# Acupuncture for chronic fatigue syndrome: a systematic review and meta-analysis

**Article** *in* Acupuncture in Medicine · June 2019

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# Acupuncture for chronic fatigue syndrome: a systematic review and meta-analysis

**Qing Zhang[1], Jing Gong[1], Haoxu Dong[1], Shabei Xu[2], Wei Wang[2] and Guangying Huang[1]**

## Abstract

**Objective:** To evaluate evidence for the efficacy of acupuncture for chronic fatigue syndrome (CFS).

**Methods:** Randomized controlled trials (RCTs) comparing acupuncture with sham acupuncture, other interventions that may have a therapeutic effect, or no intervention, for the treatment of CFS, were searched for in the following databases up to March 2018: Pubmed; Embase; the Cochrane Library; Web of Science; Wanfang database; China National Knowledge Infrastructure (CNKI); Chinese Biomedicine (CBM) database; and VIP database. Risk of bias was determined using the Cochrane tool. Meta-analyses were performed using RevMan V.5.3 software. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was adopted for levels of evidence.

**Results:** Sixteen studies with 1346 subjects were included. Most studies had low methodological quality. Meta-analyses showed a favourable effect of acupuncture on overall response rate compared with sham acupuncture (four studies, 281 participants, RR=2.08, 95% CI 1.4 to 3.1, $I^2$=64%, low certainty) and Chinese herbal medicine (three studies, 290 participants, RR=1.17, 95% CI 1.07 to 1.29, $I^2$=0%, low certainty). Acupuncture also appeared to significantly reduce fatigue severity measured by Chalder's Fatigue Scale and the Fatigue Severity Scale compared with other types of control.

**Conclusion:** Our review indicated that acupuncture was more effective than sham acupuncture and other interventions (Chinese herbal medicine, mainly), but no firm conclusion could be reached owing to limited data, poor quality and potentially exaggerated effect size evaluation. Further large, rigorously designed and reported RCTs are required.

## Keywords

acupuncture, electroacupuncture, chronic fatigue syndrome, fatigue, systematic review

Accepted 28 June 2018

## Introduction

Chronic fatigue syndrome (CFS) is a debilitating multisystem disorder characterised by persistent or repetitive fatigue for more than half a year, which cannot be improved by bed rest or explained by any other medical condition.[1] Common accompanying symptoms include musculoskeletal pain, joint pain, headaches, unrefreshing sleep, sore throat, tender lymph nodes, post-exertional malaise, difficulties with short-term memory or concentration and other impairments in the somatic or autonomic nervous, endocrine and immune systems.[2, 3] CFS affects 0.3–3.3% of the population in America,[4] 2.6% in

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the UK[5] and 3% in Hong Kong, China.[6] The underlying pathophysiology of CFS is associated with neurological and immunological dysregulation and low-grade inflammation.[7,8] No specific medications are available for patients with CFS. Pharmacological interventions, immunological or behavioural treatment, complementary and alternative medicine (CAM) are the main approaches to the treatment of CFS.[1,4]

Acupuncture is an important CAM treatment modality and a substantial part of Traditional Chinese Medicine (TCM). Acupuncture is widely available and has been used to treat diseases for at least 3000 years in China.[9] Based on the theory of TCM the treatment involves penetrating the skin with needles and stimulating them by manually lifting and twisting to induce a sensation called *deqi*, or by adding a small electric current in the case of electroacupuncture. Although evidence supporting the therapeutic effects of acupuncture is limited, an increasing number of people in Western countries have received acupuncture for its simplicity, convenience and relative safety.

The efficacy of acupuncture for the treatment of CFS has been assessed by a number of clinical trials. Some reviews focusing on diverse CAM therapies including acupuncture have been published.[10–12] However, these trials are of different quality and present divergent results, and to our knowledge there is no systematic review evaluating the efficacy of acupuncture alone for CFS. Hence, we performed a systematic review and meta-analysis to assess the efficacy of acupuncture for CFS compared with several types of control. This review was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[13]

## Methods

### Criteria for considering studies

Randomized controlled trials (RCTs) or quasi-randomized clinical trials estimating the effect of acupuncture for CFS were included. Study participants were diagnosed with CFS, irrespective of age, gender, ethnicity or nationality. The experimental group needed to have received an acupuncture intervention, which was described as needle insertion at acupuncture points with manual or electrical stimulation. Studies of acupuncture provided in conjunction with other treatments, such as moxibustion or Chinese herbs, were excluded. The control groups comprised: (1) sham acupuncture (superficial needling, needling at irrelevant traditional acupuncture points according to TCM theory, or placebo needles that mimic acupuncture without skin penetration, such as the Streitberger needle device); (2) other interventions that might have a therapeutic effect for CFS such as Western medicine, Chinese herbal medicine or cognitive behavioural therapy; and (3) no intervention or usual care, which was also received by the experimental group. Type of outcome measures included at least one or more of the following outcomes: overall response rate (the proportion of patients with complete or partially improved fatigue symptoms), fatigue severity (measured by validated scales such as Chalder's Fatigue Scale,[14] the Fatigue Severity Scale (FSS))[15] and adverse events.

### Search methods for identification of studies

We searched the following databases from their inception to March 2018: Pubmed; Ovid-Embase; the Cochrane Library; Web of Science; Wanfang database; China National Knowledge Infrastructure (CNKI) database; Chinese Biomedicine (CBM) database; and VIP database. In addition, we carefully checked the reference lists of located papers for additional records. A clinical trials registry (https://clinicaltrials.gov/) was also searched for ongoing studies. The search terms (MeSH terms combined with free terms) were as follows: fatigue syndrome, chronic; myalgic encephalomyelitis; Royal Free disease; postviral fatigue syndrome; infectious mononucleosis-like syndrome, chronic; chronic fatigue and immune dysfunction syndrome; acupuncture therapy; electroacupuncture; acupuncture and moxibustion therapy. Electronic search strategies are shown in the Supplemental material.

### Data collection and quality assessment

Two independent reviewers (QZ and HD) carefully screened all the titles, abstracts and full text for eligible studies. Disagreements were resolved by discussion to reach a consensus or by arbitration by a third reviewer (GH). Data extraction, covering information on first author, publication year, country, number and characteristics of participants, CFS diagnosis, experience of the acupuncturists, technique and principle of acupuncture intervention, treatment course, selection of acupuncture points, type of control and outcome measures, was carried out by one reviewer (QZ) and was then verified by a second reviewer (JG). For quality assessment, the risk of bias was determined using the Cochrane risk of bias assessment tool recommended by the Cochrane handbook.[16] Two reviewers (QZ and SX) independently made a judgement and disagreements were resolved by discussion.

### Data synthesis and analysis

Review Manager 5.3 software was used for the statistical analysis. Continuous outcomes were presented as mean differences (MDs) with 95% confidence intervals (CIs), while dichotomous outcomes were shown as relative risk (RR) with their 95% CIs. Heterogeneity was investigated by $\chi^2$ test and $I^2$ statistics. Data were pooled into a random effects model owing to significant between-study variability. Before starting this review, we assumed a priori hypotheses of heterogeneity: disease conditions, type of acupuncture (manual acupuncture

or electroacupuncture), theoretical principles of acupuncture points selected, fixed points or semi/unfixed points, treatment course and quality of the study. Subgroup analyses were performed to examine the potential sources of heterogeneity. A sensitivity analysis was conducted by removing low-quality studies and non-blinded studies. We planned to assess publication bias by funnel plots if sufficient studies were available. Descriptive analysis was performed where meta-analysis was not feasible. The Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach[17] was used by means of online GRADEpro GDT (https://gradepro.org/) to obtain the level of certainty of evidence and to create a summary of the findings in table form.

## Results

### Literature search

A total of 1935 articles were initially identified. After a series of procedures (removal of duplicates, screening of titles and abstracts, assessment of the full text) and applying the criteria for considering studies, 16 studies[18–33] were finally included in this systematic review. Figure 1 shows the PRISMA flow diagram of the literature search.

### Study description

Selected studies were published between 2005 and 2017. One study was conducted in Korea,[23] one in Hong Kong[18] and the others in different provinces of China. In total 1346 patients with CFS were evaluated in the 16 studies included. In 13 studies patients were diagnosed by 'diagnostic criteria for CFS' revised by the American Centre for Disease Control (CDC) in 1994,[2] and in three studies[27,30,31] the diagnostic criteria were not reported. The experience of the participating acupuncturists was reported in only two studies (over 3 years[23] and 10 years[18] of practical experience, respectively). Electroacupuncture was used in one study.[20] Fixed or semi/unfixed acupuncture points were chosen based on different theoretical principles. The most commonly used traditional acupuncture points selected in studies were ST36 (*Zusanli*), BL18 (*Ganshu*), BL23 (*Shenshu*), GV20 (*Baihui*) and BL20 (*Pishu*). The control groups comprised sham acupuncture, Chinese herbal medicine, Western medicine and usual care. All the studies reported one or more outcomes, including overall response rate, fatigue severity evaluated by Chalder's Fatigue Scale/FSS and adverse events. Assessments of quality of life, pain, anxiety and depression were also reported in some studies. Table 1 shows details of study participants, interventions and outcomes.

### Risk of bias

Ten studies clearly described appropriate methods of random sequence generation, while in the other six[24,26–28,30,31] the method and process of sequence generation were not specified. Five studies[19–21,23,29] concealed the allocation by using opaque and sealed envelopes, while the remaining studies provided no information on allocation concealment. Generally, blinding of the acupuncturist was impossible, so we paid more attention to blinding of participants. In non-sham controlled studies it was not feasible to blind participants, apart from in one study[32] comparing acupuncture plus placebo medicine with Western medicine plus sham acupuncture to attempt blinding. Among the nine sham-controlled studies, six studies ensured blinding of participants and in the other three blinding was uncertain because the way in which the sham acupuncture was designed and performed was poorly described. Blinding of outcome assessment was reported in four studies,[20–22,29] while for the remaining studies blinding was unclear. Missing data existed in some studies, whereas only one study[23] adopted the intention-to-treat principle and per-protocol set. Although none of the studies published their protocol a priori, and only one study[23] was registered, we considered four studies[19,21–23] to have a low risk of selective

**Figure 1.** PRISMA flow diagram of the literature search. CFS, chronic fatigue syndrome.

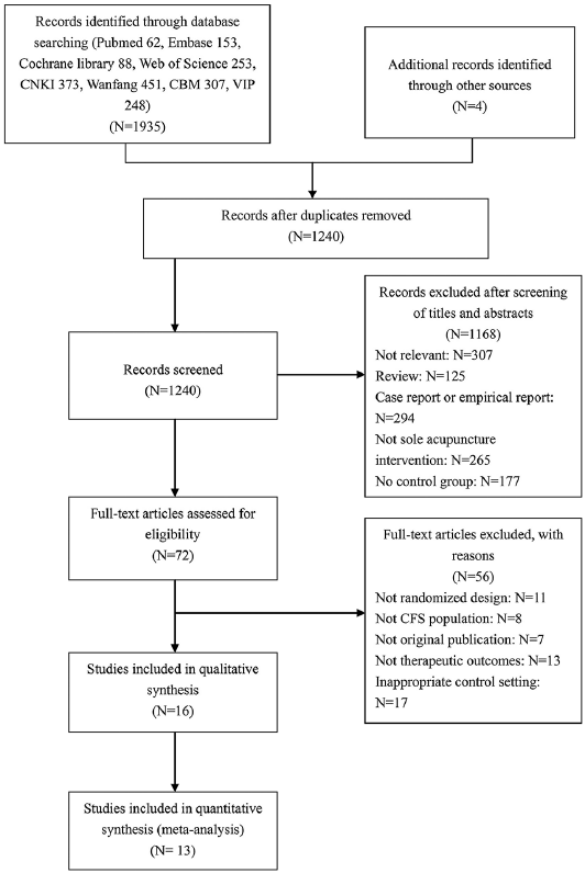


**Table 1.** Characteristic of studies of acupuncture for the treatment of chronic fatigue syndrome.

| | | Participants | | | Interventions | | |
|---|---|---|---|---|---|---|---|
| First author (year) | Diagnosis | Number (male/female) | Age (mean (±SD) or range) | Disease duration (mean±SD or range) | Experimental group (E) | Control group (C) | Outcome measures |
| Wang (2005)[24] | 1994 CDC | 100 (41/59) | E: 24–56 years<br>C: 22–54 years | E: 0.5–4 years<br>C: 0.6–4.1 years | MA: fixed points (bilateral ST36, CV6); >75 mm depths; *de qi* required; manipulated every 5 min; 30 min/session, 28 sessions for 4 weeks | CHM: Decoction of *Ten Powerful Tonics*; one dose daily for 4 weeks | Overall response rate |
| Liu (2009)[30] | Not reported | 90 (42/48) | E: 25 years<br>C: 45 years | E: 6 months–8 years<br>C: 6 months–7 years | MA: semi-fixed points; main points (GV20, CV3, CV6, ST36, HT7) and additional points (according to TCM syndrome differentiation); 30 min/session, 24–32 sessions for 2 months | CHM: Chinese herb decoctions according to syndrome differentiation; 2 months | Overall response rate |
| Zhang (2007)[28] | 1994 CDC | 50 (29/21) | E: 24–61 years<br>C: 18–57 years | E: 1–9 years<br>C: 10 months–5 years | MA: semi-fixed points; main points (BL15, BL20, BL18, BL23, BL43) and additional points (SP3, HT7, KI3, LR5); 15–25 mm depths; *de qi* required; 30 min/session, 20 sessions for 4 weeks | SA: Streitberger's placebo acupuncture* | CFS; overall response rate |
| Yao (2007)[18] | 1994 CDC | 99 (31/68) | E: 39.8±6.6 years<br>C: 42±6.5 years | Not reported | MA: fixed points (GV20, ST36, SP6); 8–30 mm depths; *de qi* required; manipulated every 10 min; 30 min/session, 8 sessions for 4 weeks | SA: Streitberger's placebo acupuncture* | CFS; SF-12 |
| Zhu (2008)[20] | 1994 CDC | 60 (16/44) | E: 38.5±7.89 years<br>C: 37.67±9.85 years | E: 15.3±5.72 months<br>C: 16.7±5.43 months | EA: fixed points (bilateral BL23, ST36); *de qi* required; 4/20 Hz current; 20 min/session; 10 sessions for 2 weeks | SA: needling non-acupuncture points superficially; 4 mm depth; *de qi* not required; 4/20 Hz current* | FSS; SF-36 |
| Chen (2010)[19] | 1994 CDC | 90 (40/50) | E: 38.31±9.89 years<br>C: 40.62±9.51 years | E: 2.06±0.98 years<br>C: 3.17±1.23 years | MA: fixed points (ST9, GV16, GV20); 15–20 mm depths; *de qi* required; manipulated every 10 min; 30 min/session, 14 sessions for 2 weeks | CHM: *Shenmai* injection; once daily for 15 days | CFS; SAS; DSI |
| Wang (2009)[21] | 1994 CDC | 64 (26/38) | E: 35.8±10.7 years<br>C: 38.8±8.8 years | Not reported | MA: fixed points (GV20, CV17, CV12, CV6, CV4, LI4, ST36, SP6, LR3, KI3, BL18, BL20); *de qi* required; 30 min/session, 14 sessions for 5 weeks | SA: Needling non-acupuncture points; *de qi* not required* | CFS; WHOQOL-BREF; VAS; adverse events |

**Table 1.** (Continued)

| First author (year) | Diagnosis | Participants | | | Interventions | | Outcome measures |
|---|---|---|---|---|---|---|---|
| | | Number (male/female) | Age (mean (±SD) or range) | Disease duration (mean±SD or range) | Experimental group (E) | Control group (C) | |
| Zheng (2012)[22] | 1994 CDC | 77 (31/46) | E: 38.73±4.11 years<br>C: 37.08±5.32 years | E: 18.41±5.34 months<br>C: 17.12±6.03 months | MA: unfixed points; *back-Shu* points (BL15, BL20, BL13, BL23, BL18, BL19) combined with *front-Mu* points (CV14, LR13, LU1, GB25, LR14, GB24) according to syndrome differentiation; 25–40 mm depth; *de qi* required; 30 min/session, 20 sessions for 4 weeks | SA: Streitberger's placebo acupuncture* | CFS, SF-36, VAS, DSI, overall response rate, immunity index |
| Zhang (2011)[29] | 1994 CDC | 120 (56/64) | E: 46.4±13.33 years<br>C: 40.22±12.42 years | E: 8.45±2.32 months<br>C: 9.09±2.15 months | MA: fixed points (bilateral BL15, BL20, BL43); 15–30 mm depth; *de qi* required; 20 min/session, 20 sessions for 4 weeks | SA: needling non-acupuncture points; 5–8 mm depth; limited acid and distension* | CFS, SF-20 |
| Ding (2012)[26] | 1994 CDC | 100 (47/53) | E: 30±10 years<br>C: 30±8 years | E: 2.4±1.2 years<br>C: 2.6±1.3 years | MA: *Huatuo Jiaji* acupuncture points; 45 min/session, 20 sessions for 4 weeks | CHM: *Shengmai* injection; 4 weeks | Overall response rate |
| Liu (2012)[34] | Not reported | 50 (35/15) | 24–45 years | Not reported | MA: unfixed points; *back-Shu* points (BL15, BL20, BL13, BL23, BL18, BL19) combined with *front-Mu* points (CV14, LR13, LU1, GB25, LR14, GB24) according to syndrome differentiation; 25–40 mm depth; *de qi* required; 30 min/session, 20 sessions for 4 weeks | SA: Streitberger's placebo acupuncture* | Overall response rate |
| An (2014)[25] | 1994 CDC | 80 (35/45) | E: 36.49±4.12 years<br>C: 37.08±4.69 years | Not reported | MA: unfixed points; compatibility of *back-Shu* points (BL15, BL20, BL13, BL23, BL18, BL19) and *front-Mu* points (CV14, LR13, LU1, GB25, LR14, GB24) according to syndrome differentiation; 25–40 mm depth; *de qi* required; 30 min/session, 20 sessions for 4 weeks | SA: Streitberger's placebo acupuncture* | CFS, VAS, DSI, immunity index |

*(Continued)*

**Table 1.** (Continued)

| First author (year) | Diagnosis | Participants | | | Interventions | | Outcome measures |
|---|---|---|---|---|---|---|---|
| | | Number (male/female) | Age (mean (±SD) or range) | Disease duration (mean±SD or range) | Experimental group (E) | Control group (C) | |
| Kim (2015)[23] | 1994 CDC | 99 (31/68) | E: 44.9±11.4 years<br>C: 41.1±11.9 years | 6 months to >5 years | MA: fixed points (GV20, GB20, BL11, BL13, BL15, BL18, BL20, BL23); *de qi* required; 15 min/session, 10 sessions for 4 weeks | Usual care | FSS, SRI, BDI, NRS for the level of fatigue, EQ-5D; adverse events |
| Guo (2017)[31] | Not reported | 104 (65/39) | 20–48 years | Not reported | MA: unfixed points; *back-Shu* points (BL15, BL20, BL13, BL23, BL18, BL19) combined with *front-Mu* points (CV14, LR13, LU1, GB25, LR14, GB24) according to syndrome differentiation; 25–40 mm depth; *de qi* required; 30 min/session, 20 sessions for 4 weeks | SA: Streitberger's placebo acupuncture* | Overall response rate |
| Wang (2017)[32] | 1994 CDC | 100 (43/57) | E: 39.05±4.25 years<br>C: 39.76±4.86 years | E: 2.65±0.68 years<br>C: 2.54±0.47 years | MA: fixed points (GV20, CV17, CV4, ST36); *de qi* required; manipulated every 5 min; 8 sessions for 4 weeks | Usual care | CFS; overall response rate |
| Jiang (2017)[33] | 1994 CDC | 63 (36/27) | 36.7±4.1 years | 4.6±2.2 years | MA: semi-fixed points plus placebo drugs; main points (GV20, ST36, SP6, CV4, CV6) and additional points (according to TCM syndrome differentiation); needling every other day for 4 months | WM: Western medicine plus needling non-acupuncture points; 4 months | Overall response rate |

*The points and treatment course in the SA group were same as in the acupuncture group.
CDC, Centres for Disease Control and Prevention; CFS, Chalder's Fatigue Scale; CHM, Chinese herbal medicine; DSI, Depression Status Inventory; EA, electroacupuncture; EQ-5D, EuroQol-5 dimension; FSS, Fatigue Severity Scale; MA, manual acupuncture; NRS, numerical rating scale; SAQ, Sleep Assessment Questionnaire; SAS, Self Rating Anxiety Scale; SF-12, SF-20, SF-36: 12, 20, 36-item short-form health survey; SPHERE, Somatic and Psychological health report; SRI, Stress Response Inventory; TCM, Traditional Chinese Medicine; VAS, Visual Analogue Scale; WHOQOL-BREF, WHO Quality of Life Assessment Instrument brief version; WM, Western medicine.

**Figure 2.** Risk of bias graph.

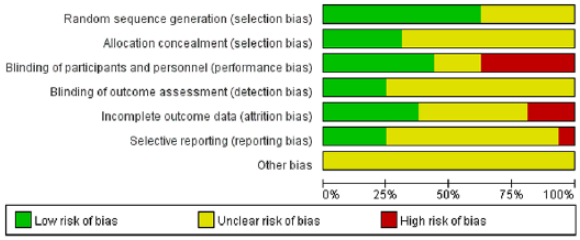
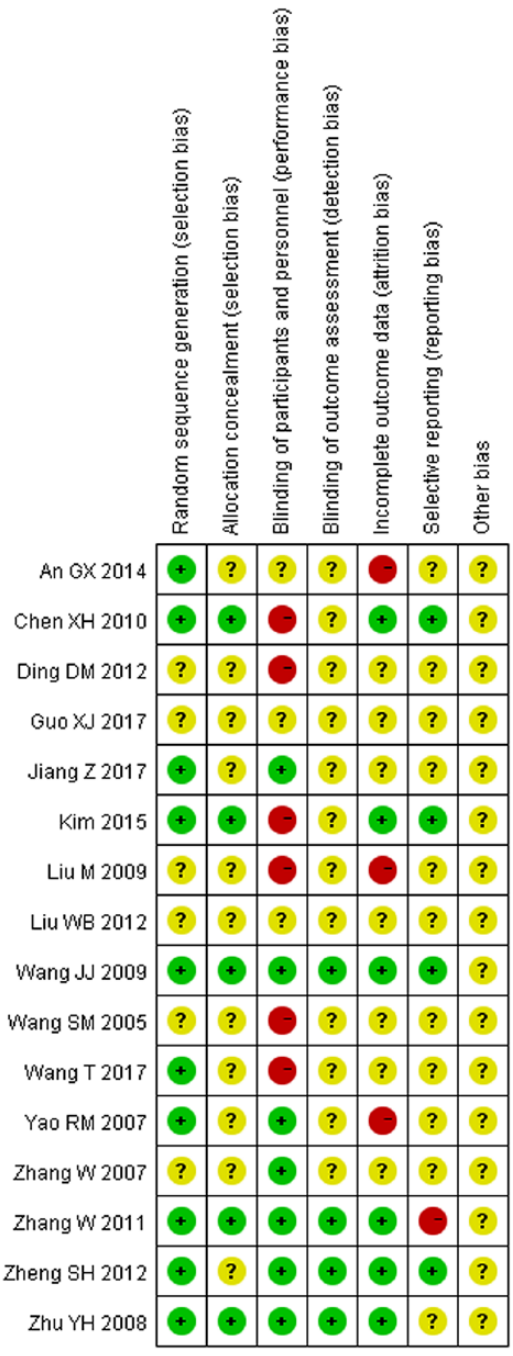



**Figure 3.** Risk of bias summary (n=16 studies).




reporting bias. Whether others forms of bias existed was unclear owing to insufficient information. Figure 2 and Figure 3 show the risk of bias among the studies.

## *Overall response rate*

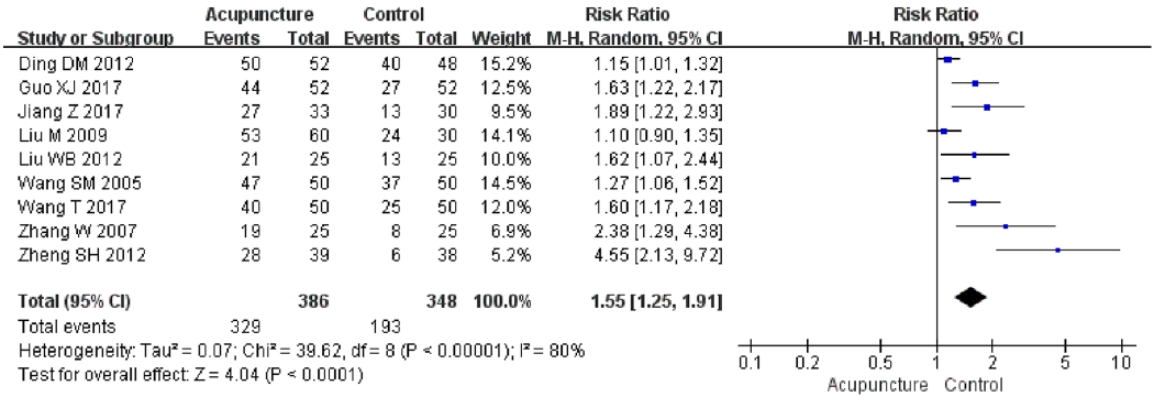
Nine studies with a total of 734 participants reported an overall response rate. Meta-analysis indicated that acupuncture was the most favourable procedure (RR=1.55, 95%CI 1.25 to 1.91; P<0.01) with high heterogeneity ($I^2$=80%, P<0.01; Figure 4). Results of subgroup and sensitivity analyses are shown in Table 2. In all subgroups acupuncture was more effective than control, with moderate to high heterogeneity. Acupuncture was more effective than sham acupuncture (four studies, 281 participants, RR=2.08, 95%CI 1.4 to 3.1, $I^2$=64%) and Chinese herbal medicine (three studies, 290 participants, RR=1.17, 95%CI 1.07 to 1.29, $I^2$=0%). Sources of heterogeneity might have been related to the type of control and quality of the studies. Sensitivity analyses performed by removing low-quality studies and non-blinded studies, respectively, showed stable results. Visual inspection of the funnel plot showed asymmetry and indicated possible publication bias.

## *Fatigue severity measured by CFS/FSS*

Data from four sham-controlled studies involving 640 participants were pooled into a meta-analysis. CFS is a 14-item, self-report scale including both physical and mental fatigue assessment.[14] In order to distinguish the two kinds of scoring methods for CFS, we marked them as CFS1 (0–1 point for each item) and CFS2 (0–4 points). Three studies favoured acupuncture with respect to the mental fatigue score of CFS1 and physical fatigue score of CFS1 but with high heterogeneity ($I^2$=81%, P<0.01 and $I^2$=70%, P<0.01; Figure 5). After examining the characteristics of these three studies, Wang et al.[21] adopted fixed points and performed sham acupuncture by needling at locations not corresponding to traditional acupuncture points, while the other two studies both adopted unfixed points and used Streitberger's placebo needle. After removal of Wang's study, the $I^2$value for the mental fatigue score of CFS1 and physical fatigue score of CFS1 both decreased ($I^2$=72%, P=0.06 and $I^2$=0%, P=0.85; data not shown), which might have explained the high heterogeneity. One study[18] showed no significant difference between the two groups measured by both mental and physical fatigue score of CFS2 (MD −1.17, 95%CI −3.03 to 0.69, P=0.22 and MD −1.41, 95%CI −3.97 to 1.15, P=0.28, respectively).

Results from the study comparing acupuncture with Chinese herbal medicine, Western medicine and usual care

**Figure 4.** Forest plot for overall response rate.




by itself are shown in Table 3. All of them were in favour of acupuncture with respect to effects on CFS or FSS.

### *Adverse events*

The majority of the included studies did not mention any adverse events. Three studies[18,21,29] claimed that no subjects experienced adverse events. One study[23] reported two mild adverse events (redness and itching, right thumb numbness and pain), which were probably associated with acupuncture.

### *Level of evidence*

The level of evidence as determined by the GRADE system ranged from very low to low. A summary of the findings is shown in Table 4.

## Discussion

Our meta-analysis showed that acupuncture appears to be more effective than sham acupuncture and Chinese herbal medicine for CFS as measured by the overall response rate. Results from several studies also favoured the effect of acupuncture on reducing fatigue severity measured by CFS and FSS and showed that acupuncture was more effective than Western medicine and usual care. However, the limited data and obvious heterogeneity prevented us from pooling them into a meta-analysis. Moreover, the safety of acupuncture remains unclear as studies generally did not report adverse events.

Previous reviews have evaluated the efficacy of acupuncture and other CAM therapies for CFS.[11,12,34] To our knowledge, ours is the first review aiming to provide quantitative evidence of the effect of manual acupuncture or electroacupuncture for the treatment of CFS. One recent review by Wang et al.[10] combined a total of 31 RCTs to evaluate the effectiveness of acupuncture plus moxibustion or acupuncture/moxibustion alone. However, as acupuncture and moxibustion are considered to be two kinds of TCM therapies, their review did not determine whether acupuncture alone is better than other treatments or not. Nevertheless, our results for the effect of acupuncture on overall response rate are consistent with theirs, which showed that moxibustion alone had a higher response rate than sham acupuncture and Chinese herbal medicine.

Currently, no specific drugs are available for the treatment of CFS. In China, many patients with CFS tend to look to TCM therapies to relieve symptoms, but efficacy seems to vary among individuals. So the results of this review showing a positive effect of acupuncture for CFS may be meaningful. According to the included studies, manual acupuncture seemed to be more popular than electroacupuncture and the most commonly used acupuncture points were ST36, BL18, BL23, GV20 and BL20. The acupuncture points commonly selected for CFS in our review were identical to those chosen in a previous review[10] and might provide some information for clinical practice. Selection of semi-fixed or unfixed acupuncture points by TCM syndrome differentiation seems more effective than using fixed acupuncture points, according to the relatively high effect size in the subgroup analysis. A different treatment course had little impact on the effect size.

Our review reflects some of the problems with existing studies evaluating the effectiveness of acupuncture for CFS. Studies were often poorly designed and variations were seen in the acupuncture intervention, control settings, the way in which sham acupuncture was performed and the outcome measures. This made it difficult to synthesise the data and might account for the observed heterogeneity. Certain a priori hypotheses regarding heterogeneity, such as disease conditions, type of acupuncture and different methods of sham acupuncture, could not be examined owing to limited data and insufficient information. Assessment of the safety of acupuncture was rarely carried out. More importantly, most of the included studies had poor methodological quality and

**Table 2.** Results of subgroup and sensitivity analyses.

| | | | Meta-analyses | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | Studies (n) | Participants (n) | RR | 95% CI | P values | $I^2$ | P values |
| Subgroup analyses | | | | | | | |
| Type of control | | | | | | | |
| SA | 4 | 281 | 2.08 | 1.40 to 3.1 | <0.01 | 64% | 0.04 |
| CHM | 3 | 290 | 1.17 | 1.07 to 1.29 | <0.01 | 0 | 0.56 |
| WM | 1 | 63 | 1.89 | 1.22 to 2.93 | <0.01 | NA | |
| UC | 1 | 100 | 1.6 | 1.17 to 2.18 | <0.01 | NA | |
| Acupuncture points selected | | | | | | | |
| Fixed | 3 | 300 | 1.28 | 1.07 to 1.52 | <0.01 | 58% | 0.09 |
| Semi-fixed | 3 | 203 | 1.63 | 0.93 to 2.87 | 0.09 | 83% | <0.01 |
| Unfixed | 3 | 231 | 2.05 | 1.24 to 3.40 | <0.01 | 74% | 0.02 |
| Treatment course (sessions) | | | | | | | |
| 10 | 1 | 100 | 1.6 | 1.17 to 2.18 | <0.01 | NA | |
| 20 | 5 | 381 | 1.86 | 1.17 to 2.98 | <0.01 | 89% | <0.01 |
| >20 | 3 | 253 | 1.3 | 1.02 to 1.64 | 0.03 | 64% | 0.06 |
| Quality of study | | | | | | | |
| High | 1 | 77 | 4.55 | 2.13 to 9.72 | <0.01 | NA | |
| Moderate | 3 | 213 | 1.78 | 1.41 to 2.24 | <0.01 | 0 | 0.49 |
| Low | 5 | 444 | 1.27 | 1.10 to 1.47 | <0.01 | 55% | 0.07 |
| Sensitivity analyses | | | | | | | |
| Excluding study of low quality | 4 | 290 | 2.17 | 1.46 to 3.21 | <0.01 | 60% | 0.06 |
| Excluding study without blinding | 5 | 344 | 1.99 | 1.48 to 2.67 | <0.01 | 51% | 0.09 |

CHM, Chinese herbal medicine; CI, confidence interval; NA, not applicable; RR, relative risk; SA, sham acupuncture; UC, usual care; WM, Western medicine.

a suspicion of publication bias, which may have resulted in an overestimated effect size.[35] Consequently, certainty about the level of evidence determined by GRADE was limited.

Our review has a number of limitations. First, although a relatively comprehensive search strategy was adopted, incomplete retrieval of identified research cannot be avoided. Second, our meta-analysis showed a positive effect of acupuncture measured by overall response rate, but this outcome is relatively non-specific for CFS. Third, a potentially high risk of bias and incomplete information limit the validity of the results. Fourth, obvious heterogeneity was present in the meta-analyses, which could not be solved by subgroup analyses; this might result from the poor quality of the studies. Finally, only one study was published in English. The others were carried out in China and published in Chinese, with most showing positive results, so selective publishing and reporting might have occurred.

Given the problems and limitations above, further RCTs with a larger sample size and more rigorous design are needed. Although it is still controversial to regard sham acupuncture as a valid placebo-controlled method,[36] it is accepted in RCTs on the condition that it is appropriately designed and performed to separate non-specific effects[37] from the specific effects of the acupuncture intervention and to ensure blinding. The

**Figure 5.** Forest plot of acupuncture versus sham acupuncture for chronic fatigue syndrome. CFS1, Chalder's Fatigue Scale scoring 0-1 points for each item; CFS2, Chalder's Fatigue Scale scoring 0-4 points for each item.

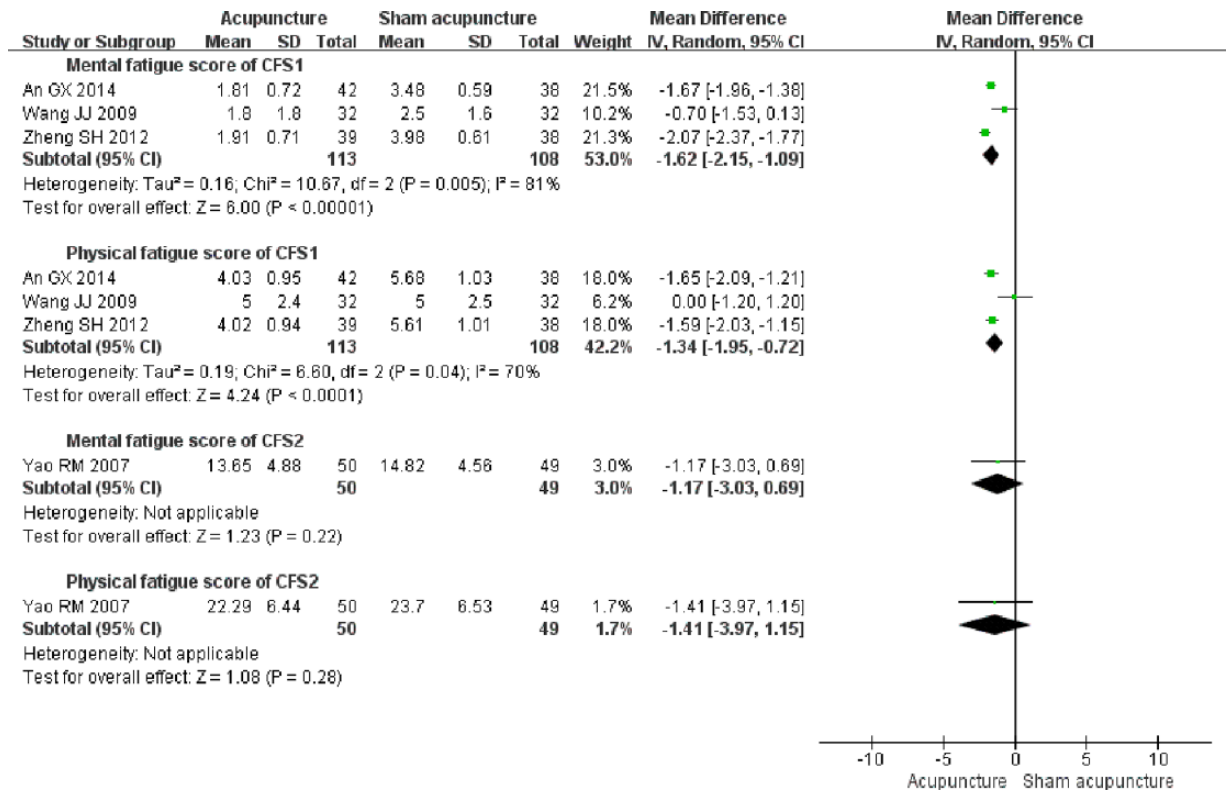



**Table 3.** Results of fatigue severity measured by CFS/FSS.

| Outcomes | Control | Study (n) | Participants (n) | MD | 95% CI | P values |
|---|---|---|---|---|---|---|
| CFS-Mental fatigue | SA | 4 | 640 | –* | | |
| | CHM | 1 | 90 | −0.15 | −0.98 to 0.02 | 0.04 |
| | UC | 1 | 100 | −3.75 | −4.42 to 3.08 | <0.01 |
| CFS-Physical fatigue | SA | 4 | 640 | –* | | |
| | CHM | 1 | 90 | −1.4 | −1.96 to 0.84 | <0.01 |
| | UC | 1 | 100 | −5.9 | −6.89 to 4.91 | <0.01 |
| FSS | SA | 1 | 60 | −12.87 | −15.86 to 9.88 | <0.01 |
| | UC | 1 | 99 | −1.09 | −1.52 to 0.66 | <0.01 |

*Shown in Figure 5.
CFS, Chalder's Fatigue Scale; CHM, Chinese herbal medicine; CI, confidence interval; FSS, Fatigue Severity Scale; MD, mean difference; SA, sham acupuncture; UC, usual care; WM, Western medicine.

comparative effect of acupuncture and standard treatment on CFS, particularly in a practical environment, is also an important topic to investigate. An outcome measure that is specific for patients with CFS and assessment of adverse events should be given more attention. It is recommended that RCTs are reported in accordance with the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines[38] and provide information about the acupuncture intervention in detail. To avoid insufficient information hindering the assessment of methodology, future RCTs should

**Table 4.** Summary of findings.

| Acupuncture group versus control group | | | | | | |
|---|---|---|---|---|---|---|
| Patient or population: patient with CFS<br>Intervention: acupuncture treatment<br>Comparison: control group | | | | | | |
| | Anticipated absolute effects* (95% CI) | | | | | |
| Outcomes | Risk with control group | Risk with acupuncture group | Relative effect (95% CI) | Nº of participants (studies) | Certainty of the evidence (GRADE) | Comments |
| Overall response rate | 555 per 1000 | **837 per 1000** (760 to 926) | **RR 1.51** (1.37 to 1.67) | 734 (nine studies) | ⊕⊕◯◯ LOW | |
| CFS - Mental fatigue | | The mean CFS - Mental fatigue in the intervention group was 1.95 lower (2.14 lower to 1.76 lower) | | 420 (five studies) | ⊕⊕◯◯ LOW | |
| CFS - Physical fatigue | | The mean CFS - Physical fatigue in the intervention group was 1.88 lower (2.17 lower to 1.6 lower) | | 420 (five studies) | ⊕⊕◯◯ LOW | |
| FSS | | The mean FSS in the intervention group was 1.33 lower (1.76 lower to 0.9 lower) | | 159 (two studies) | ⊕⊕◯◯ VERY LOW | |
| Adverse events | | | | (two studies) | | |

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI, Confidence interval; OR, odds ratio; MD, mean difference.
**GRADE Working Group grades of evidence.**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

adhere to the standards of the Consolidated Standards of Reporting Trials (CONSORT) statement[39] in reporting methodology so that results can be better appraised.

In summary, acupuncture appears more effective than sham acupuncture and Chinese herbal medicine for the treatment of CFS. However, the limited data, poor methodological quality and potentially exaggerated evaluation of effect size prevent us from drawing a firm conclusion. Further RCTs are needed including rigorous study design, sufficient sample size, valid control settings, specific outcome measures and standard reporting.

## Contributors

QZ, HD and JG were responsible for the conception and design of the study and data acquisition. QZ and SX appraised the quality of the studies and performed the meta-analyses. QZ interpreted the results of the study in collaboration with WW and GH. QZ and JG drafted the manuscript. All authors participated in critical revision of the manuscript and approved the version accepted for publication.

## Funding

TThe authors received no financial support for the research, authorship, and/or publication of this article.

## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Patient consent

Not required.

## Provenance and peer review

Not commissioned; externally peer reviewed.

## Supplemental material

Supplemental material for this article is available online.

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