

## CBT VS. TAI CHI FOR LATE LIFE INSOMNIA AND INFLAMMATORY RISK

## Cognitive Behavioral Therapy vs. Tai Chi for Late Life Insomnia and Inflammatory Risk: A Randomized Controlled Comparative Efficacy Trial

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**Study Objectives:** To investigate the comparative efficacy of cognitive behavioral therapy (CBT), Tai Chi Chih (TCC), and sleep seminar education control (SS) on the primary outcome of insomnia diagnosis, and secondary outcomes of sleep quality, fatigue, depressive symptoms, and inflammation in older adults with insomnia.

**Design:** Randomized controlled, comparative efficacy trial.

**Setting:** Los Angeles community.

**Patients:** 123 older adults with chronic and primary insomnia.

**Interventions:** Random assignment to CBT, TCC, or SS for 2-hour group sessions weekly over 4 months with follow-up at 7 and 16 months.

**Measurements:** Insomnia diagnosis, patient-reported outcomes, polysomnography (PSG), and high-sensitivity C-reactive protein (CRP) levels.

**Results:** CBT performed better than TCC and SS in remission of clinical insomnia as ascertained by a clinician ( $P < 0.01$ ), and also showed greater and more sustained improvement in sleep quality, sleep parameters, fatigue, and depressive symptoms than TCC and SS (all  $P$  values  $< 0.01$ ). As compared to SS, CBT was associated with a reduced risk of high CRP levels ( $> 3.0$  mg/L) at 16 months (odds ratio [OR], 0.26 [95% CI, 0.07–0.97]  $P < 0.05$ ). Remission of insomnia was associated with lower levels of CRP ( $P < 0.05$ ) at 16 months. TCC was associated with improvements in sleep quality, fatigue, and depressive symptoms as compared to SS (all  $P$ 's  $< 0.05$ ), but not insomnia remission. PSG measures did not change.

**Conclusions:** Treatment of late-life insomnia is better achieved and sustained by cognitive behavioral therapies. Insomnia treatment and remission reduces a marker of inflammatory risk, which has implications for cardiovascular morbidity and diabetes observed with sleep disturbance in epidemiologic surveys.

**Clinical Trial Registration:** ClinicalTrials.gov, NCT00280020

**Keywords:** insomnia, inflammation, late life, behavioral treatment, randomized controlled trial

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## INTRODUCTION

Insomnia is diagnosed by difficulty in initiating sleep or frequent awakenings and inability to return to sleep, which is associated with distress and daytime impairments due to fatigue and mood symptoms, for example.<sup>1</sup> In adults older than 55 years, the prevalence of insomnia disorder exceeds 15%, which is nearly twice that found in adults who are 30 to 50 years old.<sup>2</sup> In addition to functional impairments, sleep disturbance increases the risk for chronic disease and mortality in older adults,<sup>3,4</sup> possibly related to the association between sleep disturbance and increases in inflammation, including markers such as high sensitivity C-reactive protein (CRP). Indeed, insomnia complaints including difficulties initiating and maintaining sleep, as well as nonrestorative sleep, have been associated with increases in CRP and other markers of inflammation in epidemiologic,<sup>5–7</sup> naturalistic observational,<sup>8–11</sup> and clinical studies of patients with insomnia disorder.<sup>12–14</sup> Epidemiologic studies indicate that CRP levels in excess of 3 mg/L

predict cardiovascular events,<sup>15,16</sup> hypertension,<sup>17</sup> weight gain in older adults,<sup>18</sup> and type 2 diabetes.<sup>19,20</sup>

In adults, cognitive behavioral therapy (CBT), a multi-component behavioral intervention that provides sleep education, stimulus control (strengthening associations between bed and sleep), and therapy for anxiety-provoking beliefs about sleep, is an effective treatment for insomnia, with an efficacy that is better sustained than pharmacotherapy.<sup>21,22</sup> However, there are only two trials in the elderly with long-term follow-up,<sup>23,24</sup> and neither assessed remission of diagnostic insomnia nor daytime impairments such as fatigue. Moreover, it is not known whether such insomnia treatment is associated with decreases in inflammation, even though high levels of CRP are implicated in chronic disease risk in older adults with sleep disturbance.<sup>19</sup>

In contrast to CBT, which requires a trained clinician, Tai Chi Chih (TCC) is widely available, accessible to patients, and deliverable in a community setting. Controlled trial data have found that this movement meditation can improve sleep quality,<sup>25–27</sup> reduce fatigue, depressive symptoms, and markers of inflammation in older adults<sup>28–30</sup>; yet the efficacy of TCC in the treatment of clinical insomnia is not known. It is thought that TCC targets arousal mechanisms that contribute to insomnia.<sup>31–33</sup> The National Center for Complementary and Alternative Medicine (NCCAM) currently designates mind-body therapies as a top research priority.<sup>34</sup>

The goal of this randomized controlled trial in older adults was to evaluate the comparative benefit of CBT vs. TCC, relative to a

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sleep, hygiene education control (i.e., Sleep Seminar, SS) on the primary outcome of remission of insomnia diagnosis. Secondary sleep outcomes of sleep diary, patient-reported sleep outcomes, and polysomnographic (PSG) measures were also obtained. Additional secondary outcomes included patient-reported fatigue and sleepiness and clinician-rated depressive symptoms. Inflammation was measured by proportion of those with high CRP ( $> 3$  mg/L), given the clinical significance of this threshold. We hypothesized that CBT would be superior to TCC in the remission of insomnia and related symptoms, with effects on CRP in the long-term (i.e., one year after intervention administration). Secondly, we hypothesized that both CBT and TCC would perform better than SS on these outcomes.

## METHODS

### Trial Design

After recruitment, telephone screening, interview assessment, laboratory blood tests, and PSG evaluation for sleep apnea, eligible participants were randomly assigned to CBT, TCC, or SS. Each participated in 120 minutes of group class time weekly for 4 months, with assessments at baseline (pre-intervention), 2 and/or 3 months (mid-intervention), 4 months (post-intervention), and 7- and 16 months (follow-up). Because TCC required 4 months for participants to learn, CBT was longer than prior trials,<sup>23,24</sup> so that the duration of CBT and SS was comparable to TCC.<sup>21</sup> There were no changes to the methods after trial commencement.

### Study Participants

This randomized controlled trial was conducted from April 2006 to August 2011 following UCLA institutional review board approval. Study participants, recruited by means of advertisements, were community-dwelling adults older than 55 years of age who fulfilled criteria for primary insomnia in Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR)<sup>35</sup> and for general insomnia in the International Classification of Sleep Disorders, Second Edition.<sup>36</sup> These criteria specify difficulty in initiating or maintaining sleep or non-restorative sleep for at least one month, along with significant distress and daytime impairment.<sup>37</sup> DSM-V revised the duration criteria from 1 to 3 months<sup>1</sup>; we note that all participants also reported the presence of sleep difficulties  $\geq 3$  times per week for  $> 3$  months.

DSM-IV-TR exclusion criteria of medical and psychiatric disorders were applied. Additional exclusion criteria were: (1) presence of another sleep disorder such as sleep apnea (apnea-hypopnea index  $> 15$ ), restless legs, or periodic limb movements (movement index with arousal  $> 15$ /h) as determined by one night of PSG; (2) shift work or irregular sleep pattern; (3) regular ( $\geq 2$  times/week) use of hypnotic medications or alcohol for sleep (patients using prescribed or over-the-counter sleep medications  $< 3$  times/week were enrolled after they withdrew from medications); (4) current diagnosis of major depression, unless treated and in remission; (5) cognitive impairment with score  $< 23$  on Mini-Mental Status Examination<sup>38</sup>; (6) abnormal screening laboratory tests (i.e., complete blood count, liver function tests, thyroid function); (7) tobacco smoking; (8) body mass index  $> 35$  kg/m<sup>2</sup>; (9) debilitating condition that would

impede full participation in the study; or (10) unavailability during the study period.

### Interventions

CBT as previously described by Morin et al.<sup>21</sup> was modified to teach behavioral strategies for management of daytime activity levels and enhancement of mood, because insomnia is often accompanied by a variety of daytime complaints including mood disturbance. Whereas incorporation of a mood module expanded, theoretically and pragmatically, the scope of traditional CBT for insomnia,<sup>21</sup> this module was very compatible with the behavioral approach to insomnia treatment. The mood module was designed to promote understanding of the reciprocal relationship between sleep and mood, and how to implement strategies to improve mood either as a consequence of poor sleep or as a determinant of sleep disturbance. Addressing mood throughout the protocol in an integrated manner was believed to augment the efficacy of the intervention and also contribute to the maintenance and generalization of the intervention during follow-up. Additionally, we believed that comparability of CBT and TCC would be further optimized, in comparison with SS, because TCC has been found to improve depressive symptoms<sup>28,30</sup> in addition to its effects on sleep quality.<sup>25</sup> TCC emphasized control over physical function and arousal-related responsiveness, which is thought to contribute to insomnia,<sup>39</sup> through the performance of repetitious, nonstrenuous, slow-paced movement. Sleep seminar (SS) provided educational information related to the physical, medical, and psychosocial factors of aging and their contribution to sleep problems in aging. SS also provided education on sleep hygiene practices. Although sleep hygiene education has been found to produce modest improvements in sleep, this active control has been found to be inferior to other behavioral therapies such as CBT.<sup>21</sup> Each intervention was taught by one therapist (CBT: Motivala; TCC: Hollister; SS: Levin) who had at least one year experience in delivery of the treatment modality but no prior experience in sleep medicine, and supervised by another therapist (CBT: Nicassio; TCC: Taggart; SS: Irwin) who had extensive ( $> 10$  years) experience in the treatment modality to maintain therapist fidelity in delivery of the treatments as manualized. The supervising therapist evaluated treatment integrity and attended  $\geq 3$  sessions with rating of treatment elements; sessions on average contained  $> 95\%$  of the required elements. Supplement provides further details.

Treatment acceptance, credibility and expectation for change for each of the treatments was rated by participants after the second treatment session using a 9-item scale adapted from the original developed by Borkovic and Nau; items were scored on a 5-point Likert scale, and a score  $\geq 3$  on each of the 9 items defined treatment acceptability.<sup>40</sup>

### Primary Outcome

The primary outcome was remission of insomnia diagnosis by DSM-IV-TR criteria using a structured interview and checklist, performed by the study psychiatrist (MRI) who was blind to group assignment. Similar to the diagnostic methods to determine subject inclusion, quantitative sleep parameters were not used.

## Secondary Outcomes

Secondary outcomes included improvements in patient-reported outcomes of insomnia symptom severity and sleep quality (i.e., Pittsburgh Sleep Quality Index, PSQI; Athens Insomnia Scale, AIS) and daily diaries of sleep parameters for 2 weeks (i.e., Pittsburgh Sleep Diary). PSG was obtained as described for 2 nights after adaptation,<sup>41,42</sup> although prior trials have found little effects of CBT on PSG outcomes.<sup>23,43</sup>

Additional behavioral outcomes included insomnia-related daytime symptoms of fatigue (Multidimensional Fatigue Symptom Inventory [MDFSFI]),<sup>44</sup> sleepiness (Epworth Sleepiness Scale evaluated daytime sleepiness),<sup>45</sup> and clinician-rated depressive symptoms (i.e., Inventory of Depressive Symptomatology, IDS-C).<sup>46</sup>

Given the associations between insomnia and inflammation including levels of CRP,<sup>5-14</sup> as well as the clinical significance of high CRP in predicting cardiovascular and diabetes outcomes,<sup>47</sup> this study focused on assessment of CRP concentration, with categorization of high CRP (> 3.0 mg/L) after the intervention (4 months) and in the long-term (16 months) using methods previously published.<sup>48</sup> Blood sampling for CRP, limited to these 2 time points to minimize subject burden, occurred between 08:00 and 10:00. CRP levels are stable over time and show little diurnal variation.<sup>49</sup> If a subject reported recent (i.e., last month) infection, illness, or vaccination, the blood sampling was rescheduled. Because body mass index (BMI) and physical activity are related to CRP levels, body weight and height were obtained and physical activity was evaluated using the Yale Physical Activity Survey, as validated for use in older adults, with estimates of metabolic equivalents per week.<sup>50</sup>

## Sample Size

Based on prior meta-analytic findings in older adults and mean treatment effect (0.76),<sup>51</sup> 28 per treatment group provided the study with a statistical power of 80% ( $\alpha = 0.05$ ) to detect significant differential in insomnia diagnosis post-treatment (i.e., a sample size of 25 per group would be sufficient to compare the experimental treatments [CBT, TCC] to the control condition [SS]). Given interest in comparing CBT and TCC in the absence of information about the expected effect size, a 2:2:1 randomization schedule was used in which sufficient power (> 80%) was maintained for the primary hypothesis, and increased power for comparisons between CBT and TCC.

## Randomization

The randomization sequence was generated via computerized random number generator prior the start of the trial in blocks of 3 conditions (CBT: TCC: SS; 2:2:1). Blocks of 7-10 participants were used to ensure that allocated treatment groups were filled within 1 to 2 months of participant assessment. Once groups of 7-10 participants were accrued to be assigned either to CBT, TCC, or SS, the study coordinator requested the next group randomization. To maintain allocation concealment, none of the research staff who assessed subjects or enrolled participants had access to the randomization list; staff were specifically told that simple randomization was being used such that any of the 3 treatments was possible for each group assignment. In addition, the individual (RO), who managed the randomization list, never interacted with any participants nor

viewed any data from the participants prior to their assignment to condition.

## Blinding

Outcome assessors were unaware of group assignments.

## Statistical Methods

Intervention effects on DSM-IV-TR insomnia diagnosis were tested by  $\chi^2$  analysis. Intervention effects on the secondary continuous outcome measures were tested on an intention-to-treat basis using a mixed model approach; data from all randomized participants were included with no imputation of missing data. The mixed model approach utilizes all available data and generates unbiased estimates under the assumption that data are missing at random (MAR); or more restrictively, missing completely at random (MCAR). Because it would require information that is, by definition, not available, there are no well-established tests of the MAR assumption; hence, the MCAR assumption was tested.

*A priori* linear contrasts tested group differences from baseline to 16-month follow-up across all available time points, controlling for multiple comparisons, in which time was indexed as months of follow-up. To reduce the potential for type I error, only primary and key secondary outcomes were tested. For pairwise comparisons, the least significant difference (LSD) method was utilized. For CRP, additional analyses examined intervention effects on the proportion of those with high CRP, including evaluation of the odds ratio of CBT and TCC vs. SS. Secondary analyses evaluated the effects of insomnia remission at 4 months on CRP levels. Data were available on > 95% of the subjects at all time points among those who completed follow-up assessments. Analyses were carried out with IBM SPSS for Windows, version 19.

## Role of the Funding Source

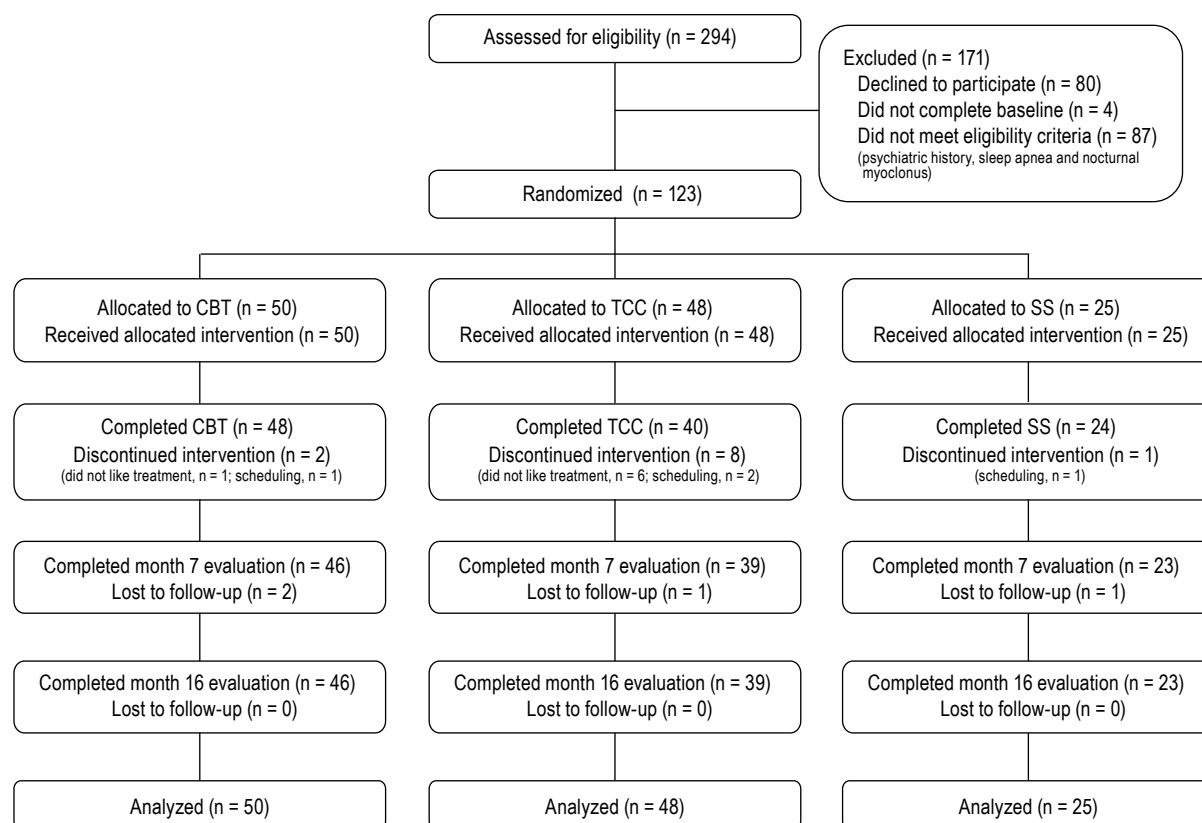
The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript.

## RESULTS

### Baseline Characteristics of the Patients

Of a total of 294 who underwent baseline assessment, 87 were identified as not eligible. Of the 207 who were eligible, 123 agreed to participate and also completed the entire baseline assessment including a night of PSG (59%; Figure 1). Treatment groups were comparable with regard to background characteristics (Table 1).

A total of 112 (92%) participants completed their assigned interventions (4 months), and 108 (89%) completed follow-up (16 months). Those who did not complete the intervention were likely to be younger ( $t_{121} = 2.12$ ;  $P < 0.05$ ) and have higher scores on the PSQI ( $t_{121} = 1.72$ ;  $P = 0.09$ ) and the MDFSFI ( $t_{121} = 1.78$ ;  $P = 0.05$ ), whereas those who did not complete the follow-up were more likely to have higher scores on the IDS-C ( $t_{110} = 2.82$ ;  $P = 0.05$ ) and the MDFSFI ( $t_{110} = 3.23$ ;  $P < 0.001$ ). Other demographic and outcome variables did not differ between the completers and non-completers at months 4



**Figure 1**—Screening, randomization, and completion of post-intervention, 7-month, and 16-month evaluations. CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.

or 16. At month 4, the drop-out rate tended to be higher in the TCC group as compared to CBT and SS ( $\chi^2(2) = 5.77$ ;  $P = 0.06$ ), but at month 16 the retention rate was similar ( $\chi^2(2) = 3.16$ ;  $P = 0.21$ ). Tests of the continuous data suggested missing values fit the MCAR assumption ( $\chi^2(486) = 523.1$ ;  $P = 0.12$ ) though EM estimates and the results regarding non-completers above suggest a slight bias toward those not completing the trial to have poorer outcomes.

The average rate of session attendance was similar (i.e., 79% in CBT; 81% in TCC and 74% in SS;  $F_{2,120} = 0.99$ ;  $P = 0.38$ ). Additionally, nearly all participants perceived the 3 interventions as acceptable treatments as defined above to improve their insomnia symptoms (98% in CBT; 94% in TCC; 95% in SS;  $\chi^2(2) = 0.58$ ;  $P = 0.74$ ). However, at the conclusion of treatment, SS and TCC participants reported significantly less confidence that their treatment would be effective for others, as compared to those in CBT ( $F_{2,91} = 10.3$ ;  $P < 0.001$ ). Nevertheless, post-treatment perception that treatments were acceptable remained high and not different (100% in CBT, 91% in TCC; 96% in SS;  $\chi^2(2) = 3.58$ ;  $P = 0.17$ ). Among the TCC participants, 90% continued to practice during the follow-up period from months 4 to 16, although average frequency of practice for  $> 30$  min decreased from 3.3 (SD, 2.2) days to 2.3 (SD, 2.0) days ( $t_{33} = 3.16$ ;  $P = 0.004$ ).

There were no significant between-group changes from baseline to post-treatment in occasional sedative-hypnotic medication use ( $F_{2,106.4} = 0.36$ ;  $P = 0.70$ ), body mass index ( $F_{2,90.9} = 1.71$ ;  $P = 0.19$ ), or physical activity (i.e., metabolic equivalents per

week as estimated by the Yale Physical Activity Survey<sup>50</sup>;  $F_{2,104.8} = 1.79$ ;  $P = 0.17$ ). Given that TCC involved a physical activity component not found in CBT or SS, the absence of within group change in physical activity in TCC suggests that participants substituted TCC for other aerobic activity.

### Primary Outcome

Diagnostic assessment of insomnia using DSM-IVTR criteria at 4 months showed that CBT resulted in a nearly two-fold greater rate of remission than TCC and SS ( $\chi^2 = 9.34$ ,  $P < 0.01$ ; Figure 2). For CBT vs. SS, the number needed to treat was 3 (95% CI, 1.8–8.5), the absolute risk reduction was 33.3% (95% CI, 11.8%–4.8%), and the relative risk reduction was 72.7% (95% CI, 19.3%–100%). This represents a medium to large effect size (estimated  $d = 0.65$ ). Results comparing CBT vs. SS were not substantively different if those lost at post-treatment were considered remitters ( $\chi^2 = 6.89$ ;  $P < 0.01$ ) or non-remitters ( $\chi^2 = 7.04$ ;  $P < 0.01$ ). More individuals failed to complete the post-treatment assessment in the TCC group; hence, as compared to effect sizes between CBT and SS, effect size differences between TCC and CBT or SS were much more variable under different assumptions of missing data at follow-up. Assuming those lost at post-treatment were all non-remitters, the effect size of CBT vs TCC was estimated  $d = 0.71$  and TCC vs. SS was estimated  $d = 0.10$ . Assuming those lost at post-treatment were all remitters, the effect size of CBT vs. TCC was estimated  $d = 0.23$  and TCC vs SS was estimated  $d = 0.54$ . The former option seems more tenable.



## Secondary Outcomes of Sleep

Insomnia symptom severity as indexed by the Pittsburgh Sleep Quality Index (PSQI), showed an overall treatment effect ( $F_{2,118.8} = 9.73$ ;  $P < 0.001$ ), in which CBT resulted in greater improvement in global sleep quality than TCC ( $t_{531.3} = 2.64$ ;  $P < 0.01$ ; estimated  $d = 0.27$ ) and SS ( $t_{522.7} = 2.70$ ;  $P < 0.01$ ; estimated  $d = 0.44$ ) from baseline to 16 months (Table S1, Figure 3). Specific time contrasts also showed that TCC resulted in improvements of global sleep quality as compared to SS at months 4 and 7 ( $P$  values  $< 0.05$ ), but not at month 16 (Figure 3). Results using the Athens Insomnia Scale were similar (Table S1). Among the TCC participants, there was no relationship between practice time and improvement in sleep quality at month 4, and no relationship between decrease in practice time from months 4 to 16 and sleep quality at month 16.

Sleep parameters (total sleep time, TST; sleep latency, SL; sleep efficiency SE; wakefulness after sleep onset, WASO) were indexed using 2 methodologies: sleep diaries and PSG. Sleep diaries showed that CBT resulted in greater improvements in SL, SE, and WASO, but not TST, from baseline to month 16 as compared to TCC and SS ( $P$  values  $< 0.05$ ; Table S1). No differences were found between TCC and SS for any of the sleep diary measures of sleep parameters (all  $P$  values  $> 0.10$ ). PSG measures of TST, SL, SE, and WASO from baseline to month 4 did not differ for the groups (all  $P$  values  $> 0.10$ ; Table S1).

## Secondary Outcomes of Fatigue and Depression

For fatigue severity as indexed by the Multidimensional Fatigue Symptom Inventory (MFSI), linear trend contrasts found that the slope of decrease of MFSI scores was greater in the CBT group as compared to TCC and SS (all  $P$  values  $< 0.05$ ; estimated  $d$ 's: 0.32 and 0.36, respectively; Table S2). Specific contrasts also showed that TCC resulted in lower levels of fatigue than SS at months 2, 4, and 7 (all  $P$  values  $< 0.05$ ). No treatment effects were found for daytime sleepiness. For clinician rated depressive symptom severity as indexed by IDS-C, CBT also resulted in greater decreases in depressive symptom severity than TCC and SS (all  $P$  values  $< 0.05$ , estimated  $d$ 's: 0.20 and 0.32, respectively; Figure 4). In addition, specific contrasts showed that TCC resulted in lower levels of depressive symptoms than SS at months 2, 3, and 4 ( $P$ 's  $< 0.05$ ; Table S2; Figure 4). Additional analyses with the IDS-C, in which items related to sleep disturbance were excluded, yielded similar results.

## Secondary Outcomes of Inflammation

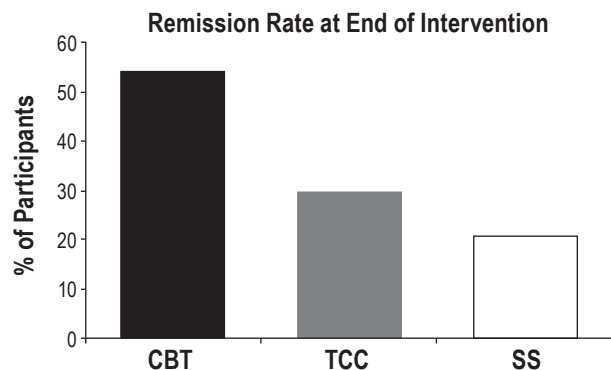
Insomnia treatment was hypothesized to reduce the risk of high CRP ( $> 3.0$  mg/L), in which insomnia remission would be

**Table 1**—Baseline characteristics of participants, by treatment group.

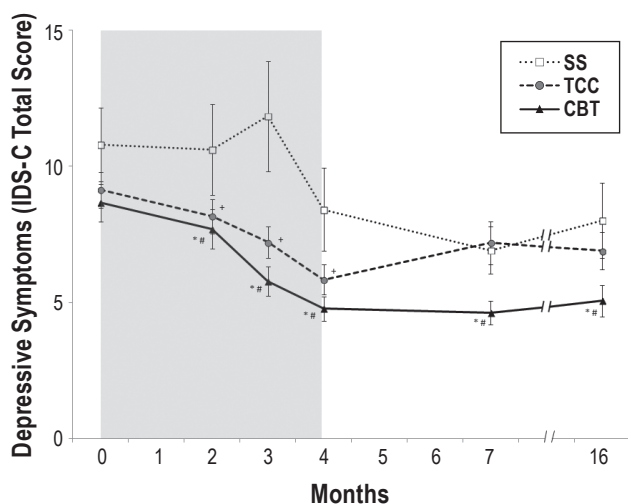
Variable <sup>†</sup>	CBT (N = 50)	TCC (N = 48)	SS (N = 25)
Age (55 to 85 years)	64.4 (6.1)	66.3 (7.4)	66.4 (7.7)
Female, n (%)	39 (78.0)	31 (64.6)	18 (72.0)
Ethnicity, Hispanic, n (%)	3 (6.0)	3 (6.4)	3 (12.5)
Race, Non-white, n (%)	6 (12.2)	7 (14.9)	4 (16.7)
Marital status, Married, n (%)	25 (50.0)	21 (43.8)	8 (32.0)
Employment			
Working, n (%)	21 (42.0)	20 (41.7)	10 (40.0)
Work hours per week	13.6 (18.5)	11.7 (18.6)	11.4 (15.3)
Education (years)	15.8 (1.4)	15.7 (1.5)	15.3 (1.5)
Body mass index (kg/m <sup>2</sup> )	25.4 (3.3)	26.4 (4.0)	26.3 (4.5)
Comorbidity			
Medical, n (%) <sup>*</sup>	19 (39.6)	22 (48.9)	14 (56.0)
Depression history, n (%)	12 (24.0)	12 (25.0)	8 (32.0)
Other psychiatric history, n (%)	9 (18.0)	6 (12.5)	3 (12.5)
Prior hypnotic drug usage, n (%)	12 (24.0)	7 (14.6)	2 (8.0)
Sleep Quality			
PSQI, total score	10.4 (2.9)	10.7 (3.1)	11.1 (2.9)
Athens Insomnia Scale	10.9 (3.1)	11.7 (5.0)	11.6 (3.0)
Total Sleep Time			
Sleep Diary (min)	339.5 (9.7)	327.1 (10.9)	342.4 (14.7)
Polysomnography (min)	370.7 (52.2)	378.9 (41.2)	356.4 (68.6)
Sleep Latency			
Sleep Diary (min)	34.8 (3.8)	39.9 (5.0)	41.3 (4.8)
Polysomnography (min)	20.4 (34.3)	25.0 (24.3)	33.6 (28.5)
Sleep Efficiency			
Sleep Diary (%)	69.6 (1.9)	67.5 (2.0)	69.6 (2.3)
Polysomnography (%)	78.5 (10.8)	80.1 (8.7)	74.5 (14.4)
Wake after Sleep Onset			
Sleep Diary (min)	73.5 (6.0)	64.4 (6.6)	80.5 (8.6)
Polysomnography (min)	81.6 (47.3)	69.2 (37.7)	88.7 (70.7)
Fatigue			
MDFS Total Score	9.8 (18.4)	8.5 (17.1)	10.4 (17.0)
Sleepiness			
Epworth Sleepiness Scale Score	7.7 (5.7)	6.7 (4.5)	7.1 (4.3)
Depressive symptoms			
IDS-C	8.7 (4.8)	9.1 (4.5)	10.8 (6.8)
Inflammation			
CRP (mg/L)	1.9 (1.9)	2.0 (2.1)	2.1 (2.2)
Proportion with high CRP ( $> 3.0$ mg/L) (%)	20.0	20.8	21.7

All values are mean (SD) unless noted with percent. Between-group differences were tested with a  $\chi^2$  test for categorical variables and one-way analysis of variance for continuous variables. <sup>†</sup>All  $P$  values were  $P > 0.19$ . <sup>\*</sup>Among those who reported medical comorbidity, 95% reported cardiovascular disease. CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar; PSQI, Pittsburgh Sleep Quality Index; MDFS, Multidimensional Fatigue Severity Index; IDS-C, Inventory of Depressive Symptoms-Clinician Rating Scale; CRP, C-reactive protein.

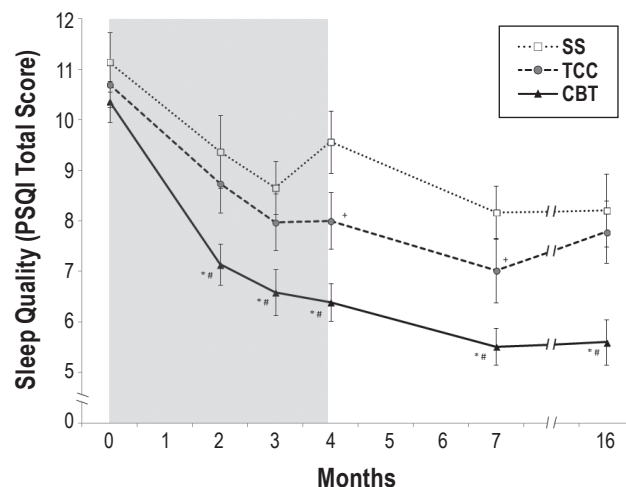
associated with a reduction of CRP. The percentage of participants with high CRP differed between the groups from baseline to month 16, in which high CRP was less likely to be found in the CBT participants as compared to TCC and SS ( $\chi^2(1) = 4.0$ ,



**Figure 2**—Percentage of participants with remission of DSM-IV-TR insomnia at 4 months (post-intervention) in the CBT, TCC, and SS treatment groups. Insomnia diagnosis was made by clinician interview using DSM-IV-TR criteria. At post-intervention, the rate of remission was 54.2% in CBT vs. 29.7% in TCC ( $\chi^2 = 7.25$ ,  $P < 0.05$ ) and 20.8% in SS ( $\chi^2 = 5.1$ ,  $P < 0.01$ ); the rate of remission was similar in the TCC and SS groups. Conversely, the percentage of participants who continued to have DSM-IV-TR insomnia was lower in the CBT group (45.8%) than in the TCC (70.3%) and SS groups (79.2%). The percentage of participants with insomnia was similar in the TCC and SS groups ( $\chi^2 = 0.60$ ,  $P = 0.44$ ). CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.



**Figure 4**—Change in depressive symptoms severity from baseline to month 16 follow-up in the CBT, TCC, and SS treatment groups. Total scores on the Inventory of Depressive Symptomatology-Clinician Rating Scale (IDS-C) range from 0 to 84, with higher scores indicating more severe depressive symptoms. Values are means; bars indicate standard error of measurement. Measurements were obtained at baseline and months 2 and 3 (mid-intervention), 4 (post-intervention), and 7 and 16 (follow-up). Shaded area indicates period of administration of intervention following baseline assessment. \* Significant linear trend contrasts between CBT vs SS ( $t_{521.1} = 1.98$ ;  $P < 0.05$ ). # Significant linear trend contrasts between CBT vs TCC ( $t_{523.0} = 1.98$ ;  $P < 0.05$ ). \* Significant pairwise comparisons between TCC vs SS. Similar results were found when the sleep disturbance items of the IDS-C were removed. CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.



**Figure 3**—Change in global sleep quality from baseline to month 16 follow-up in the CBT, TCC, and SS treatment groups. Total scores on the Pittsburgh Sleep Quality Index (PSQI) range from 0 to 21, with higher scores indicating worse sleep quality. Values are means; bars indicate standard error of measurement. Measurements were obtained at baseline and months 2 and 3 (mid-intervention), 4 (post-intervention), and 7 and 16 (follow-up). Shaded area indicates period of administration of intervention following baseline assessment. \* Significant linear trend contrasts between CBT vs SS ( $t_{522.7} = 2.70$ ;  $P < 0.01$ ). # Significant linear trend contrasts between CBT vs TCC ( $t_{531.3} = 2.64$ ;  $P < 0.05$ ). \* Significant pairwise comparisons between TCC vs SS. CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.

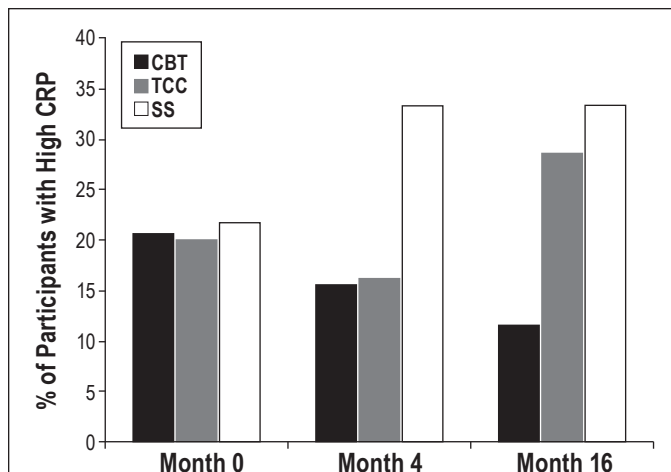
(OR, 0.26 [CI, 0.07–0.97];  $P < 0.05$ ) (Figure 5, Table S3). As compared to SS, there was a non-significant effect of TCC on lower risk of high CRP at 4 months (OR, 0.39 [CI, 0.11–1.3]  $P = 0.10$ ), but no difference was found at 16 months (OR, 0.8; [CI, 0.25–2.5]  $P = 0.47$ ). As compared to SS, the change in proportion CBT participants with high CRP from baseline to month 16 was significantly greater ( $\chi^2(1) = 4.0$ ,  $P = 0.04$ ), with a nearly 50% decrease in the CBT group. Change in proportion of TCC participants with high CRP from baseline to month 16 was similar to SS ( $P > 0.70$ ). Although CBT and SS showed a divergence in the proportion of high CRP, change in proportion of high CRP from baseline to month 16 in the SS group was not significant ( $P > 0.30$ ).

To further evaluate the association between insomnia treatment and reduction of CRP levels, the sample was stratified into those who showed a remission of insomnia disorder and those who continued to fulfill criteria for insomnia. As compared to non-remitters, those with remission of insomnia had similar levels of CRP at 4 months ( $t = 0.18$ ,  $P = 0.86$ ), but significantly lower levels of CRP at 16 months ( $t = 1.7$ ,  $P < 0.05$ ; Figure 6).

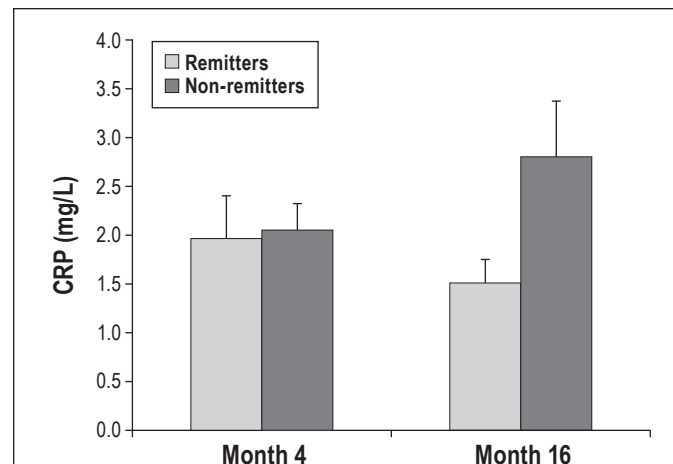
## DISCUSSION

This is the first randomized, controlled trial that has evaluated the comparative efficacy of TCC vs. CBT, a standardized behavioral intervention for insomnia. We found that CBT is more effective in the treatment of insomnia in older adults than TCC or the control intervention (SS). CBT produced a significant rate of remission of diagnostic insomnia that was nearly 2-fold greater than either TCC or SS. The additional benefits of CBT included improvements in sleep parameters, sleep

$P = 0.04$ ; Figure 5). As compared to SS, CBT was associated with a reduced risk of having high CRP at 4 months (odds ratio [OR], 0.37 [95% CI, 0.11–1.18];  $P = 0.08$ ) and at 16 months



**Figure 5**—Percentage of participants with high C-reactive protein (CRP) at baseline, 4 months, and 16 months in the CBT, TCC, and SS treatment groups. High CRP was defined by levels in excess of 3.0 mg/L. High CRP was less likely to be found in the CBT participants as compared to SS ( $\chi^2(1) = 4.0$ ,  $P = 0.04$ ). As compared to SS, CBT was associated with a reduced risk of having high CRP at 4 months (odds ratio [OR], 0.37 [95% CI, 0.11–1.18];  $P = 0.08$ ) and at 16 months (OR, 0.26 [CI, 0.07–0.97];  $P < 0.05$ ). As compared to SS, TCC was not associated with reduced risk of high CRP at 4 months (OR, 0.39 [CI, 0.11–1.3]  $P = 0.10$ ), or at 16 months (OR, 0.8; [CI, 0.25–2.5]  $P = 0.47$ ). In SS, change in percentage with high CRP from baseline to month 16 was not significant ( $P > 0.30$ ). CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.



**Figure 6**—Levels of C-reactive protein (CRP) in participants with and without remission of DSM-IV-TR insomnia. As compared to non-remitters, those with remission of insomnia had similar levels of CRP at 4 months ( $t = 0.18$ ,  $P = 0.86$ ), but significantly lower levels of CRP at 16 months ( $t = 1.7$ ,  $P < 0.05$ ).

quality, and symptoms of daytime fatigue and depression but not daytime sleepiness, which were sustained one year after treatment. Contrary to our hypothesis, and despite the fact that we had the power to detect a clinically significant effect, TCC did not yield improvements in rates of insomnia remission and sleep parameters as compared to SS. However, administration of TCC improved sleep quality, fatigue, and depression as compared to SS, although these gains were less robust than CBT and were not maintained for the duration of the follow-up.

Along with improvements in sleep outcomes, this study provides novel insight that insomnia treatment is related to decreases in a clinically relevant marker of inflammation, CRP. Given that high levels of CRP are prospectively associated with incident cardiovascular disease<sup>15,16</sup> and diabetes,<sup>52</sup> and that levels of CRP in excess of 3.0 mg/L indicate substantially elevated cardiovascular risk,<sup>47</sup> it is noteworthy that CBT treatment was associated with a significant decrease in the risk of high CRP. The proportion of participants with high CRP at baseline decreased by nearly 50% one year after treatment with an odds ratio (0.26) relative to SS, which is comparable to the benefit reported with vigorous physical activity<sup>53</sup> or weight loss.<sup>54</sup> Moreover, among those who showed remission of insomnia disorder, average levels of CRP were nearly 50% lower one year after treatment than those who continued to fulfill criteria for insomnia disorder. The maintenance of sleep improvements appears to play a critical role in the reduction of CRP; for example in TCC, the decreases of CRP that emerged at post-intervention were no longer present one year after treatment when improvements in sleep outcomes were lost. Decreases in CRP cannot be attributed to changes in body weight or physical activity because neither of these factors changed in any

of the groups. Finally, when insomnia is untreated and sleep disturbance persists (i.e., SS participants), it appears that CRP progressively increases similar to the effects of psychological stress on the inflammatory marker interleukin-6 in older adults.<sup>55</sup> Together, these findings indicate that it is even more critical to treat insomnia in this population who are already at elevated risk for aging related inflammatory disease.

The mechanism of action that leads to a reduction in the risk of high CRP following remission of insomnia is not known. However, patients with insomnia disorder show sympathetic hyperactivation, as evidenced by an absent nocturnal autonomic drop,<sup>56</sup> resulting in higher levels of sympathetic catecholamines.<sup>57</sup> In turn,  $\beta$ -adrenergic signaling can activate nuclear factor (NF)- $\kappa$ B, upregulate transcription of proinflammatory cytokine genes, and lead to increased production of interleukin-6, which drives increases in CRP.<sup>19</sup> Hence, treatment of insomnia may reduce sympathetic nervous system activity and contribute to the relative reduction in CRP. In turn, inflammatory cytokines can signal the central nervous system and alter symptoms of fatigue<sup>58–60</sup> and depression,<sup>19,61,62</sup> which suggests that reduction in proinflammatory activity may have salutary effects on these insomnia related symptoms. Finally, arousal mechanisms fail to decline from waking to sleep states in insomnia patients, which is thought to contribute to daytime fatigue.<sup>31</sup> Because nocturnal sympathetic activity is lowest during slow wave sleep and highest during REM sleep,<sup>63</sup> further research is needed to evaluate whether insomnia treatment affects nocturnal arousal mechanisms and/or the sleep architecture, with attendant effects on sympathetic activation, inflammatory biology, and fatigue.

This is one of largest controlled trials comparing behavioral therapies for insomnia in older adults. We found six published randomized controlled trials of CBT for insomnia in older adults,<sup>23,24,43,64–66</sup> and only two studies evaluated sleep using subjective and objective outcomes with long-term follow-up; one of these used a wait-list control and objectively assessed sleep with actigraphy rather than PSG.<sup>23,24</sup> The present study



replicates large effect sizes for CBT on sleep outcomes of quality and continuity; consistent with prior trials in older adults,<sup>51</sup> CBT did not alter sleep duration. This study is novel in systematic evaluation of insomnia remission, along with daytime impairments, which together comprise the diagnosis of insomnia.

CBT employed a mood enhancement module that is not typically included in other CBT therapies, which might have contributed to the improvement in the daytime depressive symptoms, and to the relative benefit of CBT as compared to TCC. However, TCC was also found to reduce depressive symptoms consistent with prior trials.<sup>28,30</sup> Additionally, in contrast to other CBT trials, sleep restriction was not used due to the known effects of short sleep duration on inflammation,<sup>41,42</sup> although long sleep has also been found to increase markers of inflammation.<sup>67</sup> Nevertheless, the effects of CBT on chronic insomnia are nearly identical to prior results,<sup>24,43</sup> in showing clinically significant remission of insomnia diagnosis. CBT has not been consistently found to alter PSG in older adults.<sup>23,43</sup> Finally, duration of CBT in this trial was long and comparable to TCC, which requires more time for participants to learn and master the movements; a typical course of CBT for insomnia is considerably shorter, lasting 6 to 8 weeks.

Consistent with prior studies that have solely targeted older adults with sleep complaints, but not clinical insomnia, TCC yields modest improvements in subjective assessments of sleep quality as compared to a control condition.<sup>25</sup> Meta-analyses show that tai chi, when regularly practiced, has a role in symptom management,<sup>68</sup> but the present findings do not support the use of TCC as a treatment for clinically significant insomnia in older adults nor as a substitute for a behavioral intervention that specifically targets insomnia symptoms.

There are limitations that require consideration. As is the case with behavior-based treatments, participants were aware of their intervention assignment, which may have introduced biases in the results. However, to minimize the influence of preexisting beliefs and expectations, participants were informed that the study was designed to test the effects of three different treatments on sleep; expectations of benefit and post-treatment acceptability were similar in the three groups. Secondly, this study used one set of therapists to deliver TCC intervention, and another set to deliver CBT and SS treatments; several therapists with expertise in all treatment modalities would have been better balanced and it is possible that differences between therapists might have contributed to the treatment effects. Third, it is possible that the scope of the CBT that included a mood enhancement component disadvantaged TCC. However, key differences between the two groups were found principally in the maintenance of benefit in the long-term after the intervention had ended. Fourth, generalizability of these results to a more diverse community sample or a primary care population are limited by recruitment of older adults by advertisement, overrepresentation of women, and exclusion of those with comorbid medical or psychiatric illness and/or an inability to stop regular use of hypnotic medications, which yielded a low participation rate. Fifth, the assessment of daytime functioning was limited to the use of questionnaires to assess fatigue, depressive symptoms, and sleepiness. Finally, there was a lack of effect of any of the treatment on PSG data. However, in clinical practice, patients with insomnia do not receive sleep

recordings and physicians base the success of any given treatment on patient reports of improved sleep.

Given its impact on insomnia related symptoms, further research is needed to evaluate whether TCC might be used as a stepped approach, for example, in the management of prodromal sleep disturbance before the onset of clinically severe, chronic insomnia in older adults. However, CBT as a sleep-focused, non-drug behavioral intervention effectively treats chronic insomnia in late life with evidence that these therapeutic gains are well maintained. Of particular importance, CBT along with remission of insomnia contributed to clinically meaningful reductions in CRP. Together our findings demonstrate that CBT for insomnia in older adults is an efficacious treatment for both achieving remission of insomnia and modifying an inflammatory marker of cardiovascular disease and diabetes risk.

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## DISCLOSURE STATEMENT

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### Description of Interventions

The cognitive behavior therapy for sleep quality (CBT) was a multicomponent (i.e., behavioral, cognitive, educational) intervention as previously described by Morin et al.,<sup>1</sup> with modification to teach behavioral strategies for management of daytime activity levels and enhancement of mood. CBT was administered in groups of 7-10 subjects by two co-therapists, a licensed

clinical psychologist and a Ph.D. level psychologist, each with specialty training in behavioral medicine. Using a manualized approach, each session dictated objectives, patient skills, and treatment activities, in which therapists provided direct role-playing and other skill-development exercises designed to increase patients' self-efficacy in managing their insomnia. CBT included five treatment modules: (1) *Biopsychosocial Model and*

**Table S1**—Primary sleep outcomes in each treatment group from baseline to 16 months

	CBT (N = 50)	TCC (N = 48)	SS (n = 25)		CBT (N = 50)	TCC (N = 48)	SS (n = 25)
<b>Sleep Quality</b>				<b>Sleep Latency</b>			
PSQI, total score <sup>†,¶</sup>				Sleep Diary <sup>††,§</sup>			
Baseline	10.4 (2.9)	10.7 (3.1)	11.1 (2.9)	Baseline	34.8 (3.8)	39.9 (5.0)	41.3 (4.8)
Month 2	7.1 (2.8)	8.7 (3.6)	9.4 (3.5)	Month 4	20.7 (2.0)	28.4 (4.2)	29.1 (4.7)
Month 3	6.6 (2.8)	8.0 (3.4)	8.7 (2.5)	Month 7	14.2 (1.2)	25.9 (3.3)	27.3 (5.6)
Month 4	6.4 (2.6)	8.0 (3.4)	9.6 (3.0)	Month 16	16.1 (1.5)	26.1 (4.0)	22.4 (3.2)
Month 7	5.5 (2.5)	7.0 (3.9)	8.2 (2.6)	Polysomnography*			
Month 16	5.6 (3.0)	7.8 (3.8)	8.2 (3.4)	Baseline	20.4 (34.3)	25.0 (24.3)	33.6 (28.5)
Athens Insomnia Scale <sup>†,¶</sup>				Month 4	19.2 (23.0)	19.0 (22.1)	22.3 (22.1)
Baseline	10.9 (3.1)	11.7 (5.0)	11.6 (3.0)	<b>Sleep Efficiency</b>			
Month 2	8.1 (4.6)	8.5 (3.5)	10.0 (4.2)	Sleep Diary <sup>††,§</sup>			
Month 3	7.3 (3.9)	7.8 (3.6)	9.0 (3.5)	Baseline	69.6 (1.9)	67.5 (2.0)	69.6 (2.3)
Month 4	6.1 (3.4)	7.6 (3.0)	9.5 (4.0)	Month 4	83.3 (1.2)	75.1 (2.3)	74.5 (3.8)
Month 7	5.3 (3.2)	6.4 (3.4)	7.9 (3.8)	Month 7	83.9 (1.2)	76.3 (2.9)	75.3 (3.9)
Month 16	5.4 (3.1)	7.0 (4.7)	7.6 (4.4)	Month 16	84.1 (1.3)	78.0 (2.4)	77.7 (3.7)
<b>Total Sleep Time</b>				Polysomnography*			
Sleep Diary <sup>§</sup>				Baseline	78.5 (10.8)	80.1 (8.7)	74.5 (14.4)
Baseline	339.5 (9.7)	327.1 (10.9)	342.4 (14.7)	Month 4	80.8 (8.9)	80.6 (11.2)	79.5 (10.3)
Month 4	381.8 (8.7)	374.5 (11.1)	372.1 (24.8)	<b>Wake after Sleep Onset</b>			
Month 7	391.0 (7.8)	391.5 (16.1)	379.0 (22.1)	Sleep Diary <sup>††,§</sup>			
Month 16	396.6 (8.1)	389.0 (12.5)	381.4 (22.1)	Baseline	73.5 (6.0)	64.4 (6.6)	80.5 (8.6)
Polysomnography*				Month 4	32.8 (3.6)	55.5 (7.8)	54.6 (8.1)
Baseline	370.7 (52.2)	378.9 (41.2)	356.4 (68.6)	Month 7	35.9 (3.7)	37.8 (6.0)	50.2 (9.3)
Month 4	383.5 (43.8)	381.3 (54.2)	378.8 (53.7)	Month 16	34.5 (4.4)	36.7 (6.4)	51.3 (9.6)
				Polysomnography*			
				Baseline	81.6 (47.3)	69.2 (37.7)	88.7 (70.7)
				Month 4	73.5 (36.1)	72.5 (52.6)	75.1 (43.0)

All values are means (SD). <sup>†</sup> Mixed repeated-measures analysis of variance (group by time) with baseline, months 2, 3, 4, 7, and 16 values indicated a significant between group difference (range  $P < 0.05$  to  $P < 0.001$ ) and time effect (all  $P < 0.001$ ) across all outcomes. Analyses were performed on an intention to treat basis. <sup>††</sup> Mixed repeated-measures analysis of variance (group by time) with baseline, months 4, 7, and 16 values indicated a significant between group difference (range  $P < 0.05$  to  $P < 0.01$ ) and time effect (all  $P < 0.001$ ) across all outcomes. Analyses were performed on an intention to treat basis. <sup>¶</sup> Pittsburgh Sleep Quality Index (PSQI) and Athens Insomnia Scale (AIS) evaluated severity and impact of insomnia symptoms on daytime functioning at baseline and months 2, 3, 4, 7, and 16. Scores on the PSQI range from 0 to 21, with higher scores indicating worse sleep quality, as indexed by individual sleep quality ratings and individual sleep parameter components including total sleep time (TST), sleep latency (SL), sleep efficiency (SE), and wakefulness after sleep onset (WASO). Scores on the AIS range from 0 to 24, with higher scores indicating more severe insomnia symptoms and impairments in daytime functioning. <sup>§</sup> Pittsburgh Sleep Diary evaluated patient reported sleep activity at baseline and months 4, 7, and 16. For two weeks at each assessment, daily reports of bed-time, wake-time, SL, and WASO, were obtained and used to calculate total sleep time (TST) and sleep efficiency (SE;  $TST/\text{time in bed} \times 100$ ). Mean values for two weeks of daily measurement at each assessment are reported. \* Polysomnography (PSG) evaluated sleep activity in a sleep laboratory as previously described using a standard PSG montage at baseline and month 4. Up to 6 nights of sleep laboratory evaluation including 3 nights at baseline, and 3 nights at months 4, with the first night serving as adaptation to the sleep laboratory and/or evaluation for sleep apnea and periodic limb movements. Scoring of PSG used standardized criteria, which focused on primary sleep continuity variables TST, SOL, SE, and WASO. Mean PSG data from the second and third nights used as an outcome. CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.



**Table S2**—Secondary outcomes of fatigue, sleepiness and depressive symptoms in each treatment group from baseline to 16 months

	CBT (N = 50)	TCC (N = 48)	SS (n = 25)
<b>Fatigue</b>			
MDFSI Total Score <sup>†</sup>			
Baseline	9.8 (18.4)	8.5 (17.1)	10.4 (17.0)
Month 2	5.5 (14.4)	2.6 (15.4)	8.5 (18.4)
Month 3	3.9 (16.8)	1.8 (14.5)	5.4 (16.1)
Month 4	0.2 (14.5)	0.4 (15.5)	6.1 (16.4)
Month 7	-2.2 (12.8)	-1.8 (13.7)	3.6 (16.2)
Month 16	-2.9 (11.0)	1.0 (19.4)	3.7 (15.6)
<b>Sleepiness</b>			
Epworth Sleepiness <sup>§</sup>			
Baseline	7.7 (5.7)	6.7 (4.5)	7.1 (4.3)
Month 2	7.1 (5.2)	6.4 (4.8)	7.6 (4.5)
Month 3	6.4 (4.4)	6.4 (4.9)	6.5 (3.8)
Month 4	6.7 (5.4)	5.5 (3.8)	6.4 (3.8)
Month 7	5.9 (4.6)	5.2 (4.0)	6.2 (3.4)
Month 16	5.8 (4.3)	5.7 (4.7)	7.1 (3.5)
<b>Depressive symptoms</b>			
IDS-C <sup>*,††</sup>			
Baseline	8.7 (4.8)	9.1 (4.5)	10.8 (6.8)
Month 2	7.7 (5.0)	8.2 (3.8)	10.6 (8.0)
Month 3	5.8 (3.3)	7.2 (3.4)	11.8 (9.9)
Month 4	4.8 (3.0)	5.8 (3.3)	8.4 (7.5)
Month 7	4.6 (2.9)	7.2 (4.9)	6.9 (4.2)
Month 16	5.1 (3.9)	6.9 (4.3)	8.0 (6.6)

All values are means (SD). <sup>†</sup> Mixed repeated-measures (group by time) with baseline, months 2, 3, 4, 7, and 16 values indicated a significant between time difference ( $P < 0.001$ ). Analyses were performed on an intention to treat basis. Linear trend contrasts found that the slope of decrease of MFSI scores was greater in the CBT group as compared to TCC and SS (all  $P$ 's  $< 0.05$ ). <sup>††</sup> Mixed repeated-measures analysis of variance (group by time) with baseline, months 2, 3, 4, 7, and 16 values indicated a significant between group difference ( $P < 0.005$ ) and time ( $P < 0.001$ ). Analyses were performed on an intention to treat basis. Specific linear trend contrasts were used to test differences between groups with significant differences between CBT vs. SS, and CBT vs. TCC (all  $P$ 's  $< 0.05$ ). <sup>†</sup> (i.e., Multidimensional Fatigue Symptom Inventory (MFSI) is a 30-item inventory, that assesses patient reported symptoms of general, physical, emotional, and mental manifestations of fatigue as well as vigor. Each subscale includes six items and each item is rated on a five-point scale indicating how true the statement was during the last week (0 = not at all, 4 = extremely). Higher scores indicate more severe fatigue, except for the Vigor subscale, where a higher score indicates less fatigue (more Vigor). The sum of General, Physical, Emotional, and Mental subscale scores minus the Vigor subscale score generates a total fatigue score. The range of possible scores for each subscale is 0–24, and the range for total fatigue score is -24 to 96.<sup>10</sup> <sup>§</sup> Epworth Sleepiness Scale is a 24-point scale that assesses subjective sense of daytime sleepiness with 8 different situations rated 0–3 according to likelihood of falling asleep with a total range from 0 to 24. Higher scores signify greater daytime sleepiness.<sup>11</sup> <sup>\*</sup> Inventory of Depressive Symptomatology–Clinician Rating Scale (IDS-C) is a 30-item questionnaire with DSM-IV diagnostic criterion items for major depressive disorder (e.g., mood, vegetative, psychomotor, and cognitive symptoms), as well as commonly associated symptoms, such as anxiety, irritability, and melancholic and atypical symptom features. The IDS-C is scored by summing the responses to 28 of 30 items (i.e., only appetite and weight increase or appetite and weight decrease are scored for a given rating), with each symptom item is scored on a scale of 0–3, with higher scores denoting greater symptom severity. The total score range is 0–84.<sup>12</sup> CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.

*Insomnia* provided sleep education and discussion of the role of biological, psychological, social, and behavioral factors that affect sleep, such as stress, cognitive arousal, poor sleep hygiene, and mood disturbance. (2) *Cognitive Restructuring and Sleep Disturbance* used cognitive restructuring principles to help patients identify maladaptive sleep cognitions, neutralize their effect, and facilitate more adaptive thinking about sleep and its importance, including training in other cognitive coping strategies such as relaxing self-talk, imagery, and distraction methods (e.g., repetition of a calming phrase, thought). (3) *Stimulus Control* targeted sleep behavior directly by instructing patients to go to bed only when sleepy; use the bed only for sleep and sexual activity and not other behaviors that compete with sleep; leave the bedroom after being unable to fall asleep within 20 minutes; repeat this process as often as necessary either before falling asleep or after awakening from sleep; and establish and adhere to a fixed time of arising each morning. The sleep restriction component was not emphasized, as shortened sleep duration may confound measures of inflammation. For example, Vgontzas et al. found that insomnia with short sleep duration is associated with increases in inflammation.<sup>2,3</sup> (4) *Mood Enhancement* assisted patients in developing behavioral goals in areas where sleep has disrupted their functioning and mood (e.g., work, social, physical activity), with the use of self-rewards (e.g., leisure, resting, relaxation), scheduling of pleasant events and mental exercises to increase awareness of positive emotional states. Whereas incorporation of this mood module expanded, theoretically and pragmatically, the scope of traditional CBT for insomnia,<sup>1</sup> this module was very compatible with the behavioral approach to insomnia as it was designed to promote understanding of the reciprocal relationship between sleep and mood, and how to implement strategies to improve mood either as a consequence of poor sleep or as a determinant of sleep disturbance. Additionally, incorporation of this module was done in an integrated manner throughout the throughout the protocol. (5) *Skill Consolidation and Adherence* was devoted to the development of individual treatment plans for follow-up, including performance of skills, and relapse prevention training methods<sup>4</sup> to help patients cope with situations that have contributed to poor sleep disturbance or that have interfered with the implementation of the insomnia management protocol.

Tai Chi Chih (TCC) is also a multicomponent intervention that integrates physical, psychosocial, emotion, spiritual, and behavioral elements to target arousal mechanisms that are thought to contribute to insomnia.<sup>5–7</sup> Because of its mind-body and “meditation through movement” attributes, TCC was well-suited to help older adults cope with fatigue,

perceived physical limitations, and negative emotional states, which are commonly associated with insomnia. In contrast with CBT, TCC did not address cognitive activity underlying appraisals of disordered sleep, but instead emphasized control over physical function and arousal-related responsiveness through the performance of repetitious, nonstrenuous, slow-paced movement. TCC was administered in groups of 7-10 subjects master's level instructor who had undergone certification by the national TCC association. Using a manualized approach,<sup>8</sup> each session provided objectives and learning activities related to sequentially learning a specific set of 20 exercises with verification of skills attainment weekly. The first 8 weeks emphasized mastery of single forms though multiple repetitions in class and at home; latter weeks focused on class consolidation of daily practice routines with natural breathing integrated into all sessions. Diary assessments were administered to assess frequency and duration of practice between sessions and at follow-up.

Sleep Seminar (SS) was an educational intervention that provided health information related to the physical, medical, and psychosocial factors that contribute to sleep problems in aging with an emphasis on sleep education and sleep hygiene practices. SS delivered some content (i.e., sleep hygiene principles) similar to that of CBT, but in contrast to CBT, SS simply provided educational information without discussion of how these practices might be used to change sleep-wake behaviors. Educational topics included during the 16 weeks were the following: (1) Sleep in late-life including discussion of changes in sleep with aging and misperceptions about sleep duration; (2) What is insomnia, including a review of the definition of insomnia, prevalence, discussion of potential causes of insomnia, and how the sleep diary can be used to evaluate insomnia; (3) Sleep basics including the sleep cycle and stages of sleep including the role of polysomnography in the evaluation of sleep; (4) Review of how sleep changes with age, and how these changes are different than insomnia with consideration of the association between sleep and medical comorbidities; (5) Other sleep disorders and sleep problems that are not insomnia, and how to assess whether they are present including sleep apnea, restless legs syndrome, and parasomnias; (6) Impact of insomnia on health including health functioning, accidents rates, and mood problems (session included discussion of the relationship between insomnia and inflammation and cardiovascular disease risk); (7) Traditional treatment for insomnia with review of medication, non-pharmacologic therapies, and role of sleep hygiene; (8) Sleep hygiene with focus on the use of alcohol, tobacco, certain non-prescription medications, and exercise; (9) Sleep hygiene II including review of age related sleep patterns, bedtime rituals, napping, and behaviors that are not compatible with good sleep such as TV watching in bed; (10) Sleep hygiene III with focus on sleep-wake principles such as the use of regular bedtime, and the impact of the environment such as light, temperature, and noise on sleep; (11) Managing daytime stress with review of certain stress management skills such as progressive muscle relaxation (without instruction), time management, problem solving; (12) Managing daytime stress II with presentation of the impact of the stress on certain disease risk including associations between stress and insomnia, depression and cardiovascular disease; (13) Nutrition and health aging, and relation to sleep with review of the relationships between alcohol, caffeine use, and tobacco

**Table S3**—Circulating levels of CRP and proportion with high CRP

% of Participants with High CRP <sup>§</sup>	CBT (N = 50)	TCC (N = 48)	SS (n = 25)
Baseline	20.6	20.0	21.7
Month 4	15.6	16.2	33.3
Month 16	11.6	28.6	33.3

<sup>§</sup> The percentage of participants with high CRP differed between the groups from baseline to month 16, in which high CRP was less likely to be found in the CBT participants as compared to TCC and SS ( $\chi^2(1) = 4.0$ ,  $P = 0.04$ ). High CRP defined as CRP levels in excess of 3 mg/L. CRP, C-reactive protein; CBT, cognitive behavioral therapy; TCC, Tai Chi Chih; SS, sleep seminar.

smoking and sleep; (14) Exercise and healthy aging with focus on the relationship between aerobic fitness and sleep; and the impact of exercise on sleep patterns as related to sleep hygiene practices; (15) How to get medical help including discussion of how to talk to your physician and access wellness educational resources; (16) Review of major topics discussed with directive question and answer session.

SS was administered in groups of 7-10 subjects as didactic presentations by physicians or licensed clinical psychologists as previously described,<sup>9</sup> followed by group discussion and self-help quizzes to assess patient learning. SS served as a control for nonspecific treatment elements such as attention, expectation for improvement, and group support that pose rival explanations for the effectiveness of CBT and TCC. As in CBT and TCC, homework was prescribed to include reading of educational materials that expanded on session information.

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