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# Exercise, Yoga, and Tai Chi for Treatment of Major Depressive Disorder in Outpatient Settings: A Systematic Review and Meta-Analysis

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## ABSTRACT

**Objective:** Exercise, yoga, and tai chi are commonly used complementary approaches for health and wellness. This review aims to synthesize the evidence for exercise, yoga, and tai chi in the outpatient treatment of major depressive disorder.

**Study Selection:** A systematic search of the Ovid MEDLINE, EMBASE, PsycINFO, and Cochrane databases was conducted for randomized controlled trials of exercise, yoga, and tai chi for major depressive disorder.

**Data Extraction:** Standardized mean differences were calculated and meta-analyzed using a random effects multilevel modeling framework. Heterogeneity and subgroup analysis was conducted.

**Results:** Twenty-five studies were included for final analysis (exercise: 15, yoga: 7, tai chi: 3). Overall, meta-analysis showed a moderate significant clinical effect. However, when only studies (6 studies) with the lowest risk of bias were included, the overall effect size was reduced to low to moderate efficacy. Overall quality of evidence was low. Heterogeneity and publication bias were high.

**Conclusions:** The current meta-analysis of outpatient exercise, yoga, and tai chi for treatment of major depressive disorder suggests that adjunctive exercise and yoga may have small additive clinical effects in comparison to control for reducing depressive symptoms. The evidence for tai chi is insufficient to draw conclusions. The concerns with quality of studies, high heterogeneity, and evidence of publication bias preclude making firm conclusions.

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Major depressive disorder (MDD) is a significant health care problem across the globe. MDD has high prevalence and recurrence and is associated with significant morbidity and mortality, loss of work productivity, increased associated health care costs, and high rates of suicide.<sup>1,2</sup> Psychopharmacology and psychotherapy are the most commonly used clinical approaches for its treatment. However, although easily available through primary care providers, antidepressants have the disadvantage of a significant side effect burden, leading to poor treatment adherence. Evidence-based psychotherapy approaches are difficult for many people to access and require significant motivational investment and psychological mindedness to be effective. Alternative and complementary therapies are commonly sought after by patients with MDD, as such treatments are perceived to be more congruent with their own values and beliefs toward health and life.<sup>3,4</sup>

Exercise represents one of the most commonly used complementary approaches for health and wellness. Exercise is defined as any activity that involves planned, structured, and repetitive bodily movement done to improve or maintain physical fitness.<sup>5</sup> Common forms of exercise involve aerobic exercise or strength training. Benefits of exercise for depression have been reported for depressive symptoms in previous systematic reviews.<sup>6-10</sup> A Cochrane review<sup>11</sup> of 35 randomized controlled trials (RCTs) of exercise for depression (diagnosed by any method of any severity) showed overall moderate clinical effect, using a random effects model standardized mean difference of  $-0.62$  (95% CI,  $-0.81$  to  $-0.42$ ). There was significant heterogeneity in effect sizes ( $I^2 = 63%$ ). However, when only methodologically sound studies were included, the positive effects disappeared.<sup>11</sup> A systematic review by Krogh and colleagues,<sup>12</sup> however, suggested no benefits of exercise for clinical depression when considering only studies with less risk of bias. Further, it has not been possible to determine what type, duration, or intensity of exercise can be clinically beneficial for those suffering with a major depressive episode.

Other forms of physical activity, particularly forms of mindful movement including yoga and tai chi, have been used increasingly as complementary health approaches.<sup>4</sup> Yoga and tai chi are traditional healing practices that come from ancient India and China, respectively. Yoga and tai chi combine the deliberate practice of repetitive movements with emphasis on controlled breathing-induced relaxation and concentration-focused meditation. Hatha yoga, the most commonly practiced yoga approach, combines movement and postures (asanas), breathing (pranayama), and meditation (dhyana). Different types of yoga vary in their

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### Clinical Points

- Adjunctive exercise and yoga combined with usual antidepressant treatment may offer low to moderate additional clinical benefit for depression.
- Two to 3 sessions of yoga per week performed according to patient capacity may be sufficient for clinical benefit.

emphasis on postures, breathing, and meditation. They include Iyengar yoga (focus on body postures), Vinyasa yoga (integrates postures and breathing—*asanas* and *pranayama*), Sudarshan Kriya yoga (predominantly breathing focused), and Sahaj yoga (meditation focused) among others. Tai chi is a Chinese martial art that involves complex, choreographed movements in coordination with breathing.<sup>13</sup> Tai chi combines concentration, coordinated body movements, deep rhythmic breathing, and meditation to attain a relaxed state of mind.

A systematic review<sup>14</sup> of yoga for treatment of MDD identified a heterogeneous group of studies comparing yoga to multiple interventions, with high risk of bias across studies. The results suggested positive effects in comparison to placebo and comparable effects to evidence-based interventions; however, considering the methodological heterogeneity, the authors<sup>14</sup> did not complete a meta-analysis. To our knowledge, there are no systematic reviews of tai chi for adjunctive treatment of MDD.

### Why Is This Review Important?

Exercise has long been believed to be effective for the treatment of depression.<sup>15</sup> Several systematic reviews and meta-analyses of exercise for the treatment of depressive symptoms suggest a small, but favorable, clinical effect when factoring for quality of studies.<sup>6-11,16</sup> However, the most recent review<sup>12</sup> raised important questions about the clinical effect of exercise interventions when considering the quality of available evidence. The authors<sup>12</sup> concluded that there was no evidence of positive effect when only higher-quality studies were included. However, the studies in this meta-analysis<sup>12</sup> included participants with major and minor depression, inpatient and outpatient studies, and a wide range of follow-up duration. Therefore, the current review attempts to reevaluate the scientific evidence, limiting inclusion to studies using standardized diagnostic criteria for diagnosing MDD and having adequate follow-up duration of at least 8 weeks in outpatient settings. We decided to evaluate whether yoga and tai chi confer additional benefits compared to traditional western exercise practices for the treatment of MDD. Since the last systematic review<sup>14</sup> of yoga, 5 RCTs of yoga for MDD have been published.

Therefore, the main objective of this systematic review is to determine the effectiveness of exercise, yoga, and tai chi compared to any intervention for treatment of MDD, meeting current episode criteria, diagnosed using standardized criteria (*ICD-10* or *DSM-IV/5*), treated in clinical settings, and followed for a sufficient period of time.

### METHODS

A systematic search of Ovid MEDLINE, EMBASE, PsycINFO, and Cochrane databases from inception to the second week of March 2019 was conducted on March 11, 2019, by a professional librarian with input from 3 study authors (A.S., M.F.T., J.M.). The search was updated on November 4, 2019. We searched database subject headings, title, and abstract with search terms that included *exercise*, *exercise therapy*, *kinesiotherapy*, *yoga*, and *tai chi* or *taiji* for MDD. We restricted our search to RCTs published in the English language and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>17</sup>

### Study Selection

The online systematic review tool Covidence was used for title screening, full-text review, and data extraction.<sup>18</sup> Title and abstract screening was done in duplicate by 2 independent reviewers (A.S. and S.O.). Conflicts were resolved by discussion. Our inclusion criteria were RCTs that included adult patients with MDD compared with any control condition, including other treatment interventions or treatment as usual (TAU), in a current episode, diagnosed using standardized diagnostic criteria with at least 8 weeks of follow-up data, in outpatient settings. We included studies of participant samples with MDD with comorbid conditions if MDD was diagnosed using standardized diagnostic criteria or by clinical interview by a specialist and identified as the primary target of treatment intervention. We excluded studies in which individuals reported depressive symptoms but were not formally diagnosed with MDD, studies that included participants with minor depression (symptoms of depression but not meeting diagnostic criteria for MDD), and those that did not provide outcome data for MDD separately. Studies were included if they provided sufficient data for calculation of effect sizes for the meta-analysis. Efforts were made to reach out to study authors in case of missing data or unclear findings. The primary outcome measure was change in depressive symptom severity assessed using standardized rating scales between the beginning and end of the treatment intervention period.

### Data Extraction

Full-text review was completed in duplicate from studies meeting inclusion criteria by 2 authors (A.S. and S.S.O.), with any disagreements resolved by discussion and reaching consensus. Risk of bias assessment was completed by 2 independent authors (A.S. and A.A.) using the Cochrane risk of bias tool.<sup>19</sup> Data were extracted by 2 independent reviewers (A.S. and A.A.), and any conflicts that arose were resolved through discussion and consensus.

### Data Synthesis

We calculated and compared standardized mean differences for each intervention group for each study using

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pre- and posttreatment mean, standard deviation (SD) or 95% confidence interval, and number of participants. We extracted the effect sizes if they were reported. Standardized mean differences were calculated using Hedges' *g* instead of Cohen *d*, as the latter is known to produce biased effect estimates for smaller samples.<sup>20</sup> Three exercise studies<sup>21–23</sup> had multiple comparison groups comprised of different exercise interventions measured against controls. We treated each comparison independently for these 3 studies. To prevent double counting of participants, we divided the sample sizes of common comparison groups within studies. One exercise study<sup>24</sup> had multiple comparison groups (ie, 5 groups) comprised of different doses (low dose vs public health dose) and duration of exercise (3 days/wk or 5 days/wk) interventions measured against control. We combined the results of the different dose arms to obtain a single comparison to the control group.<sup>24</sup>

### Statistical Analysis

R studio (R version 3.6.1)<sup>25</sup> was used to conduct meta-analysis and subgroup analysis. The inverse variance method was used for weighting studies of differing sample sizes. We used a random effects multivariate model framework to compute overall effect sizes for the meta-analysis to account for complex data structures such as multiple comparison groups within studies.

All analyses including exercise studies used the multivariate model framework. We used a random effects model to pool effect sizes using the DerSimonian-Laird estimator when analyzing yoga and tai chi studies separately, as they had single effect estimates.<sup>26</sup> All other subgroup analyses were conducted using mixed effects modeling.

### Heterogeneity and Subgroup Analysis

Heterogeneity was assessed using the Cochran *Q* statistic with  $P < .10$  used as a cutoff to attribute heterogeneity between study factors rather than by chance.<sup>27</sup> The  $I^2$  statistic was used to assess the contribution of between-study heterogeneity to the overall estimate of heterogeneity. We assigned cutoffs of 25%, 50%, and 75% for small, moderate, and large levels of heterogeneity between studies, respectively.<sup>27</sup> Sensitivity analysis was conducted after removing outliers and high-risk studies. Subgroup analysis, based on a mixed effects model, was conducted to further investigate heterogeneity between studies by stratifying studies according to types of active intervention, comparator groups (active control or attention control versus treatment-as-usual/inactive control), participant characteristics (clinical setting or volunteers from nonclinical setting), augmentation, or monotherapy.

### Publication Bias

Egger regression test and funnel plots, using the trim-and-fill method, were utilized to qualitatively and quantitatively assess publication bias.<sup>28,29</sup> We performed random effects meta-analysis using imputed data to account for effects of publication bias.

### Risk of Bias Assessment

The Cochrane risk of bias tool<sup>19</sup> was used to assess bias in the meta-analysis. This tool contains categories for sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, handling of incomplete data, selective reporting, and any other forms of bias. Cochrane guidelines recommend that all key domains be rated low risk to qualify for a global low-risk score. Even a single high or unclear risk domain confers high risk on a global scale.<sup>19</sup> Considering the nature of exercise, yoga, and tai chi interventions, blinding of participants and personnel providing interventions is not possible. We thus excluded this item from our risk of bias assessment. For this review, we classified studies as having low bias if they had low risk of bias assessed by sequence generation, allocation concealment, blinding of personnel, blinding of outcome assessment, handling of incomplete data, and selective reporting.

## RESULTS

Our search strategy resulted in 1,017 published articles. After deduplication, 689 articles were screened based on title and abstract from which 60 studies were found eligible for full-text review. Twenty-five RCTs<sup>13,21–24,30–49</sup> were included in the meta-analysis (Supplementary Figure 1). Across 15 exercise, 7 yoga, and 3 tai chi studies, 1,112 participants were enrolled in the intervention groups, while 971 participants were enrolled in the control groups. The RCTs were conducted in the United States (12),<sup>13,22,24,31,37,41,42, 44–46,48,49</sup> Brazil (1),<sup>38</sup> the United Kingdom (1),<sup>32</sup> Sweden (2),<sup>33,35</sup> Italy (2), Denmark (2),<sup>23,36</sup> Germany (1),<sup>34</sup> Portugal (1),<sup>39</sup> India (2),<sup>43,47</sup> and Iran (1).<sup>30</sup>

### Exercise

The most common exercise type was aerobic exercise (17 groups from 15 studies<sup>21–24,30,32–36,38–40,44,46</sup>) including walking, jogging, and aerobic exercise machines such as the treadmill and stationary bike, with strength training used in 3 groups (Table 1). The treatment duration for exercise studies varied between 8 and 32 weeks, with a mean study duration of 15.5 weeks (Table 1). Most of the exercise sessions (15) were group based and conducted with close supervision with other study participants. Three studies<sup>22,39,46</sup> used home-based exercise programs. In the exercise studies, there were 15 intervention groups using exercise augmentation to usual therapy and 6 intervention groups using exercise monotherapy (Table 2).

### Yoga and Tai Chi

Five yoga studies had treatment duration of 8 weeks, while 2 studies used longer treatment duration periods of 10<sup>48</sup> and 12<sup>47</sup> weeks. Five yoga studies<sup>31,41,45,47,48</sup> used Hatha yoga, while 1 study used Sudarshan Kriya yoga<sup>42</sup> and 1 used Sahaj yoga.<sup>43</sup> Five yoga studies<sup>42,43,45,47,48</sup> used yoga as an augmentation strategy, while 2 studies<sup>31,41</sup> used yoga monotherapy. All 3 tai chi studies<sup>13,37,49</sup> used 10- to

**Table 1. Characteristics of Studies Included in the Meta-Analysis**

Study	Country	Intervention	Type	Control	Medication	Duration	Mean Age, y	Sample, n (I/C)	Female, %	Depression Severity	Outcome Measure
Abdollahi et al, 2017 <sup>30</sup>	Iran	Aerobic exercise + CBT	Adjunctive	TAU-CBT	No	12 wk	51	25/29	40	Moderate	BDI-II
Belvederi Murri et al, 2015 <sup>21</sup>	Italy	Progressive aerobic exercise + sertraline	Adjunctive progressive aerobic	TAU-medication	Yes	8 wk	75	42/42	68	Moderate	HDRS
Belvederi Murri et al, 2015b <sup>21</sup>	Italy	Nonprogressive exercise + sertraline	Adjunctive nonprogressive aerobic	TAU-medication	Yes	8 wk	75	42/42	69	Moderate	HDRS
Blumenthal et al, 2007a <sup>22</sup>	United States	Aerobic exercise	Monotherapy	TAU-medication	No	16 wk	52	51/49	75	Moderate	HDRS
Blumenthal et al, 2007b <sup>22</sup>	United States	Aerobic exercise	Monotherapy	TAU-medication	No	16 wk	53	51/49	75	Moderate	HDRS
Danielsson et al, 2014 <sup>33</sup>	Sweden	Aerobic exercise	Adjunctive	TAU-medication + exercise education	Yes	10 wk	45	22/20	73	Moderate	MADRS
Dunn et al, 2005 <sup>24</sup>	United States	Aerobic exercise (multiple doses)	Monotherapy	Stretching	No	12 wk	48	67/13	63	Moderate	HDRS
Daley et al, 2015 <sup>32</sup>	United Kingdom	Aerobic exercise	Adjunctive	TAU-medication	Yes	24 wk	32	43/42	100	Moderate	EPDS
Doose et al, 2015 <sup>34</sup>	Germany	Aerobic exercise	Adjunctive	TAU-medication	Yes	8 wk	46	30/16	60	Moderate	HDRS
Hallgren et al, 2016 <sup>35</sup>	Sweden	Mixed aerobic exercise	Monotherapy	TAU-CBT	No	12 wk	43	316/312	70	Moderate	MADRS
Krogh et al, 2009a <sup>23</sup>	Denmark	Strength exercise	Adjunctive	Relaxation	Yes	16 wk	42	48/42	81	Moderate	HDRS
Krogh et al, 2009b <sup>23</sup>	Denmark	Aerobic exercise	Adjunctive	Relaxation	Yes	16 wk	38	47/42	78	Moderate	HDRS
Krogh et al, 2012 <sup>36</sup>	Denmark	Aerobic exercise	Adjunctive	Stretching	Yes	12 wk	40	56/59	67	Moderate	HDRS
Mota-Pereira et al, 2011 <sup>39</sup>	Portugal	Aerobic exercise	Adjunctive	TAU-medication	Yes	12 wk	49	19/10	65	Moderate	HDRS
Pilu et al, 2007 <sup>40</sup>	Italy	Aerobic exercise	Adjunctive	TAU-medication	Yes	32 wk	50	10/20	100	Moderate	HDRS
Singh et al, 1997 <sup>44</sup>	United States	Strength exercise	Monotherapy	TAU-medication	No	10 wk	70	9/4	70	Mild	HDRS
Moraes et al, 2020 <sup>38</sup>	Brazil	Strength exercise	Adjunctive	Strength training	Yes	12 wk	71	9/7	84	Moderate	HDRS
Szuhany and Otto, 2020 <sup>46</sup>	United States	Aerobic exercise	Adjunctive	Stretching	Yes	12 wk	34	15/16	77	Moderate	MADRS
Tolahunase et al, 2018 <sup>47</sup>	India	Yoga + meditation	Adjunctive	TAU-medication	Yes	12 wk	37	29/29	53	Moderate	BDI
Streeter et al, 2017 <sup>45</sup>	United States	Iyengar yoga	Adjunctive	Iyengar yoga-low dose	Yes	8 wk	36	15/15	83	Moderate	BDI
Sharma et al, 2005 <sup>43</sup>	India	Sahaj yoga	Adjunctive	TAU-medication	Yes	8 wk	32	15/15	36	Moderate	HDRS-17
Buttner, 2013 <sup>31</sup>	United States	Vinyasa yoga	Monotherapy	WC control	Not mentioned	8 wk	30	28/29	100	Moderate	HDRS-17
Sharma et al, 2017 <sup>42</sup>	United States	Sudarshan Kriya yoga	Adjunctive	TAU-medication	Yes	8 wk	39	13/12	70	Moderate	HDRS-17
Prathikanti et al, 2017 <sup>41</sup>	United States	Hatha yoga	Monotherapy	Education groups	No	8 wk	43	20/18	68	Mild	HDRS-17
Uebelacker et al, 2017 <sup>48</sup>	United States	Hatha yoga	Adjunctive	Health education	Yes	10 wk	46	63/59	84	Moderate	QIDS
Yeung et al, 2012 <sup>49</sup>	United States	Tai chi	Adjunctive	WC control	Yes	12 wk	55	25/13	77	Moderate	HDRS-17
Yeung et al, 2017 <sup>13</sup>	United States	Tai chi	Adjunctive	Education groups	Yes	12 wk	54	18/14	72	Moderate	HDRS-17
Lavretsky et al, 2011 <sup>37</sup>	United States	Tai chi (augmentation)	Adjunctive	Health education	Yes	10 wk	70	33/35	64	Mild	HDRS-17

Abbreviations: BDI = Beck Depression Inventory; CBT = cognitive-behavioral therapy; EPDS = Edinburgh Postnatal Depression Scale; HDRS = Hamilton Depression Rating Scale; I/C = intervention/control; MADRS = Montgomery-Asberg Depression Rating Scale; QIDS = Quick Inventory of Depression Symptomatology; TAU = treatment as usual; WC = waitlisted control.

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**Table 2. Types of Interventions Used in the Studies Included in the Meta-Analysis**

Study	Intervention		
	Minutes	Frequency	Type
Abdollahi et al, 2017 <sup>30</sup>	40	3 × wk	Aerobic exercise
Belvederi Murri et al, 2015a <sup>21</sup>	60	3 × wk	Supervised, group, progressive aerobic exercise (cycling, treadmill)
Belvederi Murri et al, 2015b <sup>21</sup>	60	3 × wk	Supervised, group, nonprogressive exercise (mat work, exercise ball, calisthenics)
Blumenthal et al, 2007a <sup>22</sup>	40	3 × wk	Supervised group walking or jogging
Blumenthal et al, 2007b <sup>22</sup>	40	3 × wk	Home-based, unsupervised, walking or jogging
Danielsson et al, 2014 <sup>33</sup>	60	2 × wk	Supervised group, cardio equipment (eg, cross-trainer, treadmill, bike)
Dunn et al, 2005 <sup>24</sup>	60	3 × wk	Supervised group, walking, self-selected intensity
Daley et al, 2015 <sup>32</sup>	30	3–5 × wk	Supervised group, walking, self-selected intensity
Doose et al, 2015 <sup>34</sup>	60	3 × wk	Self-selected intensity, outdoor, group aerobic exercise
Hallgren et al, 2016 <sup>35</sup>	60	3 × wk	Supervised group, mixed, yoga, aerobics, vigorous exercise
Krogh et al, 2009a <sup>23</sup>	90	2 × wk	Supervised strength training, circuit, targeting large muscle groups
Krogh et al, 2009b <sup>23</sup>	90	2 × wk	Supervised aerobic training, 10 different machines
Krogh et al, 2012 <sup>36</sup>	45	3 × wk	Supervised stationery bike
Mota-Pereira et al, 2011 <sup>39</sup>	30	5 × wk	1 supervised and 4 home-based unsupervised sessions
Pilu et al, 2007 <sup>40</sup>	60	2 × wk	Supervised group, cardio equipment
Singh et al, 1997 <sup>44</sup>	45	3 × wk	Supervised group, progressive resistance machines, 3 sets of 8 repetitions
Moraes et al, 2020 <sup>38</sup>	30	2 × wk	Aerobic training vs strength training
Szuhany and Otto, 2020 <sup>46</sup>	30	3 × wk	1 supervised session, 4 unsupervised home sessions
Tolahunase et al, 2018 <sup>47</sup>	120	5 × wk for 12 wk	Asanas, Pranayama, Dyana
Streeter et al, 2017 <sup>45</sup>	90	3 × wk/90 min + 4 × wk/ 30 min (homework) vs 2 × wk/90 min + 3 × wk/ 30 min (homework)	Home yoga
Sharma et al, 2005 <sup>43</sup>	30	3 × wk	Sahaj yoga, meditation
Buttner, 2013 <sup>31</sup>	60	2 × wk + home practice 1 × wk	Vinyasa yoga
Sharma et al, 2017 <sup>42</sup>	210	Week 1: 6 × wk Week 2–8: 1 × wk + 1 home session	Sudarshan Kriya yoga Sudarshan Kriya yoga
Prathikanti et al, 2017 <sup>41</sup>	60	2 × wk	Hatha Yoga
Uebelacker et al, 2017 <sup>48</sup>	80	2 × wk	Hatha Yoga
Yeung et al, 2012 <sup>49</sup>	60	× wk	Traditional Yang-style tai chi
Yeung et al, 2017 <sup>13</sup>	60	2 × wk	Traditional Yang-style tai chi
Lavretsky et al, 2011 <sup>37</sup>	120	1 × wk	Tai chi

12-week intervention periods to augment usual treatment for depression compared to control conditions.

### Sample Characteristics

All except 3 RCTs had participants diagnosed with moderate depressive episode, while 3 studies<sup>37,41,44</sup> recruited participants with mild depression based on baseline outcome measure scores. The Hamilton Depression Rating Scale (15 studies)<sup>50</sup> and Beck Depression Inventory (4 studies)<sup>51</sup> were the most common outcome measures. One RCT<sup>39</sup> recruited a sample with treatment-resistant depression. In terms of control interventions, there were 14 inactive TAU intervention groups, 7 attention-controlled education groups, 3 cognitive-behavioral therapy groups, 1 active control group of low-dose intervention (yoga), 2 active exercise interventions, and 2 active medication controls.

### Risk of Bias in Included Studies

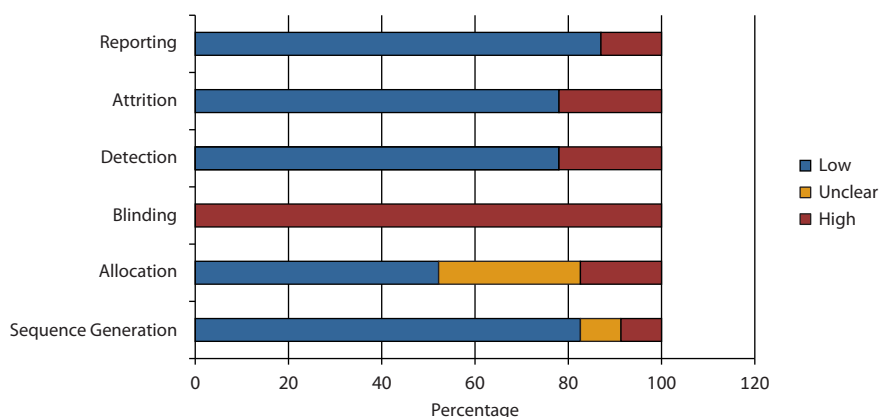
The risk of bias was assessed using Cochrane risk of bias criteria (Figure 1). Nineteen RCTs (73% of overall studies) provided details of sequence generation for randomization. However, allocation concealment was reported in only 12 studies<sup>13,21,22,24,31–33,37,41,45,47,49</sup> (48%). Overall, 3 studies<sup>34,43,46</sup> were rated as having high risk of selection bias, while 10

studies<sup>23,24,30,35,37–39,42,44,48</sup> were rated as unclear (combined 52%). The risk of detection bias was rated high or unclear for 6 RCTs<sup>13,31,34,40,42,43</sup> (24%). Six studies<sup>13,23,30,39,46,49</sup> (24%) did not report intent-to-treat statistical analysis, while 3 studies<sup>13,23,39</sup> (12%) showed reporting bias. Given that the interventions were exercise, yoga, and tai chi, blinding of participants and personnel was difficult, making the risk of bias inherently high, particularly when the control intervention was a passive or TAU condition. Overall, 6<sup>21,22,32,41,45,47</sup> of the 25 studies qualified as a high-quality study across the risk of bias criteria, excluding blinding of participants and personnel criteria.

### Effects of Interventions on Depression

Multivariate model meta-analysis revealed that, taken together, exercise, yoga, and tai chi showed efficacy in reducing depression symptoms with a moderate favorable effect in reducing depression symptoms compared to all control conditions, applying Cohen cutoff criteria (0.2: small, 0.5: moderate, 0.8: large) for effect sizes ( $k = 28$ ; Hedges'  $g = 0.63$ ; 95% CI, 0.50–0.76;  $P < .001$ )<sup>52</sup> (Figure 2). Cochran  $Q$  statistic (1,165,  $df = 27$ ,  $P < .001$ ) suggested significant heterogeneity. The  $I^2$  statistic indicated that 98% of the variance was accounted for by between-study differences

Figure 1. Risk of Bias



in effect size, with 7 studies<sup>30,33,34,39,42,44,47</sup> contributing the most to overall heterogeneity. Influence analysis removing the 7 outlier studies revealed significant influence to the pooled effect sizes. The overall effect was reduced to a small to moderate effect size ( $k=21$ ; Hedges'  $g=0.33$ ; 95% CI, 0.23–0.42;  $P<.001$ ) with a significant Cochran Q statistic (410,  $df=20$ ,  $P<.001$ ). When we included only the 6 studies meeting criteria for the lowest risk of bias (3 exercise studies and 3 yoga studies),<sup>21,22,32,41,45,47</sup> the overall effect size showed low to moderate efficacy in reducing depressive symptoms ( $k=8$ ; Hedges'  $g=0.41$ ; 95% CI, 0.14–0.66;  $P=.007$ ).

### Subgroup Analysis

**Intervention. Exercise.** Fifteen RCTs of exercise comprised of 18 groups of exercise compared to controls were included in the meta-analysis. This included 15 groups of aerobic exercise and 3 groups of strength training exercises. Fourteen groups used exercise augmentation to usual therapy, while 4 groups used exercise monotherapy. All studies recruited participants with moderate depression except 1 with mild depression.<sup>44</sup> Three studies<sup>22,39,46</sup> employed home-based facilitated exercise protocols, the majority being supervised onsite group sessions. The most common exercise frequency was 3 sessions per week, with duration ranging from 30 to 60 minutes. Compared to the control groups, multivariate model random effects meta-analysis showed that exercise-based interventions had an overall moderate effect in improving depressive symptoms at the end of the intervention period ( $k=18$ ; Hedges'  $g=0.74$ ; 95% CI, 0.06–1.40;  $P=.03$ ). There was significant heterogeneity ( $Q=113$ ,  $df=17$ ,  $P<.001$ ), with significant variance due to between-study differences in effect size ( $I^2=98\%$ ). When only the 3 high-quality studies were included,<sup>21,22,32</sup> low to moderate effect was observed (Hedges'  $g=0.31$ ; 95% CI, 0.03–0.59;  $P=.03$ ), with low heterogeneity between studies ( $Q=3.9$ ,  $df=4$ ,  $P=.4$ ). Removing 5 outlier studies<sup>30,33,34,39,44</sup> from the meta-analysis caused the effect size to decrease (Hedges'  $g=0.23$ ; 95% CI, 0.07–0.38;  $P=.007$ ), with low heterogeneity between studies ( $Q=15$ ,  $df=12$ ,  $P=.21$ ).

**Yoga.** Random effects meta-analysis of 7 RCTs of yoga with 7 treatment arms showed that yoga improved depression outcomes in comparison to control conditions with moderate effect size ( $n=260$ ; Hedges'  $g=0.69$ ; 95% CI, 0.36–1.02;  $P<.001$ ). There was significant heterogeneity ( $Q=170$ ,  $df_6=3$ ,  $P<.001$ ), with significant variance due to between-study differences in effect sizes ( $I^2=96\%$ ). When only higher-quality studies<sup>41,45,47</sup> were included in the meta-analysis, an effect size of Hedges'  $g=0.59$ ; 95% CI, 0.04–1.13;  $P=.03$  was observed. Significant between-study heterogeneity was also observed ( $I^2=93\%$ ).

**Tai Chi.** Random effects meta-analysis of 3 RCTs comparing tai chi with controls that included 2 attention control education groups and 1 waitlist control group showed no significant difference in reducing depression symptoms between tai chi and control groups ( $n=138$ ; Hedges'  $g=0.28$ ; 95% CI, -0.12–0.68;  $P=.25$ ), with high heterogeneity ( $Q=26$ ,  $df=2$ ,  $P<.001$ ,  $I^2=92\%$ ).

### Type of Control

Exercise, yoga, and tai chi (combined) were significantly superior to the active group (Hedges'  $g=0.45$ ; 95% CI, 0.26–0.63;  $P<.01$ ) and TAU group (Hedges'  $g=0.81$ ; 95% CI, 0.59–1.30;  $P<.001$ ). A mixed effects model test for subgroup differences showed significantly larger differences for TAU controls compared to active controls ( $Q=6.2$ ,  $df=1$ ,  $P<.02$ ).

### Clinical Participants or Volunteers

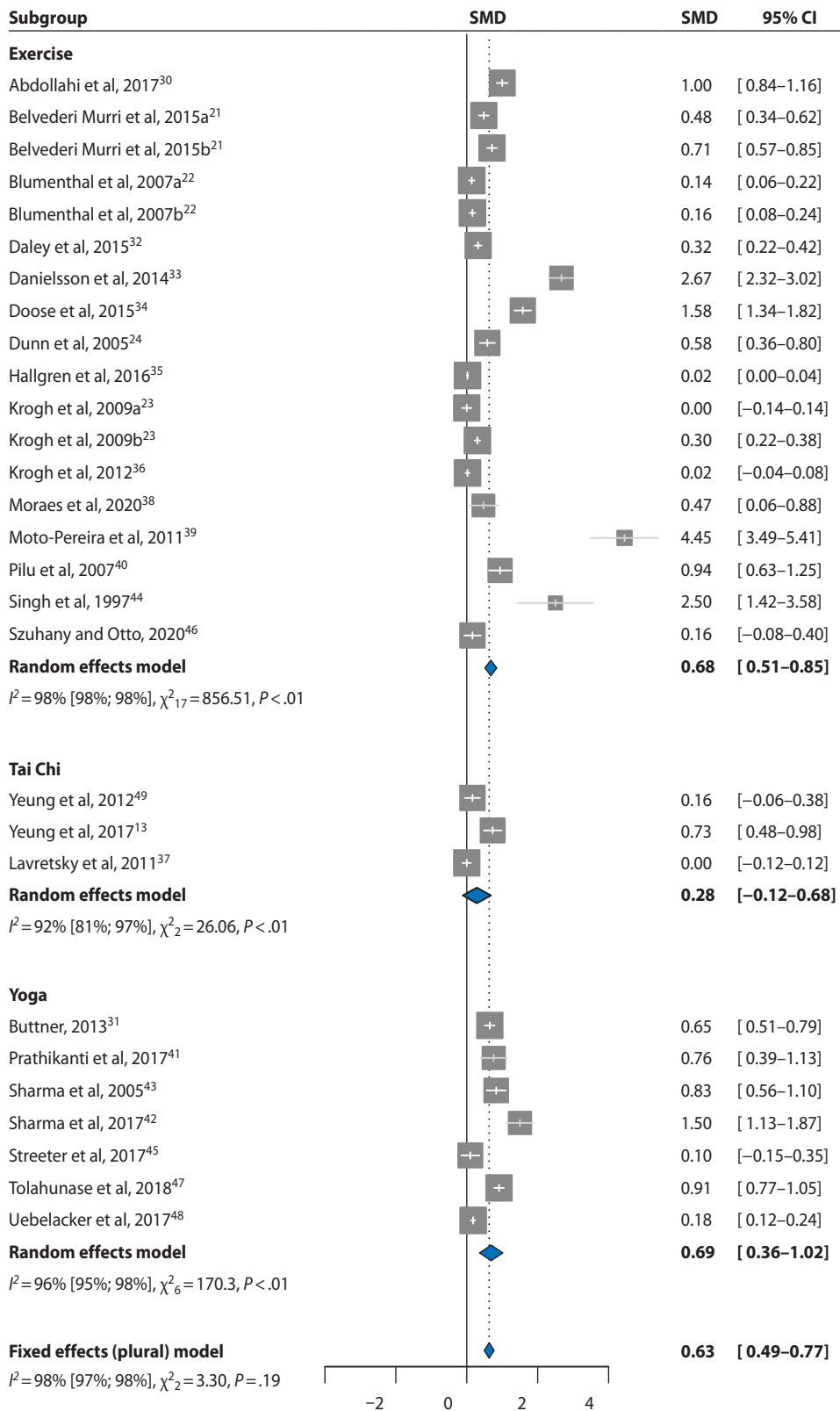
Exercise, yoga, and tai chi (combined) were significantly superior to control in the clinical group (Hedges'  $g=0.57$ ; 95% CI, 0.41–0.73;  $P<.01$ ) and volunteer group (Hedges'  $g=0.81$ ; 95% CI, 0.47–1.15;  $P<.01$ ). A mixed effects model test for subgroup differences showed significantly greater effect in volunteers compared to clinical participants ( $Q=4.8$ ,  $df=1$ ,  $P=.02$ ).

### Quality of Studies

Exercise, yoga, and tai chi (combined) were significantly superior to control in high-quality studies (Hedges'  $g=0.44$ ; 95% CI, 0.24–0.64;  $P<.01$ ) and low-quality studies (Hedges'

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Figure 2. Forest Plot Showing Mixed Effects Model Meta-Analysis Based on Type of Interventions for Depression



Abbreviation: SMD = standardized mean difference.

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$g=0.78$ ; 95% CI, 0.49–0.96;  $P<.01$ ). A mixed effects model test for subgroup differences showed significant differences based on quality of studies ( $Q=4.72$ ,  $df=1$ ,  $P=.03$ ), such that efficacy estimates were larger among low-quality studies.

### Augmentation or Monotherapy

Exercise, yoga, and tai chi (combined) were significantly superior to control when used as monotherapy (Hedges'  $g=0.40$ ; 95% CI, 0.21–0.60;  $P<.01$ ) or as augmentation to standard therapy (Hedges'  $g=0.71$ ; 95% CI, 0.53–0.96;  $P<.01$ ). A mixed effects model test for subgroup differences showed significantly greater effect with augmentation to standard therapy ( $Q=5.17$ ,  $df=1$ ,  $P=.02$ ).

### Dose or Duration of Intervention

There was no significant difference between duration of intervention sessions of duration of 30 to 45 minutes or session lengths  $>60$  minutes ( $Q=0.09$ ,  $df=1$ ,  $P=.75$ ). Similarly, there were no differences between exercise frequency  $\leq 3$  sessions per week or  $\geq 3$  sessions per week ( $Q=1.88$ ,  $df=1$ ,  $P=.38$ ).

### Publication Bias

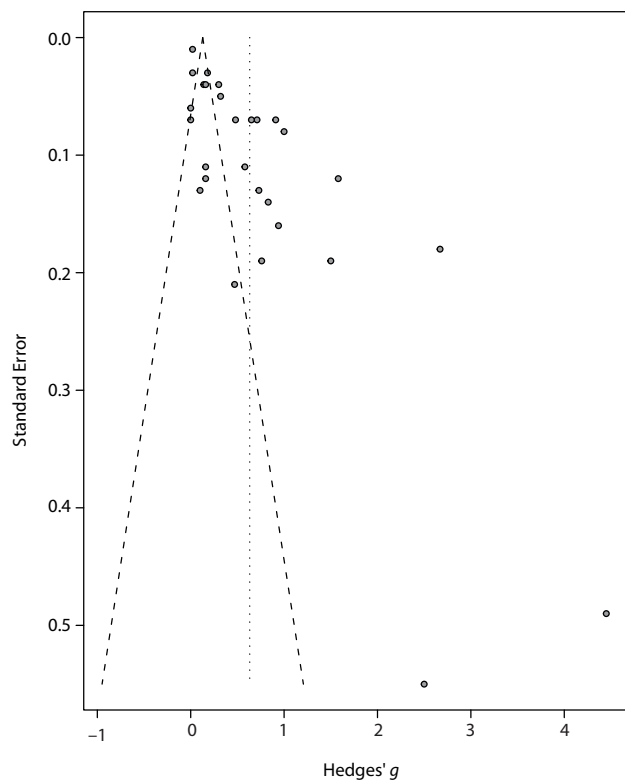
Qualitative and quantitative assessments of publication bias for studies of exercise, yoga, and tai chi using Funnel plot with trim-and-fill method and Egger regression test (intercept = 6.72; 95% CI, 4.6–8.9;  $t=6.4$ ;  $P<.001$ ) showed significant concerns with reporting bias (Figure 3). The trim-and-fill method identified and imputed 14 studies to adjust for funnel plot asymmetry. A random effects meta-analysis including the imputed data estimated the effect size for the interventions to be low (Hedges'  $g=0.11$ ; 95% CI,  $-0.03$ – $0.26$ ;  $P=.13$ ). When publication bias for studies of yoga are considered separately, an imputed model suggests a small, nonsignificant positive effect on depression (Hedges'  $g=0.32$ ; 95% CI,  $-0.005$ – $0.6$ ;  $Z=1.93$ ;  $P=.05$ ). However, considering the low number of yoga studies, this model may lack adequate statistical power to detect publication bias.

## DISCUSSION

### Summary of Main Results

The current meta-analysis of studies on exercise, yoga, and tai chi yields findings that suggest exercise and yoga may have a small additive clinical benefit as a complementary strategy to other standardized treatment modalities in the treatment of MDD. However, our study confirms the concerns expressed by previous authors<sup>11,12</sup> regarding overall quality of the published literature. Our study identified concerns for high publication bias as well. Although the overall pooled effect of exercise and yoga shows moderate clinical effect in reducing depressive symptoms in patients with a current depressive episode, this finding is based on overall low-quality evidence. When factoring in quality, the clinical effect is low in reducing depressive symptoms. When factoring for publication bias, the positive treatment effect disappears.

Figure 3. Funnel Plot of Observed Studies of Exercise, Yoga, and Tai Chi in the Treatment of Major Depressive Disorder Shows Significant Publication Bias



However, with the currently available evidence, adjunctive exercise and yoga added to usual treatment for depression may be superior to usual treatment alone. Although yoga had a better clinical effect on depression symptoms compared to exercise (after adjusting for quality and publication bias), current knowledge is inadequate to draw conclusions on its relative effect compared to traditional exercise such as aerobic exercise or strength training. Adjunctive tai chi does not appear to be an effective intervention for MDD based on current evidence.

### Overall Completeness and Applicability of Evidence

This review systematically searched the published literature in English for RCTs on exercise, yoga, and tai chi in the treatment of a current episode of MDD. We focused our review on adults diagnosed with clinical MDD. Included studies from clinical settings used clinical or standardized assessment criteria to diagnose MDD in participants. Participants in studies drawn from community volunteers were diagnosed using standardized diagnosis criteria. We excluded studies with participants reporting depressive symptoms without a formal diagnosis of MDD. While other reviews for exercise for depression exist, the last review focusing on clinical MDD was published in 2011.<sup>16</sup> This is the first review to include other modalities like tai chi and yoga, wherein additional mental processes are involved in addition to physical movements. We have updated the literature of yoga studies for MDD. This review



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focuses on the acute effects of exercise, yoga, and tai chi for depressive symptoms in MDD with a follow-up duration of at least 8 weeks. This is comparable to similar study designs of pharmacotherapy and psychotherapy interventions. However, this design does not address the longer-term effectiveness of these interventions in the treatment of MDD. We were unable to make any conclusions on optimal dose or frequency of exercise. On the basis of our analysis, we found no difference between groups based on dose or duration of exercise. One study<sup>24</sup> found that public health dose of exercise (defined by energy expenditure of 17.5 cal/kg/wk for 3–5 days a week) was no more effective than low-dose exercise (defined by energy expenditure 7 cal/kg/wk for 3 days a week) in reducing depressive symptoms. Most of the RCTs (20 studies) employed trial designs of 2 to 3 supervised sessions a week with exercise performed according to the capacity of the participants.

### Quality of the Evidence

Many of the included studies in this meta-analysis showed risk of bias. Allocation concealment bias was judged high or unclear in 48% of the studies. Six studies did not report results using intention-to-treat analysis (24%), while 6 studies showed detection bias (24%). Considering that the intervention was a form of physical activity, compared to control, there was significant risk of participant bias due to difficulty with blinding participants adequately, even when attention controlled designs were used. Overall, 6 studies qualified as high-quality across all criteria, except participant blinding. We found significant publication bias as illustrated by the asymmetric funnel plot, which likely overestimates the overall effect size of the interventions. We searched the published and gray literature and attempted to reach authors when effect size data were not clearly presented in published reports. However, we did not obtain responses to all of our requests for data.

### Agreements and Disagreements With Other Studies or Reviews

A 2013 Cochrane review and meta-analysis of exercise for depression by Cooney et al<sup>11</sup> reported moderate positive treatment effects for depression in comparison to control interventions. This effect reduced to a smaller effect when only high-quality studies were included. This review was not restricted to clinical populations or diagnosis of MDD using standardized diagnostic criteria.<sup>11</sup> The overall effect size was similar to that of the current study. A more recent meta-analysis<sup>12</sup> of exercise showed overall similar effect size (SMD = 0.66) to our current study, but also included studies with participants classified as having minor depression and inpatient participant samples. When only high-quality studies were included, no differences between exercise and control interventions were found.<sup>12</sup> In contrast, using more strict inclusion criteria of diagnosis, follow-up duration, and settings, we found evidence of a small positive effect size for studies of higher quality in our analysis.

### Implications for Practice

Our review suggests high risk of bias with the published literature of exercise, yoga, and tai chi interventions for MDD. Although the overall effect sizes suggest moderate clinical efficacy for exercise as an augmenting strategy in the treatment of MDD, when only the studies of higher quality are included, the effects of exercise are likely to be modest. Our review suggests that yoga may have a low to moderate effect on depression when used as an augmenting strategy. The effect was maintained even when only higher-quality studies were included in the analysis. We do not have enough evidence to make a judgment on effect of tai chi for MDD. Taken together, the evidence suggests that complementary exercise and yoga may offer low to moderate additional clinical benefit when added to a treatment plan for a major depressive episode. In terms of dosing, 2 to 3 sessions per week performed according to the capacity of the participants may be adequate to obtain the clinical benefit.

### Implications for Research

The role of behavioral activation in recovery from depression and the relative lack of perceived side effects from exercise have led to continued interest in use of exercise as a treatment option for patients with MDD. Adoption of complementary health practices from other regions of the world like yoga and tai chi has attracted greater interest among researchers in assessing the effects of yoga and tai chi for patients with MDD. This is evident from the multiple research publications in the last 2 years.

Larger, adequately powered studies with more robust methodology are needed to confirm early findings from the current body of studies of yoga and tai chi. Future studies of exercise, yoga, and tai chi should focus on research methodologies that use control groups utilizing evidence-based therapies or active attention-controlled groups. Trials of exercise interventions from outside Europe and North America and yoga/tai chi studies from Europe may answer whether the interventions can be applied across cultures. Additionally, head-to-head trials between exercise, yoga, and tai chi interventions may also address if one type of exercise intervention is more acceptable and feasible for people suffering from MDD. This may allow for better attention-controlled designs of RCTs.

### CONCLUSIONS

The current meta-analysis of studies of exercise, yoga, and tai chi for treatment of MDD suggest that complementary and adjunctive exercise and yoga may have a small clinical effect in comparison to treatment as usual for reducing depressive symptoms following an acute course of therapy when factoring for quality of included studies. However, the concerns with quality of studies, high heterogeneity, and evidence of publication bias found in our meta-analysis preclude making firm conclusions on clinical effect. Larger, well-designed trials with robust clinical trial

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methodologies are needed to further confirm these findings. There is insufficient evidence to make a conclusion on the effectiveness of tai chi for MDD.

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**Potential conflicts of interest:** Dr Clark has received consultant fees from Roche Diabetes Care GmbH. Dr Frye has received grant support from Assurex Health, Mayo Foundation, and Medibio; consultant fees from Actify Neurotherapies, Allergan, Intra-Cellular Therapies, Janssen, Myriad, Neuralstem, Takeda, and Teva; and CME/travel/honoraria from American Physician Institute, CME Outfitters, and Global Academy for Medical Education. Drs Seshadri, Adaji, Orth, Singh, Fuller-Tyszkiewicz, and McGillivray report no conflicts of interest related to the subject of this article.

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**Additional information:** The data that support the findings of this article are available on request from Dr Seshadri (Seshadri.Ashok@mayo.edu). The data are not publicly available due to privacy or ethical restrictions.

**Supplementary material:** See accompanying pages.

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# THE PRIMARY CARE COMPANION FOR CNS DISORDERS

## **Supplementary Material**

**Article Title:** Exercise, Yoga, and Tai Chi for Treatment of Major Depression in Outpatient Settings: A Systematic Review and Meta-Analysis

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### **List of Supplementary Material for the article**

1. Supplementary Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) 2009 Flow Diagram

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Supplementary Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) 2009 Flow Diagram

