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Impact of mind–body intervention on proinflammatory cytokines interleukin 6 and 1β: A three-arm randomized controlled trial for persons with sleep disturbance and depression

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ABSTRACT

Depressed people are prone to sleep disturbance, which may in return perpetuate the depression. Both depression and sleep disturbance influence proinflammatory cytokines interleukin (IL) 6 and 1β. Thus interventions for depression should consider the effect on sleep disturbance, and vice versa. Integrative Body-Mind-Spirit (IBMS) and Qigong interventions have been applied in a wide range of health and mental health conditions, including depression and sleep disturbance. This study aimed to evaluate the effect of these two mind–body therapies for persons with both depressive symptoms and sleep disturbance. A three-arm randomized controlled trial was conducted among 281 participants, who were randomly assigned to either IBMS, Qigong or wait list control group. Participants in IBMS and Qigong groups received eight weekly sessions of intervention. Outcome measures were plasma concentrations of IL-6 and IL-1β, and a questionnaire containing Pittsburgh Sleep Quality Index, Center for Epidemiologic Studies Depression Scale, Somatic Symptom Inventory, Perceived Stress Scale and Body-Mind-Spirit Holistic Well-being Scale. Outcomes were assessed at baseline (T0), immediate post-intervention (T1) and at three-months post-intervention (T2). Besides intervention efficacy analysis, path analysis was performed to explore the relations among perceived stress, depression, sleep disturbance, and IL-6 and IL-1β values. The study found both IBMS and Qigong reduced depression, sleep disturbance, painful and painless somatic symptoms, IL-6 and IL-1β levels, and increased holistic well-being. The effect sizes of IBMS and Qigong, mostly in the medium magnitude range, were approximatively equivalent. Path analysis models revealed a predictive role of perceived stress in depression and sleep disturbance, a bidirectional relationship between depression and sleep disturbance, and significant influence of depression and sleep disturbance on IL-6 and IL-1β. Compared with control, the findings support the efficacy of IBMS and Qigong interventions in relieving depression and sleep disturbance, and in reducing IL-6 and IL-1β levels.

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1. Introduction

High comorbidity rates and longitudinal bidirectional associations between sleep disturbance and depression have been established (Paunio et al., 2015). People with depression often experience changes in sleep neurophysiology, leading to impaired sleep (Naismith et al., 2011). Between 50% and 90% of patients with diagnosed depression have poor sleep quality (Tsuno et al., 2005). On the other hand, individuals who suffer from sleep disturbance have a high likelihood of occurrence and recurrence of depressive symptoms (Lee et al., 2013; Maglione et al., 2014). It is suggested that sleep disturbances and depression should be treated together to prevent recurrence of either disorder (Fang et al., 2019). Depressed patients and persons having poor sleep quality are prone to pain and somatic symptoms (Demyttenaere et al., 2010; Zhang et al., 2012), as well as low psychological well-being (Chu and Richdale, 2009). Therefore, it seems important that interventions for depressed persons should also consider sleep disturbance, and vice versa.

Significant increases in proinflammatory cytokine are associated with sleep impairment and depression (Irwin et al., 2013). Empirical studies have reported that disturbed sleep could predict elevations in interleukin (IL) 6 and 1β (Breitbart et al., 2014; Irwin et al., 2016). Persons with depression have also been shown to have increased plasma concentrations of IL-6 and IL-1β (Dahl et al., 2014; Dowlati et al., 2010). IL-6 and IL-1β are useful markers in the diagnosis and management of inflammatory diseases (Slaats et al., 2016). As highlighted in the review by Irwin et al. (2016), psychological care for depressed patients with sleep disturbance may improve their inflammatory functioning, although research in this area is scant.

Some studies have reported a positive effect of sleep interventions on individuals' levels of depression (Gee et al., 2019; Luca et al., 2013). However, few studies have employed a holistic psychological intervention targeting improvements in both sleep quality and depressive symptom, in order to promote integrative well-being. Chien et al. (2015) adopted a cognitive intervention combined with a breathing relaxation exercise for depressed patients with sleep disturbance, and found positive effects on participants' sleep quality and heart rate variability. However, they did not measure effects on depressive symptoms. Chan et al. (2012a) developed a Chinese Chan-based mind–body intervention for patients with depression and sleep problems, and compared the effect with cognitive-behavioral therapy. Both interventions were effective in improving participants' sleep quality and daytime energy, however the effects on depression and other physical biomarkers were not measured.

Perceived stress is a major predictor for depression and poor sleep quality (Liu et al., 2017; Wallace et al., 2017), and depressed persons with sleep disturbance often experience distressing somatic symptoms and low well-being (Chu and Richdale, 2009; Zhang et al., 2012). This study examined the effects of two mind–body interventions on perceived stress, sleep quality, depressive symptom, somatic symptom and holistic well-being of individuals with both depressive symptoms and sleep disturbances. Proinflammatory cytokines IL-6 and IL-1β levels, which indicate body inflammation status and may affect brain functions (del Rey et al., 2013), were also tested to assess the influence of psychological improvements on biochemical changes.

This study compared an Integrative Body-Mind-Spirit (IBMS) group intervention, and a Qigong exercise training group, with a waiting list control group. IBMS is a holistic intervention that combines Eastern philosophies of Buddhism, Taoism and Traditional Chinese Medicine, viewing mind, body and spirituality as a dynamically connected system (Chan et al., 2002). The cultivation of resilience, finding meaning out of suffering, and transformation through pain are some of the spiritual reflections aiming at promoting a peace of mind. IBMS contains simple movement exercises, and training on acupoint massage and meditation, to encourage the self-healing process and bring about transformative changes in individuals (Lee et al., 2009). IBMS has been applied successfully in many vulnerable groups, including cancer patients and their caregivers (Lau et al., 2018), women undergoing in vitro fertilization (Chan et al., 2012b), children with atopic dermatitis (Xie et al., 2020), and adults with repressed emotions and somatic symptoms (Ng et al., 2018). It has been applied in many countries and areas, such as Hong Kong (Chan et al., 2012b), India (Sreevani et al., 2013), and Taiwan (Hsiao et al., 2014). Empirical studies have supported the positive effects of IBMS on both psychological, social and physical dimensions of health (Yin et al., 2020).

Qigong is an ancient Chinese self-healing mind–body exercise, which contains breathing, body posture, gentle movements and Taoist philosophy of "going with the flow", i.e. let-it-be and let-go. Qigong exercise has been practiced for centuries to boost health and well-being and is popular among people in Chinese communities. Qigong aims to promote circulation of "Qi" or vital energy in the meridian system (network of channels for the flow of Qi) and facilitate balance through the regulation of body, mind and breathing (Ng and Tsang, 2009). Empirical trials have supported the positive effect of Qigong on sleep quality and depressive symptoms (Wang et al., 2016). This study adopted a Qigong exercise consisting of ten movements which has been adopted in previous clinical trials and found to be efficacious (Chan et al., 2013; Chan et al., 2019; Li et al., 2015).

The two active intervention groups were compared to a wait list control group. Participants of the control group did not receive any active intervention during the whole period of intervention and follow up. After the data collection of the study was over, participants of the control group were offered the Qigong exercise training as they were attracted to participate in this research with a motivation of receiving a holistic mind–body training. No further data collection was made while the control group participants were receiving Qigong exercise training.

Despite the importance of IL-1β in sleep regulation (Krueger et al., 2011), most studies on the impact of mind–body therapies have only focused on IL-6 (Bower and Irwin, 2016; Cheung et al., 2019). This study was among the first ones to explore the roles of an IBMS intervention and a Qigong exercise in sleep regulation using both proinflammatory cytokines IL-6 and IL-1β as physiological biomarkers. We aimed to investigate and compare the effects of IBMS intervention and Qigong exercise on subjective symptoms such as perceived stress, depressive symptoms, sleep quality, somatic symptoms and holistic well-being, as well as the inflammatory status using proinflammatory cytokines IL-6 and IL-1β in a large-scale randomized waitlist-controlled trial (n = 281). Basing on previous literature, we hypothesized that 1) both IBMS intervention and Qigong exercise can alleviate perceived stress, sleep disturbance, depressive symptoms and somatic symptom, and improve holistic well-being; 2) both the IBMS intervention and Qigong exercises can reduce proinflammatory cytokines IL-6 and IL-1β; 3) the relationship between improvements in self-reported sleep quality and depressive symptoms is bidirectional; and 4) improvements in self-reported sleep quality and depressive symptoms are associated with a reduction in IL-6 and IL-1β.

2. Methods

2.1. Study design

A three-arm randomized controlled trial (IBMS group, Qigong group and wait list control group). Due to the nature of intervention, blinding of the participants was not possible. An online blinded assessment and randomization by computer was conducted in assigning participants to the three groups. Blood was drawn by nurses who were blinded to the groups of participants as all of them were invited to draw blood at same time slots.

2.2. Ethics

The study protocol was approved by the local institutional review board (Ref. no. UW 13-485) and registered in the Hong Kong Clinical Trial Register (Registration no. HKCTR-1929). All participants signed

informed consent documents before joining the study. We followed the CONSORT checklist in designing and reporting the study (Bond et al., 2010).

2.3. Participants

We organized a press conference to promote mind–body intervention for insomnia and depression. The publicity attracted interest from 1002 Chinese adults aged between 20 and 81 years from the local community. They all completed a screening questionnaire, including Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The inclusion criteria were a PSQI score of more than five (indicating sleep disturbance) (Doi et al, 2000) and a CES-D score of 10–34 (indicating mild to moderate depression) (Santor et al., 1995). People with previous diagnosis of bipolar disorder, narcolepsy or sleep apnea were excluded. We also excluded people who had participated in IBMS intervention or Qigong practice in the past six months, or need to take medications for insomnia and depression during the intervention period.

2.4. Sample size

This was calculated using an estimated PSQI change score from T0 to T1 between each group. In order to achieve a treatment effect of −1.2 with sample variance sigma of 2.6, statistical power of 80% at a significance level of 5%, 74 participants were required in each group (Cohen, 1992; Noordzij et al., 2011). Allowing a 20% dropout, at least 93 participants in each arm were estimated as required for this study.

2.5. Interventions

Both of the IBMS and Qigong programs in this study were holistic and integrated interventions aiming at promoting physical, emotional, cognitive and spiritual well-being. Both of these programs were offered twice to about 50 participants per intervention in a big activity hall. These two intervention programs shared the same delivery schedule of three-hour weekly sessions for eight weeks, totally 24 contact hours. These programs offered short lectures and demonstrations in the first hour. Then, participants were divided into small groups of ten to twelve for small group activities, discussion and practice under the guidance of group trainers who were experienced in the IBMS intervention or Qigong practice.

The IBMS group taught culturally-relevant mind–body exercises, simple Qigong movement, self-acupressure, mindfulness practices, self-compassion, meaning making, love, forgiveness and letting-go via experimental activities, group discussion and sharing. Each session contained mind, body and spiritual reflection activities under a different theme such as mind–body connection, mastery of our own health and creating a meaningful life. Homework relating to the three aspects was also distributed each week at the end of the session. The IBMS techniques were delivered by trained therapists and small group sharing was facilitated by professional group counselors. Details of the program can be found in Lee et al. (2009) and Lee et al. (2018).

Besides the eight weekly three-hour training sessions, participants in the Qigong program were instructed to conduct 30-minute of self-practice at least three times per week, followed by self-practice for three months during the study period. The Qigong training (*Wu Xing Ping Heng Gong*, Five Elements Balance Qigong) was delivered weekly by an experienced Daoist Qigong master who had a Traditional Chinese Medicine (TCM) background. The Qigong exercise training program introduced basic TCM theories, such as the concepts of Qi, yin-yang, five elements and meridian system, and followed by teaching of the ten simple Qigong movements. More details of the Qigong exercise can be found in a previous report (Chan et al., 2013).

Participants in the wait list control group were advised to keep their lifestyle and routine as usual and refrain from joining any Qigong or mind–body training classes during the study period. After T2, they were provided with the same eight sessions of Qigong exercise training classes.

2.6. Allocation to intervention

Randomization was by computer-generated random numbers. Group allocation was assigned according to a computer-generated list of random numbers. The randomization procedure was done prior to phone contact with potential participants. We randomly contacted eligible participants by phone until the target sample size was met.

2.7. Measurement

Self-reported measures were captured through online surveys, and, at baseline (T0), immediate post-intervention (T1) and 3-month post-intervention (T2). Five self-report outcome measures and two objective outcome measures were taken. The self-report measures comprised:

2.7.1. Pittsburgh sleep quality index (PSQI)

PSQI is a widely used 19-item self-report scale to assess sleep quality and disturbances over a one-month period (Buysse et al., 1989). It contains seven components, including subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and daytime dysfunction. The total score ranges from 0 to 21, with a higher score indicating poorer sleep. A cutoff value of five has been shown to be most sensitive and specific as screening of sleep disturbance. The Chinese version of PSQI has been shown to have good validity and reliability (Tsai et al., 2005).

2.7.2. Center for epidemiologic studies depression scale (CES-D)

CES-D is a 20-item self-assessment scale designed to measure depressive symptoms during the past week in general population samples (Radloff, 1977). The range of score is 0 to 60, with a higher score indicating a greater severity of depression. A score of 16 or higher has been shown to represent clinical depression (Radloff, 1977). In this study, a CES-D score of 10–34 was used in recruiting participants with mild to moderate depressive symptoms. The Chinese version of CES-D has been shown to be reliable and valid (Chin et al., 2015).

2.7.3. Somatic symptom inventory (SSI)

SSI contains 28-item measuring somatic symptom on a Likert scale from 1 (not at all) to 5 (a great deal). It has two subscales of painful symptoms (s items) and non-painful somatic symptoms (21 items). A higher score indicates more painful and somatic symptoms (Goldstein et al., 2004). SSI has been shown to be a good instrument to measure pain and somatic symptoms among Chinese population (Zhang et al., 2012).

2.7.4. Perceived stress scale (PSS)

PSS is the most widely used psychometric instrument to measure the perception of stress. Ten-item version of PSS (PSS-10) has been shown to possess substantial reliability and validity (Cohen, 1988b). The Chinese version of the PSS-10 has been validated and confirmed to have satisfactory reliability among Hong Kong citizens (Leung et al., 2010; Ng, 2013).

2.7.5. Body-mind-spirit holistic well-being scale (HWS)

The HWS contains seven factors that correspond to the expected characteristics of affliction and equanimity and covered both psychological and somatic manifestations to measure holistic well-being. A higher score indicates more affliction and equanimity. The results showed that the scale had high alpha coefficient ranging between 0.87 and 0.92, and good concurrent validity (Chan et al., 2014).

2.7.6. The objective measures comprised plasma concentrations of IL-6 and IL-1β

Whole blood samples obtained from participants were placed into the EDTA-containing tubes (BD Vacutainer PLUS Blood Collection Tubes, BD, Franklin Lakes, NJ), followed by centrifugation at 1000g at 4 °C for 15 min. The supernatants were transferred into new tubes and stored at −80 °C. Plasma levels of IL-6 and IL-1β were measured using the Quantikine HS Human IL-6 and IL-1β/IL-1F2 immunoassay kits (R&D Systems Inc., Minneapolis, MN).

2.8. Statistical analysis

Categorical data were presented as frequency and percentage of total. Continuous data were presented as means and standard deviation (SD). The above outcome measures were treated as continuous data. Baseline differences were assessed by chi-squared test for categorical data, and one-way analysis of variance models (ANOVA) test for continuous data. The within-group differences were evaluated by pairwise *t*-test. Effect size was calculated by Cohen's *d* statistics; where values of 0.2, 0.5, and 0.8 suggest small, medium and large effect sizes respectively (Cohen, 1988a). Repeated measures univariate ANOVA (including over-time × group interactions) were constructed to test for between-group differences. Simple effect comparisons with Sidak adjustment were conducted if the interactions were significant. Two-tailed Pearson's correlation tests were performed to examine the correlation between each psychological and physical factors. All the above data analyses were conducted with Statistical Package for the Social Sciences (SPSS version 23.0, SPSS Inc., Chicago, IL).

Based on the correlation results, path analysis was employed to present the mediation relationships among outcomes. Bootstrapping method was used for mediation testing in path analysis. STDYX standardization outputs were used. The fit of the mediation model was evaluated by the ratio of chi-square/degrees of freedom (χ^2/df), comparative fit index (CFI), Tucker–Lewis index (TLI) and root mean square error of approximation (RMSEA). If the value of χ^2/df was <3, the CFI and TLI values were >0.95 and the RMSEA was <0.08, the model was considered to be robust (Fan and Sivo, 2005). Path analysis was performed using the Mplus 7.0 statistical software.

The intention-to-treat approach was applied, using the last observation carried forward method to handle missing data. Extreme outliers, which deviated from the average value by >3 times the standard deviation, were treated as missing values. Referring to the normal range of IL-6 provided by Todd et al. (2013), only IL-6 values > 7 were viewed as outliers, which may be due to inflammatory diseases.

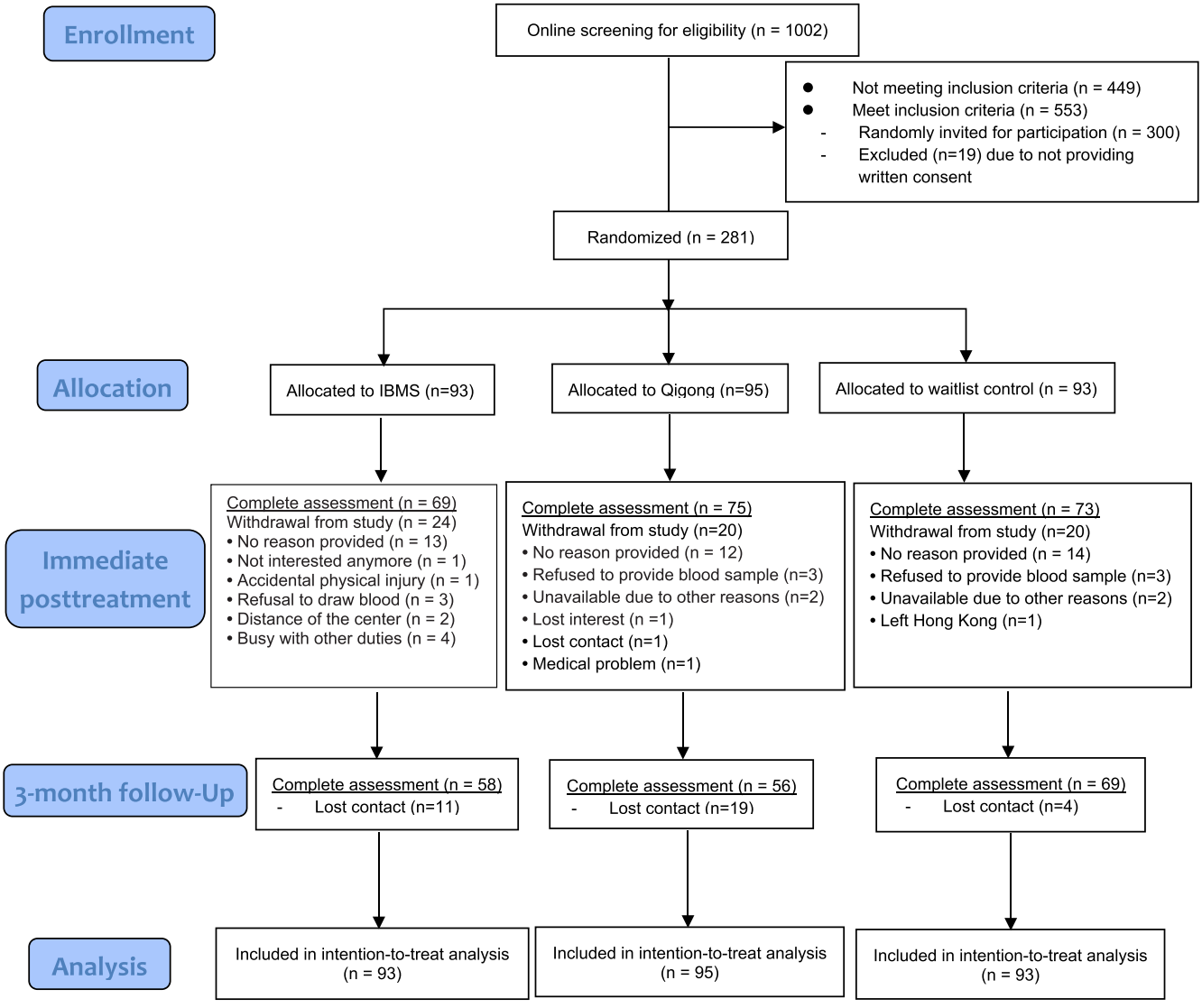

Fig. 1. CONSORT diagram of the participants flow.

3. Results

3.1. Participants characteristics

1002 adults were approached while 281 eligible participants were randomized. The whole process of participants flow was shown in Fig. 1. Sixty-nine in IBMS group, 75 in Qigong group and 73 in waitlist control group completed the post-intervention measurements. At 3-month follow-up, 11 in IBMS group, 19 in Qigong group and 4 in waitlist control group lost contact.

A total of 281 participants were analyzed (IBMS group n = 93; Qigong group n = 95; waitlist control group n = 93). Table 1 presented the baseline demographic and clinical characteristics. Age of the total sample was normally distributed ($z = 0.067$, $p > 0.05$), with a mean age of 55.49 (SD: 10.13; min: 21; max: 81). Participants were predominantly female (n = 215, 76.51%). 68.3% of participants had secondary level education or below, and 74.02% were married or cohabited. The most frequently reported duration of sleep disturbance was more than five years (n = 135, 48.04%), followed by less than one year (n = 54, 19.22%), one to three years (n = 51, 18.15%) and three to five years (n = 41, 14.59%). There were 91 participants (32.38%) whose survey scores suggesting that they had clinical depression or anxiety. There was no significant baseline difference on demographic characteristics and clinical features among the three intervention groups (Table 1).

Table 2 demonstrated that the mean PSQI and CES-D scores were similar across the IBMS, Qigong and control groups at baseline, and indicates that participants had moderate sleep disturbance and mild to moderate depression. There was no significant difference between groups in baseline sleep disturbance ($p = 0.16$), depression ($p = 0.15$), IL-6 ($p = 0.57$) and IL-1β ($p = 0.71$).

Table 3 indicated that baseline values of sleep disturbance, depression, somatic symptoms, perceived stress and the two aspects of holistic well-being were mostly interrelated. IL-6 was minimally linked to somatic symptoms ($r = -0.01$, $p < 0.05$).

Table 1
Baseline demographic and clinical characteristics.

Variables	IBMS (n = 93) n (%)	Qigong (n = 95) n (%)	Waitlist (n = 93) n (%)	Test χ^2/F	p
Age: Mean (SD)	55.91 (9.37)	55.97 (10.76)	54.59 (10.23)	0.55	0.58
Gender				1.55	0.46
Female	67 (72.04%)	75 (78.95%)	73 (78.49%)		
Education				1.25	0.53
Secondary or below	62 (66.67%)	69 (72.63%)	61 (65.59%)		
Tertiary or above	31 (33.33%)	26 (27.37%)	32 (34.41%)		
Marital status				2.91	0.23
Single/divorced/ separated	22 (23.66%)	21 (22.11%)	30 (32.26%)		
Married/cohabiting	71 (76.34%)	74 (77.89%)	63 (67.74%)		
Household monthly income (HK$*)				10.31	0.24
<20,000	39 (41.94%)	34 (35.79%)	32 (34.41%)		
20,000–39,999	8 (8.60%)	5 (5.26%)	17 (18.28%)		
≥40,000	7 (7.53%)	8 (8.42%)	7 (7.53%)		
No income	32 (34.41%)	40 (42.11%)	31 (33.33%)		
Refused to answer	7 (7.53%)	8 (8.42%)	6 (6.45%)		
Duration of sleep disturbance				2.64	0.85
1–12 month(s)	16 (17.20%)	17 (17.89%)	21 (22.58%)		
1–3 years	20 (21.51%)	16 (16.84%)	15 (16.13%)		
3–5 years	11 (11.83%)	16 (16.84%)	14 (15.05%)		
>5 years	46 (49.46%)	46 (48.42%)	43 (46.24%)		
Clinical diagnosis of anxiety/depression	28 (30.11%)	31 (32.63%)	33 (35.48%)	0.61	0.74

*Note.** 1 USD ≅ 7.8 HK$.

3.2. Intervention efficacy

Considering within-group effect on psychological measures, as shown in Table 2, the mean value of sleep disturbance, depression, painful somatic symptom, painless somatic symptom and perceived stress all reduced significantly for participants in both the IBMS and Qigong groups, at both T1 and T2 (all $p < 0.01$). Considering the two aspects (affliction and equanimity) of well-being, there were significant improvements at T1 and T2 for participants in both the IBMS and Qigong groups (all $p < 0.01$). The effect sizes of IBMS on participants' psychological health ranged from 0.35 to 0.86 at T1, and 0.30 to 0.86 at T2, 71.43% and 57.14% of which exceeded 0.5 at T1 and T2, respectively, showing a medium to large effect size according to Cohen's *d* estimation. The effect sizes of Qigong on participants' psychological health ranged from 0.39 to 0.68 at T1, and 0.30 to 0.68 at T2, 57.14% and 71.43% of which exceeded 0.5 at T1 and T2, respectively, showing a medium to large effect size. The effect sizes of IBMS intervention on sleep disturbance, depression and two aspects of holistic well-being appeared slightly larger than those of Qigong intervention, both at T1 and T2. The effect sizes of Qigong intervention on painful somatic symptom, painless somatic symptom and perceived stress appeared slightly larger than those of IBMS intervention, both at T1 and T2.

The within-group effects of IBMS and Qigong intervention on IL-6 and IL-1β were also significant both at T1 and T2 (all $p < 0.01$). The effect sizes of IBMS and Qigong on IL-6 ranged from 0.52 to 0.61, indicating a medium effect size. The effect sizes of IBMS and Qigong on IL-1β were 0.13 to 0.15, showing a small effect size. The effect sizes of IBMS and Qigong interventions on proinflammatory cytokines were approximatively equivalent, with IBMS' effect size slighter higher than Qigong at post-intervention. Fig. 2 presented the change trend of IL-6, IL-1β, sleep disturbance, and depression at the three time points of T0, T1, and T2.

The between-group effect analysis showed a significant time × group interaction in sleep disturbance ($F = 4.91$, $p = 0.001$), depression ($F = 9.97$, $p < 0.001$), painless somatic symptoms ($F = 7.44$, $p < 0.001$), affliction ($F = 4.65$, $p = 0.001$), equanimity ($F = 4.72$, $p = 0.001$), and perceived stress ($F = 5.41$, $p < 0.001$), meaning that sleep disturbance, depression, painless somatic symptom and perceived stress decreased significantly in the IBMS and Qigong groups as opposed to in the control group. Moreover, holistic well-being increased significantly over time in the IBMS and Qigong groups than that in the control group. The time × group interaction was also significant in IL-6 ($F = 5.26$, $p < 0.001$) and IL-1β ($F = 8.49$, $p < 0.001$), meaning that IL-6 and IL-1β decreased significantly over time in the IBMS and Qigong groups with reference to the control group.

Table 3 reported data that indicated that the changes of all psychological factors were interrelated both at T1 (all $p < 0.01$) and T2 (all $p < 0.05$). The change of IL-6 at T1 was correlated with sleep disturbance ($r = 0.15$, $p < 0.01$), depression ($r = 0.17$, $p < 0.01$), affliction ($r = 0.17$, $p < 0.01$) and perceived stress ($r = 0.13$, $p < 0.05$). The change of IL-1β at T1 was correlated with sleep disturbance ($r = 0.14$, $p < 0.05$), depression ($r = 0.15$, $p < 0.05$), painless somatic symptom ($r = 0.19$, $p < 0.01$) and affliction ($r = 0.16$, $p < 0.01$). The change of IL-6 at T2 was only correlated with sleep disturbance ($r = 0.13$, $p < 0.05$). The change of IL-1β at T2 was correlated with sleep disturbance ($r = 0.15$, $p < 0.05$) and affliction ($r = 0.20$, $p < 0.01$).

Table 2
Outcome measures at study time points.

	Within-group effects					Between-group effects				Time × Group interaction
	T0	T1 [a]	Effect Size Cohen's *d*	T2 [a]	Effect Size Cohen's *d*	T1-T0 [b]		T2-T0 [b]		
	Mean (SD)	Mean (SD)		Mean (SD)		Mean (SE)	*p*-value	Mean (SE)	*p*-value	*p*-value
PSQI										
IBMS (n = 93)	13.55 (2.78)	11.11 (3.78) ***	−0.71	10.60 (3.83) ***	−0.86	−2.44 (0.29)	**<0.001** [b1]	−2.95 (0.33)	**<0.001** [b1]	**0.001**
Qigong (n = 95)	14.09 (3.02)	12.37 (3.83) ***	−0.49	11.84 (4.18) ***	−0.60	−1.73 (0.28)	**0.023** [b2]	−2.25 (0.33)	**0.028** [b2]	
Waitlist (n = 93)	13.30 (2.87)	12.60 (3.12)*	−0.23	12.25 (3.11) **	−0.35	−0.70 (0.29)	0.260 [b3]	−1.05 (0.33)	0.401 [b3]	
CES-D										
IBMS (n = 93)	21.82 (6.92)	15.29 (8.12) ***	−0.86	17.83 (6.18) ***	−0.61	−6.53 (0.71)	**<0.001** [b1]	−3.99 (0.72)	**<0.001** [b1]	**<0.001**
Qigong (n = 95)	22.53 (6.58)	16.77 (9.40) ***	−0.68	18.85 (7.50) ***	−0.52	−5.76 (0.70)	**<0.001** [b2]	−3.67 (0.72)	**<0.001** [b2]	
Waitlist (n = 93)	20.68 (6.16)	19.23 (7.75)	−0.20	21.40 (6.39)	0.12	−1.45 (0.71)	0.852 [b3]	0.72 (0.72)	0.757 [b3]	
SSI-pain										
IBMS (n = 92)	15.73 (5.46)	13.87 (5.23) ***	−0.35	14.11 (5.47) **	−0.30	−1.86 (0.40)	0.400 [b1]	−1.62 (0.47)	0.462 [b1]	0.097
Qigong (n = 95)	18.05 (6.61)	15.35 (5.38) ***	−0.44	15.71 (5.35) ***	−0.38	−2.71 (0.40)	**0.019** [b2]	−2.35 (0.46)	0.066 [b2]	
Waitlist (n = 93)	16.98 (6.48)	15.86 (5.81)*	−0.18	15.85 (5.96)	−0.18	−1.12 (0.40)	0.395 [b3]	−1.13 (0.47)	0.273 [b3]	
SSI-painless										
IBMS (n = 93)	44.30 (12.73)	38.05 (10.96) ***	−0.52	38.38 (11.52) ***	−0.49	−6.25 (1.05)	**0.001** [b1]	−5.93 (1.09)	**0.005** [b1]	**<0.001**
Qigong (n = 95)	49.40 (14.76)	40.25 (12.06) ***	−0.67	40.78 (12.44) ***	−0.62	−9.15 (1.04)	**<0.001** [b2]	−8.62 (1.08)	**<0.001** [b2]	
Waitlist (n = 93)	44.02 (14.58)	42.91 (14.08)	−0.08	42.56 (13.58)	−0.10	−1.11 (1.05)	0.188 [b3]	−1.46 (1.09)	0.271 [b3]	
HWS-affliction										
IBMS (n = 92)	68.04 (19.10)	56.78 (19.25) ***	−0.59	54.58 (18.66) ***	−0.71	−11.26 (1.58)	**0.001** [b1]	−13.47 (1.76)	**0.004** [b1]	**0.001**
Qigong (n = 95)	70.04 (19.58)	58.12 (22.33) ***	−0.56	59.07 (21.84) ***	−0.53	−11.93 (1.55)	**<0.001** [b2]	−10.97 (1.73)	0.055 [b2]	
Waitlist (n = 93)	67.87 (20.78)	63.94 (20.14) *	−0.19	61.63 (20.64) **	−0.30	−3.94 (1.57)	0.764 [b3]	−6.24 (1.75)	0.312 [b3]	
HWS-equanimity										
IBMS (n = 92)	87.72 (18.27)	96.04 (20.98) ***	0.42	97.50 (21.14) ***	0.49	8.33 (1.66)	**0.001** [b1]	9.78 (1.81)	**<.001** [b1]	**0.001**
Qigong (n = 95)	86.71 (17.36)	94.35 (21.16) ***	0.39	92.87 (22.19) **	0.30	7.64 (1.64)	**0.002** [b2]	6.17 (1.78)	**0.017** [b2]	
Waitlist (n = 93)	87.87 (19.66)	88.13 (19.18)	0.01	87.99 (19.70)	0.01	0.26 (1.65)	0.769 [b3]	0.12 (1.80)	0.156 [b3]	
PSS										
IBMS (n = 93)	20.37 (4.03)	18.16 (4.73) ***	−0.50	17.52 (5.09) ***	−0.61	−2.20 (0.37)	**0.003** [b1]	−2.85 (0.43)	**0.022** [b1]	**<0.001**
Qigong (n = 95)	21.12 (3.57)	18.13 (5.32) ***	−0.62	18.08 (4.89) ***	−0.68	−2.99 (0.36)	**<0.001** [b2]	−3.03 (0.43)	**0.001** [b2]	
Waitlist (n = 93)	21.05 (4.07)	20.38 (4.44)	−0.16	19.95 (4.60)*	−0.25	−0.68 (0.37)	0.429 [b3]	−1.11 (0.43)	0.989 [b3]	
IL-6 (pg/mL)										
IBMS (n = 93)	1.24 (0.72)	1.05 (0.61)**	−0.28	1.06 (0.52)**	−0.28	−0.19 (0.06)	**0.013** [b1]	−0.18 (0.06)	0.447 [b1]	**<0.001**
Qigong (n = 95)	1.29 (0.66)	1.04 (0.56) ***	−0.40	1.11 (0.59)**	−0.29	−0.25 (0.06)	**0.015** [b2]	−0.18 (0.06)	0.628 [b2]	
Waitlist (n = 93)	1.19 (0.66)	1.30 (0.86)	0.14	1.16 (0.63)	−0.03	0.11 (0.06)	0.985 [b3]	−0.02 (0.06)	0.213 [b3]	
IL-1β (pg/mL)										
IBMS (n = 93)	0.13 (0.23)	0.07 (0.15) ***	−0.28	0.05 (0.13) ***	−0.43	−0.06 (0.01)	**<0.001** [b1]	−0.08 (0.02)	**0.020** [b1]	**<0.001**
Qigong (n = 94)	0.11 (0.18)	0.05 (0.14) ***	−0.40	0.05 (0.13) ***	−0.42	−0.07 (0.01)	**<0.001** [b2]	−0.07 (0.02)	**0.013** [b2]	
Waitlist (n = 93)	0.10 (0.27)	0.12 (0.27)	0.06	0.08 (0.27)**	−0.08	0.02(0.01)	0.998 [b3]	−0.02 (0.02)	0.898 [b3]	

Note. PSQI, Pittsburgh sleep quality index; CES-D, Center for Epidemiologic Studies Depression Scale; SSI, Somatic Symptom Inventory; HWS, body-mind-spirit Holistic Well-being Scale; PSS, perceived stress scale; IL-6, interleukin-6; IL-1β, interleukin-1β; T0, baseline; T1, immediate post-intervention; T2, 3-month post-intervention. [a] Within-group difference using paired *t*-test; [b] Between-group difference in change scores using ANOVA; [b1] IBMS vs Waitlist; [b2] Qigong vs Waitlist; [b3] IBMS vs Qigong * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 3
Pearson correlation between outcome measures at baseline (T0) and between-group change scores (Δ) from baseline to immediate post-intervention (T1-T0) and from baseline to 3-month post-intervention (T2-T0).

T0	1	2	3	4	5	6	7	8	9
1. PSQI	1								
2. CES-D	0.15**	1							
3. SSI-pain	0.13*	0.18**	1						
4. SSI-painless	0.22***	0.29***	0.80***	1					
5. HWS-Affliction	0.11	0.56***	0.34***	0.45***	1				
6. HWS-Equanimity	−0.14*	−0.37***	−0.19**	−0.22***	−0.40***	1			
7. PSS	0.04	0.50***	0.16**	0.20**	0.48***	−0.32***	1		
8. IL-6	0.05	0.02	−0.01*	−0.08	−0.12	0.01	−0.07	1	
9. IL-1β	−0.11	0.01	0.03	0.01	0.03	0.09	0.03	0.01	1
T1-T0									
1. PSQI	1								
2. CES-D	0.49***	1							
3. SSI-pain	0.26***	0.29***	1						
4. SSI-painless	0.26***	0.43***	0.74***	1					
5. HWS-Affliction	0.25***	0.49***	0.52***	0.54***	1				
6. HWS-Equanimity	−0.22***	−0.46***	−0.28***	−0.41***	−0.42***	1			
7. PSS	0.30***	0.49***	0.37***	0.42**	0.50***	−0.42***	1		
8. IL-6	0.15**	0.17**	0.06	0.08	0.17**	−0.05	0.13*	1	
9. IL-1β	0.14*	0.15*	0.10	0.19**	0.16**	−0.05	0.07	0.13*	1
T2-T0									
1. PSQI	1								
2. CES-D	0.41***	1							
3. SSI-pain	0.14*	0.16**	1						
4. SSI-painless	0.26***	0.29***	0.71***	1					
5. HWS-Affliction	0.23***	0.45***	0.31***	0.48***	1				
6. HWS-Equanimity	−0.19**	−0.24***	−0.22***	−0.29***	−0.33***	1			
7. PSS	0.30***	0.44***	0.21***	0.31***	0.44***	−0.32***	1		
8. IL-6	0.13*	0.06	−0.02	0.02	0.02	−0.05	0.04	1	
9. IL-1β	0.15*	0.11	0.05	0.09	0.20**	0.02	−0.05	0.06	1

Note. PSQI, Pittsburgh sleep quality index; CES-D, Center for Epidemiologic Studies Depression Scale; SSI, Somatic Symptom Inventory; HWS, body-mind-spirit Holistic Well-being Scale; PSS, perceived stress scale; IL-6, interleukin-6; IL-1β, interleukin-1β; *p < 0.05, ** p < 0.01, *** p < 0.001

3.3. Path analysis

Basing on the correlation tests and findings from previous studies (Maglione et al., 2014; Breitbart et al., 2014; Irwin et al., 2016; Dahl et al., 2014; Dowlati et al., 2010), two path models hypothesizing the relationship between psychological changes and physical changes were derived and tested (Fig. 3).

In model 1–1 and 1–2, the change of perceived stress at T1 was associated with change of depression at T1 (std. $\beta = 0.49$, $p < 0.001$); the change of depression at T1 was associated with change of sleep disturbance at T1 (std. $\beta = 0.49$, $p < 0.001$) and T2 (std. $\beta = 0.42$, $p < 0.001$); the change of sleep disturbance at T1 was associated with change of IL-6 (std. $\beta = 0.15$, $p < 0.01$) and IL-1β (std. $\beta = 0.14$, $p < 0.05$) at T1; the change of sleep disturbance at T2 was associated with change of IL-1β (std. $\beta = 0.15$, $p < 0.01$) at T2. Besides, the influence of perceived stress change at T1 on sleep disturbance change at T1 was fully mediated by change of depression at T1 (std. $\beta = 0.24$, $p < 0.001$); the influence of perceived stress change at T1 on sleep disturbance change at T2 was fully mediated by change of depression at T1 (std. $\beta = 0.20$, $p < 0.001$).

In model 2–1 and 2–2, the change of perceived stress at T1 was associated with change of sleep disturbance at T1 (std. $\beta = 0.30$, $p < 0.001$), and directly associated with change of depression at T1 (std. $\beta = 0.37$, $p < 0.001$) and T2 (std. $\beta = 0.20$, $p < 0.01$); the change of sleep disturbance at T1 was associated with change of depression at T1 (std. $\beta = 0.38$, $p < 0.001$) and T2 (std. $\beta = 0.30$, $p < 0.001$); the change of depression at T1 was associated with change of IL-6 (std. $\beta = 0.17$, $p < 0.01$) and IL-1β (std. $\beta = 0.15$, $p < 0.05$) at T1; however, the change of depression at T2 was not significantly correlated with IL-6 and IL-1β changes at T2. Besides, the influence of perceived stress change at T1 on depression change at T1 was partially mediated by change of sleep disturbance at T1 (std. $\beta = 0.11$, $p < 0.001$); the influence of perceived stress change at T1 on depression change at T2 was partially mediated by change of depression at T1 (std. $\beta = 0.09$, $p < 0.001$).

Model 1–1, 1–2 and 2–1 had good model fit index as shown in Table 4, and the model fit index of model 2–2 was also acceptable, meaning that both models were robust and persuasive. The structure of the two models showed that perceived stress was a major predictor of depression and sleep disturbance ($p < 0.001$); there was a bidirectional relationship between depression and sleep disturbance ($p < 0.001$); both depression and sleep disturbance would have an influence on proinflammatory cytokines of IL-6 and IL-1β ($p < 0.05$), and the influence of sleep disturbance on IL-1β was stable over time (std. $\beta = 0.14$, $p < 0.05$ at T1 and std. $\beta = 0.15$, $p < 0.01$ at T2).

4. Discussion

To the best of our knowledge, this was the first longitudinal study to compare the effects of two mind–body therapies on psychological health measures and biochemical inflammatory status (IL-6 and IL-1β). The efficacy of both interventions supported hypothesis 1, and concurred with previous studies. In this study, both the IBMS and Qigong interventions significantly alleviated perceived stress, somatic symptom, sleep disturbance and depressive symptoms, and enhanced holistic well-being over time, which was in line with the growing evidence on the benefits of Qigong and other mind–body therapies (Chow et al., 2012; Hassed, 2013; Wang et al., 2013; Wang et al., 2016). In addition, the data supported hypothesis 2 that the IBMS and Qigong interventions significantly reduced the levels of IL-1β and IL-6. This result was consistent with previous studies on the influence of Qigong and other mind–body therapies, including Taichi and Yoga, on IL-6 (Bower and Irwin, 2016; Qi et al., 2021), and studies on the influence of other mind–body interventions on IL-1β (Ng et al., 2020; Rajbhoj et al., 2015).

Path analysis results were consistent with previous studies. This study supported the proposal that perceived stress is a predictor for sleep disturbance and depression, which was in line with previous empirical studies (Liu et al., 2017; Wallace et al., 2017). Research hypothesis 3 of a

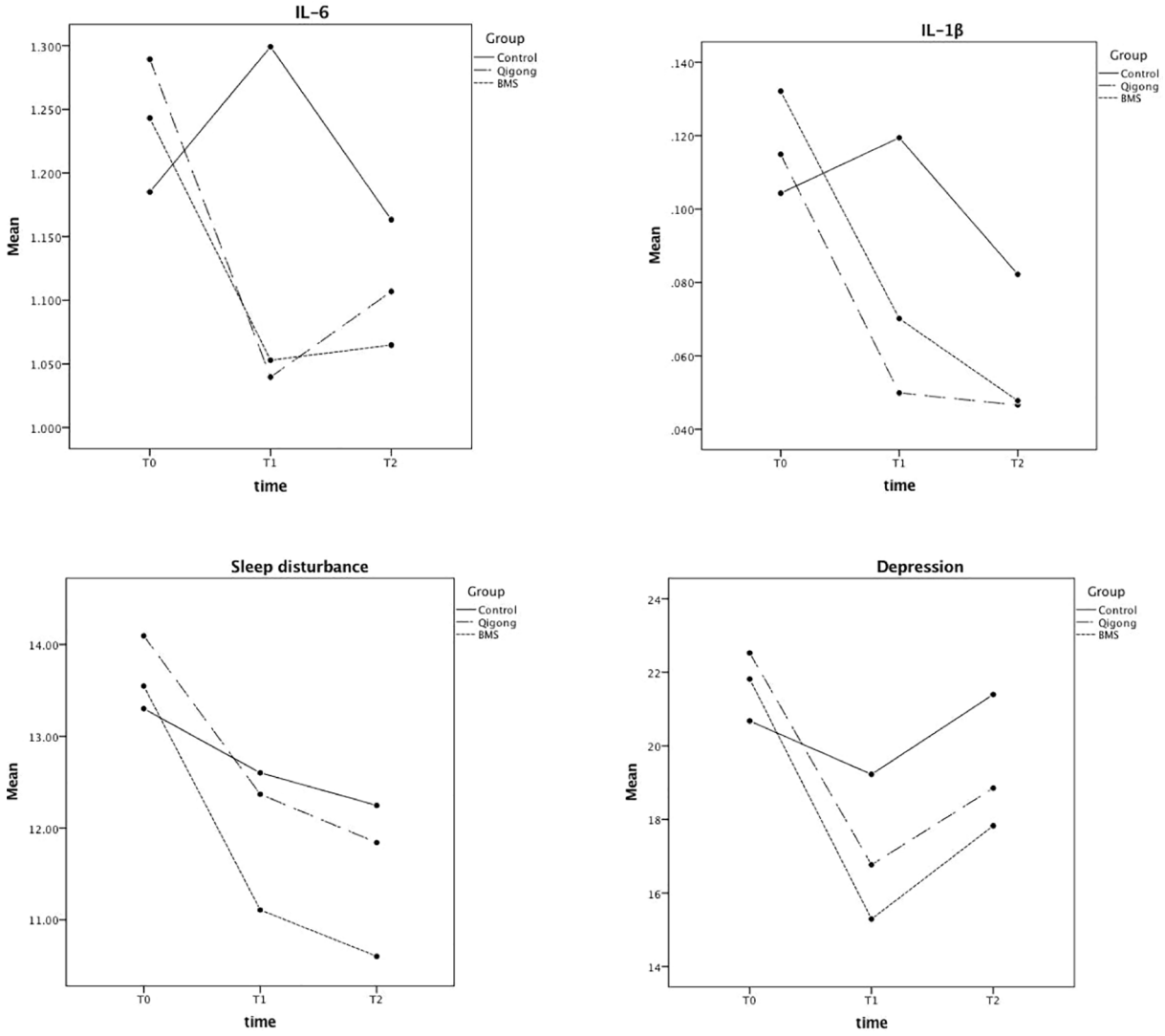

Fig. 2. Trend of IL-6, IL-1β, sleep disturbance, and depression at the three time points.

bidirectional relationship between sleep disturbance and depression was also supported, and concurred with recent findings (Fang et al., 2019). Our study was one of the first to explore the relationship between psychological health and proinflammatory cytokines using longitudinal estimates. Hypothesis 4 was supported, as both depression and sleep disturbance influenced IL-6 and IL-1β, and the influence of sleep disturbance on IL-1β was stable over time. Our longitudinal study concurred with findings from previous cross-sectional studies (Jin et al., 2020; Prather et al., 2009).

Our study showed that the IBMS intervention and Qigong exercise were both effective mind–body therapies in the psychological and physical care for persons with depression and sleep disturbance. This supported the interconnectivity between body and mind, and indicated the efficacy of the non-pharmaceutical IBMS model and Qigong exercise in reducing mental and physical distresses (Ng and Tsang, 2009; Yin et al., 2020). The IBMS intervention fosters a happy, positive and resilient attitude towards life; Qigong exercise cultivates internal harmony and advocates for a calm and non-attached attitude to maintain holistic mind–body balance. As depression and sleep quality improved over time, participants' inflammation levels decreased. This supported the pathway from psychology to biology (Bower and Irwin, 2016). Both mind–body therapies offered holistic empowerment interventions (Lee et al., 2018). After the program, intervention group participants were empowered to practice by themselves, either the IBMS techniques of self-care exercises of emotion self-management, self-acceptance, self-care, healthy lifestyle, meaning-making, acupressure, abdominal breathing, or Qigong exercises. The effective improvements found in psychological indicators and inflammation status would thus potentially be maintained in the long term because participants acquired these practices into their daily life. Although both effective, the two mind–-body interventions were slightly different. First, Qigong exercise focuses on body movements while IBMS promotes deeper sharing on spiritual growth. Besides, Qigong is easier to teach in a big group, thus, it is less labour-intensive. However, IBMS requires trainers with solid psychological counselling training.

Reduction in perceived stress helps improve depression and sleep disturbance, which are positively related to inflammation (Miller and Raison, 2016). Exposure to continuous mental stress brings depression, which leads to constant sympathetic overdrive and weakened vagal tone, and the weakened vagal tone activates proinflammatory state (Halaris, 2013). Stressful experiences negatively disrupt sleep, which then impairs brain function, increases sympathetic tone, alters the inflammatory gene expression, and upregulates in transcriptional pathways responsible for the inflammatory response, leading to the raise of proinflammatory cytokines levels (Dolsen et al., 2019). These may the underlying psycho-physiological mechanisms explaining reduction in IL-6 and IL-1β levels observed in the current intervention study.

This study is of practical and theoretical significance. Firstly, this

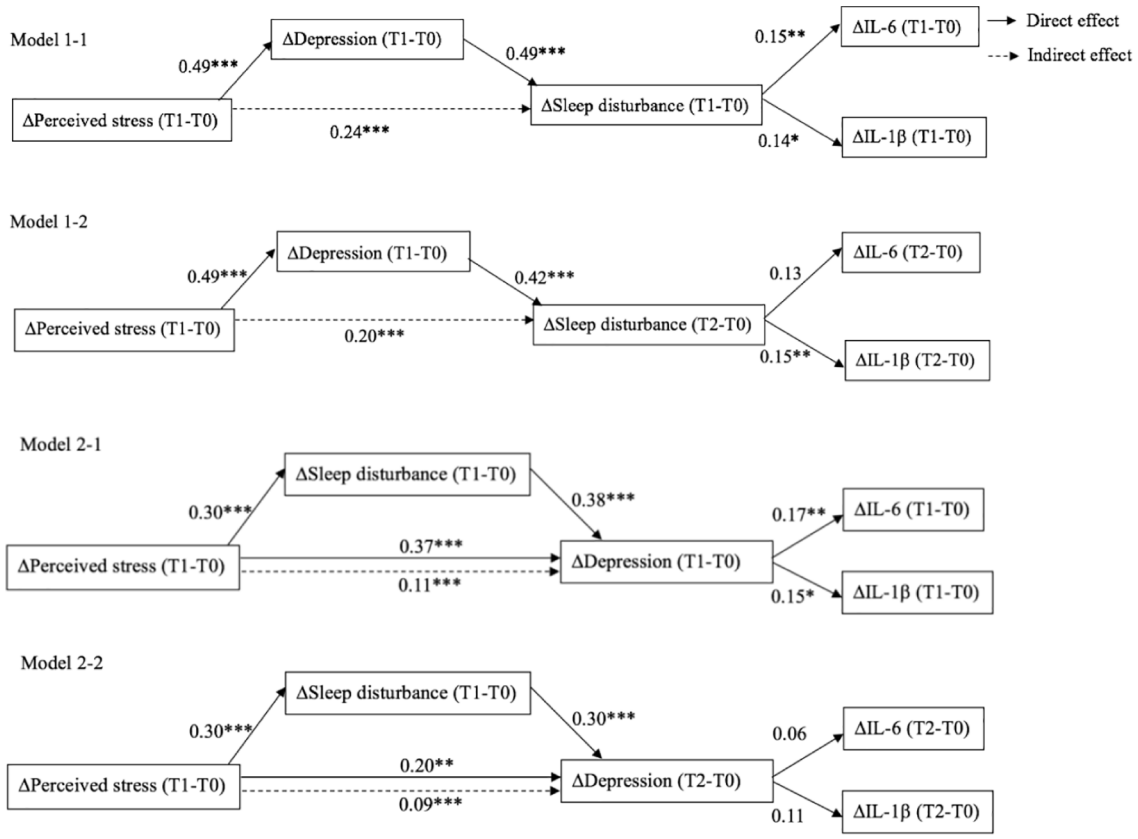

Fig. 3. Path analysis results.

Table 4
Model fit index.

	χ^2 (df)	*p*	RMSEA	CFI	TLI	SRMR
Model 1–1	7.862(5)	0.164	0.045	0.983	0.965	0.038
Model 1–2	3.469(5)	0.628	0.000	1.000	1.023	0.020
Model 2–1	3.918(4)	0.417	0.000	1.000	1.001	0.024
Model 2–2	8.286(4)	0.082	0.062	0.946	0.866	0.034

Note: df: degree of freedom; RMSEA: Root Mean Square Error of Approximation; CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; SRMR: Standardized Root Mean Square Residual.

study provides two efficacious mind–body interventions for persons with depression and sleep disturbance, which attempts to fill the research and practice gaps in non-pharmaceutical holistic treatment. Both IBMS method and Qigong exercise are gentle, long-term effective self-healing empowerment interventions without significant undesirable effects. Secondly, this research provides evidence for the bidirectional relationship between depression and sleep disturbance using a longitudinal study method, strongly supporting results of previous cross-sectional studies (Fang et al., 2019). Last but not the least, a psycho-neuro-physical link among stress, depression, sleep disturbance and proinflammatory cytokines was presented which provides a platform for future research.

The study had limitations. Firstly, participants were included basing on a community sample with self-reported sleep disturbance and depression symptoms. The favorable findings of the current study may not be generalizable to clinical populations. Future studies using clinical samples and standardized pre-intervention interviews should be pursued. Secondly, this study only investigated the relationship between proinflammatory cytokines and self-reported sleep disturbance and depression. Further studies using polysomnography for more objective assessment of sleep are warranted. Besides, other cytokines like C-reactive protein, tumor necrosis factor-α, and so on, may also be tested. Thirdly, the effects of IBMS method and Qigong exercise on sleep and proinflammatory markers may be a consequence of non-specific factors, such as mutual support, social interaction and expectancy effects. Future studies should consider adopting an active control, such as psycho-education, so that three active interventions can be compared. Last but not the least, the Hawthorne effect and the Pygmalion effect are difficult to control in our psychosocial interventions.

5. Conclusion

This paper presented results from a large-scale three-arm randomized controlled trial which suggests that mind–body intervention is significantly better than being on a waiting list, in improving depression, sleep quality and biochemical markers of inflammation. This provides evidence to support the efficacy of either group-based IBMS intervention method and Qigong exercise on psychological health and inflammation status in adults with mild-moderate depression symptoms and sleep disturbance. The feasibility and significance of these non-pharmaceutical mind–body therapies in holistic care and treatment is proposed.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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