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Title page/Running title

Acupuncture for breathlessness in advanced diseases:

A systematic review and meta-analysis

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Abstract

Context. Non-pharmacological approaches are effective strategies for difficult to palliate breathlessness. Whilst acupuncture is effective for dyspnoea in early-stage COPD, little is known about its effects in patients with advanced (non-)malignant diseases.

Objectives. To identify and examine the evidence of acupuncture on breathlessness in advanced malignant and non-malignant diseases.

Methods. Systematic literature review of randomised controlled trials of acupuncture and acupressure searched in five databases. Included were adult participants with at least 25% having advanced diseases such as cancer or COPD with severe breathlessness. Primary outcome was severity of dyspnoea on visual analogue or Borg scale. Secondary outcomes included quality of life, function and acceptability. Data were pooled using a random effects model of standardised mean differences.

Results. 12 studies with 597 patients (347 COPD, 190 advanced cancer) were included. For breathlessness severity significant differences were obtained in a meta-analysis (10 studies with 480 patients; SMD= -1.77 (95% CI -3.05,-0.49; p=0.007; I^2= 90%)) and in a subgroup analysis of using sham acupuncture control groups and a treatment duration of at least three weeks (6 studies with 302 patients; SMD= -2.53 (95% CI -4.07,-0.99; p=0.001; I^2 =91%)). Exercise tolerance (6MWT) improved significantly in the acupuncture group (6 studies with 287 patients; SMD=0.93 (95% CI 0.27,1.59; p=0.006; I^2= 85%)). In four of six studies quality of life improved in the acupuncture group.

Conclusion. Acupuncture improved breathlessness severity in patients with advanced diseases. The methodological heterogeneity, low power and potential morphine-sparing effects of acupuncture as add-on should be further addressed in future trials.

Key words:

dyspnoea; acupuncture; advanced disease; systematic review; meta-analysi

Introduction

Breathlessness is one of the most common symptoms in patients with chronic lung or heart diseases of malignant or non-malignant origin. Its incidence increases in patients with advanced disease (1). Fifty to 70% of advanced cancer patients experience significant breathlessness (2,3). In COPD patients, breathlessness is one of the most distressing symptoms, and is associated with a significant decrease in quality of life (4) and reduced survival (5).

Breathlessness can be a common and distressing symptom in other advanced diseases, such as interstitial lung disease, motor neuron disease, amyotrophic lateral sclerosis, chronic heart failure, cystic fibrosis or cryptogenic fibrosing alveolitis, motor neuron disease, and advanced cancer, increasing in particular at the end of life (6). Dyspnoea in advanced diseases is often associated with non-reversible or non-identifiable conditions or complex interactions with other organ dysfunction (e.g. heart failure). In these cases, causal treatment becomes very difficult and palliative symptom control is needed (5).

Use of medication is often limited or may even be harmful due to side effects (e.g. drowsiness, constipation, nausea, vomiting), inadequate usage or insufficient effectiveness. Beside the pharmacological treatment of breathlessness, many other non-pharmacological interventions have been tested. Some of them (e.g. breathing training, chest wall vibration, use of a hand-held fan) have shown effectiveness in relieving breathlessness (6). These non-pharmacological treatments are usually used supplementary to standard medication or oxygen.

Acupuncture is a widely used technique in traditional Chinese medicine (TCM) and numerous randomised, controlled trials (RTCs) have evaluated the clinical efficacy of acupuncture (7). The concept of TCM is based on the harmonious flow of “Qi”, commonly translated as “life energy”. Disease or distress occurs if the continuous flow of Qi in some of these meridians is somehow disrupted. Specific acupuncture points (acupoints) are located on the meridians. Stimulation of these points by needles (acupuncture), finger pressure (acupressure) or other methods (laser, electric stimulation) may restore the continuous flow of energy and may maintain health by enhancing robustness (8). As has been reported, acupuncture is effective in treating common symptoms in supportive and palliative care, such as cancer-related fatigue, leukopenia and chemotherapy-induced nausea and vomiting and acupuncture may be effective in treating cancer-related pain and improving quality of

life in palliative patients (7,9,10). Only insufficient evidence for the effectiveness of acupuncture for cancer-related dyspnoea has been reported (11,12). Similar results were published in a Cochrane Review in 2008, showing mixed results with low strength of evidence regarding acupuncture for breathlessness in advanced diseases (6). However, some acupuncture techniques were not included and a meta-analysis was not performed. The recent systematic review with meta-analyses by Wang (13) showed improved functional effects and quality of life in COPD patients, but did not focus on breathlessness. In a review by Coyle (14), it was assumed that acupuncture can be effective in treating COPD-related breathlessness. However, the Coyle review included patients at early stages of COPD with findings not applicable to later COPD stages (14). Although acupuncture can offer palliation in early stage COPD-related breathlessness, it remains unclear if this is also the case for breathlessness in more advanced diseases.

Currently, there is no single physiological correlate that will accurately predict dyspnoea or reflect the far-reaching effects of breathlessness and various subjective clinical and psychophysical scales and questionnaires are typically used to measure breathlessness (15). Accordingly, it is recommended to combine a unidimensional scale such as the Borg scale in conjunction with other disease-specific methods (16).

Therefore, the current review with meta-analyses aims to systematically review and evaluate the effectiveness of acupuncture or acupressure in reducing breathlessness and improving physical function and quality of life in advanced malignant and non-malignant diseases with dyspnoea.

Methods

Design

A systematic review and meta-analysis was conducted according to the Cochrane (17) and *Preferred Reporting of Items for Systematic Reviews and Meta-Analyses* (PRISMA) (18) guidelines.

Search strategy

The following databases were searched: MEDLINE (1946-2019), PsycINFO (1806-2019) and Embase (1974-2019) via Ovid, Web of Science (1900-2019), CINAHL and AMED (via EBSCOhost, 1980-2019) and the Cochrane Database of Abstracts of Reviews of Effects (via Cochrane Library, 2019). A sample of search strategies with all used search strings can be found in the Appendix. The search strategy used a combination of key words, medical subject headings (MeSH, exploded) and title- or abstract free-text words: “dyspnoea”, “breathlessness”, “shortness of breath” AND “cancer”, “neoplasms”, “chronic obstructive pulmonary disease”, “chronic heart failure”, “motor neuron disease”, “interstitial lung disease” AND “acupuncture”, “acupressure”. No restrictions as to date, language or country were placed on the searches.

The references of relevant articles, systematic reviews and included studies and their citations were also searched and entered into the Google scholar database, Scopus and Ovid databases to identify further relevant studies. Key researchers within the field were contacted to identify further unpublished studies. Furthermore, grey literature was hand searched, including searches for studies which were not yet published on clinicaltrials.gov and the ISRCTN (International Standard Randomised Controlled Trial Number) registry.

Selection of studies

Inclusion criteria

Any study fulfilling the following characteristics was included in the review:

1. Research design: All types of RCTs. Original published full-text articles were included.
2. Intervention: Studies using any form of acupuncture or acupressure.

3. Control group: Control groups may receive no treatment, treatment as usual; non-penetrative sham (i.e. non-invasive treatment); penetrative sham (i.e. invasive treatment at non-acupuncture points).
4. Participants: Adult participants (>18 years of age) with breathlessness due to advanced malignant or non-malignant diseases. Since the term advanced disease is not uniformly defined in the scientific medical literature (6), types of included diseases were:

- advanced cancer (cancer of any origin in advanced local or metastatic stage, e.g. breast cancer stage III or higher, lung cancer stage II or higher)
- severe COPD (FEV1 should be below 50%, respectively COPD GOLD III-IV (19))
- chronic heart failure (NYHA Stage III or IV (20))
- interstitial lung disease (any stage, if associated with breathlessness)
- motor neuron disease (any stage, if associated with breathlessness)

At least 25% of the study population should meet the criteria mentioned above.

5. Primary outcome: Any subjective measurement of breathlessness severity made on a validated rating scale (visual analogue scale (VAS) (21), numerical rating scale (NRS)) or on the Borg Scale (22).
6. Secondary outcomes:

- Exercise tolerance was measured via the 6-minute walk test (6MWT) (23).
- Quality of life was assessed with any validated questionnaire.
- Anxiety or depressions were measured on any validated scale.
- Acceptability was assessed by comparing the number of drop-outs or withdrawals.
- Tolerability was assessed by comparing the number of adverse events.

Exclusion criteria

Studies with following characteristics were excluded:

1. Research design: All quasi-experimental studies, observational research and case studies as well as systematic reviews were excluded.
2. Intervention: All other therapies (like qigong or herbal remedies) not manipulating acupoints, were excluded. Studies with other complex interventional elements as acu-TENS or moxibustion were excluded.

3. Participants: Study samples with less than 25% in the advanced stages or not comprising the diseases defined above. Studies of patients with asthma or other potentially curable diseases or exacerbations of a chronic disease (e.g. decompensation of chronic heart failure or acute exacerbations of COPD) were excluded.
4. Outcome: Studies were excluded if they did not use validated scales to measure breathlessness severity.

Data collection and data extraction

Searches were run in 2016 by one reviewer and up-dated in June 2019. References were imported into Zotero (Version 5.0.59) and duplicates removed. All potentially eligible studies were identified from the literature searches, using the eligibility criteria to determine study inclusion. First, the titles and abstracts of all retrieved studies were screened for eligibility. If it was not clear from the title or abstract that the study needed to be rejected, the full text of the study was obtained and reviewed.

Data extraction and assessment were carried out by two reviewers. Data extraction was done using a prespecified and piloted format in Microsoft Excel. The following information was extracted from original studies: study characteristics (year, country of origin), study design (type of RCT, number and nature of trial arms), study participants and case-mix criteria (age, disease, stage etc.), information regarding the content and delivery characteristics of the intervention and the control treatment, primary and secondary outcomes (name of measure, outcome data for both groups). Data extraction for meta-analysis from original studies included means and standard deviations. If possible, means and standard deviations were calculated from other reported data (such as change scores, range, standard errors, confidence intervals and p-values) using guidance in the appendix of the Cochrane Handbook (17) and from the systematic review textbook by Cooper et al. (24). If information on means and standard deviations could not be inferred, the study was only included in the qualitative synthesis.

Quality assessment

Studies were assessed for methodological quality using Cochrane's risk of bias scale (17). This scale assesses six domains – sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and

other bias. One reviewer rated the risk of bias in each study, defined as “low risk of bias”, “high risk of bias” or “unclear risk of bias”, and another reviewer independently checked the scoring. Results of quality assessment were integrated into data synthesis.

Data analysis

For continuous outcomes, data were pooled in meta-analyses using the inverse variance weighting method and a random-effects model. We used random-effects models since a heterogeneous set of advanced conditions was included and thus more than one true effect was to be estimated for this population. Data analysis was conducted using Review Manager 5.1 (25). Meta-analysis used standardised mean difference (SMD) with 95% confidence intervals as the effect size for random-effects models. However, if outcome data was presented primarily as a binary outcome (number of adverse events, number of drop-outs) we used this dichotomous data to calculate odds ratios (ORs) with 95% confidence intervals as the effect size.

The Chi^2 test (26) and the I^2 statistic (27) were used to investigate heterogeneity. The Chi^2 test assesses whether observed differences in the results of the included studies are compatible with chance alone. The I^2 statistic describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance. We followed the recommendations from the Cochrane Handbook on the interpretation of I^2: “0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity” (17).

As we expected relatively low numbers of included studies, we did not plan to investigate sources of heterogeneity by statistical means, i.e. meta-regression. Rather, we tabulated possible influences on heterogeneity, such as methodological sources, variability in included patient samples, variation in the intervention delivery and dose, to determine sources of heterogeneity on the main effect. To investigate the possible influence of treatment duration on the effect sizes we planned to integrate treatment duration into subgroup analyses.

Funnel plots were used to examine potential publication bias and small study effects.

If enough studies reported a secondary outcome such as exercise tolerance or number of adverse events in intervention and control group, these results were pooled across studies using meta-analyses with the methods detailed above. Trial

data that could not be included in the meta-analyses were evaluated in qualitative synthesis of findings.

Results

Search results and study characteristics

The literature search was performed in November 2016 and updated in June 2019. As outlined in Figure 1, the searches of English-language databases identified 691 references. After removal of duplicates, the titles and abstracts of the remaining 658 were reviewed for eligibility. The full text was retrieved for 30 studies and 12 published studies met the eligibility criteria.

[Insert Figure 1]

Characteristics of the twelve included studies with a total number of 597 participants completing the studies are outlined in Table 1. In nine studies (n = 470 patients), the intervention consisted of acupuncture (28–36). Three studies with a total of 127 patients used acupressure (37–39). Four studies originated from the UK (28,33–35), three from Taiwan (37–39), two from Japan (29,30), one from US (32), one from Ireland (31), and one from China (36).

Ten studies included patients with advanced COPD (stage III and IV) (Table 1). Vickers' study included advanced lung and breast cancer patients with dyspnoea (32) and Minchom's patients with advanced lung cancer and mesothelioma (35).

[Insert Table 1]

Assessment of risk of bias

We determined the Cochrane "risk of bias" score for each study (see Fig. 2 and Fig. 3). Fifty percent of the included studies were rated as having a high or unclear risk of performance bias (blinding of participants and personnel) (Fig. 2 and Fig. 3). Eight studies performed single-blinding for patients by using true and sham techniques to stimulate acupoints (Table 1) and seven studies reported about blinded assessors (Fig. 2 and Fig. 3). However, no study was double-blinded as it is difficult to blind the acupuncture therapist. Fifty percent of the studies showed an unclear or high risk of bias regarding allocation concealment (Fig. 2). Other sources of bias were not reporting the number of drop-out (30,31,34,37–39), not stating the primary outcome (33,37), change of protocol during the course of the trial (32), potential carryover effects in crossover studies (28,39), problems with the statistical analysis of results

and optimistic conclusions (36). Furthermore, possible selection biases with inclusion of patients influenced by physicians (30), may have occurred.

[Insert Figure 2 and Figure 3]

Primary outcome: Breathlessness severity

Ten out of twelve studies provided numerical data for breathlessness severity and were included in a meta-analysis (Fig. 4). Three studies (28,35,39) used a visual analogue scale (VAS), four studies (29–31,34) a Borg-Scale, two (33,36) a modified (inversed) Borg-Scale, and one (32) a numerical rating scale. For the three-arm studies the acupuncture in combination with pulmonary rehabilitation arm was compared with the pulmonary rehabilitation only arm (31) and the acupuncture-alone arm was compared with the morphine-alone arm (35) respectively. The meta-analysis of the ten studies (n = 480 patients) (Fig. 4) showed a significant effect favouring the acupuncture group. The standardised mean difference (SMD) was -1.77 (95% CI -3.05,-0.49; p=0.007) and heterogeneity (I^2 = 90%) high.

[Insert Figure 4]

The treatment duration between all studies included in this systematic review ranged from just a single acupuncture session to a treatment course of 12 weeks' duration (Table 1). The median duration was 25 days. As can be seen in Figure 4, all studies with treatment duration of at least 2 weeks favoured the acupuncture group. In the two studies that showed non-significant SMDs (32,34), the duration of treatment was only 7 days or less.

A subgroup analysis explored expectancy effects by including only sham controlled studies (Figure 5). These six studies (n = 302) with sham control groups and a treatment duration of at least 3 weeks (28,29,33,36,37,39) demonstrated a significant improvement in dyspnoea SMD= -2.53 (95% CI -4.07,-0.99; p=0.001) and high heterogeneity (I^2 =91%).

[Insert Figure 5]

Exercise tolerance measured by the 6MWT

In six studies the six-minute walk test (6MWT) was measured to assess exercise tolerance (29,30,33,36,37,39). In the meta-analysis in Fig. 6, of 143 patients treated with acupuncture, 6MWT data were compared to data of 144 control patients. The

SMD was 0.93 (95% CI 0.27 to 1.59), showing a significant group difference favouring the acupuncture group (p=0.006). However, heterogeneity was relatively high (I^2 =85%).

[Insert Figure 6]

Quality of life and anxiety

Owing to study heterogeneity and insufficient data, meta-analyses of quality of life and anxiety could not be performed. In six studies quality of life was measured (28,29,31,33,35,36). Different scales to measure quality of life were used: St. George's respiratory questionnaire SGRQ (4 studies, (28,29,31,36)), the EORTC (European Organisation for Research and Treatment of Cancer) quality-of-life questionnaire (QLQ-30 lung-specific module) (40) (1 study, (35)), the EuroQol (EQ-5D-3L) (1 study, (31)) a general wellbeing scale (1 study, (33)). Heterogeneity in effects on quality of life was observed across studies. There were only small reductions of the SGRQ score within the groups, which did not reach the minimal clinically important difference (41). In four studies (29,31,35,36) beneficial effects were reported for the acupuncture arms and in two studies (28,33) no significant changes were found between the treatment groups. In two sham controlled studies (29,36) the total SGRQ score in the real acupuncture group improved more compared to the sham groups. In the three-arm studies the SGRQ score was still persistent for the 3 month follow-up only in the acupuncture arm (30) and EORTC global health improvements were observed for both acupuncture-inclusive arms (35).

Four studies provided data for anxiety using different scales (34,35,37,38). No significant changes in VAS anxiety were found between the treatment groups (34), anxiety improved in the acupressure arms compared to the controls (37,38), and Lar anxiety improved in both acupuncture-arms compared to the morphine-alone arm (35).

Acceptability and tolerability

Acceptability could be assessed for six studies (28,29,32,33,35,36). The odds ratio was 0.61 (95% CI 0.31 to 1.20; p=0.15) and heterogeneity was low (I^2 =2%). However, six studies (30,31,34,37–39) were excluded from this analysis due to failure to report the number of drop-outs and withdrawals.

[Insert Figure 7]

Seven studies reported data on tolerability. However, five studies did not report whether there were any adverse events (31,33,36–38). Three studies reported that there were no adverse events (32,34,39). Four studies reported minor adverse events in the intervention group (e.g. transitory bruising or pain) (28–30,35). In the meta-analysis of seven studies no significant differences between the groups were observed (Fig. 8).

[Insert Figure 8]

Sensitivity analysis

In a funnel plot the effect sizes versus their standard errors were plotted for the primary outcome breathlessness severity to assess publication bias (Appendix, Fig. 1). The funnel plot shows evidence of publication bias with negative and small effects being underrepresented.

To check the robustness of findings sensitivity analysis was conducted (Appendix, Figs 2 and 3). Pooling together five studies with SMD higher than 2.0 showed very low heterogeneity (I^2=4%). The analysis of five studies with SMD 2.0 or lower showed a heterogeneity of I^2=27%.

Discussion

This systematic review of randomised controlled trials was conducted to evaluate the effectiveness of acupuncture on breathlessness in advanced diseases with dyspnoea. Twelve RCTs were identified and meta-analyses for breathlessness severity and secondary outcomes were performed. Overall, there was a significant effect for acupuncture reducing breathlessness severity in patients with advanced diseases. Furthermore, the meta-analysis on the 6MWT, including 6 studies showed a significant treatment effect of acupuncture compared to the control group. In addition, in four out of six studies measuring quality of life, beneficial effects were observed for the acupuncture group.

The findings of this review were primarily based on a limited number of studies (n = 12). There was also large heterogeneity regarding types of acupuncture interventions and treatment durations. Methodological quality varied widely between the included studies. Most of the meta-analyses showed considerable heterogeneity (I^2 = 75% or higher).

Acceptability was comparable in acupuncture and control groups. However, half the studies missed information on number of drop-outs. Only few adverse events were reported in the interventions and no significant differences between groups were observed. Minchom et al. (35) reported fewer side-effects for acupuncture than for morphine and it was assumed that acupuncture might have morphine-sparing properties (35). Due to a lack of reporting of adverse events in half of included studies, overall tolerability or safety of acupuncture treatment remains uncertain.

The interventions itself varied widely across the 12 included studies. Some were based on traditional Chinese medicine (TCM) diagnosis with individually chosen acupuncture points in two studies (30,33). The majority of studies utilised a symptom-based treatment concept and used standardised (not individually chosen) locations of acupoints for all patients. Furthermore, different kinds of needles were used and standardised acupoints for breathlessness differed between studies. Hence, only a small number of acupoints was consistently used across studies (LU1, LU10, ST36 and LI4).

Despite this heterogeneity across studies in the intervention, the aim of this review was to evaluate the effect of manipulating acupoints for relieving breathlessness. All included techniques to manipulate acupoints referred to the principles of TCM. It was therefore regarded as a sufficiently homogeneous concept of treatment. Pooling together several different acupuncture techniques is also a common approach used

in past systematic reviews (11,13,14,42). A focus on acupuncture with needle-insertion only and exclusion of acupressure would have been a more homogeneous approach, but would have resulted in only a small number of studies to be included in this review.

Since breathlessness is one of the most distressing symptoms in various advanced diseases and is associated with a significant decrease in functional effects and quality of life, we chose breathlessness severity as the primary outcome for our review. Many different assessment tools measured breathlessness severity (e.g. Borg-scale, VAS) for different time-intervals. These variabilities caused difficulties in interpretation of the outcome measurements. Additionally, the measurement scales did not always use standardised scaling (i.e. using an inversed scale with 10 as the best possible score on the Borg scale). This will have contributed to the high amount of heterogeneity between studies observed in the meta-analyses (Fig. 4 and Fig. 5).

In the meta-analysis of our secondary outcome 6MWT a significant treatment effect of acupuncture compared to the control group was observed (Fig. 6). Preferably, one would choose the 6MWT as a primary outcome for a future review as the 6MWT is a standardised and widely used measurement tool.

Contrary to two previous reviews of acupuncture for COPD patients (13,14), our review focusses on patients with advanced diseases only. Similar to Coyle et al. (14) our review also shows a significant improvement in breathlessness in addition to the significant improvement in health-related quality of life reported in other reviews (13,14). Estimated group differences in the 6MWT were slightly higher than in our review.

Acupuncture has been shown to be effective in an elderly population not suffering from breathlessness. For example, in hospitalised geriatric patients acupuncture reduced low back pain (43) and led to fewer medication-related side-effects than in the control group. Acupressure has also been shown to improve quality of sleep in elderly patients living in residential homes (44). However, no studies to date have investigated acupuncture for breathlessness specifically in an elderly population.

Opioids have shown promising effects for the relief of breathlessness in advanced COPD (45). Nonetheless, the risks of opioid drug use in particular the side-effects may increase deleterious outcomes in older patients with COPD (46).

The observed heterogeneity could also stem from different comorbidity status in included study populations. It is known that COPD patients suffer from multiple

comorbidities such as muscle wasting, cachexia, ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes (47). Only two studies (33,39) of our review reported the number of comorbidities. Therefore, the role of comorbidities affecting our results remains unclear.

Two recent reviews did not recommend acupuncture for cancer-related breathlessness (48,49). However, both reviews only included the study by Vickers and co-authors (32). In addition, we also considered the study by Minchom et al. (35) reporting relief of dyspnoea in patients with advanced non-small cell lung cancer and mesothelioma.

Limitations of the review

This systematic review is restricted by the fact that the primary search and review was done by one author only. The update of the search, data extraction and methodological quality assessment, however, were also independently performed by a second reviewer. The main literature search was performed in 2016. Two more studies were added (35,36) when the search was updated in June 2019. Additionally, searches of grey literature and hand search were performed but due to limited resources and lack of time, some possibly relevant publications may not have been identified. Furthermore, language barriers and high costs associated with translation prevented the author from including non-English literature. Chinese databases were not searched. However, Ernst warns of a country-specific bias with almost all Chinese acupuncture trials showing positive results (50) while not meeting reporting and quality standards for RCTs. Therefore, we do not think that searches of these databases would have prevented the publication bias observed in this review.

The definition of palliative patients respectively patients with advanced diseases is not clearly defined. Advanced stages should be defined independently for every malignant or non-malignant disease (6). We followed these recommendations. However, other disease-specific definitions of advanced diseases would have led to different outcomes.

Many studies did not report complete outcome data. A large amount of outcome data had to be imputed from reported standard error, range and confidence intervals, and mean changes (with standard deviations inferred from the standard deviation of

change). Hence, most meta-analyses might lack precision and validity, have high heterogeneity and should be interpreted with caution.

Conclusion

In advanced diseases, acupuncture significantly reduced breathlessness severity.

The high level of heterogeneity of the included studies and the limited amount of studies did not provide rigorous evidence to allow recommendations on the use of acupuncture in this field.

Although current evidence is insufficient, potentially beneficial effects of acupuncture on dyspnoea, anxiety, quality of life and exercise capacity, as well as potential morphine-sparing effects, justify further research.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Figures and tables legend

(greyscale print possible for all tables and figures)

Fig. 1. Flow Chart.

Table 1. Included studies.

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Fig. 4. Forest plot of comparison: Acupuncture vs. Control, Outcome: Breathlessness severity.

Fig. 5. Forest plot of comparison Subgroup: Acupuncture vs. Sham Control, treatment duration $\geq$ 3 weeks, Outcome: Breathlessness severity.

Fig. 6. Forest plot of comparison: Acupuncture vs. Control, Outcome: Exercise tolerance measured by 6MWT.

Fig. 7. Forest plot of comparison: Acupuncture vs. Control, Outcome: Number of drop-outs.

Fig. 8. Forest plot of comparison: Acupuncture vs. Control, Outcome: Number of adverse events.

Appendix: sample search strategy

Appendix:

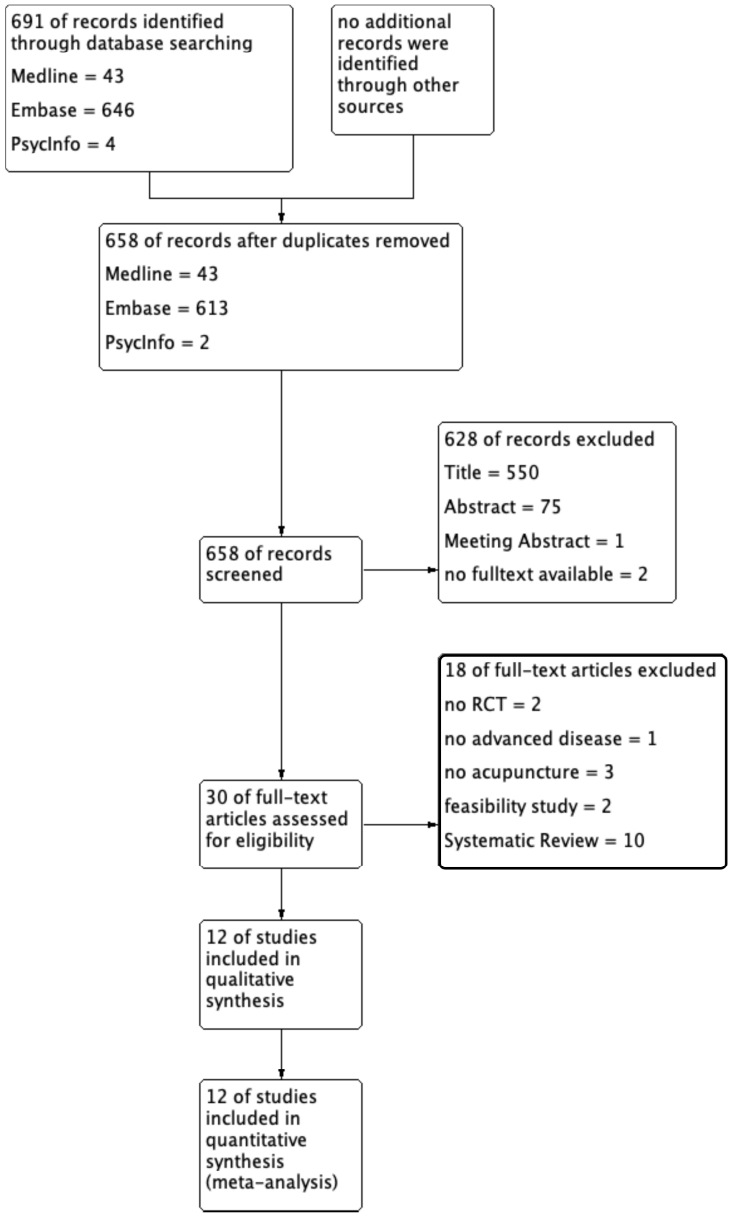
Fig. 1. Funnel plot for primary outcome (Breathlessness severity): Publication Bias.

Fig. 2. Forest plot of comparison: Acupuncture vs. Control, Outcome: Breathlessness severity, Sensitivity Analysis: Ranking by effect size (SMD > 2.0)

Fig. 3. Forest plot of comparison: Acupuncture vs. Control, Outcome: Breathlessness severity, Sensitivity Analysis: Ranking by effect size (SMD $\leq$ 2.0)

Figures:

Fig. 1. Flow Chart.



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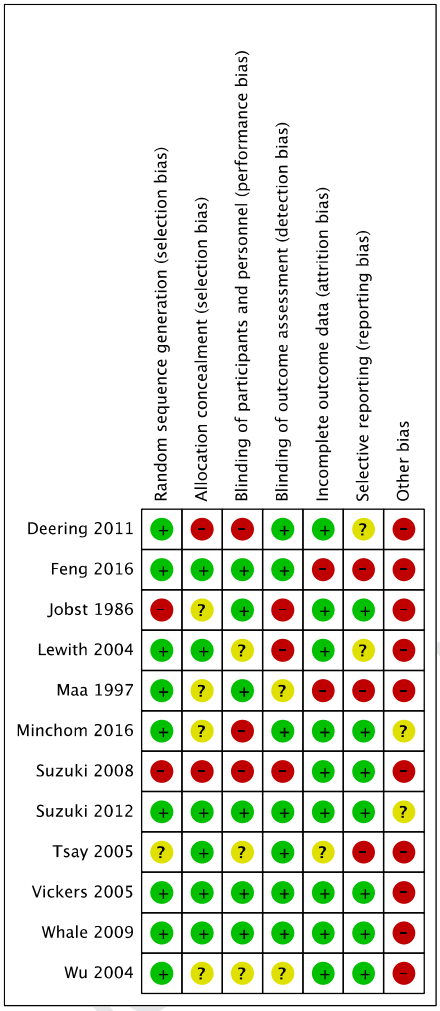

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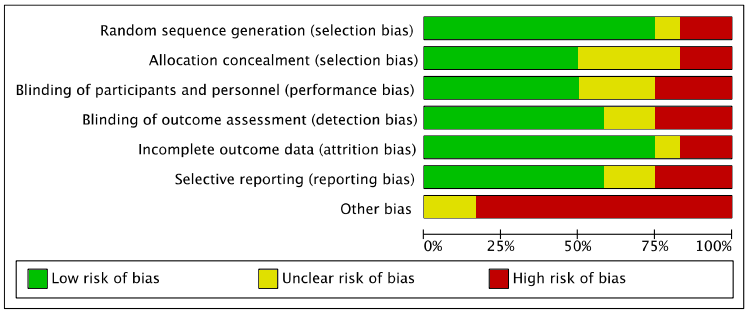


Fig. 4. Forest plot of comparison: Acupuncture vs. Control, Outcome: Breathlessness severity.

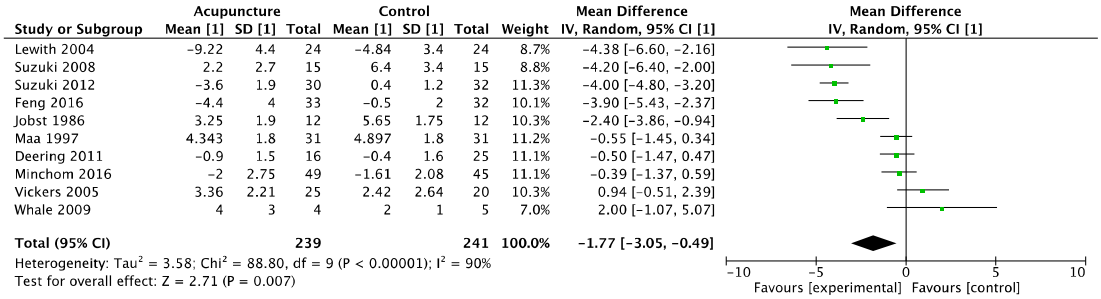


Fig. 5. Forest plot of comparison Subgroup: Acupuncture vs. Sham Control, treatment duration ≥ 3 weeks, Outcome: Breathlessness severity.

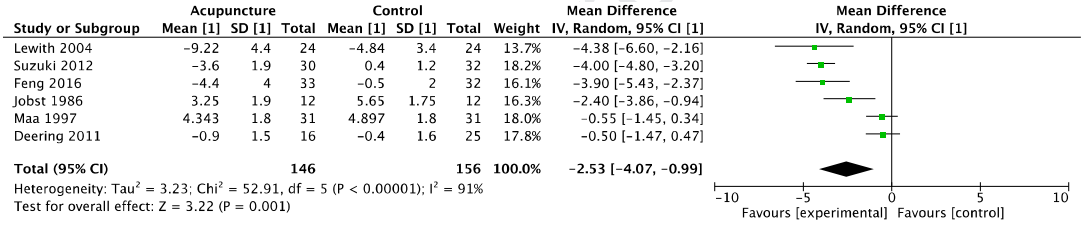


Fig. 6. Forest plot of comparison: Acupuncture vs. Control, Outcome: Exercise tolerance measured by 6MWT.

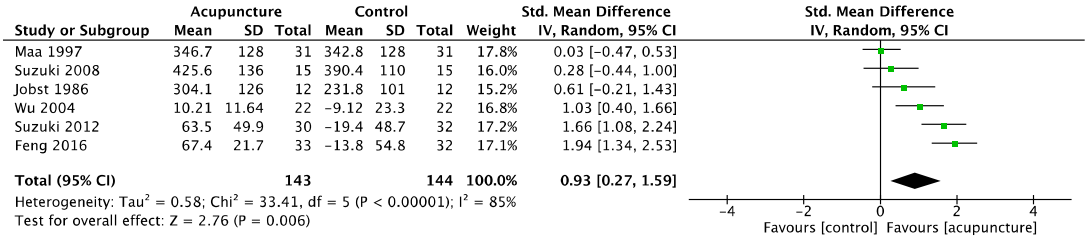


Fig. 7. Forest plot of comparison: Acupuncture vs. Control, Outcome: Number of drop-outs.

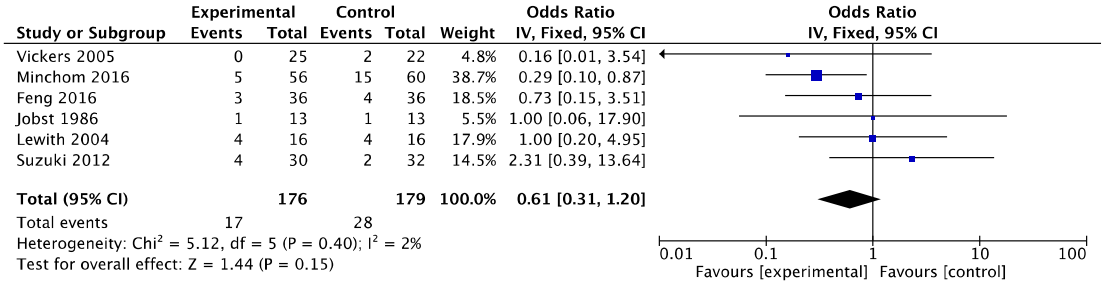
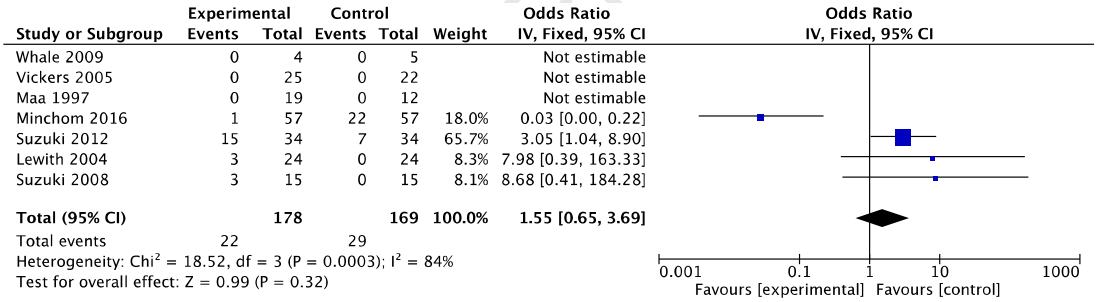


Fig. 8. Forest plot of comparison: Acupuncture vs. Control, Outcome: Number of adverse events.



Tables:

Table 1. Included studies.

Study	Mean age	Disease	number of patients completed the study	Intervention	treatment duration	number of sessions	Control	Breathlessness measures	Other outcome measures	Results
Suzuki, 2012	73	COPD	62	Acupuncture	12 weeks	12	Sham Acupuncture (Park Sham Device)	Borg Scale	6MWT, SGRQ, SpO_2	Substantial improvements of Borg Scale and 6MWD and a significant decrease of SGRQ were observed for the real acupuncture group.
Suzuki, 2008	71	COPD	30	Acupuncture	10 weeks	10	Conventional medication only	Borg Scale	6MWT, SpO_2	Significant improvements of Borg Scale (p=0.0001), 6MWD (p=0.0002), SpO_2 (p=0.0001) were observed for the acupuncture group
Feng, 2016	67	COPD	65	Acupuncture	8 weeks	24	Sham Acupuncture (Park Sham Device)	Borg Scale	6MWT, SGRQ	Signicant improvements of Borg Scale, 6MWD, and SGRQ ($p < 0.01$) were observed for the real acupuncture group.
Deering, 2011	67	COPD	60*	acupuncture in combination with pulmonary Rehabilitation	7 weeks	7	Pulmonary Rehabilitation only and no intervention*	Borg Scale	SGRQ, EQ-5D	No statistically significant differences in outcomes between groups. The acupuncture group remained less breathless for a longer period and improvement of SGRQ was longer persistent than in the pulmonary rehabilitation alone group.
Maa, 1997	67	COPD	31"	Acupressure	6 weeks	42	Sham Acupressure (Acupressure of non-points)	Borg Scale, VAS, Bronchitis-Emphysema symptom checklist	6MWT	A significant improvement of VAS (p= 0.009) and reduction of decathexis (p=0.044) were observed for the real acupressure treatment frames.
Wu, 2004	74	COPD	44	Acupressure	4 weeks	20	Sham Acupressure (different Acupoints)	Pulmonary Functional Status and Dyspnoea Questionnaire-modified	6MWT, SpO_2, Spielberger Anxiety scale, respiratory rate	Significant improvements ($p< 0.001$) in dyspnoea, anxiety, 6MWT, SpO_2, and respiratory rates were observed in the real acupressure group.
Jobst, 1986	64	COPD	24	Acupuncture	3 weeks	13	Sham Acupuncture (needling of non-points)	modified Borg Scale	6MWT, general wellbeing scale	A significant improvement of modified Borg Scale and 6MWD ($p < 0.05$) were observed for the acupuncture group.
Lewith, 2004	67	COPD	30"	Acupuncture	3 weeks	6	Sham Acupuncture (Mock TENS)	VAS	SGRQ	VAS improved significantly for all treatment groups, no statistically significant differences in outcomes between treatment frames.
Minchom, 2016	73	Lung cancer	145*	Acupuncture in combination with morphine* and acupuncture alone with rescue morphine	2 weeks	1#	Morphine alone	VAS	Lar-Anxiety and relaxation, EORTC QLQ-C30, HADS	No statistically significant differences between arms. Significant improvements of relaxation ($p < 0.001$) and anxiety (p=0.003) were observed for the acupuncture groups.
Tsay, 2005	74	COPD, receiving mechanical ventilation	52	Acupressure + Massage	10 days	10	Massage and handholding only	VAS	VAS-Anxiety, heart rate, respiratory rate	Significant improvements of dyspnoea (p= 0.009), anxiety (p=0.011), heart and respiratory rates ($p < 0.0001$) were observed for the real acupressure treatment frames.
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Whale, 2009	68	COPD	9	Acupuncture	3 days	3	Sham Acupuncture (Park Sham Device)	modified Borg Scale, VAS	VAS-Anxiety	No statistically significant differences in outcomes between groups
Total	70	347 COPD 190 advanced cancer	597	9 acupuncture 3 acupressure	median duration 25 days	median 10 sessions	8 sham acu-studies 4 conventional only			

COPD: chronic obstructive pulmonary disease; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality-of-life scores; EQ-5D: Measurement of health status, developed by the EuroQoL group; HADS: Hospital Anxiety and Depression Scale; Lar-Anxiety: line analogue rating Anxiety; SGRQ: St. George's Respiratory Questionnaire; SpO_2: oxygen saturation; VAS: Visual Analogue Scale; 6MWT: six minute walk test; *three-arm study; "cross-over design; #semi-permanent acupuncture studs

Appendix: sample search strategy

MEDLINE (from 1946), **PsycINFO** (from 1806), **Embase** (from 1974) **via OVID**

1. exp dyspnea/
2. ((dyspnoea or dyspnea or dyspnoeic or breathing) adj3 labour$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tc, id, tm, tn, dm, mf, dv, kw]
3. breathless$.mp.
4. Shortness of breath.mp.
5. Breathing difficult$.mp.
6. or/1-5
7. exp Neoplasms&/
8. exp respiratory tract neoplasms/
9. exp lung neoplasms/
10. Lung cancer.mp.
11. (Lung adj3 carcinoma$).mp.
12. cancer.mp.
13. carcino*.mp.
14. or/7-13
15. exp pulmonary disease, chronic obstructive/
16. COPD.ab,ti.
17. Chronic obstructive Pulmonary Disease.mp.
18. or/15-17
19. exp heart failure, congestive/
20. congestive heart failure.mp.
21. chronic heart failure.mp.
22. dilated cardiomyopathy.mp.
23. CHF.ab,ti.
24. or/19-23
25. exp pulmonary fibrosis/
26. pulmonary fibrosis.mp.
27. cryptogenic fibrosing alveolitis.mp.
28. or/25-27
29. exp motor neuron disease/
30. MND.ab,ti.
31. ALS.ab,ti.

32. (((((advanced adj3 disease$) or advanced) adj3 cancer$) or terminal$) adj3 ill$).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, tc, id, tm, tn, dm, mf, dv, kw]
33. or/28-31
34. 14 or 18 or 24 or 28 or 33
35. acupunct*.mp.
36. exp acupuncture/
37.exp acupuncture needle/
38. exp electroacupuncture/
39. electroacupunctur*.mp.
40. exp electrostimulation/
41. exp electrostimulation therapy/
42. electro-acupunctur*.mp.
43. acupoint*.mp.
44. exp transcutaneous nerve stimulation/
45. transcutaneous nerve stimulat*.mp.
46. exp percutaneous electrical nerve stimulation/
47. percutaneous electrical nerve stimulat*.mp.
48. TENS.mp.
49. auriculoacupunctur*.mp.
50. or/35-50
51. 6 and 34 and 50

Appendix:

Fig. 1. Funnel plot for primary outcome (Breathlessness severity): Publication Bias.

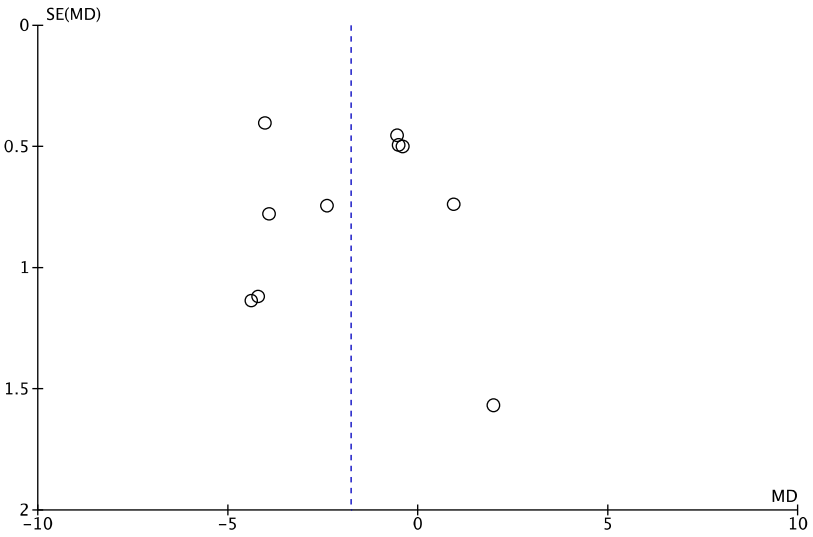
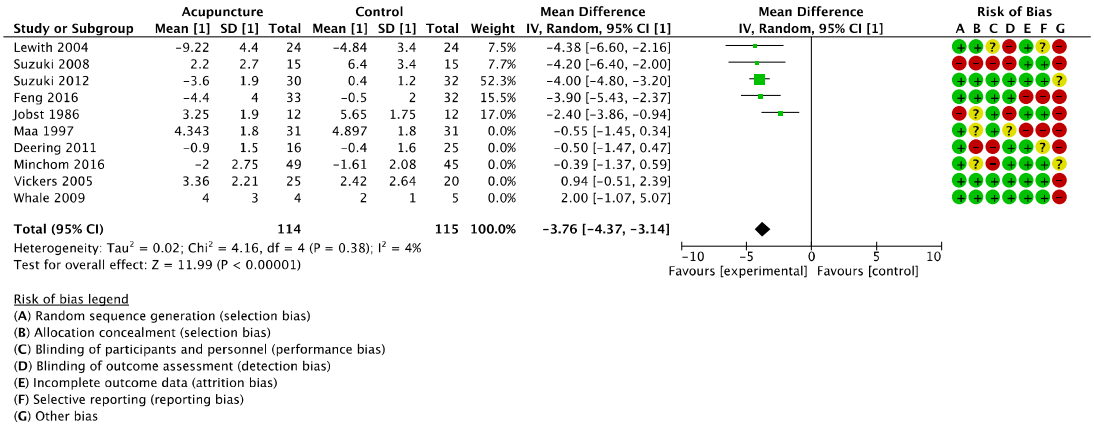
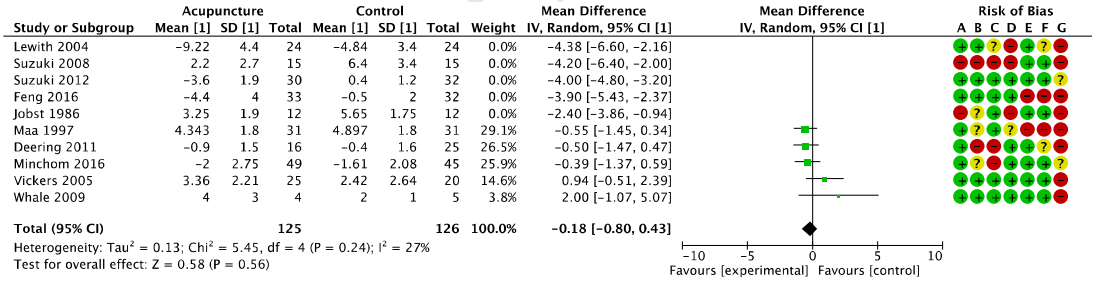


Fig. 4. Forest plot of comparison: Acupuncture vs. Control, Outcome: Breathlessness severity, Sensitivity Analysis: Ranking by effect size (SMD > 2.0)



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fig. 5. Forest plot of comparison: Acupuncture vs. Control, Outcome: Breathlessness severity, Sensitivity Analysis: Ranking by effect size (SMD ≤ 2.0)



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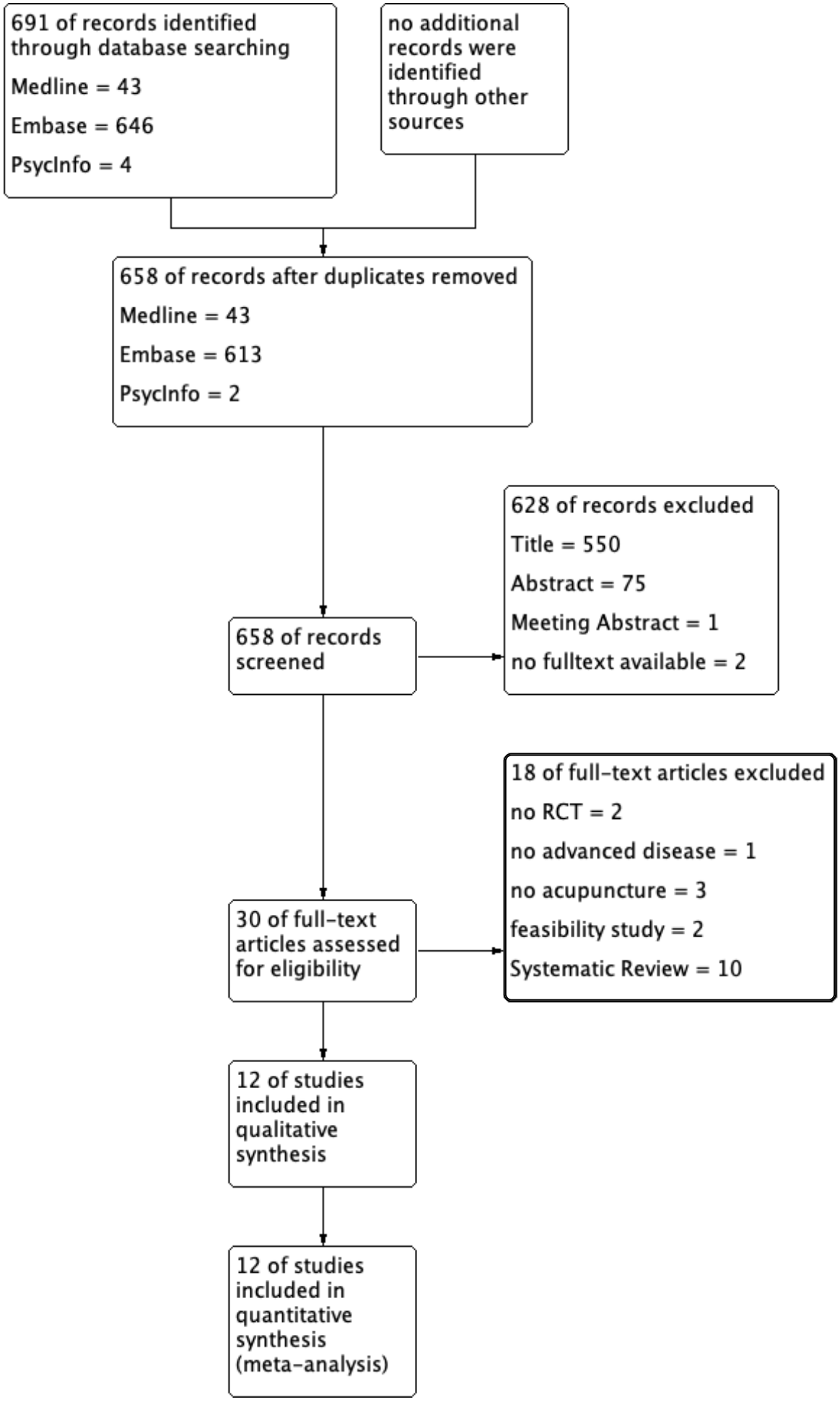
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Embase = 646
PsycInfo = 4
no additional records were identified through other sources
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Embase = 613
PsycInfo = 2
628 of records excluded
Title = 550
Abstract = 75
Meeting Abstract = 1
no fulltext available = 2
658 of records screened
18 of full-text articles excluded
no RCT = 2
no advanced disease = 1
no acupuncture = 3
feasibility study = 2
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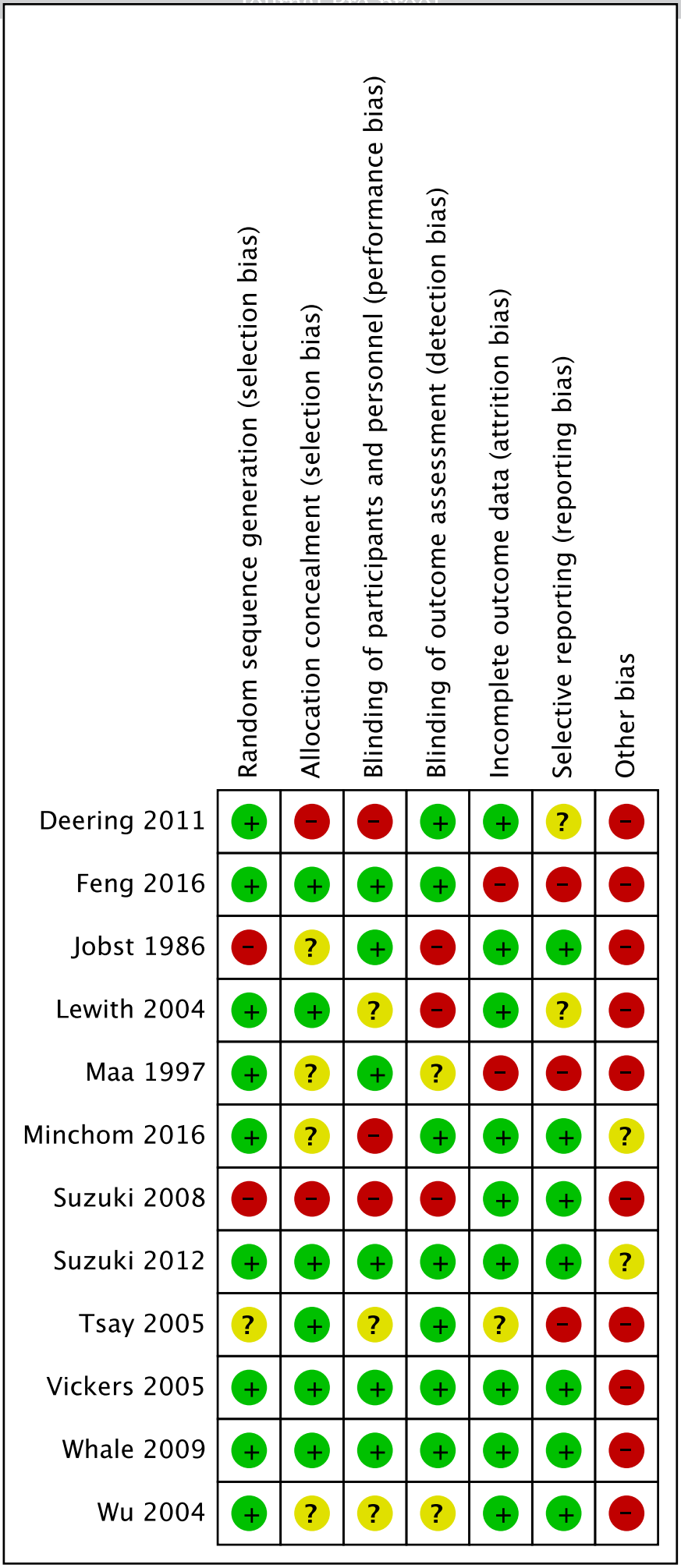
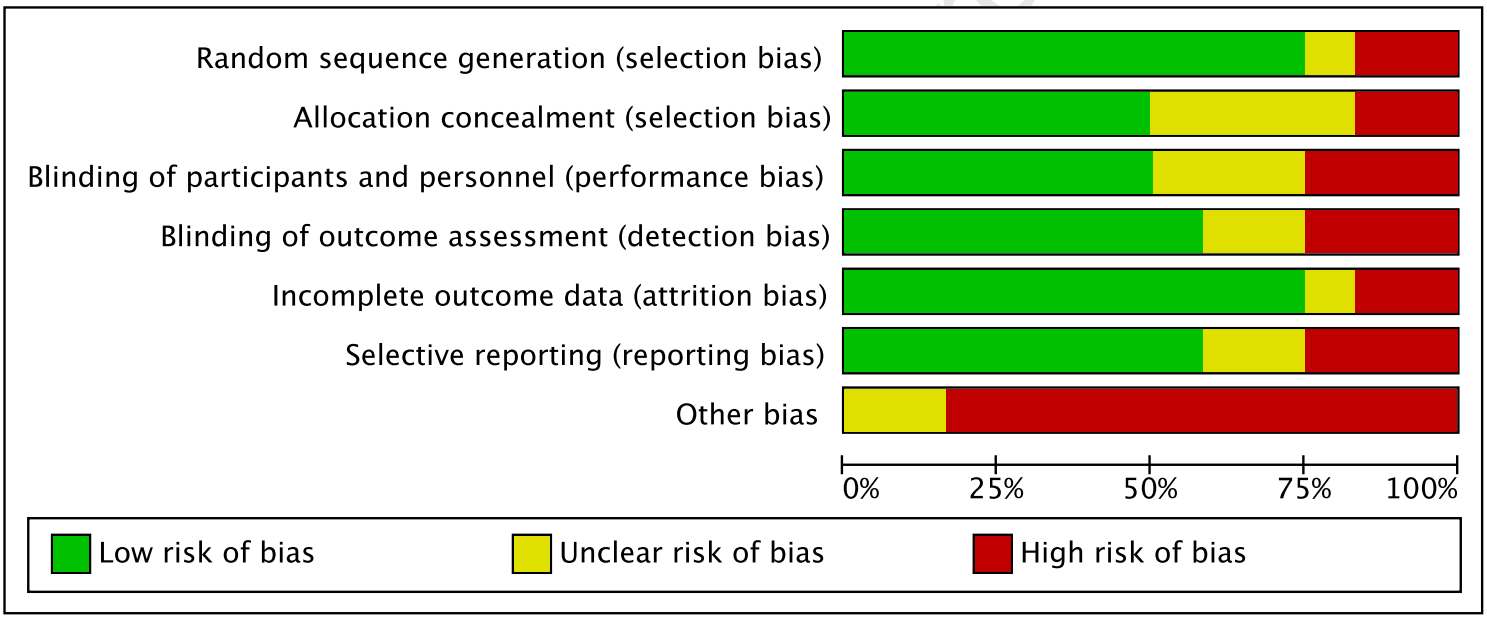
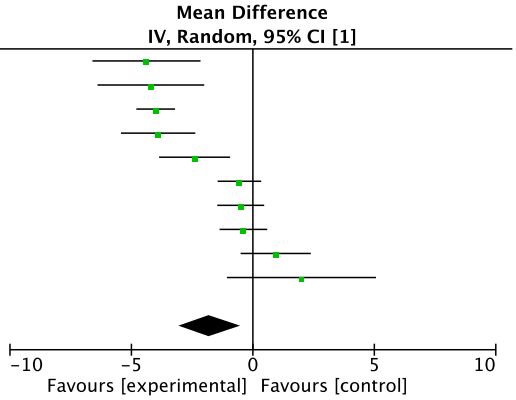
12 of studies included in qualitative synthesis
12 of studies included in quantitative synthesis (meta-analysis)




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
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Study or Subgroup	Acupuncture Mean [1]	SD [1]	Total	Control Mean [1]	SD [1]	Total	Weight	Mean Difference IV, Random, 95% CI [1]
Lewith 2004	-9.22	4.4	24	-4.84	3.4	24	8.7%	-4.38 [-6.60, -2.16]
Suzuki 2008	2.2	2.7	15	6.4	3.4	15	8.8%	-4.20 [-6.40, -2.00]
Suzuki 2012	-3.6	1.9	30	0.4	1.2	32	11.3%	-4.00 [-4.80, -3.20]
Feng 2016	-4.4	4	33	-0.5	2	32	10.1%	-3.90 [-5.43, -2.37]
Jobst 1986	3.25	1.9	12	5.65	1.75	12	10.3%	-2.40 [-3.86, -0.94]
Maa 1997	4.343	1.8	31	4.897	1.8	31	11.2%	-0.55 [-1.45, 0.34]
Deering 2011	-0.9	1.5	16	-0.4	1.6	25	11.1%	-0.50 [-1.47, 0.47]
Minchom 2016	-2	2.75	49	-1.61	2.08	45	11.1%	-0.39 [-1.37, 0.59]
Vickers 2005	3.36	2.21	25	2.42	2.64	20	10.3%	0.94 [-0.51, 2.39]
Whale 2009	4	3	4	2	1	5	7.0%	2.00 [-1.07, 5.07]
Total (95% CI)			**239**			**241**	**100.0%**	**-1.77 [-3.05, -0.49]**

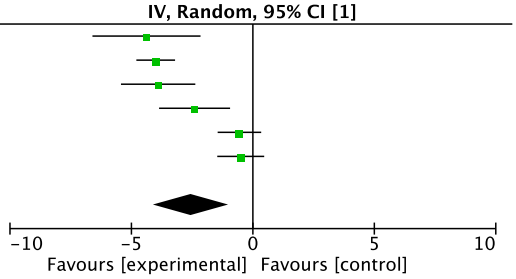
Heterogeneity: $Tau^2 = 3.58$; $Chi^2 = 88.80$, df = 9 ($P < 0.00001$); $I^2 = 90\%$
Test for overall effect: $Z = 2.71$ ($P = 0.007$)



Study or Subgroup	Acupuncture Mean [1]	SD [1]	Total	Control Mean [1]	SD [1]	Total	Weight	Mean Difference IV, Random, 95% CI [1]
Lewith 2004	−9.22	4.4	24	−4.84	3.4	24	13.7%	−4.38 [−6.60, −2.16]
Suzuki 2012	−3.6	1.9	30	0.4	1.2	32	18.2%	−4.00 [−4.80, −3.20]
Feng 2016	−4.4	4	33	−0.5	2	32	16.1%	−3.90 [−5.43, −2.37]
Jobst 1986	3.25	1.9	12	5.65	1.75	12	16.3%	−2.40 [−3.86, −0.94]
Maa 1997	4.343	1.8	31	4.897	1.8	31	18.0%	−0.55 [−1.45, 0.34]
Deering 2011	−0.9	1.5	16	−0.4	1.6	25	17.8%	−0.50 [−1.47, 0.47]
Total (95% CI)			**146**			**156**	**100.0%**	**−2.53 [−4.07, −0.99]**

Heterogeneity: $Tau^2 = 3.23$; $Chi^2 = 52.91$, df = 5 ($P < 0.00001$); $I^2 = 91\%$

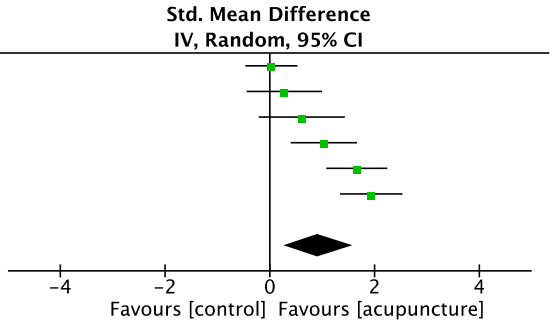
Test for overall effect: $Z = 3.22$ ($P = 0.001$)



Study or Subgroup	Acupuncture Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Maa 1997	346.7	128	31	342.8	128	31	17.8%	0.03 [-0.47, 0.53]
Suzuki 2008	425.6	136	15	390.4	110	15	16.0%	0.28 [-0.44, 1.00]
Jobst 1986	304.1	126	12	231.8	101	12	15.2%	0.61 [-0.21, 1.43]
Wu 2004	10.21	11.64	22	-9.12	23.3	22	16.8%	1.03 [0.40, 1.66]
Suzuki 2012	63.5	49.9	30	-19.4	48.7	32	17.2%	1.66 [1.08, 2.24]
Feng 2016	67.4	21.7	33	-13.8	54.8	32	17.1%	1.94 [1.34, 2.53]
Total (95% CI)			**143**			**144**	**100.0%**	**0.93 [0.27, 1.59]**

Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 33.41$, df = 5 ($P < 0.00001$); $I^2 = 85\%$

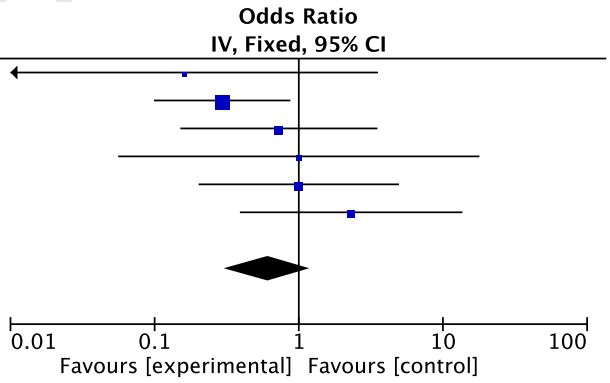
Test for overall effect: $Z = 2.76$ ($P = 0.006$)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Vickers 2005	0	25	2	22	4.8%	0.16 [0.01, 3.54]
Minchom 2016	5	56	15	60	38.7%	0.29 [0.10, 0.87]
Feng 2016	3	36	4	36	18.5%	0.73 [0.15, 3.51]
Jobst 1986	1	13	1	13	5.5%	1.00 [0.06, 17.90]
Lewith 2004	4	16	4	16	17.9%	1.00 [0.20, 4.95]
Suzuki 2012	4	30	2	32	14.5%	2.31 [0.39, 13.64]
Total (95% CI)		**176**		**179**	**100.0%**	**0.61 [0.31, 1.20]**
Total events	17		28			

Heterogeneity: $Chi^2 = 5.12$, df = 5 (P = 0.40); $I^2 = 2\%$

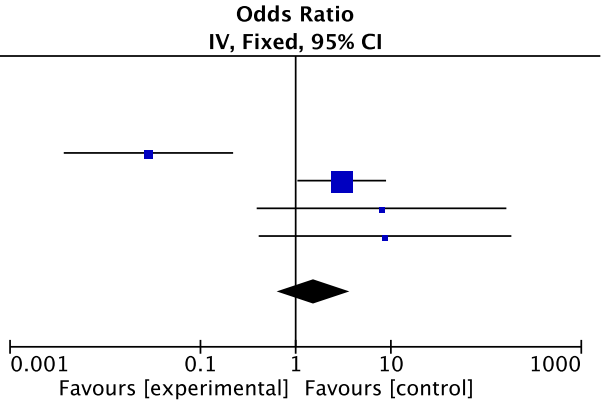
Test for overall effect: Z = 1.44 (P = 0.15)

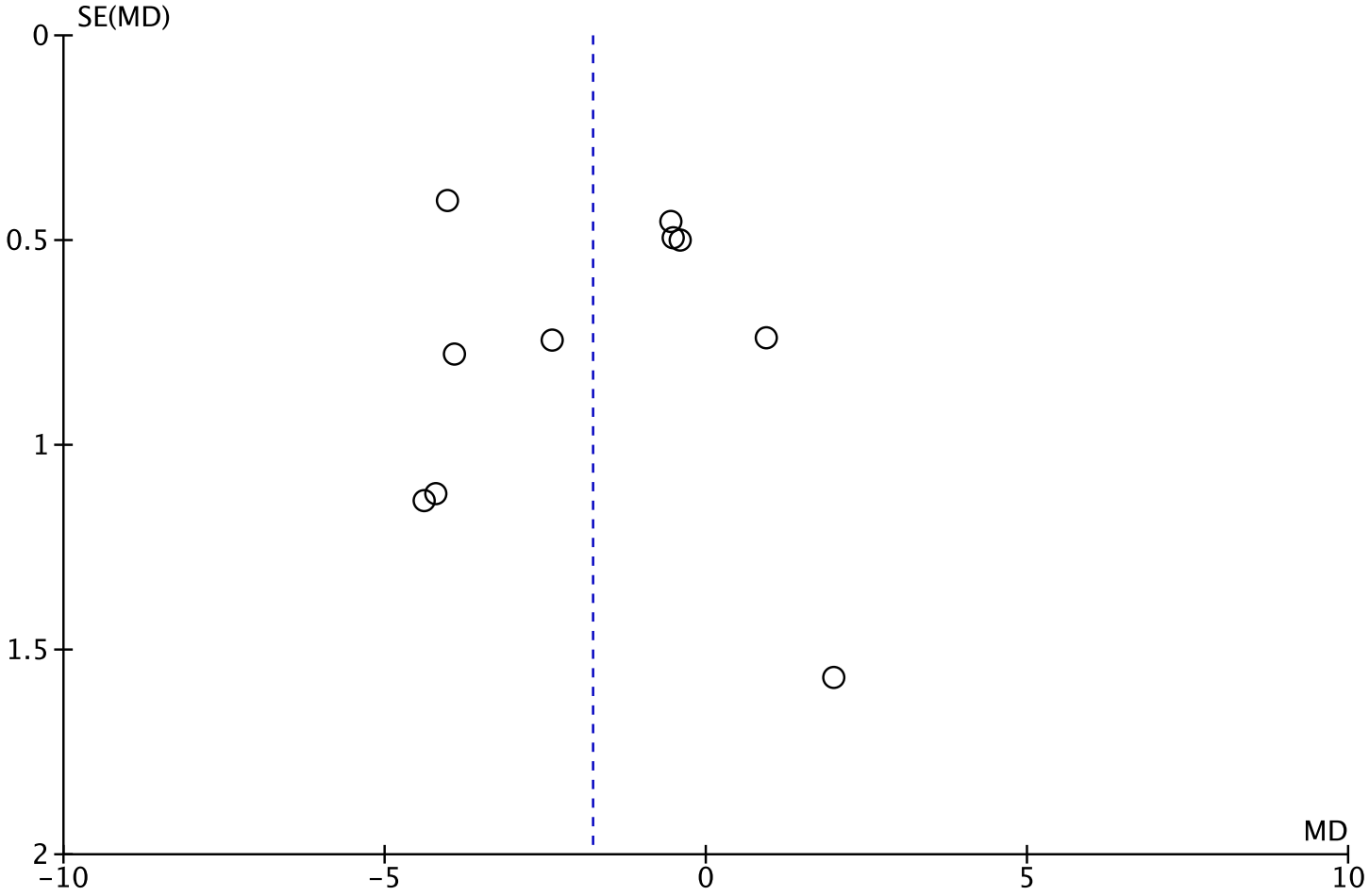


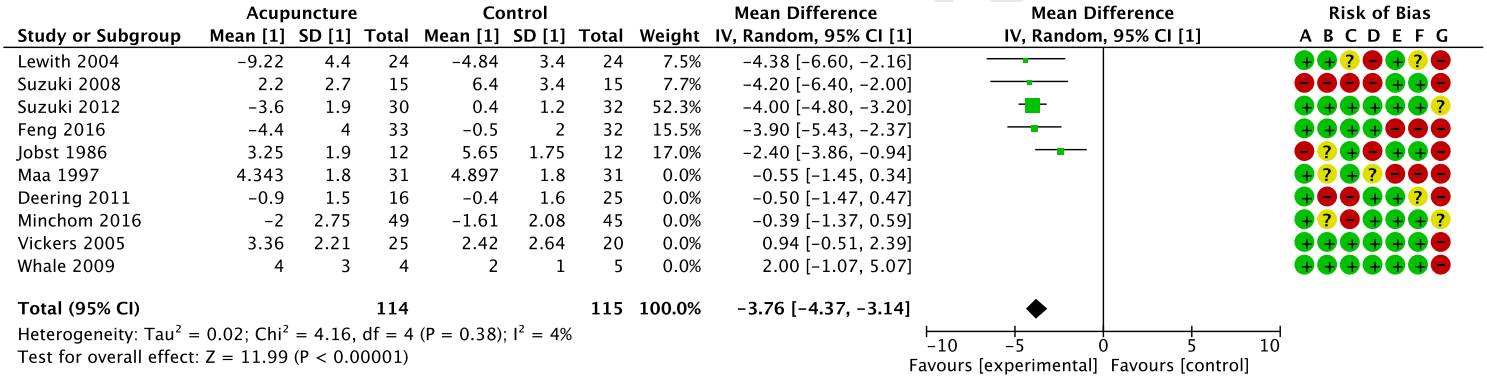
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio IV, Fixed, 95% CI
Whale 2009	0	4	0	5		Not estimable
Vickers 2005	0	25	0	22		Not estimable
Maa 1997	0	19	0	12		Not estimable
Minchom 2016	1	57	22	57	18.0%	0.03 [0.00, 0.22]
Suzuki 2012	15	34	7	34	65.7%	3.05 [1.04, 8.90]
Lewith 2004	3	24	0	24	8.3%	7.98 [0.39, 163.33]
Suzuki 2008	3	15	0	15	8.1%	8.68 [0.41, 184.28]
Total (95% CI)		**178**		**169**	**100.0%**	**1.55 [0.65, 3.69]**
Total events	22		29			

Heterogeneity: Chi^2 = 18.52, df = 3 (P = 0.0003); I^2 = 84%

Test for overall effect: Z = 0.99 (P = 0.32)




SE(MD)
0
0.5
1
1.5
2
MD
−10
−5
0
5
10



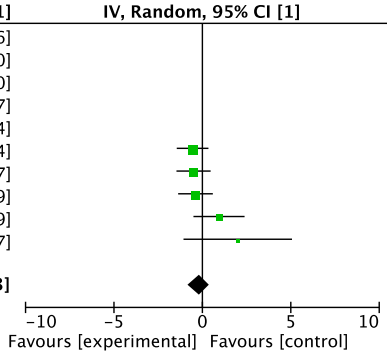
Study or Subgroup	Acupuncture Mean [1]	SD [1]	Total	Control Mean [1]	SD [1]	Total	Weight	Mean Difference IV, Random, 95% CI [1]
Lewith 2004	−9.22	4.4	24	−4.84	3.4	24	7.5%	−4.38 [−6.60, −2.16]
Suzuki 2008	2.2	2.7	15	6.4	3.4	15	7.7%	−4.20 [−6.40, −2.00]
Suzuki 2012	−3.6	1.9	30	0.4	1.2	32	52.3%	−4.00 [−4.80, −3.20]
Feng 2016	−4.4	4	33	−0.5	2	32	15.5%	−3.90 [−5.43, −2.37]
Jobst 1986	3.25	1.9	12	5.65	1.75	12	17.0%	−2.40 [−3.86, −0.94]
Maa 1997	4.343	1.8	31	4.897	1.8	31	0.0%	−0.55 [−1.45, 0.34]
Deering 2011	−0.9	1.5	16	−0.4	1.6	25	0.0%	−0.50 [−1.47, 0.47]
Minchom 2016	−2	2.75	49	−1.61	2.08	45	0.0%	−0.39 [−1.37, 0.59]
Vickers 2005	3.36	2.21	25	2.42	2.64	20	0.0%	0.94 [−0.51, 2.39]
Whale 2009	4	3	4	2	1	5	0.0%	2.00 [−1.07, 5.07]
Total (95% CI)			**114**			**115**	**100.0%**	**−3.76 [−4.37, −3.14]**

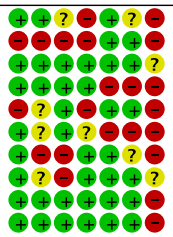
Heterogeneity: Tau² = 0.02; Chi² = 4.16, df = 4 (P = 0.38); I² = 4%
Test for overall effect: Z = 11.99 (P < 0.00001)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Study or Subgroup	Acupuncture Mean [1]	SD [1]	Total	Control Mean [1]	SD [1]	Total	Weight	Mean Difference IV, Random, 95% CI [1]
Lewith 2004	-9.22	4.4	24	-4.84	3.4	24	0.0%	-4.38 [-6.60, -2.16]
Suzuki 2008	2.2	2.7	15	6.4	3.4	15	0.0%	-4.20 [-6.40, -2.00]
Suzuki 2012	-3.6	1.9	30	0.4	1.2	32	0.0%	-4.00 [-4.80, -3.20]
Feng 2016	-4.4	4	33	-0.5	2	32	0.0%	-3.90 [-5.43, -2.37]
Jobst 1986	3.25	1.9	12	5.65	1.75	12	0.0%	-2.40 [-3.86, -0.94]
Maa 1997	4.343	1.8	31	4.897	1.8	31	29.1%	-0.55 [-1.45, 0.34]
Deering 2011	-0.9	1.5	16	-0.4	1.6	25	26.5%	-0.50 [-1.47, 0.47]
Minchom 2016	-2	2.75	49	-1.61	2.08	45	25.9%	-0.39 [-1.37, 0.59]
Vickers 2005	3.36	2.21	25	2.42	2.64	20	14.6%	0.94 [-0.51, 2.39]
Whale 2009	4	3	4	2	1	5	3.8%	2.00 [-1.07, 5.07]
Total (95% CI)			**125**			**126**	**100.0%**	**-0.18 [-0.80, 0.43]**

Heterogeneity: Tau^2 = 0.13; Chi^2 = 5.45, df = 4 (P = 0.24); I^2 = 27%
Test for overall effect: Z = 0.58 (P = 0.56)





Risk of bias legend
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