

## Original Article

# Effects of mindfulness-based stress reduction on the anxiety, depression and quality of life of patients with intrauterine adhesion: a randomized controlled trial

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**Abstract:** Objective: This study aimed to investigate effects of mindfulness-based stress reduction (MBSR) on anxiety, depression and quality of life in patients with intrauterine adhesion. Methods: Patients who received therapy for intrauterine adhesion (IUA) were recruited and randomized into MBSR group and Wait-List group (WL group). 71 women who received routine physical examination were recruited as healthy controls. Patients in MBSR group received MBSR training for 8 weeks. Results: There were 76 patients in MBSR group, 75 patients in WL group and 71 subjects in control group. When compared with control group, the scores of anxiety and depression increased significantly and the score of quality of life reduced significantly before intervention. In patients, the scores of quality of life in all the domains were negatively related to the scores of anxiety and depression ( $P<0.05$ ). After MBSR for 8 weeks, there was a significant time and group interaction for the anxiety score ( $F=55.168$ ,  $P<0.001$ ) and depression score ( $F=252.485$ ,  $P<0.001$ ). The MBSR group showed a decrease in the anxiety and depression score, while the WL group did not. The quality of life (except for bodily pain) in the MBSR group was also significantly improved. The recurrence rate in the MBSR group was 18.4%, which was significantly lower than that in WL group (34.7%;  $P=0.024$ ). Conclusion: IUA patients have evident anxiety and depression, which significantly reduces the life quality of patients. MBSR may improve the anxiety and depression of IUA patients during therapy, promote the post-operative recovery and improve their quality of life.

**Keywords:** Intrauterine adhesion, mindfulness-based stress reduction, anxiety, depression, quality of life

## Introduction

Asherman's syndrome has been reported and studied for more than one century. In 2008, Yu et al [1] reported that the incidence of IUA was about 2.2% in women. Six years later, Xiao et al [2] found that 36.8% of 9295 women who received hysteroscopy were diagnosed with IUA. In China, the abortion rate is at a high level (29%) [3], and the incidence and detection rate of IUA are also increasing in recent years. Currently, the therapeutic efficacy of IUA is still poor, and treatment of IUA is long lasting, complicated. In addition, IUA has been found as a cause of infertility. These significantly add social and family burden to IUA patients. Long-term psychological pressure may not only affect the quality of life and physical health, but also cause infertility [4].

Mindfulness is a psychological training method for self-regulation. It has been described as "bringing one's complete attention to the present experience on a moment-to-moment basis" and as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" [5]. Mindfulness based stress reduction (MBSR) is a mindfulness based, systemic training method and can improve the individual pressure and mood [6]. MBSR has been a new and promising therapy for the daily life related or chronic disease induced anxiety and pressure without any adverse effect [7]. To date, no study has been conducted to investigate the therapeutic effects of MBSR on IUA, but it has been shown to attenuate psychological pressure in patients with diseases other than IUA [8].

IUA has a poor prognosis and may affect the fertility. Thus, we speculate that IUA may cause anxiety and depression. In the present study, the psychological health and quality of life were evaluated in IUA patients, and MBSR was also employed as a tool for the therapy of anxiety and depression in these patients. This study aimed to investigate whether MBSR was able to attenuate anxiety and depression, improve the quality of life and reduce the recurrence of IUA.

## Materials and methods

### *Study design*

This study was registered as a clinical trial (NCT02746679). This was a parallel, two-arm, randomized and controlled trial and IUA patients were randomly assigned into MBSR group and WL group at a ratio of 1:1. This study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University (No: [2015]122). Zung Self-Rating Anxiety Scale (ZSAS), Zung Self-Rating Depression Scale (ZSDS) and 36-Item Short Form Health Survey (SF-36) were employed to evaluate the anxiety, depression and quality of life, respectively, in these subjects. Evaluation in the MBSR group was done 1 day before MBSR and on the day of MBSR ending by face to face interviewing. In control group, the time interval of evaluation was similar to that in the MBSR group. In healthy control group, evaluation was done on recruitment.

### *Subjects*

Patients who were diagnosed with IUA by hysteroscopy and met the inclusion criteria were recruited from our hospital between January 2015 and January 2016. All the patients received systemic therapy (trans-cervical resection of adhesion + post-operative placement of intrauterine balloon + post-operative hormonal treatment) in our hospital. In addition, healthy subjects who received routine physical examination were recruited as healthy controls.

Inclusion criteria: IUA was diagnosed according to the diagnostic criteria for intrauterine adhesion developed by the European Society of Gastrointestinal Endoscopy (ESGE) [9]. Patients had consciousness and could correctly respond to the survey. Exclusion criteria: patients with a history of mental disease, administration of

psychotherapy, acute mental disorder or special stress related life events within 6 months were excluded from this study.

Subjects meeting the inclusion criteria were recruited after informed consent was obtained. The clinical characteristics were collected from IUA patients: endometrial thickness, menstrual cycle, and findings in hysteroscopy. The endometrial thickness was measured with ultrasound in the mid of menstrual cycle. Visual analogue scale (VAS) was employed for the self-evaluation of menstruation with 100 for normal and 0 for amenorrhea. The intrauterine examination by hysteroscopy was done 3 months after surgery.

### *Randomization and blindness*

The random number table was generated by a computer and then IUA patients were randomly assigned into MBSR group and WL group with this table. The investigator who randomized patients was blind to this study. In addition, the investigator who conducted the survey was also blind to the study.

### *Psychological intervention*

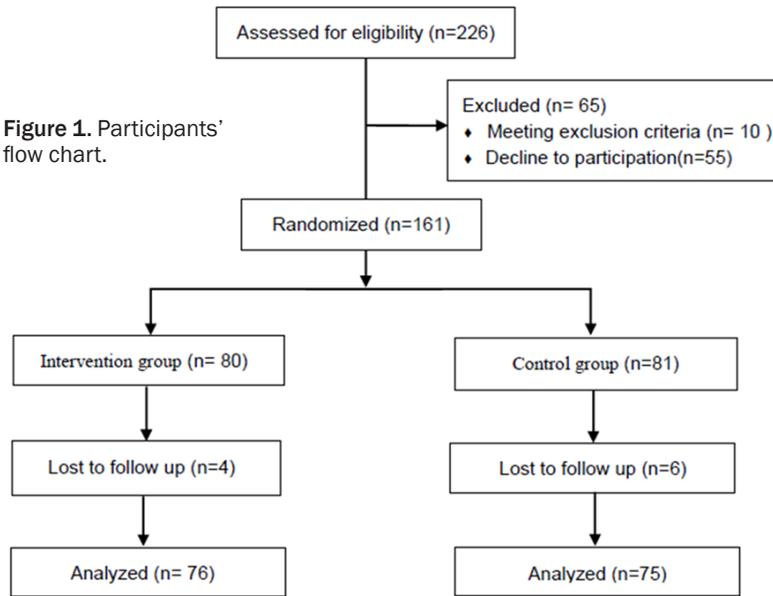
After randomization, IUA patients in the MBSR group received MBSR and a survey was conducted. MBSR was done with the program developed by Kabat-Zinn [10]. In brief, group training was performed for 2.5 h once weekly in which the mindfulness meditation skills were taught for 30 min, patients practiced for 1 h, group discussion was done for 30 min and group meeting was done for 0.5 h. The skills taught included body scan, mindfulness, Hatha yoga postures and mindfulness during ordinary activities like walking, standing, and eating. Participants in MBSR are instructed to practice these skills outside group meetings for at least 30-45 min per day, six days per week, and the patients were asked to timely feed back the effects of MBSR.

### *Determination of effects of MBSR*

General information such as age, education, salary per month and marriage status was collected. Zung's Self-Rating Anxiety Scale (ZSAS) was first developed by William WK Zung in 1971 and is mainly used to evaluate the level of anxiety in patients with anxiety related symptoms

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**Figure 1.** Participants' flow chart.



**Table 1.** Demographics characteristics

		MBSR Group (n=76)	WL Group (n=75)	Healthy control (n=71)	P-value
Age		30.7±5.5	31.1±6.5	29.7±5.6	NS
Education	<9 years	5	8	5	NS
	≥9 years	71	67	66	
Marriage	Single	12	7	8	NS
	Married	64	68	63	
Salary per month	<¥ 5000	16	15	10	NS
	>¥ 5000	60	60	61	

Note: MBSR = mindfulness-based stress reduction; WL = wait-list.

[11]. According to the standards in Chinese population, the score of <50 is suggestive of no anxiety, 50-59 is suggestive of mild anxiety, 60-69 is indicative of moderate anxiety and >70 indicates severe anxiety.

Zung's Self-Rating Depression Scale (ZSDS) is mainly used to evaluate the severity of depression [12]. According to the standards in Chinese population, score of <53 is indicative of no depression, 53-62, mild depression, 63-72, moderate depression and 72, severe depression.

36-Item Short-Form Health Survey (SF-36) is usually used for the evaluation of quality of life [13]. The individual scores are converted into z-scores and standardized combined scores are obtained: converted scores = (original scores-possible lowest scores)/possible score range ×100. The scores may reflect the quality

of life: the higher the score, the better the quality of life is. Each domain was analyzed independently in this study.

## Statistical analysis

Statistical analysis was done with SPSS version 22.0. Quantitative data are expressed as mean ± standard deviation. Student's t test was used to compare the quantitative data. Qualitative data were compared with chi square test or Fisher's exact test. Repeated measures analysis of variance was employed to evaluate the interaction between time and group of depression/anxiety/quality of life. Cohen's d index was used to calculate the effect size. A value of two-sided P<0.05 was considered statistically significant.

## Results

### Recruitment of IUA patients

A total of 226 patients with IUA were recruited into present study within 12 months. Of them, 10 met the exclusion criteria and 55 patients refused to participate in this study. Finally, 161 patients were randomized into MBSR group (n=80) and WL group (n=81). During the follow up period, 4 patients in the MBSR group and 6 patients in the WL group were lost to follow up. The flow chart of recruitment of IUA patients is shown in **Figure 1**.

### Baseline characteristics

A total of 151 patients with IUA and 71 healthy women of child-bearing age were recruited into present study. The demographics of these subjects are shown in **Table 1**. There were no significant differences in the demographics among three groups. In addition, the anxiety score, depression score and quality of life were comparable between MBSR group and WL group before MBSR (**Table 3**) (P>0.05).

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**Table 2.** Anxiety/depression symptoms according to the Zung self-rating anxiety scale/Zung self-rating depression scale n (%)

Healthy control			Before MBSR		After MBSR	
			MBSR Group	WL Group	MBSR Group	WL Group
Anxiety symptoms (a)	Normal	65 (91.5%)	53 (69.7%)	43 (57.3%)	70 (92.1%)	41 (54.7%)
	Mild	5 (7%)	20 (26.3%)	29 (38.7%)	5 (6.6%)	28 (37.3%)
	Moderate	1(1.4%)	3 (3.9%)	3 (4.0%)	1 (1.3%)	6 (8.0%)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	$\chi^2_a/P_a$		11.207 <sup>1</sup> /0.002 <sup>1</sup>	23.383 <sup>1</sup> / $<0.001^1$	28.050 <sup>2</sup> / $<0.001^2$	
Depression symptoms (b)	Normal	51 (71.8%)	37 (48.7%)	36 (48.0%)	55 (73.7%)	39 (52.0%)
	Mild	18 (25.4%)	31 (40.8%)	34 (45.3%)	16 (21.1%)	29 (38.7%)
	Moderate	2 (2.8%)	8 (10.5%)	5 (6.7%)	4 (5.3%)	7 (9.3%)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	$\chi^2_b/P_b$		11.207 <sup>1</sup> /0.008 <sup>1</sup>	8.967 <sup>1</sup> /0.01 <sup>1</sup>	7.610 <sup>2</sup> /0.022 <sup>2</sup>	

Note: 1. MBSR Group and WL Group compared with the healthy controls before MBSR. 2. MBSR Group compared with the WL Group after MBSR. MBSR = mindfulness-based stress reduction; WL = wait-list.

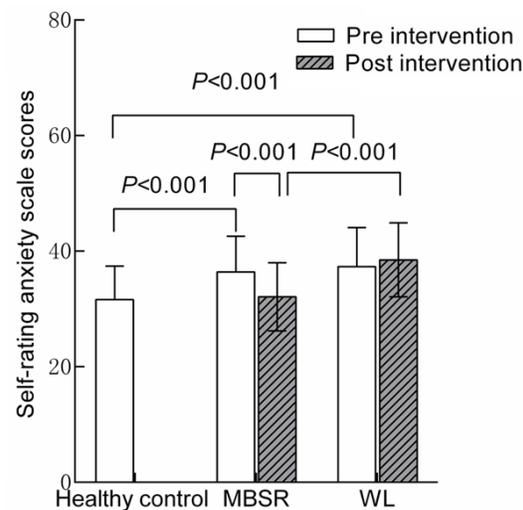
**Table 3.** Anxiety, depression, quality of life and clinical parameters in MBSR group and WL group before and after MBSR

	MBSR Group (n=76)	WL Group (n=75)	95% C.I.	Effect size	P-value
Anxiety/Depression					
SAS					$<0.001^1$
Pre	36.4±6.2	37.3±6.8	-2.94, 1.22	0.138	NS
Post	32.1±5.9	38.5±6.4	-8.42, -4.43	1.039	$<0.001$
SDS					$<0.001^1$
Pre	40.3±7.2	39.7±6.2	-1.56, 2.75	0.089	NS
Post	37.1±7.4	40.9±6.0	-5.69, -1.47	0.564	0.001
SF-36					
Physical functioning					
Pre	86.5±13.7	88.1±12.5	-5.75, 2.64	0.122	NS
Post	90.9±10.7	85.3±11.3	1.97, 9.07	0.509	0.003
Role-physical					
Pre	61.5±38.2	60.3±35.9	-10.7, 13.1	0.032	NS
Post	74.7±26.6	55.7±34.3	9.12, 28.88	0.619	$<0.001$
Bodily pain					
Pre	71.3±15.1	70.4±16.3	-4.14, 5.97	0.057	NS
Post	72.5±11.1	68.5±14.6	-0.21, 8.24	0.308	0.062
General health					
Pre	56.9±17.7	58.9±19.0	-7.94, 3.88	0.109	NS
Post	66.5±16.0	57.1±17.6	4.05, 14.84	0.559	0.001
Vitality					
Pre	67.2±19.5	64.5±19.8	-3.61, 9.02	0.137	NS
Post	74.9±11.6	62.3±18.6	7.53, 17.54	0.813	$<0.001$
Social functioning					
Pre	78.1±19.6	80.3±18.0	-11.2, 0.83	0.117	NS
Post	86.2±13.9	80.5±18.6	0.38, 10.98	0.347	0.036
Role-emotional					
Pre	65.4±34.2	64.0±35.0	-9.77, 12.5	0.04	NS
Post	78.5±22.9	62.7±30.0	0.72, 18.69	0.592	$<0.001$

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Mental health					<0.001 <sup>1</sup>
Pre	64.6±16.3	64.9±16.8	-6.60, 4.06	0.018	NS
Post	72.9±13.0	63.9±16.5	4.24, 13.76	0.606	<0.001
Clinical parameters					
Menstrual pattern					NS <sup>1</sup>
Pre	43.9±22.5	44.8±27.8	-12.97, 10.30		NS
Post	68.5±22.0	69.2±24.8	-10.92, 9.54		NS
Endometrial thickness					NS <sup>1</sup>
Pre	4.4±2.5	4.1±2.4	-0.65, 1.42		NS
Post	5.7±1.4	5.2±1.4	-0.22, 1.09		NS
Adherence recurrence <sup>2</sup>					
Post	14/18.4	26/34.7	5.116		0.024

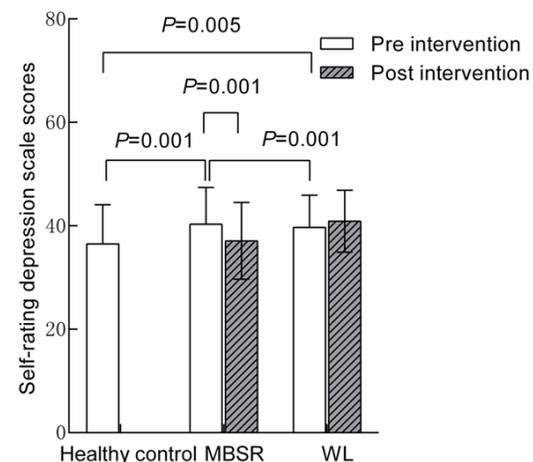
Note: 1. *P*-value indicates the interaction between time and group. 2. Adhesions recurrence and adhesions recurrence rate. MBSR = mindfulness-based stress reduction; WL = wait-list.



**Figure 2.** Zung self-rating depression scale scores in the three groups before an after MBSR. Note: MBSR = mindfulness-based stress reduction; WL = wait-list.

### Anxiety and depression status in IUA patients before MBSR

A total of 222 people completed ZSAS/ZSDS questionnaire. Compared with healthy controls, the incidence of anxiety/depression was significantly higher in the MBSR group and the WL group (Table 2). As shown in Figure 2, ZSAS score in the MBSR group (36.4±6.2,  $P<0.001$ ) and the WL group (37.3±6.8,  $P<0.001$ ) were significantly higher than in healthy control group (31.6±5.8). ZSDS score was 40.3±7.1 in the MBSR group and 39.7±6.2 in the WL group, which were markedly higher than in healthy control group (37.5±7.4;  $P=0.001/0.005$ ) (Fi-



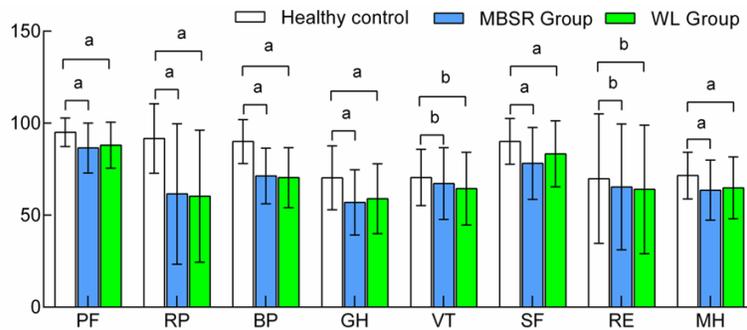
**Figure 3.** Zung self-rating in the three groups before and after MBSR. Note: MBSR = Mindfulness based stress reduction; WL = wait-list.

gure 3). The incidence of anxiety/depression was similar between the MBSR group and the WL group and there were no marked differences in the ZSAS score and ZSDS score between the MBSR group and the WL group.

### Quality of life in IUA patients and healthy controls before MBSR

The quality of life in healthy controls and IUA patients before MBSR is shown in Figure 4. As compared to healthy controls, the quality of life in each domain reduced in IUA patients, and significant differences were observed in physical functioning, Role-physical, bodily pain, general health, social functioning and mental health ( $P<0.05$ ). It is suggested that the quality

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**Figure 4.** Quality of life in the three groups. <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P > 0.05$ . MBSR = mindfulness-based stress reduction; WL = wait-list; PF = Physical functioning; RP = Role-physical; BP = Bodily pain; GH = General health; VT = Vitality; SF = Social functioning; RE = role-emotional; MH = Mental health.

of life of IUA patients at most domain is poorer than that in healthy controls. The correlation between ZSAS/ZSDS score and quality of life is shown in **Figures 5** and **6**. In MBSR group, WL group and healthy control group, the quality of life in each domain was negatively related to the SAS score and SDS score ( $P < 0.05$ ), suggesting that the quality of life in IUA patients reduces may be due to anxiety and depression.

### ZSAS score, ZSDS score and quality of life score

Repeated measures analysis of variance showed the anxiety ( $F = 55.168$ ,  $P < 0.001$ ), depression ( $F = 252.485$ ,  $P < 0.001$ ), physical functioning ( $F = 11.072$ ,  $P = 0.001$ ), role-physical ( $F = 9.273$ ,  $P = 0.003$ ), general health ( $F = 11.982$ ,  $P = 0.001$ ), vitality ( $F = 8.365$ ,  $P = 0.004$ ), social functioning ( $F = 13.665$ ,  $P < 0.001$ ), role-emotional ( $F = 5.184$ ,  $P = 0.024$ ), mental health ( $F = 16.164$ ,  $P < 0.001$ ) displayed interaction between time and group (**Figures 2, 3; Table 3**), but the Bodily pain score was comparable between two groups.

### Effect of MBSR on the clinical prognosis of IUA

In MBSR group, the IUA recurrence rate (18.4%) was significantly lower than in WL group (34.7%;  $P = 0.024$ ), but MBSR seemed to have no influence on the post-operative menstruation and endometrial thickness (**Table 3**).

### Discussion

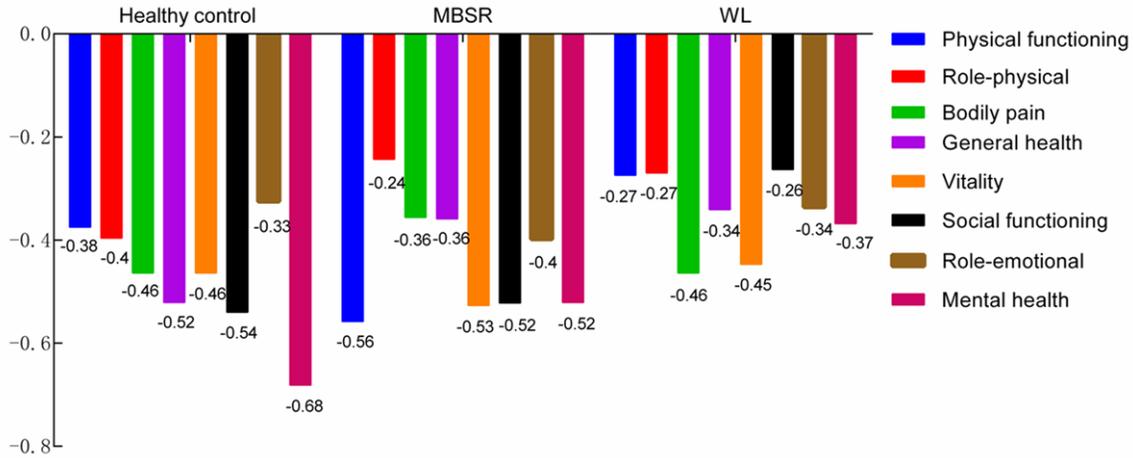
IUA has been regarded as a consequence of base layer destruction of the endometrium. IUA

may cause infertility and amenorrhea and significantly affects the reproductive health [14]. For women of childbearing age, reproduction is a normal physiological process. When the reproduction is disordered, the individual will develop some negative emotions and bear enormous psychological pressure. Mental and psychological factors play an important role in the pathogenesis of reproductive dysfunction [15]. MBSR is a mindfulness training system used

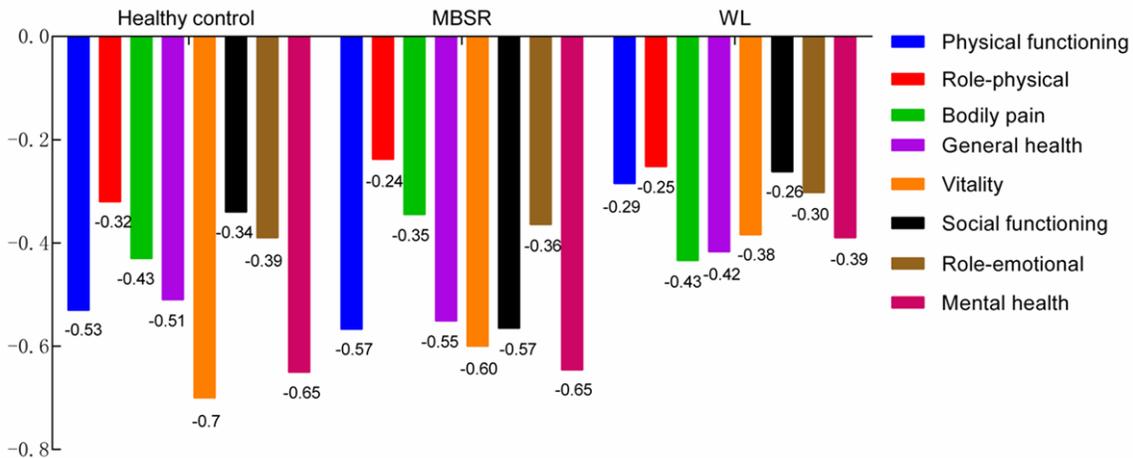
to ease pressure and manage emotion to improve the clinical therapeutic efficacy of a disease [16]. In recent years, increasing attention has been paid to the MBSR in medicine.

There is evidence showing that anxiety and depression are common negative emotions in patients with infertility [17]. The anxiety score and depression score in infertility patients are usually higher than in health controls [18]. IUA may also cause infertility. However, how is the psychological health in IUA patients? As shown in our study, the anxiety score and depression score in IUA patients were significantly higher than in healthy controls before MBSR. In addition, the incidence of anxiety and depression was also higher in IUA patients, suggesting that the anxiety and depression play an important role in IUA patients. These negative emotions might affect the hormone level and in turn the change in sexual hormones may affect the ovulation and endometrial repair, resulting in infertility in women. This forms a vicious cycle in IUA patients. Thus, it is necessary to effectively reduce the anxiety and depression in IUA patients. Kolahkaj et al [19] treated multiple sclerosis patients with MBSR and found it was able to significantly improve the anxiety and depression in these patients. Würtzen et al [20] reported that MBSR could improve the anxiety and depression of breast cancer patients, which lasted for more than 1 year. Our results also showed that the symptoms of anxiety and depression were significantly improved in MBSR group as compared to WL group. It is suggested that MBSR is able to improve the anxiety and depression in IUA patients to a certain extent. MBSR is a therapeutic modality

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**Figure 5.** Correlations between Zung self-rating anxiety scale scores and quality of life. The quality of life at each domain was negatively correlated with the SAS anxiety scores in MBSR group, WL group and healthy control group ( $P < 0.05$ ). MBSR = mindfulness-based stress reduction; WL = wait-list.



**Figure 6.** Correlations between Zung self-rating depression scale scores and quality of life. The quality of life at each domain was negatively correlated with the SDS depression scores in MBSR group, WL group and healthy control group ( $P < 0.05$ ). MBSR = mindfulness-based stress reduction; WL = wait-list.

that can alter the understanding and may help patients to manage the adverse emotions. Although MBSR is unable to avoid the occurrence of negative thoughts and emotions, it may gradually increase mindfulness state and capability to regulate cognitive ability, which then alters the cognitive biases and increases the active cognitive reappraisal [21]. There is evidence showing that the density of left hippocampal gray matter increases and the density of posterior cingulate cortex, temporoparietal junction and cerebellum increases significantly after MBSR as shown in MRI [22]. Hippocampus is closely related to the regula-

tion of emotion. Thus, MBSR may exert protective effects via neurophysiological mechanisms.

In addition, our results also showed MBSR could improve the quality of life in IUA patients. It has been reported that MBSR can improve the quality of life in patients with polycystic ovary syndrome [8], breast cancer in early stage [23] and chemical-induced lung injury [24]. On one hand, quality of life can be explained as the survival status related to goal, expectation and concerns of an individual and the sense of approval and gratification obtained

during the comparison of current functional status with expected functional status. The mindfulness theory holds that the thought can be regarded as thought alone but not as fact when the individual finds the threat, harm or loss of a specific event overwhelm his/her capability. In MBSR, the thoughts, especially the negative thoughts, are not analyzed or replaced with other ideas, but the individual keeps calm to observe and stay with the status peacefully, which finally eases pressure and acquires the sense of acceptance on the current status [25]. When the mindfulness increases in IUA patients, they can accept the IUA and other adverse events and keep patient to stay with this status. Gradually, the understanding of IUA is improved, and the quality of life increases. On the other hand, long lasting anxiety and depression may increase the harmful personality characteristics such as sense of accident, denial, anxiety, depression, compulsion, fear, paranoia and hypochondria, which may reduce the interest on other life activities and cause social disorders, interpersonal tension/indifference, reduction in self-esteem, and increases in frustration, loneliness and sense of guilt [17]. These may finally compromise the quality of life. It has been reported that diseases such as gastroesophageal reflux disease [26], diarrhea-predominant irritable bowel syndrome [27] and autoimmune hepatitis [28] may significantly reduce the quality of life. These findings were consistent with our result that the quality of life in IUA patients reduced significantly as compared to healthy controls. Before MBSR, the score of quality of life at most domains in IUA patients was significantly lower than in healthy controls. Further analysis showed the score of anxiety/depression was negatively related to the quality of life at each domain in SF-36 survey. Yang et al [29] reported anxiety/depression was negatively related to the quality of life. However, MBSR could reduce the level of anxiety/depression in IUA patients and then improves the quality of life. In the SF-36 survey, only the bodily pain was not significantly improved after MBSR, but the bodily pain in patients with chronic pain [30] and fibromyalgia [31] is significantly improved after MBSR. This may be explained as the difference in the disease between studies (IUA vs chronic pain) and the pain is not a major symptom of IUA patients.

After surgery, the menstrual blood volume, endometrial thickness in the mid menstrual cycle and recurrence of adhesion are the concerns of clinicians and patients on IUA. Our results showed the recurrence rate of IUA was 18.4% in MBSR group and 34.7% in WL group, showing significant difference ( $P=0.024$ ). This suggests that MBSR can reduce the recurrence rate of IUA. Turakitwanaka et al [32] found that MBSR could reduce the serum cortisol. In addition, in pathological study on cardiac fibrosis, results showed mood related norepinephrine could promote the proliferation of fibroblasts and induce their secretion of collagen and fibronectin [33]. This might be the molecular mechanism underlying the therapeutic effects of MBSR on the recurrence of IUA. There is evidence showing that the recurrence rate of IUA is as high as 28.7% after therapy [34]. Thus, MBSR may be promoted in the post-operative recovery of IUA patients.

There were still limitations in this study due to time and condition limitations. The sample size was small, and the duration of MBSR and observation was short. Thus, more studies with large sample size and long term follow up are required to confirm the long term efficacy of MBSR in IUA patients.

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### Disclosure of conflict of interest

None.

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