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Nonpharmacologic interventions for improving sleep disturbances in patients with lung cancer: a systematic review and meta-analysis

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Abstract

Context. Lung cancer patients suffer from higher levels of sleep disturbances compared to other cancer patients and this leads to greater distress, poorer function and lower quality of life. Nonpharmacologic interventions have demonstrated improvements in the context of breast cancer but their efficacy in the lung cancer population is unclear.

Objectives. The aim of this review was to determine the effects of any nonpharmacologic intervention on sleep quality of lung cancer patients.

Methods. Intervention studies of any design that reported primary or secondary outcomes on sleep quality were included. Databases searched were Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL and PsycINFO. Risk of bias was assessed regarding randomization, allocation concealment, blinding, incomplete outcome data, selective reporting and other biases.

Results. 22 studies were identified with total of 1272 participants. Pittsburgh Sleep Quality Index was the most common instrument used. Statistically significant results were observed for all intervention categories examined in the short-term follow-up period; exercise and rehabilitation programs (SMD: −0.43, 95% CI: −0.68, −0.19, p=0.0005), information, psychoeducation and symptom screening interventions (SMD: −0.87, 95% CI: −1.21, −0.54, p<0.00001) and mind-body interventions (SMD: −0.88, 95% CI: −1.59, −0.16, p=0.02). However, effectiveness was lower and non-significant when evaluated over one month after completion.

Conclusion. Limitations include the high heterogeneity of interventions and outcome measures, in addition to small sample sizes and high risk of bias within studies. Since they do not allow for a clear interpretation of the results, it is recommended that every patient should be assessed individually to guide a possible referral.

Key Words

lung cancer, sleep disturbances, nonpharmacologic interventions

Running title: Interventions for sleep disturbances in lung cancer patients

Introduction

Disturbed sleep is a common complaint among lung cancer patients and survivors. Across observational studies that used questionnaires, the prevalence of poor overall sleep quality and clinical insomnia syndrome ranged from 52% to 96%[1–5] and 36.8% to 52%[6–8] respectively. Results from actigraphic recordings show that lung cancer patients experience disturbed sleep/activity patterns with significantly lower daily activity, lower sleep efficiency and higher sleep fragmentation than healthy controls[2,9,10]. They are reported as having the highest or second highest level of sleep disturbances relative to other patients with solid tumors, including being overly fatigued (56.1%), using sleeping pills (40.4%) and being overly sleepy (39.5%)[7], while their sleep architecture resembles that of insomniacs[11], with more stage I sleep and a higher index of awakenings compared with breast cancer patients[12]. Sleep disturbances are also a common cause of distress and have an impact on quality of life (QOL), as they have been independently associated with impaired cognitive function and poorer functional status[4]. Insomnia, among other symptoms, was found to be a predictor of survival in newly diagnosed lung cancer patients[13,14].

Although nonpharmacologic interventions for the long-term management of sleep disturbances in cancer have been previously reviewed[15–19] and evidence-based recommendations for clinical practice have been proposed, the vast

majority of studies that supported those interventions assessed patients with breast or mixed cancers, with low representation of lung cancer. Regarding QOL issues, lung cancer patients are a unique cancer population under many terms. They experience higher symptom burden[20,21] and greater psychological distress[22] than cancer patients of other common primary sites, and symptoms like pain, fatigue and emotional distress have been linked with sleep disturbance, forming a frequently encountered symptom cluster[23]. Chronic obstructive pulmonary disease, a comorbidity most often associated with lung cancer than other malignancies, can be complicated by a variety of sleep disorders causing poor sleep quality, such as insomnia, sleep-related hypoxemia or hypoventilation, obstructive sleep apnea (termed “overlap syndrome”) and restless leg syndrome[24], that may precede or be exacerbated after the cancer diagnosis. These individuals require more careful evaluation and screening, complex diagnostic modalities and even specific treatment, different from the usual pharmacologic or nonpharmacologic therapies. Furthermore, lung cancer patients were found to have significant higher risk for poorer functional status[25] and cognitive performance[26] compared to patients with other common cancers, so that physically or mentally demanding interventions may have different appropriateness and impact on them than the rest cancer population. Keeping in mind the high prevalence and severity of sleep disorders in lung cancer patients and their particular characteristics, as mentioned before, this review aims to clarify if the existing interventions are feasible and effective in this population.

The purpose of this systematic review is to examine which nonpharmacologic interventions have shown efficacy in improving sleep/wake disturbances in lung cancer patients and survivors based on the evidence from intervention studies that evaluated sleep quality as a primary or secondary outcome regardless of the study design or the instrument used for measurement.

Methods

Eligibility criteria, information sources and study selection

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[27]. The review included intervention studies of any design (randomized controlled trials, quasi-experimental studies or single-arm trials) that involved lung cancer patients or survivors of any stage and at any time before, during or after any kind of treatment, as long as they comprised over 25% of the study sample size. All nonpharmacologic interventions were eligible for inclusion, while studies qualified if they reported primary or secondary outcomes on sleep disturbance or sleep quality, assessed by either subjective or objective measures. No language or publication status restrictions were imposed.

Studies were identified from electronic bibliographic databases including the Cochrane Central Register of Controlled Trials, MEDLINE (via Ovid), EMBASE (via Ovid), CINAHL (via EBSCO) and PsycINFO (via Ovid) from the earliest date available to December 2016. Additional unpublished trials were identified through WHO International Clinical Trials Registry Platform Search Portal and

ClinicalTrials.gov. Search terms included “lung cancer”, “sleep”, “insomnia”, “intervention”, “program”, “trial”, “random”, “control”, “treatment” and “therapy” in all applicable combinations. The search strategy used for Ovid platform is presented in Supplementary Table 1 and it was adapted for use in the other databases.

Two review authors (DP, AP) independently examined the titles and abstracts of all studies identified using the search strategy to determine eligibility for inclusion and disagreements were resolved by consensus or discussion with a third author (MK).

Data collection and risk of bias in individual studies

Two review authors (DP, AP) extracted data from all studies fulfilling the inclusion criteria using a standardized form. Information was extracted from each included study on study design and setting, participant characteristics (sample size, age, gender distribution, stage of cancer, conventional treatment, screening condition), intervention details (type, components, dose, duration, control group) and outcomes (instrument, type of measure, time of assessment and follow-up, results, adverse events). When necessary, outcome data values were approximated from figures in the reports.

For assessing risk of bias in included studies we used the Cochrane Collaboration’s “Risk of Bias” Tool[28] and in each domain, the study was judged as having low, high or unclear risk of bias. The assessment was performed independently by two review authors (DP, AP) and disagreements were resolved

by consensus or discussion with a third author (MK). For all included studies, an additional search in appropriate databases, registries or other online sources was implemented in order to identify protocols or other reports and acquire the above relevant information.

Summary measures and synthesis of results

Standardized mean differences (SMD) together with their corresponding standard errors (SE) were calculated from post-intervention outcomes and used as the primary measure of effect across studies.

In order to synthesize the treatment effect estimates, we performed a meta-analysis of included controlled trials using the "Review Manager 5.3" software and the random-effects method. We ran separate analyses based on the intervention category and the follow-up time after the intervention that the outcome of interest was assessed, including three time frames: short-term (before one month), medium-term (between one and three months) and long-term (after three months). For studies that compared two relevant intervention groups to a control condition, we combined the groups to a single comparison. When studies reported multiple subscales of the same outcome, we performed the analysis with the most clinically relevant outcome measurement, according to reviewers' judgement. Cross-over trials were treated as parallel studies by analyzing only the first period to avoid cross-over effects.

Results from intention-to-treat analyses were preferred over those from per-protocol analyses, as long as they were suitable for inclusion. In both cases, raw

data or unadjusted estimates were preferred against adjusted values to eliminate possible heterogeneity. When studies reported non-parametric data (e.g. medians and interquartile range), they were transformed by using the following formulas: mean=median, standard deviation=interquartile range/1.35, assuming their distributions were not highly skewed[28]. In order to include dichotomous data, we calculated the log odds ratio and its corresponding SE and transformed them to SMD (SE) by multiplying both by $\sqrt{3}/\pi$[28]. In the case where only baseline values and change scores were available, we calculated the post-intervention mean and imputed the standard deviation using the median of the pooled standard deviations of the other included trials that used the same measurement scale. Heterogeneity between studies was assessed with the chi-square test and measured with the I^2 statistic.

Risk of bias across studies and additional analyses

A funnel plot of SMD by their associated SE was generated for each comparison for the purpose of assessing possible publication bias. When significant visual asymmetry was found, an Egger's regression test[29] was conducted to formally evaluate publication bias, in the presence of a sufficient amount of studies.

Sensitivity analysis was performed excluding studies of high or unclear risk of selection bias, small sample size, non-English language, involving mixed cancer populations and reporting sleep disturbances as secondary outcome or as subscale of an original scale. We also undertook subgroup analysis based on

intervention components, control condition, instrument used, intervention delivery method, duration and dose. A narrative synthesis was conducted for interventions and outcomes that could not be pooled and therefore were not included in meta-analyses. Quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The PRISMA checklist was completed and shown in Supplementary Table 2.

Results

Study selection and characteristics

A total of 22 studies[30–51] were identified for inclusion in the review. The search of all the databases for studies published until December 2016 provided a total of 1250 records, while 9 studies were added from trial registries. After adjusting for duplicates and multiple publications 852 remained. We discarded 807 records based on title and abstract and assessed 45 full texts and conference abstracts for eligibility. After applying the review criteria, a further 23 studies were excluded for involving mixed cancer populations with low representation of lung cancers (n=13), having no outcome on sleep (n=7) and presenting preliminary results of ongoing trials (n=2) or feasibility results of subsequent trials (n=1) (Fig. 1).

The majority of the included studies (Table 1) were randomized or quasi-randomized controlled trials, while four studies[34,41,45,46] had a single group design. All but two[32,44] were single-centered and most of them were conducted in Asian countries. They involved total of 1272 participants, 1048 (82.4%) of whom had lung cancer diagnosis. Six studies[31,35,36,40,43,49] had mixed cancer participants

with high enough representation of lung cancer (range 27.8%-51.5%), allowing us to include them in the review. In most of the studies, over 2/3 of the participants had advanced stage (III or IV) cancer and concurrently underwent conventional treatment (surgery, chemotherapy or radiation therapy). Four studies[31,36,40,43] implemented screening tools when recruiting participants, although only in two[40,43] of them they were specific for measuring sleep disturbance. We recognized a wide range of nonpharmacologic interventions that can be classified into three broader categories: standard exercise and rehabilitation programs[30–34] (n=5), information, psychoeducation and symptom screening interventions[35–39] (n=5) and mind-body interventions[40–51] (n=12), the latter further categorized into acupuncture and related practices[40,48,51] (n=3), cognitive/behavioral strategies[43,44,47,50] (n=4) and mind-body fitness training[41,42,45,46,49] (n=5). A more detailed description of the intervention components in each study is presented in Supplementary Table 3. The control groups were given mostly standard care or no intervention[30,32,33,37,38,42,47,51] (n=8), as well as attention control (n=3)[35,44,50], sham therapy[36,48] (n=2), wait-list[31,43] (n=2) and active control[40,49] (n=2). The instruments used to measure sleep disturbance were the Pittsburgh Sleep Quality Index (PSQI)[30,32,38,40,41,43,45–48] (n=10), the Insomnia Severity Index (ISI)[36] (n=1), the Self-Rating Scale of Sleep (SRSS)[42] (n=1), the Pittsburgh Sleep Symptom Questionnaire-Insomnia (PSSQ_I)[44] (n=1), numeric rating scales[31,35,43,49] with range 0-10 (n=4) and sleep subscales of various cancer-specific[33,37,50,51] (n=4) or general[34] (n=1) QOL or

depression[39] (n=1) scales. Only one study[30] used objective sleep measures via sleep diary and actigraphy.

Risk of bias in included studies

Risk of bias was assessed for the 18 controlled clinical trials included and only for the sleep outcome. When there was insufficient information to permit judgment of low or high risk from the study reports, the study was rated at unclear risk of bias (Fig. 2).

Six studies[30,31,35,43,49,51] reported the use of a computer random number generator, two studies[40,50] referred to a random number table and two studies[32,44] performed a minimization procedure in order to randomize participants to treatment arms. Three studies[30,31,43] used sequentially numbered, opaque, sealed envelopes to conceal the allocations and three trials[32,35,44] performed central allocation. One study[48] employed a coin flipping process to ensure randomization and allocation concealment, while three studies described a non-random generation sequence, based on the date of informed consent[36] and the hospital record number[37,39], so that it was possible for investigators to foresee assignments. Four[33,38,42,47] and eight studies[33,38,40,42,47,49–51] did not report the specific method for randomization and allocation concealment respectively.

Eight studies[31,32,35,39,43,44,47,49] stated that participants were not blinded, while six more studies[30,33,38,40,42,51] have not addressed this issue, although it was clear that they were unable to maintain blinding. One study[37] stated that participants were not informed of their assignment, however it is likely that blinding was

broken due to obvious differences between the groups. One trial[48] used a sham control group to blind participants but one of the intervention arms was offered an additional feature that may have led to breaking of the blinding. One study[50] reported the blinding of key personnel (oncologists) and the administration of intervention by the same person (psychologist) to both groups, but it was not clarified if participants were aware of their allocation. Only one study[36] using a sham-control material of equal characteristics with the active treatment is believed to have effectively blinded participants. Five trials[30,31,44,48,49] reported blinding of personnel responsible for data collection or entry, while none performed blinding of research coordinators or personnel delivering the interventions; however, since sleep disturbances were a patient-reported outcome in all included studies and participants served also as outcome assessors, only their blinding was considered significant enough to avoid bias.

Six studies[33,38–40,42,47] reported no missing data and four studies[30,35,36,44] had balanced, in number and reason, between arms drop-out rates. Two studies[37,51] did not provide reasons for attrition. Four studies reported differences in number of missing cases between groups; of them two studies successfully implemented an intention-to-treat approach, one[31] by use of regression-based imputation and the other[48] employing a statistical model accounting for missing data, one study[43] used an inappropriate imputation method (last value carried forward) and one study[49] performed per-protocol analysis. We also judged two studies at high risk of attrition bias because of imbalance in reasons for drop-out between arms (control group missing assessments more often than experimental group)[32] and

substantial withdrawal proportion of participants[50], despite the intention-to-treat analysis performed in both cases. All of the included studies reported results on the sleep outcome that was described in their protocol or the "Methods" section.

Five studies were rated at high risk of bias due to other sources. Three open-label trials[30,31,43] used blocked randomization, which could lead to prediction of group assignment at recruitment, despite adequate allocation concealment. In one study[36], a significant between-group difference at baseline was demonstrated (history of cancer surgery), while one study[40] used a drug for the control group that causes insomnia as side effect. Finally, insufficient information about baseline balance between arms, delivery of interventions and occurrence of contamination in the remaining studies does not allow a precise assessment.

Synthesis of results

Sleep outcome data extracted from each study are presented in Table 2. Since only one study reported objective sleep outcomes, we synthesized the subjective sleep ratings across the 18 included controlled trials. All of them presented non-significant baseline differences between arms, however two trials[44,48] reported adjusted estimates at follow-up. In one study[39] that involved a comparison between three interventions, we chose one of them (group C) as the control condition, based on what is generally considered standard care. Pooled results are presented below, categorized by intervention category, together with assessment of risk of bias across studies and additional analyses. The rating of

quality of evidence according to the GRADE system is presented in Supplementary Table 4 (evidence profile) and 5 (summary of findings).

Standard exercise and rehabilitation programs Exercise and rehabilitation programs significantly improved sleep disturbances of lung cancer patients compared to control in the short-term follow-up period (SMD: −0.43, 95% CI: −0.68, −0.19, p=0.0005) with no evidence of heterogeneity across studies (p=0.5, I^2=0%). However, non-significant differences were observed in the medium-term (SMD: −0.21, 95% CI: −0.46, 0.04, p=0.11) and long-term (SMD: −0.68, 95% CI: −1.747,0.37, p=0.20) follow-up periods. Heterogeneity was absent in the first case (p=0.39, I^2=0%) and large in the second (p=0.004, I^2=88%), that included only two trials (Fig. 3). Inspection of the funnel plots were inconclusive due to the low amount of studies. Eliminating one study[33] of low methodological quality and small sample size (<50) or one study[31] with mixed cancer participants did not affect the results. Only one trial[30] examined sleep quality as a primary outcome. No significant subgroup differences regarding choice of control condition and instrument used or intervention delivery mode, duration and dose were found between studies across all periods.

Information, psychoeducation and symptom screening interventions Interventions in this category were evaluated only in short-term follow-up period. Pooled results showed significant differences compared to control (SMD: −0.87, 95% CI: −1.21, −0.54, p<0.00001) and low non-significant heterogeneity (p=0.17,

I^2=38%) (Fig. 4). No evidence of asymmetry was found examining the funnel plot. Results remained significant after removing three non-English studies[37–39], two small-sized studies[36,39], two studies[35,36] involving mixed cancer participants and three studies[36,37,39] not reporting sleep disturbance as primary outcome. All but one trials in this category were judged at high or unclear risk of selection bias. In subgroup analysis, a significant difference was noted regarding intervention delivery mode; interventions delivered at site were more effective than those offered at home (p=0.04), while both groups presented homogeneous (Supplementary Fig. 1).

Mind-body interventions Mind-body interventions had a significant large effect in treating sleep disturbances of lung cancer patients in the short-term follow-up period (SMD: −0.88, 95% CI: −1.59, −0.16, p=0.02), which was lost in the medium-term period (SMD: −0.13, 95% CI: −0.94, 0.69, p=0.76), that consisted only of two studies evaluating less than 100 patients. Significant heterogeneity was noted both in short-term (p<0.00001, I^2=93%) and medium-term (p=0.08, I^2=68%) follow-up period (Fig. 5). In the first period, we observed signs of asymmetry in the funnel plot (Fig. 6), but Egger's regression test excluded it (intercept: −2.328, 95% CI: −7.905, 3.250, p=0.357), while the limited amount of trials prevented an evaluation of publication bias in the second period. Sensitivity analysis was performed by deleting six[40,42,47,49–51] low-quality, three[44,49,50] small-sized, three[40,43,49] mixed-cancer studies and five studies[44,48–51] using secondary sleep outcomes, that did not alter the significance of the findings. Heterogeneity

disappeared in the first case (p=0.39, I^2=0%) and the remaining studies yielded lower effect of interventions (SMD: −0.40, 95% CI: −0.72, −0.08, p=0.01). On the other hand, the effect was significantly higher in studies with large (>50) compared to those with small sample size (p=0.02), but heterogeneity was significant (p<0.00001, I^2=93%) (Supplementary Fig. 2). Including only publications in English[40,43,44,48,49], we found non-significant results in the short-term period (SMD: −0.52, 95% CI: −1.45, 0.41, p=0.28), but also with high heterogeneity (p<0.00001, I^2=92%). Subgroup analysis revealed that only interventions in the acupuncture subcategory had significant short-term effect (SMD: −1.49, 95% CI: −2.29, −0.68, p=0.003) and that interventions delivered more frequently (>3 times per week) showed a larger short-term effect than those delivered more rarely (p=0.008), although heterogeneity was still an issue (Supplementary Fig. 3).

Narrative synthesis Regarding objectively measured sleep quality, one study[30] found that a walking exercise program improved all sleep parameters measured via actigraphy compared to a usual care group, but the difference was statistically significant only for sleep onset latency at the medium-term follow-up (SMD: −0.49, SE: 0.23, p=0.03). Commenting on the included non-controlled studies, three yoga interventions[41,45,46] failed to show significant results in overall sleep quality, but they were pilot trials with low sample sizes, while the in-patient chest physiotherapy program[34] significantly reduced symptoms of disturbed sleep, although its effectiveness in out-patient populations is unknown. Adverse events

were reported in four studies[30–32,51] and totaled nine cases, all of them minor and self-resolved.

Discussion

Summary of evidence

This is the first systematic review to investigate the efficacy of nonpharmacologic interventions in the treatment of sleep disturbances in lung cancer patients and survivors. 22 studies were included with 1272 participants that evaluated sleep quality or insomnia symptoms in lung cancer patients of all stages and at any time through the disease course. We identified three different intervention categories, each one of them containing diverse interventions in both components and dose/duration. All of them assessed sleep disturbances with subjective measures, although with varied instruments and only five of them had sufficient follow-up measurements to test long-term effectiveness. Moreover, all studies used questionnaires instead of sleep diary recordings which are considered a more reliable source of assessment and only two studies used a screening tool for identification of insomnia or poor sleep quality in the inclusion criteria. Risk of bias analysis of the included controlled clinical trials revealed high performance and detection biases and a high proportion of unclear risks basically due to poor reporting.

The exercise and rehabilitation programs were found effective in reducing the sleep disturbances of lung cancer patients compared to conventional treatment shortly after the intervention (SMD: −0.43, 95% CI: −0.68, −0.19, p=0.0005).

However, the effect was not significant in the medium- and long-term follow-up periods examined. For the short- and medium-term periods, quality of evidence was moderate, lessened only by the lack of blinding, which means that the true effect is likely to be close to the estimate of the effect from this meta-analysis. A possible explanation for the smaller effect in the medium-term period is the deconditioning that is usually observed in the course of the disease, which can reverse the obtained benefit in physical activity from an exercise intervention after its discontinuation. On the contrary, quality of evidence for the long-term follow-up period was very low, since studies that assessed this outcome were heterogeneous and involved a small number of patients, besides failing of blinding. Interventions were reported safe, even in patients with advanced cancer. A common pitfall is that fitter patients generally accept to participate more frequently and are more likely to complete such programs compared to frailer individuals, so caution should be taken in the effort to generalise the results. In general oncology settings, one meta-analysis[52] found a significant effect of walking exercises on subjective sleep disturbances (SMD: −0.52), while another[53] tested a wide range of exercise interventions and revealed no significant differences compared to control either on subjective or on objective sleep measures. Oncology Nursing Society's (ONS) guidelines[54] currently rate exercise interventions as "Likely to Be Effective" for sleep-wake disturbances in cancer patients. Since effective blinding is very difficult to achieve in this kind of programs, future research should focus on well-designed randomized controlled trials, utilizing more specific instruments and examining longer follow-up periods.

Information, psychoeducation and symptom screening interventions significantly improved sleep quality and reduced insomnia symptoms in lung cancer patients compared to usual care or attention-placebo control (SMD: −0.87, 95% CI: −1.21, −0.54, p<0.00001). It was also evident that interventions had greater impact when delivered at site by a physician or nurse rather than at home via telephone or e-mail, as face-to-face contact is expected to provide an additional positive effect. These interventions were not evaluated in medium- or long-term periods of follow-up and were reported as feasible and easy to implement in standard medical and nursing care. Quality of evidence was low, since most of the included trials had high risk of bias for being quasi-randomized and unblinded. Moreover, components of these programs were striking different and none was used specifically for addressing sleep disturbances. In a systematic review[55] that assessed the effectiveness of non-invasive interventions in improving symptoms, psychological functioning and quality of life in patients with lung cancer, authors concluded that psychoeducation, counselling and nurse follow-up programs may help patients cope with emotional symptoms and improve their quality of life. A meta-analysis[17] for sleep disturbances in general oncology patients included only two trials examining informational/educational interventions and found a small effect size (SMD: −0.23). ONS guidelines[54] currently rate psychoeducational interventions as “Effectiveness Not Established” for sleep-wake disturbances in cancer patients. It is clear that more studies are needed to draw a more definite conclusion.

Mind-body interventions also improved significantly the sleep disturbances of lung cancer patients compared either to active or inactive control in the short-term follow-up period (SMD: −0.88, 95% CI: −1.59, −0.16, p=0.02), while those delivered at increased dose showed higher effectiveness. High risk of bias within studies due to lack of blinding and high heterogeneity across studies because of differences in intervention components, control conditions and instruments used were identified and led to a low rating of overall quality of evidence. In the medium-term period, results were not significant and quality of evidence was very low, since the two studies that assessed this outcome had, except from the above-mentioned limitations, also a small sample size. Examining different intervention types separately, we observed significant effect for acupuncture and related practices, but not for cognitive/behavioral strategies or mind-body fitness training (yoga, qigong/tai-chi). Two systematic reviews[56,57] addressing the effectiveness of acupuncture in the general setting of cancer found also positive impacts in sleep parameters but quality issues prevented the authors from giving strong recommendations for its use in sleep disturbances. In a meta-analysis[58] regarding mind-body interventions for sleep in cancer patients, mindfulness therapies, including yoga, mindfulness-based stress reduction, meditation, hypnosis and mind-body bridging yielded significant effects on improving sleep quality (SMD: −0.43), while in another[59] that focused on breast cancer patients, small, non-significant effects of yoga on sleep disturbances were observed (SMD: −0.26). On the contrary, two systematic reviews[60,61] examining specifically cognitive-behavioral therapy for insomnia in cancer concluded that it provides

significant and long-lasting improvement in patients' sleep disturbances and is recommended as standard care. In ONS guidelines[54], cognitive/behavioral interventions are "Recommended for Practice", mindfulness-based stress reduction is rated as "Likely to Be Effective" and all the other practices have "Effectiveness Not Established" for sleep disturbances in cancer patients. Preliminary results from an uncompleted randomized controlled trial[62] on nurse-delivered cognitive-behavioral therapy for lung cancer survivors with insomnia (ISI score>7), that was not included in the review, revealed improvements in all subjective sleep measures compared to attention control. Further research is needed to establish the efficacy of mind-body interventions in this sensitive population with higher-quality studies using validated screening and measurement tools.

Limitations

The main limitation of this review is the high variability in characteristics of participants (cancer stage, treatment status), interventions (type, dose, duration, mode of delivery) and outcome measurement (type, instrument, assessment time) across studies. Small sample sizes, high risk of bias and poor reporting in included studies also contribute to limited applicability of the results in general practice. Another potential drawback could be the inclusion of studies that evaluated mixed cancer populations, where the intervention effect could not be estimated separately for lung cancer patients; however, sensitivity analysis showed that excluding those trials did not significantly influenced the results.

Finally, some degree of publication bias may have occurred based on possible missing of studies with negative results on sleep outcomes.

Conclusions

Pharmacological management of disease symptoms and conventional treatment's adverse events has been the mainstream of therapeutic approach for years, although drug side effects and questionable long-term efficacy limit its applicability. This systematic review proved that nonpharmacologic interventions are feasible and effective in improving sleep quality or disturbances of lung cancer patients, though limitations at study and outcome level across studies as mentioned above do not allow us to provide firm recommendations for implementation in standard medical and nursing lung cancer care. Referrals to any of these programs should be considered individually based on assessment of patient characteristics, needs and desires, exclusion of other possible reasons for poor sleep quality (sleep disordered breathing, etc.) and availability of interventions. Future research should concentrate on larger sample sizes, randomized and blinded study designs, validated screening and measurement tools including use of the sleep diary, interventions of optimal dose and duration and larger follow-up periods.

In the era of targeted therapy and prolonged survival of lung cancer patients, QOL issues emerge as an important factor for both adherence to treatment and prognosis. In conclusion, nonpharmacologic interventions may represent a useful

adjunctive therapeutic modality, aiming in improving patients' QOL in a broader context of multidisciplinary management of lung cancer.

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Figure Legends

Fig. 1. Review flow diagram.

Fig. 2. Risk of bias summary.

Fig. 3. Forest plot of exercise and rehabilitation programs for treating sleep disturbances in the short-term (A), medium-term (B) and long-term (C) follow-up periods.

Fig. 4. Forest plot of information, psychoeducation and symptom screening interventions for treating sleep disturbances in the short-term follow-up period.

Fig. 5. Forest plot of mind-body interventions for treating sleep disturbances in the short-term (A) and medium-term (B) follow-up periods.

Fig. 6. Funnel plot of mind-body interventions for treating sleep disturbances in the short-term follow-up period.

Supplementary Fig. 1. Forest plot of information, psychoeducation and symptom screening interventions for treating sleep disturbances in the short-term follow-up period grouped by delivery mode of intervention.

Supplementary Fig. 2. Forest plot of mind-body interventions for treating sleep disturbances in the short-term follow-up period grouped by sample size.

Supplementary Fig. 3. Forest plot of mind-body interventions for treating sleep disturbances in the short-term follow-up period grouped by dose of intervention.

Table 1

Characteristics of included studies

Author/Year	Design	Setting	Participants	Intervention	Control	Assessment	Sleep measure (instrument)
Exercise and rehabilitation programs							
Chen 2016[30]	RCT	Single center Taiwan	111 (IG 56/CG 55) mean age 64.64±11.54/62.51±9.64 male 24/25 stage I 34/38, II 5/4, III 5/5, IV 5/4 treatment: surg 30/31, chemo 3/5, RT 2/2, chemoRT 2/1	Home-based walking exercise program duration: 12 weeks dose: 3 times per week (40 min)	usual care	baseline, 3 and 6 months	Sleep quality (PSQI, sleep diary, actigraphy)
Cheville 2013[31]	RCT	Single center USA	66 (IG 33/CG 33) mean age 63.8±12.5/65.5±8.9 male 16/19 treatment: chemo 15/14, RT 3/2 screening: pain NRS<6, AM-PAC CAT score 50-75 lung: 34 (51.5%) IG 16/CG 18 stage IV 34	Home-based exercise program duration: 8 weeks dose: at least 4 days a week	wait list	before and after	Sleep quality (NRS)
Dhillon 2017[32]	RCT	5 centers Australia	111 (IG 56/CG 55) median age 64 (38-80)/64 (34-76) male 29/32 stage III 3/2, IV 53/53 treatment: chemo 44/43	Physical activity (PA) program duration: 2 months dose: once per week supervised PA (45 min) and behavior change (15 min) sessions + home-based PA	usual care	baseline, 2, 4 and 6 months	Sleep quality (PSQI)

Li 2013[33]	2 group RM	Single center China	48 (IG 24/CG 24) mean age 57.2±8.9/55.9±8.5 male 20/19 stage II 7/8, III 17/16 treatment: surg	Systematic rehabilitation program duration-dose: variable (perioperative period and until discharge)	standard medical and nursing care	baseline, 3 and 6 months	Insomnia symptoms (EORTC QLQ-C30 insomnia subscale)
Ozalevli 2010[34]	1 group pre-post	Single center Turkey	18 mean age 66.17±7.33 male 15 stage III 3, IV 15 treatment: chemo 4, RT 3, chemoRT 11	In-patient chest physiotherapy program duration: variable (mean 16.2±9.7days) dose: twice per day (20-30 min)	-	before and after	Sleep quality (NHP sleep subcategory)
Information, psychoeducation and symptom screening interventions							
Cleeland 2011[35]	RCT	Single center USA	79 (IG 38/CG 41) mean age 59.2±13.6/60.9±11.8 male 21/21 treatment: surg lung 36 (45.6%) IG 16/CG 20	Automated symptom alerts duration: 4 weeks dose: twice per week calls	attention (symptom assessment twice per week)	baseline and at each call	Sleep disturbance (MDASI disturbed sleep score)
Lee 2014[36]	2 group pre-post	Single center Korea	36 (IG 19/CG 17) median age 58 (34-71) male 16 stage I 2, II 5, III 6, IV 23 treatment: chemo screening: HADS-A or HADS-D≥11 lung: 10 (27.8%)	Tablet PC-based psychoeducation duration: 20 min dose: single session at chemotherapy day	sham-control movie clip	baseline and next cycle	Insomnia intensity (ISI)
Miao 2012[37]	2 group RM	Single center	70 (IG 38/CG 32) mean age 56.16±11.35/56.25±8.72	Extended nursing care duration: 3 months	no intervention	baseline, 1 and 3	Insomnia symptoms (EORTC QLQ-C30

		China	male 24/26	dose: twice per week calls, once per month lectures and additional on-demand services (mean 6.37±1.63 h)		months	insomnia subscale)
Tong 2013[38]	2 group pre-post	Single center China	60 (IG 30/CG 30) mean age 67.5±8 male 31 stage III 39, IV 21	Psychological counseling	conventional nursing	before and after	Sleep quality (PSQI)
Wang 2008[39]	3 group pre-post	Single center China	43 (A 11/B 23/C 9) mean age 57.5±10.8/59.3±9.6/ 55.9±11.1 male 7/18/7 stage III 43 treatment: none	A: completely unknowing state of illness B: partly knowing state of illness C: completely knowing state of illness duration: 1 week dose: once per day (25-30 min)	-	before and after	Sleep disturbance (HAMD sleep disturbance score)
Mind-body interventions							
Feng 2011[40]	RCT	Single center China	80 (IG 40/CG 40) mean age 63.8±5.47/63.6±4.26 male 26/27 screening: SDS>50, HAMD>7, PSQI≥8 lung: 30 (37.5%) IG 14/CG 16	Acupuncture duration: 30 days dose: once per day (20-30 min)	fluoxetine 20mg per day	before and after	Sleep quality (PSQI)
Fouladbakhsh 2014[41]	1 group RM	Single center USA	9 mean age 67±6.5 male 3 stage I 3, II 3, III 3	Viniyoga duration: 8 weeks dose: once per week (40 min)	-	week 1-14	Sleep quality (PSQI)

			treatment: none				
Jiang 2013[42]	2 group pre-post	Single center China	60 (IG 30/CG 30) mean age 64.4±2.8/65.6±2.5 male 14/16	Tai Chi duration: 30 days dose: twice per day (30 min)	conventional nursing	before and after	Sleep quality (SRSS)
Kwekkeboom 2012[43]	RCT	Single center USA	86 (IG 43/CG 43) mean age 60.44±10.76/60.14±11.54 male 14/21 treatment: chemo 30/32, RT 9/10, chemoRT 4/1 screening: MDASI score≥3 for at least 2 of the 3 symptoms (pain, fatigue and sleep disturbance) lung 25 (29%) IG 10/CG 15	Patient-controlled brief cognitive-behavioral strategies via MP3 player duration: 2 weeks dose: as needed but at least once per day (mean 13.65±6.98 times)	wait list	before and after	Sleep disturbance (summary score from MDASI disturbed sleep score and a single PSQI item subscore)
Lehto 2014[44]	RCT	3 centers USA	40 (IG 20/CG 20) mean age 64.5±9.25/67.9±9.5 male 7/6 stage III 6/7, IV 14/13 treatment: chemo 12/8, RT 2/3, chemoRT 6/9	Home-based mindfulness therapy duration: 6 weeks dose: once per week (45 min)	attention (symptom assessment once per week)	baseline, 7 and 11 weeks	Sleep quality and interference from sleep impairment (PSSQ_I)
Milbury 2015[45]	1 group pre-post	Single center USA	10 mean age 71.22±6.16 male 5 stage I 3, III 7 treatment: RT 3, chemoRT 7	Tibetan yoga duration: 5-6 weeks dose:2-3 sessions per week (45-60 min)	-	before and after	Sleep quality (PSQI)
Milbury	1 group	Single	9	Vivekananda yoga	-	before and	Sleep quality (PSQI)

2015[46]	pre-post	center USA	mean age 62.16±14.03 male 5 stage III 9 treatment: chemoRT	duration: 5-6 weeks dose: 2-3 sessions per week (60 min)		after	
Tang HK 2014[47]	2 group RM	Single center China	100 (IG 50/CG 50) mean age 54.28±5.59/54.28±5.18 male 17/18 treatment: chemo	Music therapy duration: 5 days dose: specific protocol	routine treatment	baseline, 1 and 5 days	Sleep quality (PSQI)
Tang WR 2014[48]	RCT	Single center Taiwan	57 (A 17/B 24/C 16) mean age 53.9±9.8/54.8±9.5/ 66.1±8 male 9/12/12 stage I 1/1/2, II 1/1/0, III 3/7/3, IV 12/15/11 treatment: chemo	A: acupressure + essential oils B: acupressure duration: 5 months dose: once per day (6 min)	C: sham acupressure	baseline, 3rd and 6th chemo cycle	Sleep quality (PSQI)
Vanderbyl 2017[49]	cross-over RCT	Single center Canada	24 (IG 11/CG13) mean age: 66.1±11.7/63.7±7.7 male 7/7 stage III 4/4, IV 7/9 treatment: chemo 8/9 lung 12 (50%) IG 7/CG 5	Medical Qigong duration: 6 weeks dose: twice per week supervised group sessions (45 min) + 1 h per day home practice	SET dose: twice per week supervised sessions + 1 h per day walking	baseline, after first and second arm	Sleep quality and sleepiness (ESAS)
Villoria 2012[50]	RCT	Single center Spain	90 (IG 50/CG 40) mean age 61.64±9.57/60.92±8.33 male 37/36 stage II 3/0, III 28/26, IV 18/14 treatment: chemo	Behavioral activation therapy duration: 4 chemo cycles dose: 45 min sessions before each cycle	attention (QOL assessment sessions before each cycle)	each cycle and after 3 months	Insomnia symptoms (EORTC QLQ-C30 insomnia subscale)

Zhang 2016[51]	RCT	Single center China	65 (IG 33/CG 32) mean age 57±11/54±10 male 21/21 stage I 2/1, II 6/5, III 13/15, IV 12/11 treatment: none	Moxibustion duration: 6 weeks dose: once per day	no intervention	before and after	Insomnia symptoms (EORTC QLQ-C30 insomnia subscale)

RCT=randomized controlled trial, RM=repeated measures, IG=intervention group, CG=control group, RT=radiation therapy, SET= standard endurance and strength training, PSQI=Pittsburgh Sleep Quality Index, NRS=Numeric Rating Scale, AM-PAC CAT=Ambulatory Post Acute Care Computer Adaptive Test, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, NHP=Nottingham Health Profile, MDASI=M.D. Anderson Symptom Inventory, HADS-A=Hospital Anxiety and Depression Scale-Anxiety, HADS-D=Hospital Anxiety and Depression Scale-Depression, ISI=Insomnia Severity Index, HAMD=Hamilton Depression Rating Scale, SDS=Self-rating Depression Scale, SRSS=Self-Rating Scale of Sleep, PSSQ_I=Pittsburgh Sleep Symptom Questionnaire-Insomnia, ESAS=Edmonton Symptom Assessment Scale.

Table 2

Unadjusted results (except when noted) on sleep outcomes at each time frame in included studies and associated measure of effect size

Author/Year	Scale (range)	Time frame	N		Metric	Baseline and follow-up scores			Change from baseline scores			SMD (SE)
			IG	CG		IG	CG	p	IG	CG	p	
Chen 2016[30]	PSQI (0-21)	Baseline	56	55	m±sd	9.25±4.55	8.82±4.26					
		STFU	47	48		6.26±3.14	8.90±4.91					−0.63 (0.21)
		MTFU	43	46		6.49±3.71	8.33±4.67					−0.43 (0.21)
	TST (min)	Baseline	52	54		380.32±96.39	395.06±88.21					
		STFU	43	41		380.72±78.30	375.94±92.40					−0.05 (0.22)
		MTFU	39	40		401.76±72.84	369.29±107.21					−0.35 (0.23)
	SE (%)	Baseline	52	54		88.94±9.67	88.36±10.73					
		STFU	43	41		89.14±8.69	87.10±14.29					−0.17 (0.22)
		MTFU	39	40		88.18±10.78	85.07±15.38					−0.23 (0.23)
	SOL (min)	Baseline	52	54		27.14±40.48	31.85±30.05					
		STFU	43	41		28.29±31.93	42.78±38.75					−0.41 (0.22)
		MTFU	39	40		22.15±23.00	37.88±38.05					−0.49 (0.23)
	WASO (min)	Baseline	52	54		45.86±33.17	50.56±45.30					
		STFU	43	41		44.37±33.11	53.53±54.53					−0.20 (0.22)
		MTFU	39	40		52.61±43.96	63.92±66.42					−0.20 (0.23)
Cheville 2013[31]	NRS (0-10)	Baseline	33	33	m±sd	5.97[a]	6.74[a]					
		STFU (raw)	26	30		7.61±**2.44**[a]	6.71±**2.44**[a]	0.05	1.46±1.88	−0.10±1.71	0.002	−0.36 (0.27)
		STFU (imp.)	28	31		7.55±**2.44**[a]	6.66±**2.44**[a]					−0.36 (0.26)
Dhillon 2017[32]	PSQI (0-21)	Baseline	56	55	m	9.59	10.06					
		STFU			md (CI)	−0.99 (−2.17, 0.18)		0.098				−0.31 (0.19)
		MTFU				−0.43 (−1.67, 0.82)		0.499				−0.13 (0.19)

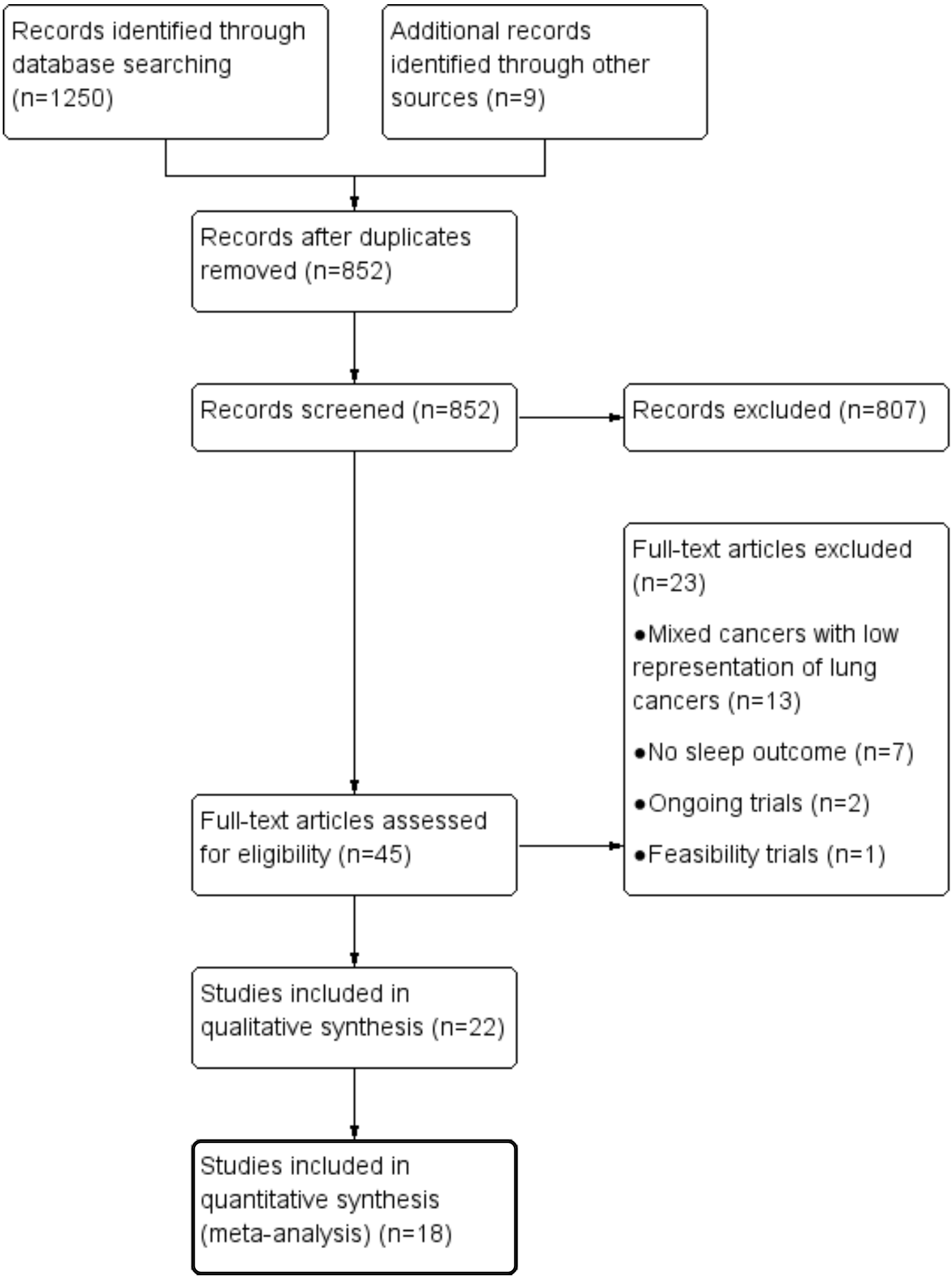
		LTFU				−0.64 (−1.97, 0.69)		0.342			−0.18 (0.19)
Li 2013[33]	EORTC QLQ-C30 (0-100)	Baseline	24	24	m±sd	9.4±8.7	11.2±10.4	0.259			
		MTFU				37.2±15.0	36.9±10.8	0.468			−0.02 (0.29)
		LTFU				15.6±12.8	38.2±21.6	0.000			−1.25 (0.32)
Ozalevli 2010[34]	NHP (0-100)	Baseline	18		m±sd	51.86±38.68		0.01			
		STFU				27.85±30.36					
Cleeland 2011[35]	MDASI (0-10)	Baseline	38	41	events score>5	11[a]	19[a]				
		STFU				11[a]	25[a]				−0.74 (0.26)
Lee 2014[36]	ISI (0-28)	Baseline	19	17	m±sd	11.53±6.27	14.94±6.27				
		STFU	19	16		8.58±5.71	14.56±7.38		−2.95±3.75	−0.44±4.56	−0.90 (0.36)
Miao 2012[37]	EORTC QLQ-C30 (0-100)	Baseline	38	32	m±sd	26.31±25.88	22.91±19.74				
		STFU				43.85±26.96	56.24±23.09				−0.48 (0.24)
Tong 2013[38]	PSQI (0-21)	STFU	30	30	m±sd	11.1±**3.73**	16.5±**3.73**				−1.43 (0.29)
Wang 2008[39]	HAMD (0-6)	Baseline	11	9	m±sd	2.26±2.44	2.03±1.00	0.11			
			23			2.88±1.71					
		STFU	11	9		2.19±2.13	4.26±2.50	<0.01			−0.96 (0.39)
			23			2.22±1.96					
Feng 2011[40]	PSQI (0-21)	Baseline	40	40	m±sd	14.48±1.71	13.92±2.59				
		STFU				7.92±1.22	11.44±1.89	<0.01			−2.19 (0.29)
Fouladbakhsh 2014[41]	PSQI (0-21)	Baseline	9		m	2.43					
		STFU				2.43					
Jiang 2013[42]	SRSS (10-50)	Baseline	30	30	m±sd	28.367±5.798	27.667±5.274	0.627			
		STFU				24.900±5.418	28.033±5.269	0.046			−0.58 (0.26)
Kwekkeboom 2012[43]	Summary score (0-10)	Baseline	36	42	m±sd	5.04±2.49	5.25±2.59				
		STFU				3.71±2.15	4.39±2.70				−0.27 (0.23)

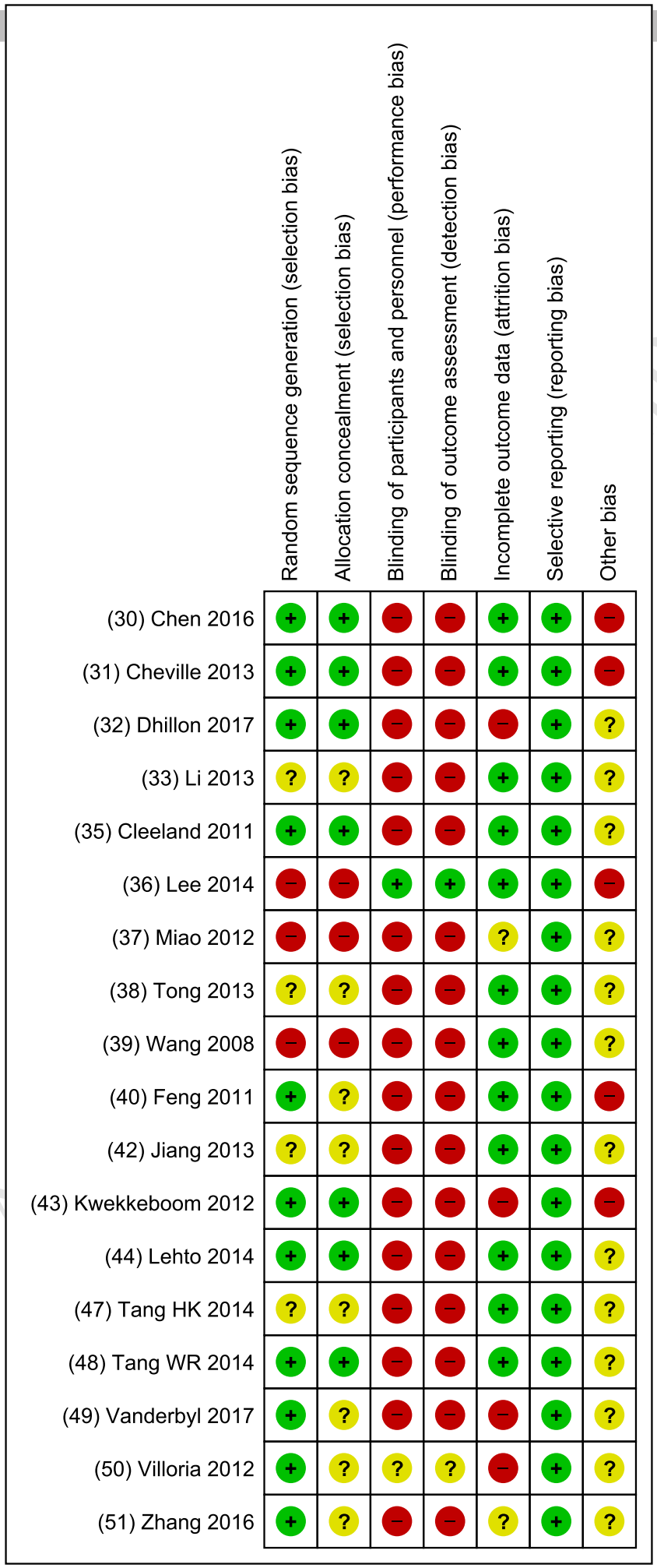
Lehto 2014[44]	PSSQ_I quality (0-25)	Baseline	16	16	m±sd	14.47±6.84	11.65±7.53					
		STFU[b]			m (se)	8.71 (2.14)	10.62 (1.95)					−0.23 (0.35)
		MTFU[b]				8.17 (2.08)	12.93 (1.99)					−0.57 (0.36)
	PSSQ_I interference (0-32)	Baseline			m±sd	10.63±8.05	6.37±6.18					
		STFU[b]			m (se)	5.99 (1.55)	6.45 (1.47)					−0.07 (0.35)
		MTFU[b]				6.28 (1.55)	9.26 (1.54)					−0.47 (0.36)
Milbury 2015[45]	PSQI (0-21)	Baseline	10		m±sd	12.82±3.34		0.11				
		STFU				10.70±3.34						
Milbury 2015[46]	PSQI (0-21)	Baseline	9		m±sd	12.00±5.04		0.34				
		STFU				11.00±4.93						
Tang HK 2014[47]	PSQI (0-21)	Baseline	50	50	m±sd	18.10±2.76	18.56±2.07					
		STFU				9.84±3.02	18.66±2.91					−2.95 (0.29)
Tang WR 2014[48]	PSQI (0-21)	Baseline	17	16	m±sd	8.82±4.63	9.44±3.76					
			24			9.63±4.72						
		STFU (raw)	15	14		7.53±4.29	10.09±4.76					−0.55 (0.33)
			16			7.47±4.88						
		STFU (est.)[c]	17	16	md (se)	−3.62 (**1.10**)			−3.00 (1.73)		0.083	−0.75 (0.30)
			24			−2.06 (**1.10**)			−2.25 (1.10)		0.040	
Vanderbyl 2017[49]	ESAS poor sleep (0-10)	Baseline	11	13	M (IQR)	2.5 (4)	3 (4)	0.26				
		STFU			m±sd	2.4±**2.44**	−0.1±**2.44**		−0.1±2.4	−3.1±3.0	0.03	0.99 (0.44)
	ESAS sleepiness (0-10)	Baseline			M (IQR)	2 (2.8)	3 (5)	0.11				
		STFU			m±sd	2±**2.44**	2.5±**2.44**		0±3.0	−0.5±2.4	0.71	−0.20 (0.41)
Villoria 2012[50]	EORTC QLQ-C30 (0-100)	STFU (raw)	11	9	m±sd	21.21±30.81	29.63±30.93					−0.26 (0.45)
		STFU (est.)	23	22	md (CI)	−10.57 (−36.95, 15.80)		0.43				−0.23 (0.30)
		MTFU (raw)	8	7	m±sd	29.17±33.03	4.76±12.60					0.89 (0.55)

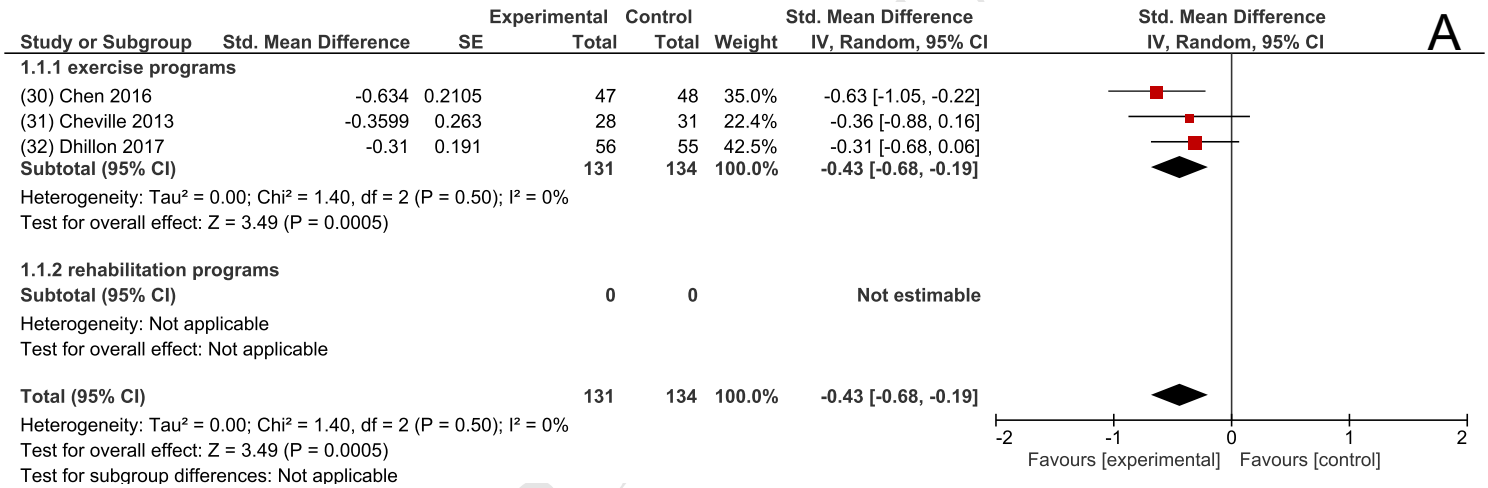
		MTFU (est.)	23	22	md (CI)	14.25 (−16.73, 45.22)		0.36	0.26 (0.30)
Zhang 2016[51]	EORTC QLQ-C30 (0-100)	Baseline	33	32	M (IQR)	100 (33.3)	100 (25)		
		STFU				66.7 (33.3)	100 (25)		−1.51 (0.28)

m=mean, sd=standard deviation, se=standard error, M=median, IQR=interquartile range, md=mean difference, CI=confidence interval, SMD=standardized mean difference of follow-up scores, IG=intervention group, CG=control group, STFU=short-term follow-up, MTFU=medium-term follow-up, LTFU=long-term follow-up, TST=total sleep time, SE=sleep efficiency, SOL=sleep onset latency, WASO=wake after sleep onset, PSQI=Pittsburgh Sleep Quality Index, NRS=Numeric Rating Scale, EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, NHP=Nottingham Health Profile, MDASI=M.D. Anderson Symptom Inventory, ISI=Insomnia Severity Index, HAMD=Hamilton Depression Rating Scale, SRSS=Self-Rating Scale of Sleep, PSSQ_I = Pittsburgh Sleep Symptom Questionnaire-Insomnia, ESAS=Edmonton Symptom Assessment Scale.

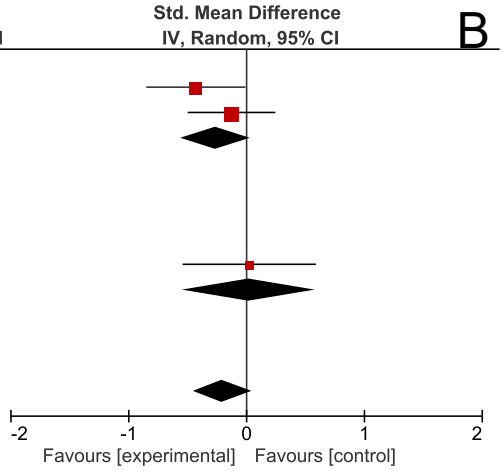
Imputed values are shown in bold. [a]data from graph, [b]adjusted for baseline values, [c]adjusted for age, baseline values and adherence.


Records identified through database searching (n=1250)
Additional records identified through other sources (n=9)
Records after duplicates removed (n=852)
Records screened (n=852)
Records excluded (n=807)
Full-text articles excluded (n=23)
•Mixed cancers with low representation of lung cancers (n=13)
•No sleep outcome (n=7)
•Ongoing trials (n=2)
•Feasibility trials (n=1)
Full-text articles assessed for eligibility (n=45)
Studies included in qualitative synthesis (n=22)
Studies included in quantitative synthesis (meta-analysis) (n=18)

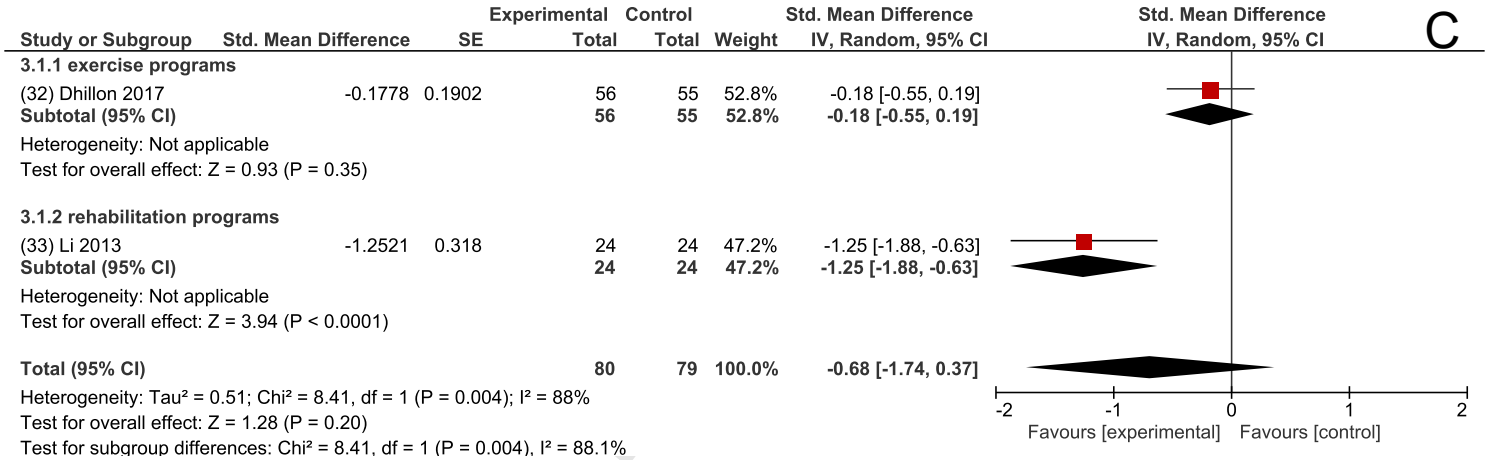

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
(30) Chen 2016
(31) Cheville 2013
(32) Dhillon 2017
(33) Li 2013
(35) Cleeland 2011
(36) Lee 2014
(37) Miao 2012
(38) Tong 2013
(39) Wang 2008
(40) Feng 2011
(42) Jiang 2013
(43) Kwekkeboom 2012
(44) Lehto 2014
(47) Tang HK 2014
(48) Tang WR 2014
(49) Vanderbyl 2017
(50) Villoria 2012
(51) Zhang 2016

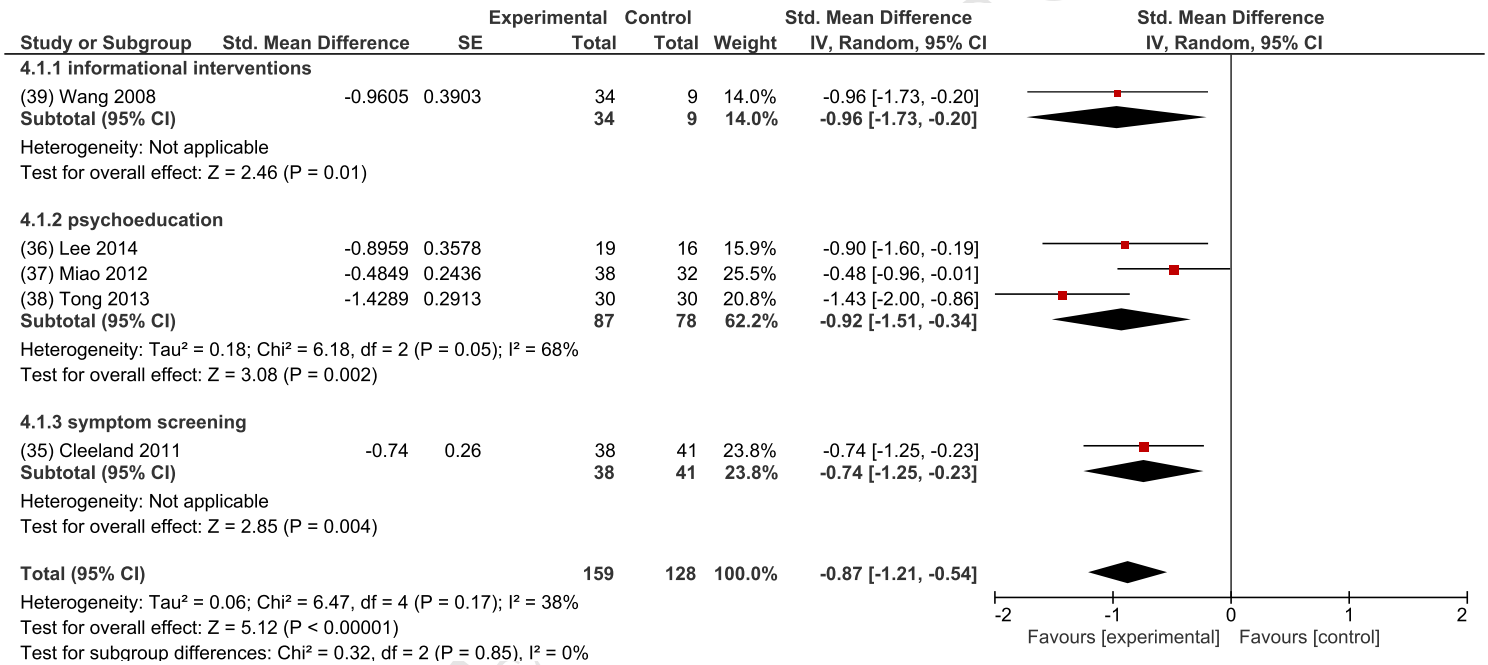

Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup
Std. Mean Difference
SE
Total
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
A
1.1.1 exercise programs
(30) Chen 2016 -0.634 0.2105 47 48 35.0% -0.63 [-1.05, -0.22]
(31) Cheville 2013 -0.3599 0.263 28 31 22.4% -0.36 [-0.88, 0.16]
(32) Dhillon 2017 -0.31 0.191 56 55 42.5% -0.31 [-0.68, 0.06]
Subtotal (95% CI) 131 134 100.0% -0.43 [-0.68, -0.19]
Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)
1.1.2 rehabilitation programs
Subtotal (95% CI) 0 0 Not estimable
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Total (95% CI) 131 134 100.0% -0.43 [-0.68, -0.19]
Heterogeneity: Tau² = 0.00; Chi² = 1.40, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.49 (P = 0.0005)
Test for subgroup differences: Not applicable
-2
-1
0
1
2
Favours [experimental]
Favours [control]

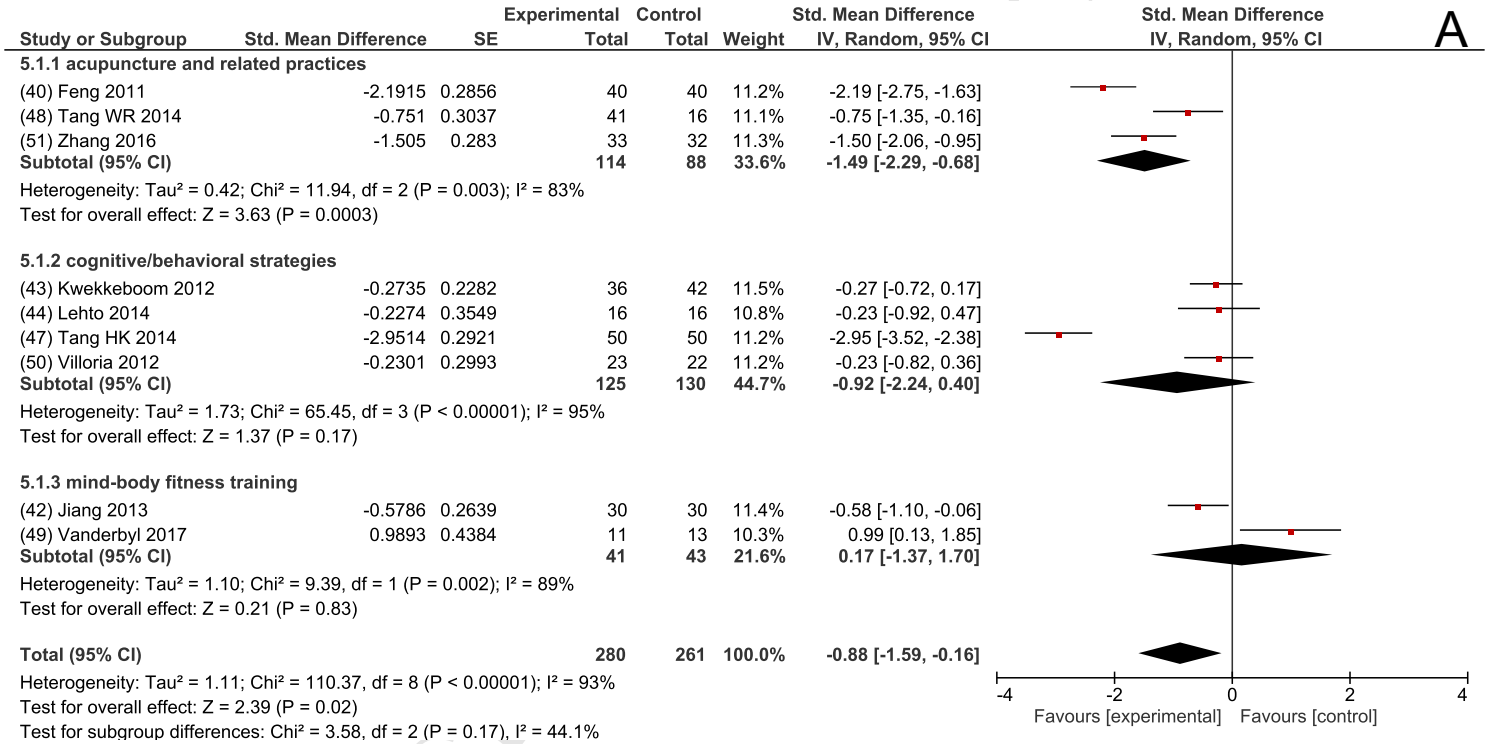
Study or Subgroup	Std. Mean Difference	SE	Experimental Total	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 exercise programs						
(30) Chen 2016	-0.4308	0.2147	43	46	35.3%	-0.43 [-0.85, -0.01]
(32) Dhillon 2017	-0.1281	0.19	56	55	45.1%	-0.13 [-0.50, 0.24]
Subtotal (95% CI)			**99**	**101**	**80.5%**	**-0.26 [-0.56, 0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 1.75 (P = 0.08)						
2.1.2 rehabilitation programs						
(33) Li 2013	0.0226	0.2887	24	24	19.5%	0.02 [-0.54, 0.59]
Subtotal (95% CI)			**24**	**24**	**19.5%**	**0.02 [-0.54, 0.59]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)			**123**	**125**	**100.0%**	**-0.21 [-0.46, 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.61 (P = 0.11)						
Test for subgroup differences: Chi² = 0.77, df = 1 (P = 0.38), I² = 0%						

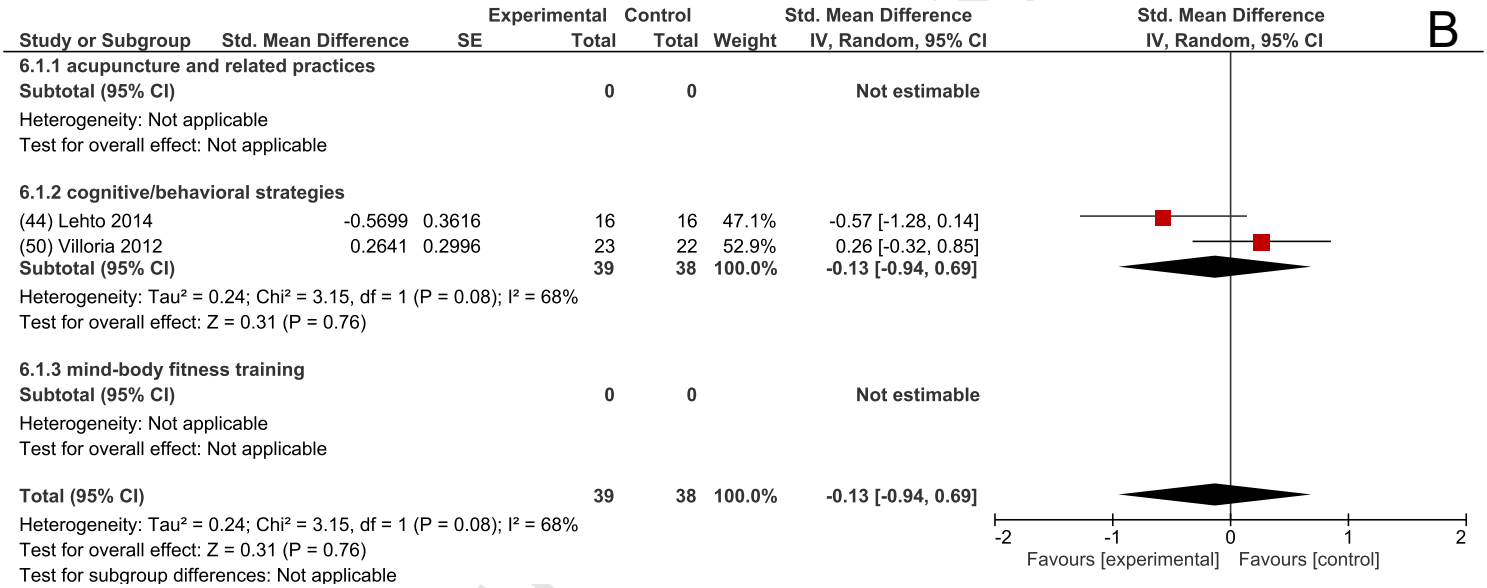


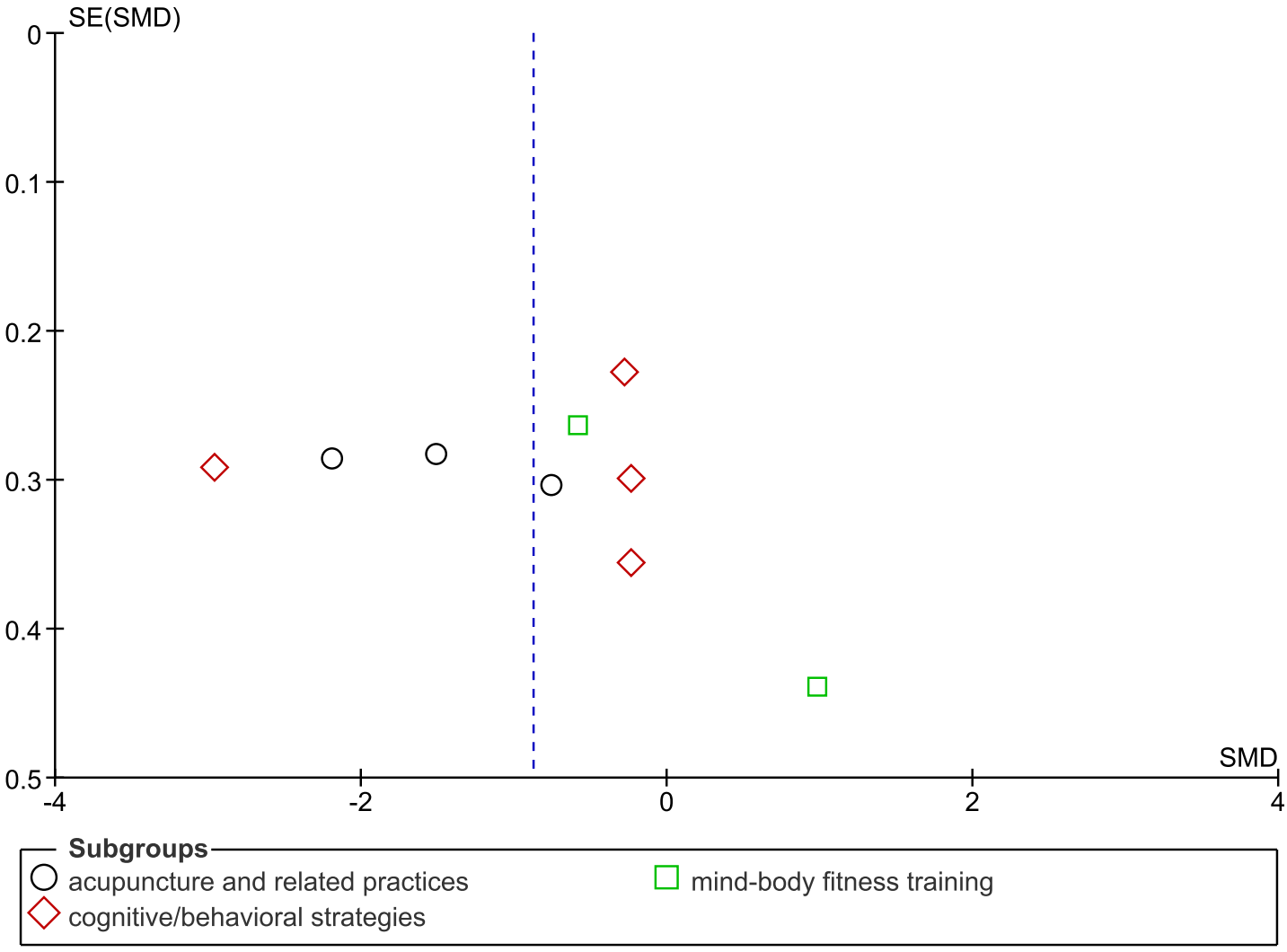
B


Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup
Std. Mean Difference
SE
Total
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
C
3.1.1 exercise programs
(32) Dhillon 2017 -0.1778 0.1902 56 55 52.8% -0.18 [-0.55, 0.19]
Subtotal (95% CI) 56 55 52.8% -0.18 [-0.55, 0.19]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)
3.1.2 rehabilitation programs
(33) Li 2013 -1.2521 0.318 24 24 47.2% -1.25 [-1.88, -0.63]
Subtotal (95% CI) 24 24 47.2% -1.25 [-1.88, -0.63]
Heterogeneity: Not applicable
Test for overall effect: Z = 3.94 (P < 0.0001)
Total (95% CI) 80 79 100.0% -0.68 [-1.74, 0.37]
Heterogeneity: Tau² = 0.51; Chi² = 8.41, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Chi² = 8.41, df = 1 (P = 0.004), I² = 88.1%
-2
-1
0
1
2
Favours [experimental]
Favours [control]








SE(SMD)
0
0.1
0.2
0.3
0.4
0.5
-4
-2
0
2
4
SMD
Subgroups
acupuncture and related practices
cognitive/behavioral strategies
mind-body fitness training