



The Feasibility and Efficacy of a Brief Integrative Treatment for Adults With Depression and/or Anxiety: A Randomized Controlled Trial

Adrian L. Lopresti, PhD^{1,2} , Stephen J. Smith, MA^{1,2}, Alexandra P. Metse, PhD¹, Tiffany Foster, MA¹, and Peter D. Drummond, PhD¹

Abstract

The aim of this study was to investigate the efficacy and suitability of a brief integrative intervention, Personalized Integrative Therapy (PI Therapy), for the treatment of adult depression and/or anxiety. In this 6-week, 3-arm, parallel-group, randomized trial, PI Therapy delivered alone or with nutritional supplements (PI Therapy + Supps) was compared to cognitive behavior therapy (CBT) in 48 adults with depression and/or anxiety. All treatments were delivered as a 1-day workshop plus 6 weeks of reminder phone text messages to reinforce topics and skills covered in the workshop. Affective symptoms decreased significantly and to the same extent in all 3 conditions. At the end of treatment, 33% to 58% of participants reported levels of depressive symptoms in the normal range, and 50% to 58% reported nonclinical levels of anxiety. Compared to CBT and PI Therapy, PI Therapy + Supps was associated with significantly greater improvements in sleep quality. These findings suggest that a brief integrative intervention with or without supplements was comparable to CBT in reducing affective symptoms in adults with depression and/or anxiety. However, sleep quality improved only in the PI Therapy + Supps condition. These findings will require replication with a larger cohort.

Keywords

integrative treatment, depression, anxiety, nutrition, holistic, exercise, clinical trial

Received February 27, 2020. Received revised April 21, 2020. Accepted for publication June 7, 2020.

The most common treatments for adult depression and anxiety comprise psychological therapy and pharmaceutical antidepressants. Psychological therapies target change in unhelpful thoughts and coping skills, with a review of meta-analyses indicating cognitive behavioral therapy (CBT) is the “gold standard” psychological treatment for affective disorders.^{1,2} Pharmaceutical antidepressants are believed to target neurotransmitters such as serotonin and noradrenaline, with the most popular antidepressant classes comprising selective-serotonin reuptake inhibitors and selective-noradrenaline reuptake inhibitors.³ However, while these treatments are effective, there remains a significant portion of individuals who experience either no or only partial response. In a meta-analysis of 34 studies and 2500 participants, a response rate (defined as $\geq 50\%$ reduction in depression scores from baseline) of 49% (95% confidence interval 42% to 56%) was reported following an average of 10 sessions of CBT.⁴ An average remission rate of 45% (95% confidence interval 39% to 51%) from CBT was

also reported in this meta-analysis. In a comparison of CBT with second-generation antidepressants, outcome rates were found to be similar with response rates of 44% and 45%, and remission rates of 41% and 48%, respectively.⁵

In addition to their moderate rates of efficacy, CBT and antidepressant medications are associated with several treatment barriers and/or adverse effects. CBT requires sound intellectual competence, insight into personal affective and cognitive processes, a willingness to disclose personal information, transportation to attend sessions, and time and

¹ Murdoch University, Perth, Western Australia, Australia

² Clinical Research Australia, Perth, Western Australia, Australia

Corresponding Author:

Adrian L. Lopresti, College of Science, Health, Engineering and Education, Murdoch University, Perth, Western Australia 6150, Australia.
 Email: a.lopresti@murdoch.edu.au



willingness to attend regular sessions ranging from 10 to 20 sessions.^{6,7} Pharmaceutical antidepressants are associated with several adverse effects including nausea, weight gain, fatigue, headache, sedation, and sexual dysfunction.⁸ Adverse effects are cited as common reasons for treatment refusal and early discontinuation.^{9,10} Developing new interventions and/or delivery formats that overcome some of these barriers to successful treatment are, therefore, important to increase treatment efficacy and accessibility.

Depression and anxiety are influenced by many factors including psychological, biological, lifestyle, and dietary factors.¹¹ For example, associations between diet,¹² physical activity,¹³ sleep,¹⁴ and social relationships¹⁵ have been confirmed in depression and anxiety. Targeting these factors for intervention may, therefore, boost treatment efficacy. Indeed, in a recently published psychiatry commission, the need for developing holistic interventions for people with a mental disorder, including treatments that optimize physical and mental health was highlighted.¹⁶ As an adjunct to pharmacotherapy, exercise,¹⁷ dietary,¹⁸ and nutraceutical/herbal interventions such as saffron, folate, vitamin D, and omega-3 polyunsaturated fatty acids¹⁹⁻²¹ are associated with greater treatment efficacy. However, there has been limited investigation into the efficacy of an integrative intervention that targets a combination of individually chosen psychological, dietary, lifestyle, medical, social, and spiritual factors. Based on the available limited evidence, positive results from a 12-week open-label study consisting of several lifestyle interventions (eg, diet, exercise, and mindfulness)²² and an 8-week mindfulness-based program with elements of nutrition and exercise²³ for the treatment of depression and anxiety were identified. However, in a 12-week randomized controlled trial there were no differences in mental health outcomes in adults with depression and/or anxiety treated with a lifestyle intervention comprising dietary, exercise, and other lifestyle changes compared to an attention control with scheduled telephone contact.²⁴ Moreover, a 12-week lifestyle program provided to patients with a mental illness (major depressive disorder or bipolar disorder) and comorbid metabolic syndrome was associated with no significant changes in mental health measures, although there was a significant reduction in body mass index and abdominal circumference.²⁵

Even though CBT is often delivered via regular attendance at face-to-face individual or group therapy sessions, other formats of delivery are available and have some evidence to support their efficacy. These include internet delivery, telephone counselling, or through smartphone applications.²⁶⁻²⁸ There is also evidence that CBT delivered as a 1-day workshop can effectively reduce depressive symptoms and improve mood in adults with depression with gains maintained for up to 2 years.²⁹⁻³¹

The aim of this study was to assess the efficacy and feasibility of Personalized Integrative Therapy (PI Therapy), an integrative intervention for adults with depression and anxiety, including any additive benefits of dietary supplements. Treatment was delivered as a 1-day workshop plus 6 weeks of regular follow-up phone text messaging. The efficacy of PI Therapy (with or without supplements) was compared to CBT to examine changes

in affective symptoms, sleep quality, overall life quality, diet, and exercise habits. Due to increasing positive findings associated with nutraceutical and herbal supplementation on depressive and anxiety symptoms, a PI Therapy plus supplements arm was included in this study to examine whether the addition of supplements to an integrative intervention could enhance treatment outcomes. In several meta-analyses, it has been confirmed that supplementation with saffron,³² curcumin,³³ probiotics,³⁴ and omega-3 fatty acids³⁵ are associated with reduced depressive and/or anxiety symptoms. However, most studies have been stand-alone interventions and the efficacy of supplementation as a component of a comprehensive integrative intervention has received little attention in the scientific literature. Moreover, in nutraceutical and herbal clinical trials, the efficacy of single supplements is most commonly examined. However, consumers may take several supplements at a time. By better emulating real-world behaviors associated with supplementation, we examined the acceptability and tolerability of a treatment comprising multiple supplements. Because depression and anxiety are associated with multiple physiological disturbances (ie, neurotransmitter disturbances, hypothalamic-pituitary-adrenal axis dysregulation, mild chronic inflammation, and increased oxidative stress)³⁶ herbs and nutraceuticals targeting these various mechanisms were also chosen. It was hypothesized that PI Therapy would be at least comparable to CBT in improving mood, anxiety, and relevant behaviors that can influence mental and physical well-being. Moreover, the addition of supplements was hypothesized to increase treatment outcomes associated with mood and sleep quality.

Materials and Methods

Study Design

A 6-week, 3-arm, parallel-group, randomized trial, with a 6-week follow-up, was undertaken (Figure 1). Participants were informed that the goal of the study was to compare the efficacy of a lifestyle-based treatment with a validated standard treatment for depression and/or anxiety, and that they would be allocated randomly into 1 of 3 groups. Participants became aware of treatment allocation on attendance of the 1-day workshop; however, they were not aware of the content covered in the other workshops. Study investigators were aware of treatment group allocation. However, this is unlikely to have introduced bias as all outcome measures were completed online by participants.

In this trial, the sample size was influenced by resource availability and was therefore likely underpowered. However, as the goal of this trial was to investigate the efficacy and feasibility of PI Therapy, delivered via a brief intervention, it still enabled the formation of preliminary conclusions and will help establish future directions for research in more adequately powered studies.

Recruitment and Randomization

Participants were recruited across Perth, Western Australia, through social media advertisements between May and June 2019. Interested participants were directed to a website landing page providing details about the study and a link to complete an initial online screening questionnaire. This online questionnaire screened for current

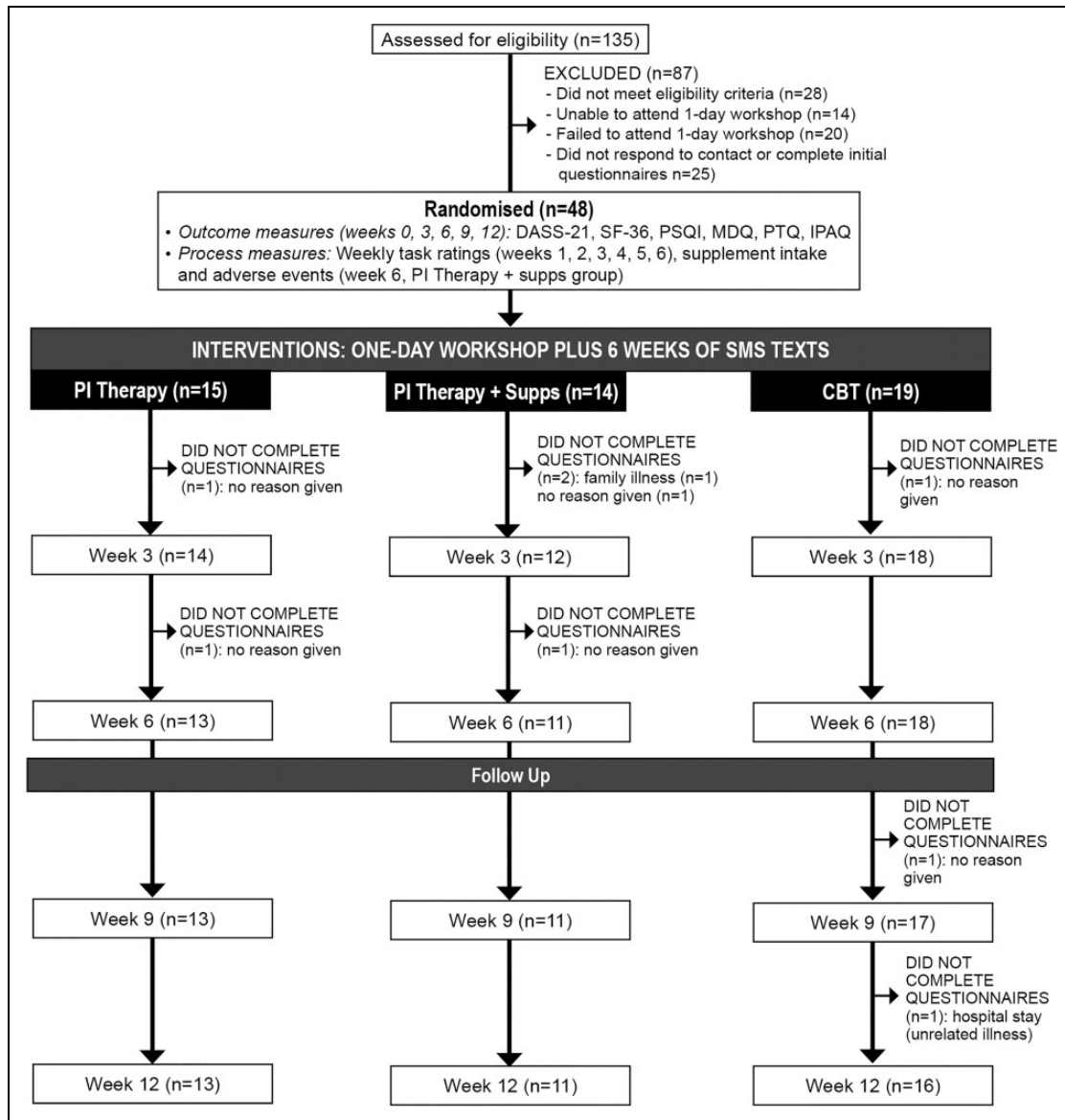


Figure 1. Systematic illustration of study design.

depressive and/or anxiety symptoms, medication use, suicidal ideation, self-harm behaviors, history of medical/psychiatric disorders, alcohol, nicotine, and other drug use, supplement and vitamin intake, and pregnancy/breastfeeding status. If assessed as likely eligible, volunteers participated in a phone interview with an investigator. The phone interview comprised a structured series of questions examining the eligibility criteria specified below.

Eligible and consenting participants completed baseline assessments and were randomly assigned to 1 of 3 groups (PI Therapy, PI Therapy + Supps, or CBT) using a randomization calculator (<http://www.randomization.com>). The randomization calculator ensured sequence concealment. The randomization structure comprised 5 randomly permuted blocks, containing 10 participants per block. The participant identification number was allocated according to the order of participant enrolment in the study. Participants were informed of a date to attend a workshop but were not informed of treatment allocation until the day of attendance.

Participants

Inclusion Criteria. Male and female participants aged 18 to 65 years with self-reported mild to moderately severe depression and/or anxiety as assessed by the DASS-21 were recruited for this trial (ie, DASS-21 depression score from 10 to 28 and/or anxiety score from 8 to 22). If participants were taking psychotropic medication, they were required to be taking a stable dose for at least 8 weeks. Participants were also required to be fluent in English and to have consented (via an electronic consent form) to all pertinent aspects of the trial.

Exclusion criteria. Participants with a reported DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) diagnosis of bipolar disorder, schizophrenia, psycho-organic syndromes, eating disorders, substance abuse, or dependence disorders were ineligible to participate in the study. Participants who were engaging in self-harm behaviors and/or reported serious suicidal ideation were also

excluded from the study. Participants with a major medical illness affecting their ability to implement many of the lifestyle, dietary, and psychological changes covered in the program were also excluded. Medical disorders included but were not limited to cancers, serious cardiovascular disease, neurodegenerative disorders (eg, Alzheimer's disease, multiple sclerosis, and Parkinson's disease), and unmanaged metabolic disorders such as diabetes. Participants currently receiving psychological therapy for depression or anxiety by a mental health practitioner or who had a known allergy or significant intolerance to natural supplements were also ineligible to participate in the study.

Interventions

All participants attended a 1-day workshop (PI Therapy, PI Therapy + Supps, or CBT). Each workshop was held on a weekend and lasted approximately 6 hours. The content of each workshop is provided in Supplementary Table 1. Participants were provided with 3 handouts consisting of (1) copies of slides, (2) checklists and questionnaires that were completed during the workshop, and (3) goal-setting and monitoring sheets that participants were asked to complete for 6 weeks. Throughout the workshop, attendees were required to evaluate their skills/behavior in specified areas by completing relevant questionnaires or reflection sheets, each of which was tailored to content delivered in respective workshops. The goal was for attendees to identify factors that may be contributing to his/her depression and/or anxiety and to establish potential future goals for change. The goal-setting and monitoring workbook was completed at the end of the workshop. Specifically, participants were asked to set 3 to 5 goals for the forthcoming week based on the content covered in the workshop. Throughout the week, participants were asked to record whether they achieved their goal on the monitoring chart provided. At the completion of each week, participants were asked to review their goals and set new ones. New goals could include setting the same goal again, making the goal easier or more difficult based on their previous week's performance, and/or setting a completely new goal based on other areas covered in the workshop. The goal-setting and monitoring booklet was held by participants and copies were not given to investigators.

After the workshops, all participants were sent phone text messages every 2 to 3 days reminding them of content covered in the workshop, encouraging them to continue to work on their goals, or reminding them to complete weekly rating forms or relevant outcome measures. The texts sent to PI Therapy and PI Therapy + Supps groups were identical apart from one text which was sent to the PI Therapy + Supps group, which reminded participants about their supplement intake. In total, each participant received approximately 25 text messages during the first 6 weeks. No messages were sent after week 6 apart from reminders to complete questionnaires at weeks 9 and 12.

Three group facilitators attended all workshops, although one facilitator (AL) presented the material and coordinated group exercises during all workshops. This facilitator is a clinical psychologist with 22 years of clinical experience, significant training and experience in CBT, and the founder of PI Therapy.

All participants in the PI Therapy + Supps condition were provided with several supplements at the end of the workshop. These supplements were unbranded, listing only the ingredients and directions for use. All supplements were provided by Metagenics (Aust) Pty Ltd and produced in an Australian-approved, Good Manufacturing Practice facility. The supplements included the following:

1. Fish oil (2 capsules daily, taken at one time or in divided doses). Each capsule delivered 500 mg of eicosapentaenoic acid and 200 mg of docosahexaenoic acid.
2. B-complex (1 tablet taken in the morning). Each tablet delivered 450 mg of ascorbic acid (vitamin C), 300 mg calcium pantothenate (vitamin B₅), 50 mg citrus bioflavonoids extract, 50 mg thiamine hydrochloride (vitamin B₁), 50 mg nicotinamide (vitamin B₃), 50 mg pyridoxal 5-phosphate monohydrate (vitamin B₆), 20 mg riboflavin sodium phosphate (vitamin B₂), 500 µg Biotin, 200 µg levomefolic acid (5-methyltetrahydrofolate), 200 µg mecobalamin (co-methylcobalamin; vitamin B₁₂).
3. Probiotic (1 capsule daily taken at any convenient time). Each capsule delivered total live organisms—25 billion colonizing forming units (CFUs) comprising 11.5 billion CFUs *Lactobacillus acidophilus* (NCFM), 11.5 billion CFUs *Bifidobacterium lactis* (Bi-07), and 2 billion CFUs *Lactobacillus rhamnosus* (LGG).
4. Magnesium powder formula (1 serve taken in water in the evening). Each serve delivered 350 mg of magnesium as magnesium bisglycinate, 3 g of taurine, 2 g of glutamine, 362 mg of potassium as potassium citrate, 500 mg of vitamin C as calcium ascorbate dihydrate, 25 mg of thiamine hydrochloride (vitamin B₁), 25 mg of riboflavin (vitamin B₂), 25 mg of nicotinamide (vitamin B₃), 25 mg of pyridoxal 5-phosphate monohydrate (vitamin B₆), and 10 mg of zinc as amino acid chelate (zinc bisglycinate).
5. Saffron and curcumin (1 capsule, twice daily). Each capsule delivered 15 mg of a saffron extract (affron) and 500 mg of a curcumin extract (BCM-95).

Outcome Measures

All outcome measures (except weekly task ratings) were completed at baseline (1 to 7 days prior to workshop attendance) and 3, 6, 9, and 12 weeks after the workshop. All measures were completed via self-directed online surveys.

Primary outcome measures

Depression, Anxiety, and Stress Scale—21 (DASS-21). The DASS-21 is a validated self-report measure assessing symptoms of stress, anxiety, and depression.³⁷ Twenty-one questions are rated on a 4-point scale (0-3), ranging from never to almost always (lower scores indicate a reduction in symptoms).

Secondary Outcome Measures

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a reliable and valid 19-item self-report questionnaire that assesses sleep quality over the previous month.^{38,39} Scores are calculated to derive 7-component scores comprising sleep duration, sleep disturbance, sleep latency, sleep efficiency, daytime dysfunction, subjective sleep quality, use of sleeping medication, and overall global sleep quality.

Short Form-36 Health Survey (SF-36). The SF-36 is a self-report measure assessing the quality of life. It consists of 8 scaled scores measuring (1) vitality, (2) physical functioning, (3) bodily pain, (4) general health perceptions, (5) physical role functioning, (6) emotional role functioning, (7) social role functioning, and (8) mental health. The SF-36 is a commonly used outcome measure of quality of life with strong psychometric properties.^{40,41} Scoring for the SF-36 was based on the algorithm developed by RAND Health Care.⁴²

Table 1. Baseline Demographic Details of Participants.

		PI Therapy (n = 15)	PI Therapy + Supps (n = 14)	CBT (n = 19)	P value
Age, mean (SE)		39.8 (2.98)	40.07 (3.47)	39.32 (2.95)	.985 ^a
BMI		30.29 (1.77)	30.01 (1.55)	29.22 (1.77)	.884 ^a
Gender	Female	67%	86%	84%	.354 ^a
Marital status	Single	27%	14%	42%	.392 ^b
	Married	40%	29%	37%	
	Divorced	20%	29%	5%	
	De facto	13%	29%	16%	
Educational level	Secondary	47%	57%	58%	.933 ^b
	Tertiary	33%	21%	21%	
	Postgraduate	20%	21%	21%	
	Yes	60%	43%	37%	
Antidepressant use	Depression	13%	7%	5%	.941 ^b
	Anxiety	27%	29%	32%	
	Combined	60%	64%	63%	
Duration of depression/anxiety	6 to 12 months	13%	0%	5%	.060 ^b
	1 to 2 years	13%	7%	0%	
	2 to 5 years	0%	0%	16%	
	5 to 10 years	0%	36%	16%	
	10+ years	73%	57%	63%	
Last time depression/anxiety free	1 to 2 years	27%	7%	0%	.032 ^b
	2 to 5 years	0%	29%	21%	
	5 to 10 years	7%	29%	32%	
	10+ years	67%	36%	47%	
DASS-21 scores	Depression	16.67 (2.11)	20.29 (2.29)	20.63 (2.27)	.400 ^a
	Anxiety	11.33 (1.83)	14.29 (2.55)	13.89 (2.14)	.605 ^a
	Stress	21.47 (1.79)	23.71 (2.06)	21.05 (1.72)	.569 ^a
	Total	49.47 (4.23)	58.29 (5.06)	55.58 (5.07)	.461 ^a
PSQI	Duration	1.07 (0.28)	1.00 (0.28)	1.26 (0.25)	.764 ^a
	Disturbance	1.40 (0.16)	1.5 (0.17)	1.58 (0.14)	.713 ^a
	Latency	1.2 (0.30)	1.79 (0.30)	1.58 (0.27)	.383 ^a
	Dysfunction	1.47 (0.17)	1.86 (0.10)	1.74 (0.13)	.144 ^a
	Efficiency	0.93 (0.34)	1.14 (0.29)	1.37 (0.27)	.579 ^a
	Subjective sleep quality	1.47 (0.24)	1.64 (0.17)	1.63	.769 ^a
	Medications	1.00 (0.35)	0.57 (0.27)	0.53 (0.22)	.430 ^a
	Global Score	8.53 (1.11)	9.50 (0.97)	9.68 (1.02)	.708 ^a
SF-36	Physical functioning	85.67 (4.57)	90.71 (3.95)	82.89 (3.83)	.410 ^a
	Role limitations due to physical health	75.00 (9.76)	71.43 (10.10)	72.37 (9.91)	.969 ^a
	Role limitations due to emotional problems	31.07 (9.48)	30.79 (7.39)	24.58 (6.69)	.790 ^a
	Energy/fatigue	34.33 (5.04)	29.64 (4.46)	24.47 (3.22)	.239 ^a
	Emotional well-being	50.13 (2.64)	46.00 (3.50)	45.05 (3.55)	.525 ^a
	Social functioning	56.93 (5.45)	51.14 (4.02)	52.16 (5.67)	.727 ^a
	Pain	67.93 (3.01)	61.21 (6.00)	67.84 (5.70)	.682 ^a
	General health	56.33 (5.47)	55.71 (5.74)	49.47 (4.42)	.559 ^a
	Perseverative Thinking Qu	36.93 (1.97)	37.57 (2.37)	37.42 (2.29)	.980 ^a
	Mediterranean Diet Qu	15.93 (0.91)	17.00 (1.13)	17.11 (1.04)	.685 ^a
IPAQ	Vigorous activity (MET minutes/week)	357.33 (145.04)	1204.57 (533.57)	484.21 (305.61)	.221 ^a
	Moderate activity (MET minutes/week)	318.67 (155.20)	791.43 (311.92)	287.37 (115.14)	.151 ^a
	Walking (MET minutes/week)	829.55 (147.37)	1716.68 (455.65)	1057.74 (251.88)	.127 ^a
	Category low	13%	21%	26%	.255 ^b
	Category medium	60%	36%	63%	
Category high	27%	42%	11%		

Abbreviations: PI Therapy, Personalized Integrative Therapy; CBT, cognitive behavior therapy; SE, standard error; BMI, body mass index; DASS-21, Depression, Anxiety, and Stress Scale-21; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form-36 Health Survey; IPAQ, International Physical Activity Questionnaire.

^aOne-way ANOVA.

^bPearson χ^2 test.

Perseverative Thinking Questionnaire (PTQ). The PTQ is a 15-item measure of repetitive, intrusive negative thinking that people find difficult to disengage from. Repetitive thoughts are also defined as unproductive and capture significant mental capacity. The PTQ is a reliable and valid measure that correlates positively with depressive

symptoms as measured by the Beck Depression Inventory and the Inventory of Depressive Symptomatology.⁴³

Mediterranean Diet Adherence Questionnaire (MDAQ). The MDAQ is a 14-item questionnaire designed to assess adherence to a

Mediterranean diet. The MDAQ is validated against the more comprehensive and validated Food Frequency Questionnaire that is commonly used in epidemiological studies.^{44,45}

International Physical Activity Questionnaire, Short Form (IPAQ). The IPAQ is a 7-item self-report measure assessing physical activity patterns over the last 7 days. Metabolic equivalent of task scores (METs) for vigorous activity, moderate activity, and walking is calculated. The IPAQ has sound psychometric properties.⁴⁶

Process Measures

Weekly task ratings. To assess attitudes toward treatments, from weeks 1 to 6 participants rated primary topics covered in each workshop. Participants were required to rate on a 5-point scale how important a task was for the week, how much effort was allocated to the task, and how much success was achieved. In the 2 PI Therapy groups, participants rated the following: improve my diet, take my supplements (PI Therapy + Supps group only), improve my sleep, increase my physical activity, improve my psychology and coping skills, improve my social connections, increase my life purpose and meaning, and improve medical and physical conditions that might be affecting my mental health. In the CBT group, participants rated the following: identify my triggers, identify my thoughts, change my thoughts, accept my thoughts, increase my activity, learn a relaxation skill, and increase exposure to situations I avoid.

Supplement intake. To monitor supplement intake, at week 6 participants in the PI Therapy + Supps group recorded the number of tablets or powder they had remaining.

Adverse events. Tolerability of supplement intake by participants in the PI Therapy + Supps group was assessed at week 6 through an online question querying adverse effects that were believed to be associated with supplement intake. Participants were also requested to contact researchers immediately if any adverse effects were experienced.

Treatment fidelity. To monitor adherence to the content and tasks planned for each 1-day workshop, one cofacilitator in attendance of all workshops completed a checklist at the end of the workshop. This checklist was designed to monitor adherence to the content covered in each workshop by the primary workshop facilitator.

Statistical Analysis

A 1-way ANOVA was used to compare demographic variables across the 3 treatment groups for continuous variables, and Pearson's χ^2 was used to compare categorical data. Total and subscale scores (where relevant) on the DASS-21, PSQI, SF-36, PTQ, MDAQ, and IPAQ were analyzed for time (baseline and mean score across weeks 3, 6, 9, and 12) and group (PI Therapy versus PI Therapy + Supps; PI Therapy conditions combined vs CBT) using a repeated-measures analysis of variance (ANOVA). Scores were averaged across weeks 3 to 12 as preliminary analyses indicated that treatment effects were present from week 3 onwards and did not change appreciably throughout follow-up (Supplementary Tables 2-5). To examine the clinical relevance of treatment effects, the percentage change from baseline was calculated. Eta-squared was calculated to examine effects sizes. The percentage of participants with depression or anxiety subscale scores in the normal range on the DASS-21 was also calculated and a Pearson's χ^2 analysis was conducted to compare between-group differences. This was conducted after excluding participants who

scored in the normal range at baseline. As an exploratory analysis, for participants allocated to the PI Therapy conditions, Spearman's ρ correlations between change in DASS-21 total score (from baseline to mean of weeks 3 to 12) and weekly ratings of effort, importance, and success were conducted.

The Shapiro-Wilk normality test was conducted to examine the normality of group data. This demonstrated that data were not normally distributed, and transformations were unable to normalize data. However, a repeated-measures ANOVA was considered the most appropriate option for statistical analyses as it is relatively robust to violations of normality.⁴⁷ Where necessary, degrees of freedom were adjusted using the Greenhouse-Geisser approach to correct for violations of the sphericity assumption. Data from participants were included in analyses if questionnaire data were obtained at week 3 (last observation carried forward [LOCF] from week 3 for missing values). All data were analyzed using SPSS (version 24; IBM, Armonk, NY).

Results

Study Population

Baseline Questionnaire and Demographic Information. From 135 people completing the initial online screening questionnaire, 48 volunteers attended a 1-day workshop. A total of 87 individuals were either ineligible or did not attend the 1-day workshop for the following reasons: 28 people did not meet the eligibility criteria, 20 people failed to attend the 1-day workshop despite meeting the eligibility criteria and agreeing to participate in the study, 14 people were unable to attend the 1-day workshop at the allocated times, and 25 people did not respond to contact by the investigator or did not complete the initial questionnaires.

Data from 44 participants were used for statistical analyses and 40 participants completed all questionnaires over the 12-week period. Six participants withdrew or did not complete questionnaires during the 6-week intervention and 2 people withdrew during the follow-up period (ie, weeks 6 to 12). There were no significant differences in dropout rates across groups. Reasons for withdrawal included failure to complete questionnaires with no reason given ($n = 6$), illness of a family member ($n = 1$), and hospitalization for an unrelated medical illness ($n = 1$). No participants withdrew from the study due to reported adverse events associated with supplement intake.

Outcome Measures

DASS-21 (Primary Outcome Measure)

Changes in DASS-21 total and subscale scores across the 3 treatment groups and repeated-measures ANOVA significance levels are detailed in Table 2 and Figure 2. All treatments were associated with statistically significant reductions in DASS-21 total and subscale scores. Mean percentage improvements from baseline ranged from 22% (DASS-21 stress score in the CBT group) to 41% (DASS-21 depression score in the PI Therapy + Supps group). A 38%, 59.7%, and 26.8% variance from baseline, as measured by η^2 , was observed in the DASS-21 total score in the PI Therapy, PI Therapy + Supps, and CBT conditions, respectively. As detailed in Table 2, between-group

Table 2. Change in DASS-21 Scores.

		Repeated-measures ANOVA						
DASS-21 Scores		Week 0	Mean score (weeks 3 to 12)	Mean % improvement, weeks 0 to 12	P value (within-group, weeks 0 to 12)	η^2 (%)	P value (Time \times PI Therapy [combined] vs CBT interaction) ^a	P value (Time \times PI Therapy + Supps interaction) ^a
Depression	PI Therapy (n = 14)	Mean 17.14 SE 2.41	11.57	32.49%	.033	30.3	.794	.360
	PI Therapy + Supps (n = 12)	Mean 21 SE 2.61	12.38	41.07%	.003	57.5		
	CBT (n = 18)	Mean 21.44 SE 2.24	15.25	28.87%	.036	23.3		
Anxiety	PI Therapy (n = 14)	Mean 11.43 SE 1.96	7.39	35.32%	.009	41.7	.805	.542
	PI Therapy + Supps (n = 12)	Mean 14.83 SE 2.83	9.17	38.19%	.038	33.7		
	CBT (n = 18)	Mean 13.56 SE 2.23	9.31	31.37%	.032	24.4		
Stress	PI Therapy (n = 14)	Mean 21.57 SE 1.92	16.75	22.35%	.036	29.7	.410	.216
	PI Therapy + Supps (n = 12)	Mean 24.33 SE 2.16	15.79	35.09%	.002	61.0		
	CBT (n = 18)	Mean 21.11 SE 1.82	16.50	21.84%	.023	26.9		
Total	PI Therapy (n = 14)	Mean 50.14 SE 4.48	35.71	28.77%	.014	38.0	.634	.280
	PI Therapy + Supps (n = 12)	Mean 60.17 SE 5.52	37.33	37.95%	.002	59.7		
	CBT (n = 18)	Mean 56.11 SE 5.33	41.06	26.83%	.023	26.8		

Abbreviations: PI Therapy, Personalized Integrative Therapy; CBT, cognitive behavior therapy; SE, standard error; DASS-21, Depression, Anxiety, and Stress Scale-21.

^aBetween-group repeated-measures ANOVA interaction (week 0 to mean of weeks 3 to 12 scores).

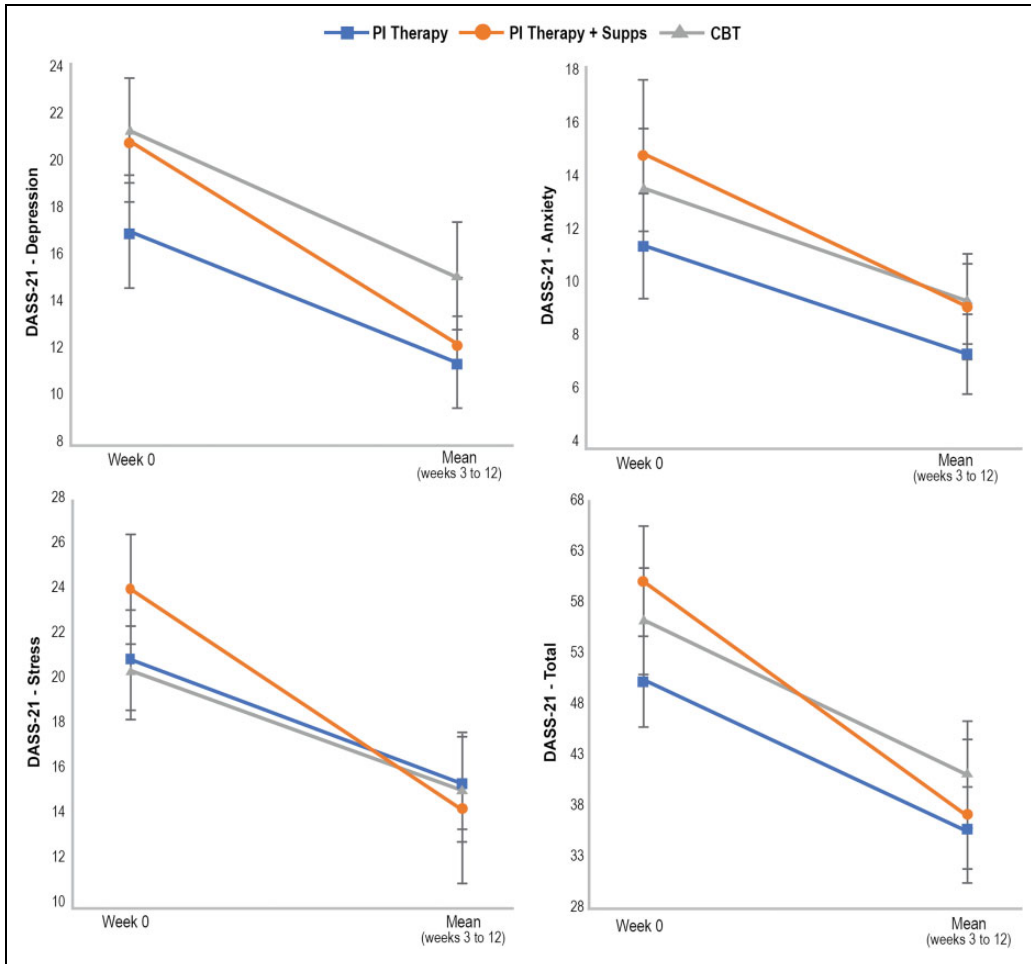


Figure 2. Change in DASS-21 scores (error bars depict standard error).

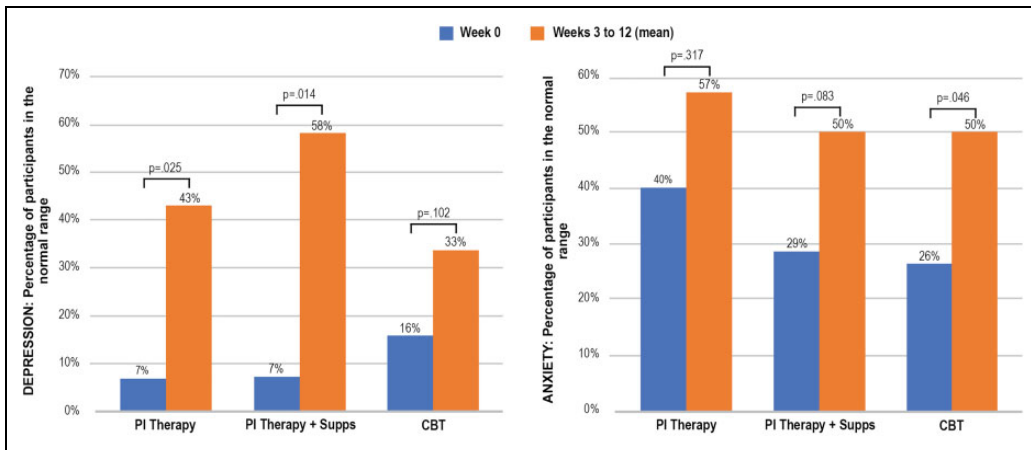


Figure 3. Percentage of participants in the normal range (DASS-21 scores).

analyses on all DASS-21 scores revealed nonsignificant time × group interactions in PI Therapy versus PI Therapy + Supps and PI Therapy combined versus CBT.

The percentage of participants scoring in the normal range on the DASS-21 depression and anxiety subscale scores is detailed in Figure 3. A Wilcoxon signed-rank test revealed

there were statistically significant increases in the number of participants scoring in the normal range for depression in the PI Therapy ($P = .025$) and PI Therapy + Supps ($P = .014$) conditions but not the CBT condition ($P = .102$). A statistically significant increase in the number of participants scoring in the nonclinical range for anxiety occurred in the CBT condition (P

= .046), but not the PI Therapy ($P = .317$) or PI Therapy + Supps condition ($P = .083$). However, a Pearson's χ^2 analysis revealed no statistically significant between-group differences between PI Therapy combined and CBT for depression, $\chi(1) = .621, P = .431$, or anxiety, $\chi(1) = .068, P = .794$. There were also no statistically significant between-group differences between PI Therapy and PI Therapy + Supps for depression, $\chi(1) = .851, P = .356$, or anxiety, $\chi(1) = .032, P = .858$.

SF-36 (Secondary Outcome Measure 1)

Changes in SF-36 subscale scores across the 3 treatment groups and repeated-measures ANOVA significance levels are detailed in Table 3. In the PI Therapy condition, statistically significant treatment effects were observed in role limitations due to physical health ($F_{1,13} = 4.72, P = .049, \eta^2 = 26.6\%$), energy/fatigue ($F_{1,13} = 4.92, P = .045, \eta^2 = 27.5\%$), emotional well-being ($F_{1,13} = 8.20, P = .013, \eta^2 = 38.7\%$), and general health ($F_{1,13} = 4.92, P = .045, \eta^2 = 27.5\%$). In the PI Therapy + Supps condition, statistically significant treatment effects were observed in role limitations due to emotional problems ($F_{1,11} = 5.05, P = .046, \eta^2 = 31.4\%$), energy/fatigue ($F_{1,11} = 13.35, P = .004, \eta^2 = 54.8\%$), emotional well-being ($F_{1,11} = 7.76, P = .018, \eta^2 = 41.4\%$), pain ($F_{1,11} = 12.92, P = .004, \eta^2 = 54\%$), and general health ($F_{1,11} = 12.53, P = .005, \eta^2 = 53.3\%$). In the CBT condition, statistically significant treatment effects were observed in role limitations due to emotional problems ($F_{1,17} = 11.84, P = .003, \eta^2 = 41.1\%$), emotional well-being ($F_{1,17} = 8.34, P = .010, \eta^2 = 32.9\%$), and social functioning ($F_{1,17} = 3.06, P = .022, \eta^2 = 15.3\%$). As detailed in Table 3, between-group analyses on all SF-36 scores revealed nonsignificant time \times group interactions in PI Therapy versus PI Therapy + Supps and PI Therapy combined versus CBT. However, a near-significant interaction was observed in pain scores between PI Therapy versus PI Therapy + Supps condition ($F_{1,24} = 4.029, P = .056, \eta^2 = 14.4\%$).

PSQI (Secondary Outcome Measure 2)

Changes in PSQI subscale scores across the 3 treatment groups and repeated-measures ANOVA significance levels are detailed in Table 4. As detailed in Table 4, between-group analyses revealed significant time \times group interactions in sleep latency for PI Therapy versus PI Therapy + Supps ($F_{1,24} = 5.30, P = .030, \eta^2 = 18.1\%$) and PI Therapy combined vs CBT ($F_{1,42} = 5.71, P = .021, \eta^2 = 12\%$). There were also statistically significant time \times group interactions in global sleep for PI Therapy versus PI Therapy + Supps ($F_{1,24} = 4.41, P = .046, \eta^2 = 15.5\%$) and PI Therapy combined versus CBT ($F_{1,42} = 5.22, P = .027, \eta^2 = 11.1\%$). No statistically significant treatment effects were observed in the CBT group on any subscale score. In the PI Therapy condition, a statistically significant treatment effect occurred in subjective sleep quality ($F_{1,13} = 4.79, P = .047, \eta^2 = 26.9\%$) and a near-significant effect in global sleep quality ($F_{1,13} = 4.28, P = .059, \eta^2 = 24.8\%$). In the PI Therapy + Supps condition statistically-significant treatment effects

were observed in sleep disturbance ($F_{1,11} = 9.43, P = .011, \eta^2 = 46.2\%$), sleep latency ($F_{1,11} = 9.81, P = .010, \eta^2 = 47.1\%$), sleep dysfunction ($F_{1,11} = 7.86, P = .017, \eta^2 = 41.7\%$), subjective sleep quality ($F_{1,11} = 8.19, P = .015, \eta^2 = 42.7\%$), and global sleep score ($F_{1,11} = 22.24, P = .001, \eta^2 = 66.9\%$).

IPAQ (Secondary Outcome Measure 3)

Changes in IPAQ subscale scores across the 3 treatment groups and repeated-measures ANOVA significance levels are detailed in Table 5. There were no statistically-significant increases in vigorous activity, moderate activity, or walking in any treatment condition.

MDAQ (Secondary Outcome Measure 4)

Changes in MDAQ total score across the 3 treatment groups and repeated-measures ANOVA significance levels are detailed in Table 5. As detailed in Table 5, between-group analyses revealed a significant time \times group interaction between PI Therapy combined versus CBT ($F_{1,42} = 16.13, P < .001, \eta^2 = 27.8\%$) but not between PI Therapy versus PI Therapy + Supps ($F_{1,24} = 0.042, P = .840, \eta^2 = 0.2\%$).

Statistically significant increases in MDAQ total score were observed in the PI Therapy ($F_{1,13} = 21.08, P = .001, \eta^2 = 61.8\%$) and PI Therapy + Supps conditions ($F_{1,11} = 20.46, P = .001, \eta^2 = 65\%$), but not the CBT group ($F_{1,17} = 1.45, P = .245, \eta^2 = 7.9\%$).

PTQ (Secondary Outcome Measure 5)

Changes in the PTQ total score across the 3 treatment groups and repeated-measures significance levels are detailed in Table 5. Statistically significant reductions in PTQ total scores were observed in the PI Therapy ($F_{1,13} = 11.63, P = .005, \eta^2 = 47.2\%$), PI Therapy + Supps ($F_{1,11} = 20.05, P = .001, \eta^2 = 64.6\%$), and CBT conditions ($F_{1,17} = 10.20, P = .005, \eta^2 = 37.5\%$). As detailed in Table 5, there were no significant time \times group interactions for PI Therapy versus PI Therapy + Supps and PI Therapy combined versus CBT.

Mean Weekly Ratings (Process Measure)

Mean weekly ratings (weeks 1 to 6) on the primary topics/skills covered in each 1-day workshop are detailed in Supplementary Table 6. Although statistical analyses were not undertaken due to the small sample sizes, in the PI Therapy group, highest importance, effort and success ratings were given for improving diet quality, followed by improving coping skills and sleep quality. In the PI Therapy + Supps group, the highest importance, success, and effort ratings were provided for taking supplements, followed by improving coping skills and diet quality. In the CBT group, the highest ratings were provided for changing thoughts, followed by identifying thoughts, increasing activity, and learning relaxation skills.

Table 3. Change in SF-36 Scores.

		Repeated-measures ANOVA						
Short Form-36		Week 0	Mean score (weeks 3 to 12)	Mean % improvement, weeks 0 to 12	P value (within-group, weeks 0 to 12)	η^2 (%)	P value (Time \times PI Therapy [combined] vs CBT interaction) ^a	P value (Time \times PI Therapy vs PI Therapy + Supps interaction) ^b
Physical functioning	PI Therapy (n = 14)	Mean 84.64	85.45	0.95%	.817	0.4	.575	.326
		SE 4.79	3.63					
	PI Therapy + Supps (n = 12)	Mean 94.17	90.94	-3.43%	.089	24.0		
Role limitations due to physical health	CBT (n = 18)	Mean 85	85.97	1.14%	.766	0.5		
		SE 3.38	2.55					
	PI Therapy (n = 14)	Mean 73.21	67.41	-7.92%	.652	1.6	.953	.667
Role limitations due to emotional problems	PI Therapy + Supps (n = 12)	Mean 10.31	8.79	1.09%	.912	0.1		
		SE 77.08	77.92					
	CBT (n = 18)	Mean 9.95	6.13	-4.55%	.735	0.7		
Energy/fatigue	PI Therapy (n = 14)	Mean 9.58	6.57	66.39%	.049	26.6	.756	.632
		SE 33.29	55.39					
	PI Therapy + Supps (n = 12)	Mean 33.17	63.31	90.87%	.046	31.4		
Emotional well-being	CBT (n = 18)	Mean 8.22	7.58	133.27%	.003	41.1	.203	.406
		SE 22.22	51.83					
	PI Therapy (n = 14)	Mean 35.71	48.48	35.77%	.045	27.5		
Social functioning	PI Therapy + Supps (n = 12)	Mean 5.21	3.97	68.77%	.004	54.8	.575	.510
		SE 28.33	47.81					
	PI Therapy (n = 14)	Mean 24.72	32.92	33.16%	.074	17.6		
Pain	PI Therapy + Supps (n = 12)	Mean 3.39	3.83	22.47%	.013	38.7	.416	.515
		SE 50.86	62.29					
	PI Therapy (n = 14)	Mean 2.73	3.70	35.56%	.018	41.4		
General health	PI Therapy + Supps (n = 12)	Mean 4.46	4.77	24.13%	.010	32.9	.598	.056
		SE 44.22	54.89					
	PI Therapy (n = 14)	Mean 5.83	6.09	9.57%	.485	3.8		
General health	PI Therapy + Supps (n = 12)	Mean 51.25	63.98	24.84%	.129	19.7		
		SE 4.46	7.57					
	PI Therapy (n = 14)	Mean 50.89	66.18	30.05%	.011	32.7		
General health	PI Therapy + Supps (n = 12)	Mean 66.36	69.30	4.44%	.507	3.5	.598	.056
		SE 6.42	5.72					
	PI Therapy (n = 14)	Mean 62	77.17	24.46%	.004	54.0		
General health	PI Therapy + Supps (n = 12)	Mean 6.39	4.46	7.94%	.292	6.5	.278	.649
		SE 69.78	75.32					
	PI Therapy (n = 14)	Mean 5.5	64.91	18.02%	.045	27.5		
General health	PI Therapy + Supps (n = 12)	Mean 59.17	71.77	21.30%	.005	53.3		
		SE 6.12	4.42					
	PI Therapy (n = 14)	Mean 50.56	56.60	11.94%	.125	13.3		
	SE 4.54	3.92						

Abbreviations: PI Therapy, Personalized Integrative Therapy; CBT, cognitive behavior therapy; SE, standard error; SF-36, Short Form-36 Health Survey.

^aBetween-group repeated-measures ANOVA interaction (week 0 to mean of weeks 3 to 12 scores).

Table 4. Change in Pittsburgh Sleep Quality Scores.

Pittsburgh Sleep Quality Index	Duration	Week 0	Mean score (weeks 3 to 12)	Mean % improvement, weeks 0 to 12	P value (within-group, weeks 0 to 12)	η^2 (%)	Repeated-measures ANOVA	
							P value (Time \times PI Therapy vs CBT interaction) ^a	P value (Time \times PI Therapy + Supps interaction) ^a
Disturbance	PI Therapy (n = 14)	Mean 1.07	0.77	28.24%	.268	9.3	.157	.679
	SE	0.29	0.25					
	PI Therapy + Supps (n = 12)	Mean 0.92	0.46	50.18%	.100	22.7		
Latency	SE	0.32	0.24					
	CBT (n = 18)	Mean 1.33	0.25	-0.25%	1.00	0.0		
	SE	0.26	0.25					
Dysfunction	PI Therapy (n = 14)	Mean 1.43	1.23	13.84%	.264	9.5	.709	.211
	SE	0.17	0.12					
	PI Therapy + Supps (n = 12)	Mean 1.58	1.08	31.43%	.011	46.2		
Efficiency	SE	0.18	0.10					
	CBT (n = 18)	Mean 1.61	1.35	16.32%	.109	14.4		
	SE	0.15	0.12					
Subjective Sleep Quality	PI Therapy (n = 14)	Mean 1.14	0.93	18.55%	.165	14.3	.021	.030
	SE	0.32	0.20					
	PI Therapy + Supps (n = 12)	Mean 1.83	0.88	52.19%	.010	47.1		
Global Sleep Score	SE	0.34	0.26					
	CBT (n = 18)	Mean 1.56	1.63	-4.17%	.718	0.8		
	SE	0.28	0.25					
Medications	PI Therapy (n = 14)	Mean 1.43	1.21	15.08%	.281	8.9	.717	.172
	SE	0.15	0.17					
	PI Therapy + Supps (n = 12)	Mean 1.83	1.21	33.97%	.017	41.7		
Duration	SE	0.16	0.22					
	CBT (n = 18)	Mean 1.78	1.46	18.07%	.091	15.9		
	SE	0.13	0.15					
Efficiency	PI Therapy (n = 14)	Mean 0.79	0.82	-3.98%	.913	0.1	.519	.217
	SE	0.31	0.25					
	PI Therapy + Supps (n = 12)	Mean 1.08	0.56	47.92%	.101	22.5		
Subjective Sleep Quality	SE	0.33	0.26					
	CBT (n = 18)	Mean 1.44	1.42	1.62%	.862	2.0		
	SE	0.27	0.26					
Global Sleep Score	PI Therapy (n = 14)	Mean 1.43	1.05	26.32%	.047	26.9	.133	.186
	SE	0.2	0.18					
	PI Therapy + Supps (n = 12)	Mean 1.67	0.85	48.85%	.015	42.7		
Medications	SE	0.22	0.23					
	CBT (n = 18)	Mean 1.67	1.43	14.34%	.080	16.9		
	SE	0.18	0.14					
Duration	PI Therapy (n = 14)	Mean 0.86	0.45	48.09%	.170	13.9	.108	.832
	SE	0.3	0.22					
	PI Therapy + Supps (n = 12)	Mean 0.67	0.33	50.25%	.132	19.4		
Global Sleep Score	SE	0.32	0.25					
	CBT (n = 18)	Mean 0.56	0.57	-1.69%	.914	0.1	.027	.046
	SE	0.26	0.20					
Efficiency	PI Therapy (n = 14)	Mean 8.14	6.46	20.59%	.059	24.8		
	SE	1.12	0.87					
	PI Therapy + Supps (n = 12)	Mean 9.58	5.38	43.89%	.001	66.9		
Subjective Sleep Quality	SE	1.21	1.01					
	CBT (n = 18)	Mean 9.94	9.18	7.64%	.209	9.1		
	SE	0.99	1.07					

Abbreviations: PI Therapy, Personalized Integrative Therapy; CBT, cognitive behavior therapy; SE, standard error.

^aBetween-group repeated-measures ANOVA interaction (week 0 to mean of weeks 3 to 12 scores).

Table 5. Change in Physical Activity, Diet Quality and Perseverative Thinking.

	Repeated-measures ANOVA									
	Week 0		Mean score (weeks 3 to 12)	Mean % improve- ment, weeks 0 to 12	P value (within-group, weeks 0 to 12)	η^2 (%)	P value (Time \times PI Therapy (combined) vs CBT interaction) ^a	P value (Time \times PI Therapy vs PI Therapy + Supps interaction) ^a		
	Mean	SE								
International Physical Activity Questionnaire	Vigorous Activity (METS)	PI Therapy (n = 14)	Mean	280	442.14	57.91%	.050	26.4	.729	.331
			SE	379.05	120.84					
		PI Therapy + Supps (n = 12)	Mean	1165.33	769.58	-33.96%	.525	3.8		
			SE	409.42	226.10					
		CBT (n = 18)	Mean	506.67	535.61	5.71%	.832	0.3		
			SE	334.29	245.11					
		PI Therapy (n = 14)	Mean	315.71	504.64	59.84%	.299	8.3	.267	.392
			SE	179.03	143.97					
		PI Therapy + Supps (n = 12)	Mean	623.33	539.79	-13.40%	.762	0.9		
			SE	193.38	236.37					
		CBT (n = 18)	Mean	298.89	612.22	104.83%	.047	21.3		
			SE	157.89	151.19					
Perseverative Thinking Questionnaire	Walking (METS)	PI Therapy (n = 14)	Mean	818.09	897.01	9.65%	.762	0.7	.493	.897
			SE	308.79	237.41					
		PI Therapy + Supps (n = 12)	Mean	1656.29	1780.18	7.48%	.591	2.7		
			SE	333.53	453.43					
		CBT (n = 18)	Mean	1089	1000.57	-8.12%	.691	1.0		
			SE	272.33	219.23					
		PI Therapy (n = 14)	Mean	36.86	28.77	21.95%	.005	47.2	.649	.504
			SE	2.46	3.00					
		PI Therapy + Supps (n = 12)	Mean	36.33	25.98	28.49%	.001	64.6		
			SE	2.66	3.25					
		CBT (n = 18)	Mean	37.5	29.67	20.89%	.005	37.5		
			SE	2.17	2.34					
Mediterranean Diet Questionnaire	PI Therapy (n = 14)	Mean	15.71	20.18	28.44%	.001	61.8	<.001	.840	
		SE	1.07	1.01						
	PI Therapy + Supps (n = 12)	Mean	17.25	21.44	24.28%	.001	65.0			
		SE	1.16	0.69						
	CBT (n = 18)	Mean	17.61	18.26	3.71%	.245	7.9			
		SE	0.95	1.00						

Abbreviations: PI Therapy, Personalized Integrative Therapy; CBT, cognitive behavior therapy; SE, standard error.

^aBetween-group repeated-measures ANOVA interaction (week 0 to mean of weeks 3 to 12 scores).

Spearman's ρ correlations between mean ratings (from weeks 1 to 6) in importance, effort, and success with a change in the total DASS-21 score are detailed in Supplementary Table 7 (for PI Therapy groups only). Higher ratings of importance ($r = .482, P = .013$) and effort ($r = .394, P = .047$) but not success ($r = .239, P = .240$) in improving diet quality were positively associated with improvements in the total DASS-21 score. Higher ratings in effort ($r = .443, P = .023$) and success ($r = .443, P = .027$) in improving medical and physical conditions that might affect mental health were positively associated with improvements in total DASS-21 score. Higher success ratings ($r = .533, P = .005$) in changing psychological and coping skills were associated with improvements in DASS-21 score.

Intake of Supplements

At week 6, participants in the PI Therapy + Supps group recorded their quantity of remaining supplements. All participants reported taking greater than 80% of their supplements except one participant who only consumed 10% of her curcumin/saffron capsules but took greater than 80% of the remaining supplements.

Adverse Events

No significant adverse events were reported by participants, with similar dropout rates across the 2 conditions. No participants withdrew from the study due to concerns associated with supplement intake.

Treatment Fidelity

The treatment fidelity checklist completed by a co-facilitator confirmed that the primary workshop facilitator adhered to content and exercises planned for each workshop, as outlined in Supplementary Table 1.

Discussion

In this 6-week, randomized, 3-arm trial, an integrative treatment for depression and/or anxiety (PI Therapy) with or without nutritional supplements was found to be at least as effective as a similarly delivered format of CBT. Treatment was provided as a 1-day workshop followed by regular phone texts over a 6-week period, reminding participants of topics covered in the workshop and encouraging them to set weekly goals for change.

Affective symptoms, as measured by the DASS-21 total and subscale scores, improved in all treatment groups and there were no statistically significant differences among the treatment conditions. However, this study was likely underpowered to detect any but large between-group differences. In this population of adults with mild-to-moderate severity of depression and/or anxiety, 33% to 58% of participants reported levels of depressive symptoms in the normal range at the end of treatment, and 50% to 58% reported nonclinical levels of anxiety. Even though confirmation is required in a larger clinical trial with clearly defined mental health populations and validated self-report and

clinician-administered outcome measures, these results are comparable to those obtained from standard delivery CBT and pharmaceutical interventions. For example, in a meta-analysis of 34 studies, CBT delivered for an average of 10 sessions was associated with a remission rate of 45% in adults with depression.³ An average remission rate of 48% was also identified in a meta-analysis on second-generation antidepressants.⁴

Despite improvements in affective symptoms occurring in all treatment conditions, improvements in sleep quality were detected only in the PI Therapy + Supps condition. Compared to CBT and PI Therapy, PI Therapy + Supps was associated with significantly greater improvements in sleep latency and global sleep quality, as measured by the PSQI. Overall, participants in the PI Therapy + Supps condition reported improvements in sleep disturbance, sleep latency, sleep dysfunction, subjective sleep quality, and global sleep quality. PI Therapy alone was associated with a statistically significant improvement in subjective sleep quality and a near-significant improvement in global sleep quality. However, there were no statistically significant changes in sleep quality following participation in CBT. These results suggest that supplementation comprising magnesium, B-vitamins, omega-3 fish oil, probiotics, saffron, and curcumin may enhance sleep quality. As these supplements were taken in combination it cannot be determined if changes in sleep quality were due to one or a combination of these ingredients. Moreover, as there was no placebo control, it is feasible that the simple act of taking supplements may have contributed to improvements in sleep quality. However, this is unlikely given the large, clinically meaningful changes in sleep quality. Supplementation with magnesium,⁴⁸ saffron,⁴⁹⁻⁵¹ omega-3-polyunsaturated fatty acids,⁵² and probiotics⁵³ have been associated with improvements in sleep quality. Even though further research is required to understand how these nutrients and plant extracts improve sleep quality, their sleep-enhancing effects may be due to their influence on serotonergic, hypothalamic-pituitary-adrenal axis activity, and anti-inflammatory mechanisms. For example, omega-3 fatty acid and magnesium supplementation is associated with reduced inflammation and cortisol concentrations.⁵⁴⁻⁵⁶ Saffron and probiotics have also been shown to lower inflammation and cortisol concentrations and may influence serotonergic activity.⁵⁵⁻⁵⁹ Alterations in these physiological mechanisms have been identified in insomnia and other sleep disturbances.⁶⁰⁻⁶² It is important to note that treating poor sleep leads to improvements in affective and anxious symptoms among people with mental disorders and increases the effectiveness of evidence-based treatments for depression and anxiety.^{63,64} As a result, sleep improvements seen in the PI + Supps group may moderate a greater improvement in mental health symptoms, and this requires investigation via a longer-term follow-up.

Improvements in quality of life, as measured by the SF-36, and perseverative thinking were observed across all treatment groups, with no statistically significant, between-group differences, apart from a near-significant greater improvement in pain in the PI Therapy + Supps group compared to PI Therapy. Increases in diet quality as measured by the MDAQ were

observed in the 2 PI Therapy conditions. A higher score on the MDAQ indicates an increase in a Mediterranean dietary pattern characterized by increased consumption of fruits, vegetables, legumes, whole-grains, olive oil, and a reduced intake of processed foods, sweets, and soft drinks. The importance of dietary changes was not covered in the CBT workshop, and as expected, no change in dietary patterns was reported by participants in the CBT condition. No changes in physical activity, as measured by the IPAQ was observed in any treatment condition.

While these treatment effects should be considered tentative until confirmed in larger, adequately powered, and controlled studies, the results are certainly encouraging. In this study, the eligibility criteria were relatively broad to increase the likelihood of recruiting a representative sample of mostly moderate-to-severely depressed and/or anxious adults motivated to make changes to improve their mental well-being. In fact, approximately 60% of participants reported experiencing depression and/or anxiety for greater than 10 years and almost 50% were currently taking a pharmaceutical antidepressant. Despite this, approximately 40% to 60% of participants in the PI Therapy conditions reported that levels of depression and/or anxiety had decreased to within the normal range following treatment. Even more encouraging is the efficient, cost-effective intervention that was offered to participants which included attending a 1-day workshop and automated SMS texts every 2 to 3 days to remind participants of topics covered in the workshop and to encourage them to set weekly goals for change. These improvements were also maintained during a 6-week follow-up.

PI Therapy comprising personalized goal-setting targeting diet, sleep, physical activity, psychological coping skills, life purpose and meaning, social connections, and general physical/medical health was well received by participants. The process of empowering people to choose a target for change, rather than a clinician deciding what to change, might be an important factor in facilitating change and increasing treatment acceptability for participants.⁶⁵ In a meta-analysis of 23 studies, it was confirmed that when patients exercise control over their health care decisions, there are improved treatment outcomes and an approximate 50% reduced likelihood of treatment dropout.⁶⁶ No participants withdrew from the study due to the content covered in the workshop. In fact, improving diet and taking supplements, along with enhancing psychological coping skills were rated by participants as the most important components of the intervention, and the ones they reported exercising the greatest effort and success in changing. The importance of diet in enhancing mental health was further highlighted by an exploratory analysis of weekly ratings by participants in the PI Therapy conditions where higher ratings in importance and effort to change diet quality were positively associated with greater improvements in mood. However, no such associations were found in participants ratings associated with improving sleep, increasing physical activity, improving psychological coping skills, increasing social connections, or increasing purpose and life meaning. This suggests that attitudes and behaviors associated with improving diet quality may be important components of change. This will require further investigation in controlled experimental studies.

Emerging research suggests a protective effect of healthy diets such as the Mediterranean diet on depression.^{67,68} The results from 2 dietary interventions in depressed adults also indicate that dietary changes can effectively lower depressive and anxiety symptoms.^{18,69}

In addition to diet, the results of this study indicate that in participants receiving PI Therapy, the more effort and success an individual reported in improving medical and physical conditions, the greater the improvement in affective symptoms as measured by the total DASS-21 score. This suggests that allocating efforts at improving physical health can have a positive effect on mental health. Self-rating of success (but not importance or effort) at improving psychological coping skills was also positively associated with improved mental health. These results require more comprehensive investigation in future clinical trials, as understanding the most essential components of an intervention can help improve treatment models.

Despite encouraging participants to increase physical activity, no significant increases in physical activity (eg, walking, moderate, and vigorous activity) were found in any treatment condition. Changes in physical activity were assessed with the IPAQ, a self-report measure of physical activity. While this is a validated instrument with sound psychometric properties, significant variability in respondents' estimates of activity was noted by investigators. Seasonal changes in physical activity may also have impacted on changes in activity as the workshops were conducted in autumn and follow-up assessments of physical activity occurred in winter months.

Limitations and Directions for Future Research

In this study, encouraging effects of an integrative, brief intervention (PI Therapy) to reduce depressive and anxiety symptoms in adults with depression and/or anxiety were identified. However, these findings should be considered preliminary and require confirmation in larger well-controlled trials. The lack of a no-treatment control group precludes an analysis of the extent of improvements associated with the passage of time or placebo effects. This study was also underpowered, and based on the effect sizes achieved in this study, it is anticipated that a total sample size of approximately 160 would be required to detect between-group differences in affective symptoms between PI Therapy and CBT. Moreover, the therapeutic effects of this integrative intervention delivered in different formats should be investigated. All treatments were delivered as a 1-day, 6-hour workshop, plus 6-weeks of SMS texts. Both PI Therapy interventions were found to be at least comparable to CBT. However, CBT is most often delivered as a weekly group or individual intervention ranging from 10 to 20 sessions. Examining the differing efficacy of PI Therapy delivered as a weekly individual or group intervention ranging from 6 to 20 sessions will allow an analysis of the costs to benefits associated with different treatment delivery formats. It will also allow a comparison of PI Therapy to CBT when delivered in its most-validated format.

The addition of nutritional supplements (B-complex, magnesium, curcumin, saffron, fish oil, and a probiotic) was well tolerated by participants and may have enhanced treatment efficacy. In particular, greater improvements in sleep quality, physical function, and pain were reported by participants in the PI Therapy + Supps group. In the future, a placebo-controlled comparison will be important to determine the robustness of this finding.

It is important that PI Therapy is investigated in different populations to determine its efficacy and feasibility. Advertising for this study occurred via social media where participants were informed that the purpose of the study was to compare the effects of a lifestyle-based intervention with a validated intervention for depression and anxiety. While participants were not provided with details about the treatments, it is possible that a population interested in lifestyle and dietary interventions was recruited. To evaluate the generalizability of study results, it is therefore important that the efficacy of PI Therapy is evaluated in participants with a range of demographic and psychographic characteristics, and levels of readiness to make changes.

PI Therapy comprises several areas of intervention covering the following domains: diet and nutrition, lifestyle and environment, psychology and coping skills, social and spiritual, and medical and physical. Targeting change in several areas that can influence mental well-being may be associated with greater treatment efficacy. However, utilizing an intervention consisting of multiple components prohibits analysis of the most effective components of an intervention. Whether improvements in mental health were due to one or several components within PI Therapy could not be determined. One remedy is to investigate the efficacy of each intervention in isolation. However, this approach opposes a primary assumption of an integrative intervention where multiple, small changes can have large therapeutic effects. This will require consideration in future studies.

Finally, investigators in this study were not blinded, which may potentially impact on outcomes. However, outcome measures comprised online, self-report measures. Following the 1-day workshop, investigators had no personal contact with participants. This limits the likelihood of investigator influence on study outcomes. However, it may be prudent in future studies for outcomes to be assessed by investigators blinded to treatment conditions. In addition, objective outcome measures may be helpful. This may include the collection of actigraphy and polysomnography data to assess changes in physical activity and sleep patterns.

Acknowledgments

The authors gratefully acknowledge Metagenics (Aust) Pty Ltd for providing part-funding for the project and supplying the nutritional supplements used in this study.

Author Contributions

All authors have contributed to the conception and design of the study, drafting of the article, and have approved the final article submitted for publication.


Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: ALL is the founder of PI Therapy. ALL has previously received speaker fees from Metagenics (Aust) Pty Ltd. All other authors declare they have no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Nutritional supplements used in this study were provided by Metagenics (Aust) Pty Ltd. Metagenics (Aust) Pty Ltd also provided partial funding for this study. Metagenics (Aust) Pty Ltd was not involved in the design of the research, analysis of data, or the writing of the report.

ORCID iD

Adrian L. Lopresti  <https://orcid.org/0000-0002-6409-7839>

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Trial Registration

The trial protocol was approved by the Human Research Ethics Committee at Murdoch University, Western Australia (Approval Number 2019/003), and was prospectively registered with the Australian New Zealand Clinical Trials Registry (Trial ID: ACTRN12619000452190).

Supplemental Material

Supplemental material for this article is available online.

References

- Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. *Cognit Ther Res*. 2012;36:427-440.
- David D, Cristea I, Hofmann SG. Why cognitive behavioral therapy is the current gold standard of psychotherapy. *Front Psychiatry*. 2018;9:4.
- Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry*. 2017;4:409-418.
- Santoft F, Axelsson E, Öst LG, Hedman-Lagerlöf M, Fust J, Hedman-Lagerlöf E. Cognitive behaviour therapy for depression in primary care: systematic review and meta-analysis. *Psychol Med*. 2019;49:1266-1274.
- Amick HR, Gartlehner G, Gaynes BN, et al. Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. *BMJ*. 2015;351:h6019.
- Mohr DC, Hart SL, Howard I, et al. Barriers to psychotherapy among depressed and nondepressed primary care patients. *Ann Behav Med*. 2006;32:254-258.

7. Fernandez E, Salem D, Swift JK, Ramtahal N. Meta-analysis of dropout from cognitive behavioral therapy: magnitude, timing, and moderators. *J Consult Clin Psychol*. 2015;83:1108-1122.
8. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. *Drugs Context*. 2015;4:212290.
9. Kostev K, Rex J, Eith T, Heilmaier C. Which adverse effects influence the dropout rate in selective serotonin reuptake inhibitor (SSRI) treatment? Results for 50 824 patients. *Ger Med Sci*. 2014;12:Doc15.
10. Jacob SA, Ab Rahman AF, Hassali MA. Attitudes and beliefs of patients with chronic depression toward antidepressants and depression. *Neuropsychiatr Dis Treat*. 2015;11:1339-1347.
11. Lopresti AL. It is time to investigate integrative approaches to enhance treatment outcomes for depression? *Med Hypotheses*. 2019;126:82-94.
12. Li Y, Lv MR, Wei YJ, et al. Dietary patterns and depression risk: a meta-analysis. *Psychiatry Res*. 2017;253:373-382.
13. Schuch F, Vancampfort D, Firth J, et al. Physical activity and sedentary behavior in people with major depressive disorder: a systematic review and meta-analysis. *J Affect Disord*. 2017;210:139-150.
14. Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. *Depress Anxiety*. 2015;32:664-670.
15. Garipey G, Honkaniemi H, Quesnel-Vallee A. Social support and protection from depression: systematic review of current findings in Western countries. *Br J Psychiatry*. 2016;209:284-293.
16. Firth J, Siddiqi N, Koyanagi A, et al. The Lancet Psychiatry Commission: a blueprint for protecting physical health in people with mental illness. *Lancet Psychiatry*. 2019;6:675-712.
17. Kvam S, Kleppe CL, Nordhus IH, Hovland A. Exercise as a treatment for depression: a meta-analysis. *J Affect Disord*. 2016;202:67-86.
18. Jacka FN, O'Neil A, Opie R, et al. A randomised controlled trial of dietary improvement for adults with major depression (the "SMILES" trial). *BMC Med*. 2017;15:23.
19. Lopresti AL, Smith SJ, Hood SD, Drummond PD. Efficacy of a standardised saffron extract (Affron[®]) as an add-on to antidepressant medication for the treatment of persistent depressive symptoms in adults: a randomised, double-blind, placebo-controlled study. *J Psychopharmacol*. 2019;33:1415-1427.
20. Sarris J, Murphy J, Mischoulon D, et al. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. *Am J Psychiatry*. 2016;173:575-587.
21. Firth J, Teasdale SB, Allott K, et al. The efficacy and safety of nutrient supplements in the treatment of mental disorders: a meta-review of meta-analyses of randomized controlled trials. *World Psychiatry*. 2019;18:308-324.
22. Null G, Pennesi L. Diet and lifestyle intervention on chronic moderate to severe depression and anxiety and other chronic conditions. *Complement Ther Clin Pract*. 2017;29:189-193.
23. Griffin KH, Johnson JR, Kitzmann JP, Kolste AK, Dusek JA. Outcomes of a multimodal resilience training program in an outpatient integrative medicine clinic. *J Altern Complement Med*. 2015;21:628-637.
24. Forsyth A, Deane FP, Williams P. A lifestyle intervention for primary care patients with depression and anxiety: a randomised controlled trial. *Psychiatry Res*. 2015;230:537-544.
25. Murphy JA, Oliver G, Ng CH, et al. Pilot-testing of "Healthy Body Healthy Mind": an integrative lifestyle program for patients with a mental illness and co-morbid metabolic syndrome. *Front Psychiatry*. 2019;10:91.
26. Health Quality Ontario. Internet-delivered cognitive behavioural therapy for major depression and anxiety disorders: a health technology assessment. *Ont Health Technol Assess Ser*. 2019;19:1-199.
27. Mohr DC, Ho J, Duffecy J, et al. Effect of telephone-administered vs face-to-face cognitive behavioral therapy on adherence to therapy and depression outcomes among primary care patients: a randomized trial. *JAMA*. 2012;307:2278-2285.
28. Firth J, Torous J, Nicholas J, et al. The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials. *World Psychiatry*. 2017;16:287-298.
29. Brown JS, Elliott SA, Boardman J, Andiappan M, Landau S, Howay E. Can the effects of a 1-day CBT psychoeducational workshop on self-confidence be maintained after 2 years? *A naturalistic study*. *Depress Anxiety*. 2008;25:632-640.
30. Brown JS, Elliott SA, Boardman J, Ferns J, Morrison J. Meeting the unmet need for depression services with psycho-educational self-confidence workshops: preliminary report. *Br J Psychiatry*. 2004;185:511-515.
31. Horrell L, Goldsmith KA, Tylee AT, et al. One-day cognitive-behavioural therapy self-confidence workshops for people with depression: randomised controlled trial. *Br J Psychiatry*. 2014;204:222-233.
32. Marx W, Lane M, Rocks T, et al. The effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. *Nutr Rev*. 2019;28:nuz023.
33. Fusar-Poli L, Vozza L, Gabbiadini A, et al. Curcumin for depression: a meta-analysis. *Crit Rev Food Sci Nutr*. Published online August 19, 2019. doi:10.1080/10408398.2019.1653260
34. Goh KK, Liu YW, Kuo PH, Chung YE, Lu ML, Chen CH. Effect of probiotics on depressive symptoms: a meta-analysis of human studies. *Psychiatry Res*. 2019;282:112568.
35. Liao Y, Xie B, Zhang H, et al. Efficacy of omega-3 PUFAs in depression: a meta-analysis. *Transl Psychiatry*. 2019;9:190.
36. Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. *Neuro Endocrinol Lett*. 2011;32:7-24.
37. Brown TA, Chorpita BF, Korotitsch W, Barlow DH. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. *Behav Res Ther*. 1997;35:79-89.
38. Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh Sleep Quality Index as a screening tool for sleep dysfunction in clinical and non-clinical samples: a systematic review and meta-analysis. *Sleep Med Rev*. 2016;25:52-73.
39. Grandner MA, Kripke DF, Yoon IY, Youngstedt SD. Criterion validity of the Pittsburgh Sleep Quality Index: investigation in a non-clinical sample. *Sleep Biol Rhythms*. 2006;4:129-139.

40. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30:473-483.
41. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993;31:247-263.
42. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Econ*. 1993;2:217-227.
43. Ehling T, Zetsche U, Weidacker K, Wahl K, Schonfeld S, Ehlers A. The Perseverative Thinking Questionnaire (PTQ): validation of a content-independent measure of repetitive negative thinking. *J Behav Ther Exp Psychiatry*. 2011;42:225-232.
44. Martinez-Gonzalez MA, Garcia-Arellano A, Toledo E, et al. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. *PLoS One*. 2012;7:e43134.
45. Schroder H, Fito M, Estruch R, et al. A short screener is valid for assessing Mediterranean diet adherence among older Spanish men and women. *J Nutr*. 2011;141:1140-1145.
46. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. *Int J Behav Nutr Phys Act*. 2011;8:115.
47. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. 5th ed. Allyn; 2007.
48. Abbasi B, Kimiagar M, Sadeghniai K, Shirazi MM, Hedayati M, Rashidkhani B. The effect of magnesium supplementation on primary insomnia in elderly: a double-blind placebo-controlled clinical trial. *J Res Med Sci*. 2012;17:1161-1169.
49. Umigai N, Takeda R, Mori A. Effect of crocetin on quality of sleep: a randomized, double-blind, placebo-controlled, crossover study. *Complement Ther Med*. 2018;41:47-51.
50. Nishide A, Fujita T, Nagaregawa Y, et al. Sleep enhancement by saffron extract in randomized control trial. *Jpn Pharmacol Ther*. 2018;46:1407-1415.
51. Lopresti AL, Smith SJ, Metse AP, Drummond PD. Effects of saffron on sleep quality in healthy adults with self-reported poor sleep: a randomized, double-blind, placebo-controlled trial. *J Clin Sleep Med*. Published online February 14, 2020. doi:10.5664/jcsm.8376
52. Jahangard L, Sadeghi A, Ahmadpanah M, et al. Influence of adjuvant omega-3-polyunsaturated fatty acids on depression, sleep, and emotion regulation among outpatients with major depressive disorders—results from a double-blind, randomized and placebo-controlled clinical trial. *J Psychiatr Res*. 2018;107:48-56.
53. Nishida K, Sawada D, Kawai T, Kuwano Y, Fujiwara S, Rokutan K. Para-psychobiotic *Lactobacillus gasseri* CP2305 ameliorates stress-related symptoms and sleep quality. *J Appl Microbiol*. 2017;123:1561-1570.
54. Delarue J, Matzinger O, Binnert C, Schneiter P, Chiolero R, Tappy L. Fish oil prevents the adrenal activation elicited by mental stress in healthy men. *Diabetes Metab*. 2003;29:289-295.
55. Calder PC. Omega-3 fatty acids and inflammatory processes. *Nutrients*. 2010;2:355-374.
56. Dmitrasinovic G, Pesic V, Stanic D, Plecas-Solarovic B, Dajak M, Ignjatovic S. ACTH, cortisol and IL-6 levels in athletes following magnesium supplementation. *J Med Biochem*. 2016;35:375-384.
57. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the manipulation of bacteria-gut-brain signals. *Trends Neurosci*. 2016;39:763-781.
58. Lopresti AL, Drummond PD. Saffron (*Crocus sativus*) for depression: a systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Hum Psychopharmacol*. 2014;29:517-527.
59. Wang H, Lee IS, Braun C, Enck P. Effect of probiotics on central nervous system functions in animals and humans: a systematic review. *J Neurogastroenterol Motil*. 2016;22:589-605.
60. van Dalen JH, Markus CR. The influence of sleep on human hypothalamic-pituitary-adrenal (HPA) axis reactivity: a systematic review. *Sleep Med Rev*. 2018;39:187-194.
61. Cespuoglio R. Serotonin: its place today in sleep preparation, triggering or maintenance. *Sleep Med*. 2018;49:31-39.
62. Fernandez-Mendoza J, Baker JH, Vgontzas AN, Gaines J, Liao D, Bixler EO. Insomnia symptoms with objective short sleep duration are associated with systemic inflammation in adolescents. *Brain Behav Immun*. 2017;61:110-116.
63. Franzen PL, Buysse DJ. Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. *Dialogues Clin Neurosci*. 2008;10:473-481.
64. Kallestad H, Hansen B, Langsrud K, et al. Impact of sleep disturbance on patients in treatment for mental disorders. *BMC Psychiatry*. 2012;12:179.
65. Yeung V, Sharpe L, Geers A, Colagiuri B. Choice, expectations, and the placebo effect for sleep difficulty. *Ann Behav Med*. 2020;54:94-107.
66. Swift JK, Callahan JL. The impact of client treatment preferences on outcome: a meta-analysis. *J Clin Psychol*. 2009;65:368-381.
67. Lassale C, Batty GD, Baghdadli A, et al. Healthy dietary indices and risk of depressive outcomes: a systematic review and meta-analysis of observational studies. *Mol Psychiatry*. 2018.
68. Nicolaou M, Colpo M, Vermeulen E, et al. Association of a priori dietary patterns with depressive symptoms: a harmonised meta-analysis of observational studies. *Psychol Med*. Published online August 14, 2019. doi:10.1017/S0033291719001958
69. Parletta N, Zarnowiecki D, Cho J, et al. A Mediterranean-style dietary intervention supplemented with fish oil improves diet quality and mental health in people with depression: a randomized controlled trial (HELFIMED). *Nutr Neurosci*. 2019;22:474-487.