectin's significant role in mediating running-triggered enhancement of hippocampal neurogenesis and in alleviating depression. Collectively, these results raised the possibility of

applying adiponectin as a biomarker for predicting and evaluating Qigong exercise intervention in depression.

The significant associations between adiponectin levels and body weight, BMI, waist circumference, hip circumference, waist/hip ratio, and gender were observed in CFS-like illness, which might also relate to the pathogenesis of depression. Further investigations involving other types of exercise or other populations are warranted before introducing adiponectin to clinical practice as an objective biomarker.

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