Acupuncture for hot flushes in perimenopausal and postmenopausal women: a randomised, sham-controlled trial

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Abstract

Objectives To determine the effect of acupuncture in treating hot flushes in perimenopausal or postmenopausal women.

Methods The study was a randomised single-blind sham-controlled clinical trial. Perimenopausal or postmenopausal women with moderate or severe hot flushes were randomised to receive real or sham acupuncture. Both groups underwent a 4-week run-in period before the treatment. The real acupuncture group received 11 acupuncture treatments for 7 weeks, and the control group underwent sham acupuncture on non-acupuncture points during the same period. Both groups were followed for 8 weeks after the end of treatment period. Changes from baseline in the hot flush scores at week 7, measured by multiplying the hot flush frequency and severity, were the primary outcome. Hot flush frequency, severity and menopause-related symptoms measured with the Menopause Rating Scale Questionnaire were regarded as secondary outcomes.

Results 54 participants were randomised into the real acupuncture group (n=27) and the sham acupuncture group (n=27). The mean change in hot flush scores was −6.4±5.2 in the real acupuncture group and −5.6±9.2 in the sham group at week 7 from values at the start of the acupuncture treatment (10.0±8.1 vs 11.7±12.6), respectively (p=0.0810). No serious adverse events were observed during the whole study period.

Conclusions Compared to sham acupuncture, acupuncture failed to show significantly different effects on the hot flush scores but showed partial benefits on the hot flush severity. Further consideration is needed to develop appropriate strategies for distinguishing non-specific effects from observed overall effectiveness of acupuncture for hot flushes. Whether acupuncture has point-specific effects for hot flushes should be also considered in designing future researches.

INTRODUCTION

Hot flushes are among the most disturbing vasomotor symptoms in menopausal women, which profoundly impacts their quality of life. They are accompanied by a sudden sensation of heat, flushing, sweating and sleep disturbance and often lead to decreased social activity and emotional embarrassment. The prevalence of hot flushes varies according to ethnicity and geographic region,2 3 and studies have revealed that over 60% of South Korean menopausal women have experienced hot flushes.4 5 Currently, the most effective treatment for menopausal hot flushes is hormone replacement therapy (HRT), which reduces vasomotor symptoms by up to 80% compared to pretreatment.6 However, long-term use of HRT has been reported to be associated with increased risks of cancer and stroke,7 8–10 Non-hormonal agents, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, clonidine and gabapentin, have been used to manage hot flushes, although the adverse effects and cost may limit their use for many women.11 Accordingly, many women have paid considerable attention to complementary and alternative medicine (CAM) to relieve hot flushes without adverse effects.12 13 CAM to alleviate hot flushes includes black cohosh, Chinese herbal medicine, soy products, phytoestrogen, yoga and acupuncture, although the data are insufficient to support the effectiveness and long-term safety for menopausal hot flushes.14 Acupuncture is a common form of CAM for menopausal hot flushes.15 However, the current evidence supporting the use of acupuncture for menopausal hot flushes remains controversial. Two large randomised controlled trials (RCTs) showed that acupuncture plus usual care could improve hot flushes, menopause-related symptoms and health-related quality of life in perimenopausal or postmenopausal women compared to usual care alone.16 17 Meanwhile, most sham-controlled acupuncture trials and systematic reviews have reported no significant benefits of acupuncture for hot flushes.18 19 Some possible reasons for the contrasting overall effectiveness but lack of efficacy of acupuncture are the non-specific effects from the high expectation of study participants and the unintended neurophysiological effects of penetrating/non-penetrating...
sham acupuncture used in studies. Nevertheless, the reasons for these disparities remain yet to be determined and require further elucidation.

To date, a few sham-controlled acupuncture RCTs for hot flushes have been published and have shown almost identical results (ie, no significant effects between real and sham acupuncture). However, it is worth replicating the methods of the acupuncture RCTs in a different context because, in principle, one particular study result cannot be generalised to a different situation. Furthermore, several factors including patients’ expectations, practitioners’ enthusiasm and the social acceptability of the theoretical framework of acupuncture treatment can differ in different cultural backgrounds and affect the outcome of treatment. In Korea, acupuncture has been used to manage a range of women’s health problems, including primary dysmenorrhea, infertility and emotional distress.

We developed an acupuncture treatment protocol for menopausal hot flushes through a consensus among five gynaecologists practicing traditional Korean medicine. In this study, we aimed to evaluate the specific effect of acupuncture on hot flushes and menopausal symptoms in perimenopausal or postmenopausal women by conducting a randomised sham-controlled clinical trial.

**METHODS**

**Study design and participants**

This study was a randomised single-blind sham-controlled trial in perimenopausal or postmenopausal women suffering from moderate to severe hot flushes. Recruitment occurred between April and July 2007, and acupuncture treatments were conducted between May and October 2007 at the Dongguk University Ilsan Korean Medicine Hospital (DUIH). This protocol was approved by the DUIH Institutional Review Board (SR08).

We recruited participants from the Ilsan and Seoul areas by advertisements in newspapers and hospital postings at the DUIH. Before enrolment, the trial information was provided to the participants, and all participants signed an informed consent. Participants were instructed to record the frequency and severity of hot flushes in a diary for 4 weeks before enrolment to minimise non-specific effects from the natural remission of hot flushes.

The inclusion criteria were as follows: perimenopausal and postmenopausal women (perimenopausal status defined as ≥3 months of self-reported menstrual irregularity; postmenopausal status was defined as amenorrhea for ≥12 months), 45–60 years of age; desire to receive treatment for hot flushes; hot flushes defined as sensations of heat with sweating that were moderate (able to continue activities) or severe (not able to continue activities), as defined by the Food and Drug Administration in the USA. All women were asked not to take new drugs or dietary supplements during the trial and agreed not to change the doses of currently administered drugs or supplements.

The exclusion criteria were as follows: total hysterectomy or anticancer treatment due to malignancy; history of cancer within 5 years; metallic allergy; hyperthyroidism; known psychiatric disorders; any conventional medication (eg, HRT or SSRIs) for hot flushes within the 8 weeks prior to the study; and medical conditions not appropriate for this study (eg, thromboembolic disease, heart disease, uncontrolled hypertension, diabetes mellitus or vaginal bleeding of unknown origin within 6 months).

The study lasted a total of 19 weeks. The study protocol involved 4 weeks before acupuncture treatment (screening and 4-week waiting period), 7 weeks of acupuncture treatment and 8 weeks of follow-up assessment.

**Randomisation**

Random allocation software V.1.0 (Department of Anaesthesia, Isfanhan University of Medical Science) was used to randomise patients into two groups. A block size of 4 was used. The allocation of each patient was concealed by placing each random code in an opaque, sealed envelope. These envelopes were opened after the enrolment of the patient.

**Treatments**

One traditional Korean medicine doctor, as qualified by the Korean Ministry of Health and Welfare and having more than 4 years of clinical experience, provided all treatments of real and sham acupuncture. All participants were treated in the supine position and received 11 treatments over 7 weeks. Real or sham acupuncture treatment was provided twice a week in the first 4 weeks and once a week in the remaining 3 weeks in both groups. The needle retention time was 20±3 min per each treatment. Sterile disposable 0.30×30 mm acupuncture needles (The Korean Oriental Medicine Distribution Company, Sungnam, Korea) were used for all participants. Infrared irradiation was also applied to gently warm the lower abdomens of participants in both groups, as it is a routine adjunct in the clinical practice of acupuncture in Korea.

For the active treatment group, 13 acupuncture points were used, based on an extensive traditional and contemporary literature review and the consensus of traditional Korean medicine doctors who were experts in treating gynaecological conditions (table 1). For the real acupuncture group, needles were inserted to a depth of 0.2–10 mm, according to the location of the points and manually stimulated, eliciting the de qi sensation (a dull, aching sensation around the needling points). For the sham treatment group, 12 non-acupuncture points were needled on predefined non-acupuncture points without stimulation, to not elicit the de qi sensation (table 2).

Each participant was in a separate room with an eye bandage (Black, CS Beria, Seoul, Korea) to minimise the risk of unblinding due to the possible communication about the perceived experience or sensation of the study acupuncture among participants in different groups. During the acupuncture treatment, no patient–practitioner communication was allowed to minimise potential non-specific effects from patient–practitioner interactions. A blinded assessor collected the patient diaries and performed the outcome assessment.
HT8 Ren mai Up to 1 cun* On the midline 3 cun below the umbilicus

SP6 Spleen Toward of the contralateral G 39 to 5–8 fen, bilateral

ST36 Stomach Toward of the contralateral SP 9 to 5–8 fen, bilateral

LI4 Large intestine Toward the second, bilateral metacarpal bone to 5–8 fen, bilateral

HT7 Heart Up to 3 fen, bilateral Between the fourth and fifth metacarpal bones

PC6 Pericardium Up to 5–8 fen, bilateral 2 cm above the transverse crease of the wrist, between the tendon of musculus palmaris longus and musculus flexor radialis

LI11 Heart Up to 3 fen, bilateral At the ulnar end of the transverse crease of the wrist

ST36 Stomach Toward of the contralateral SP 9 to 5–8 fen, bilateral On the dorsum of the hand, between the first and second metacarpal bones, approximately in the middle of the second metacarpal bone

SP6 Spleen Toward of the contralateral G 39 to 5–8 fen, bilateral On the lateral side of the shank, one finger breadth from the anterior crest of the tibia

CV4 Ren mai Up to 1 cun* On the midline 3 cun below the umbilicus

*A cun is a relative body measure in traditional Korean medicine. It is the distance between the transverse creases of the interphalangeal bone of the thumb when the finger is slightly flexed. 1 fen = 1/10 cun.

### Table 1  
Table 1  Acupuncture points of the active treatment group

<table>
<thead>
<tr>
<th>Point</th>
<th>Meridian</th>
<th>Depth of needling</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC6</td>
<td>Pericardium</td>
<td>Up to 5–8 fen, bilateral</td>
<td>2 cm above the transverse crease of the wrist, between the tendon of musculus palmaris longus and musculus flexor radialis</td>
</tr>
<tr>
<td>HT8</td>
<td>Heart</td>
<td>Up to 3 fen, bilateral</td>
<td>Between the fourth and fifth metacarpal bones</td>
</tr>
<tr>
<td>HT7</td>
<td>Heart</td>
<td>Up to 3 fen, bilateral</td>
<td>At the ulnar end of the transverse crease of the wrist</td>
</tr>
<tr>
<td>LI4</td>
<td>Large intestine</td>
<td>Toward the second, bilateral metacarpal bone to 5–8 fen, bilateral</td>
<td>On the dorsum of the hand, between the first and second metacarpal bones, approximately in the middle of the second metacarpal bone</td>
</tr>
<tr>
<td>ST36</td>
<td>Stomach</td>
<td>Toward of the contralateral SP 9 to 5–8 fen, bilateral</td>
<td>On the lateral side of the shank, one finger breadth from the anterior crest of the tibia</td>
</tr>
<tr>
<td>SP6</td>
<td>Spleen</td>
<td>Toward of the contralateral G 39 to 5–8 fen, bilateral</td>
<td>3 cm above the medial malleolus, dorsal to the posterior border of the tibia</td>
</tr>
<tr>
<td>CV4</td>
<td>Ren mai</td>
<td>Up to 1 cun*</td>
<td>On the midline 3 cun below the umbilicus</td>
</tr>
</tbody>
</table>

### Table 2  
Table 2  Acupuncture points of the sham treatment group

<table>
<thead>
<tr>
<th>Location</th>
<th>Needling</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 cm below and 1 cm behind the SP9</td>
<td>5–8 fen, bilateral</td>
</tr>
<tr>
<td>2 cm above and 1 cm behind the L11</td>
<td>3–5 fen, bilateral</td>
</tr>
<tr>
<td>2 cm above the umbilicus and 3 cm lateral point</td>
<td>Up to 1 cun*, bilateral</td>
</tr>
<tr>
<td>2 cm above the umbilicus and 6 cm lateral point</td>
<td>Up to 1 cun, bilateral</td>
</tr>
<tr>
<td>2 cm below the umbilicus and 3 cm lateral point</td>
<td>Up to 1 cun, bilateral</td>
</tr>
<tr>
<td>2 cm below the umbilicus and 6 cm lateral point</td>
<td>Up to 1 cun, bilateral</td>
</tr>
</tbody>
</table>

*A cun is a relative body measure in traditional Korean medicine. It is the distance between the transverse creases of the interphalangeal bone of the thumb when the finger is slightly flexed. 1 fen = 1/10 cun.

### Outcomes

The primary outcome measure was changes in the hot flush scores at week 7 from the start of treatment. Hot flush scores were calculated by multiplying the hot flush frequency and severity on a daily basis. Measuring hot flush scores is a reliable and validated method for evaluating hot flush activities.28 On the first visit, we distributed a hot flush diary to the participants. Participants were asked to document the total number of 24 h hot flushes and the severity of hot flushes on 0–10 Visual Analogue Scale (0 referring to no discomfort and 10 to extreme discomfort) in a daily diary during the whole study period. The hot flush diary is a reliable and valid tool that has been used in multiple clinical studies pertaining to hot flushes.28

The secondary outcomes included the frequency and severity of hot flushes, the Menopause Rating Scale (MRS) and patients’ global assessments. MRS is a validated vasomotor symptom assessment tool comprised of 11 questions divided into three subscales (ie, psychological, somatic and urogenital).29

All outcomes were measured at screening (week −4), baseline (week 0), post-treatment (week 7) and follow-up (week 15) visits by a blinded assessor who did not participate in the treatment process in either group.

Additionally, the serum level of follicle stimulating hormone (FSH), luteinising hormone (LH) and oestradiol (E2) were measured at the screening and post-treatment visits to identify any hormonal changes related to acupuncture treatment.

### Sample size calculation

This study was based on the results of our previous study in 2006.30 The score differences of the hot flush Visual Analogue Scale (ranging 0–100) were 15, and the SDs of the study and control groups were 3.9 and 3.8, respectively. According to this result, 20.4 patients would be required in each group to detect significant differences (p=0.05, power=0.8). Assuming a 20% dropout rate, it was necessary to have at least 27 patients in each group.

### Statistical methods

Differences in participant characteristics at screening and at baseline were tested using the χ² test for dichotomous variables and the t test for continuous variables. The primary analysis was based on the intention-to-treat principle, which included all randomised participants who measured the baseline value of the primary outcome and received at least one acupuncture treatment (regardless of real or sham acupuncture assignment). The last observation carried forward was used for the imputation of the missing value. For primary and secondary outcomes, the mean intergroup differences from baseline to each time point were assessed by using two-sample t tests or Wilcoxon rank sum tests. For each participant, we computed the percentage reduction in the daily hot flush scores from baseline to each of the two time points (weeks 7 and 15). The percentage reduction in the daily hot flush scores was defined as 100 times the reduction in the mean daily hot flush scores at a specific time point divided by the baseline score. A similar method was also used in a previous study.31 32 Analyses were conducted using the SAS statistical package, version 9.1.3, and two-sided p<0.05 was considered significant.

### RESULTS

#### Participant flow

We screened 60 women for eligibility and excluded six women. Fifty-four eligible participants were randomised into the real acupuncture group (n=27) or sham acupuncture group (n=27). A 4-week run-in period was included to observe any spontaneous remissions of hot flushes under the study context. One patient in the treatment...
group dropped out due to the disappearance of hot flushes during the observation period. Following the 4-week run-in period, 53 participants received real or sham acupuncture treatments. Among them, 25 participants in the real acupuncture group and 26 in the sham acupuncture group completed 11 treatment sessions over 7 weeks. One patient in the real acupuncture group dropped out due to the loss of hot flushes, and one in the sham acupuncture group dropped out due to initiating HRT. Forty-eight participants finished the 8-week follow-up period after the end of 11 treatment sessions. Three participants in the sham acupuncture group were lost to follow-up. Post-hoc exclusion from analysis for hot flush activities was performed due to the lack of baseline values of hot flush scores in three patients (two in the real and one in the sham acupuncture groups) (figure 1).

Baseline data
The baseline characteristics of participants are shown in table 3. There were no significant between-group differences in the baseline characteristics except for age and height.

Effects of acupuncture on hot flush activities
The baseline values and the mean differences at each follow-up point for the hot flush scores, percentage changes in hot flush scores, hot flush frequency and severity are presented in table 4, figure 2 and 3. No significant intergroup differences were observed in the hot flush scores, frequency and severity scores either at screening or at baseline. No significant intergroup differences were found for any outcome at any of the times, except for hot flush severity at week 7 (p=0.0150). Within-group differences in each outcome showed significant changes from baseline at each time point in both the real and sham acupuncture groups (results not shown).

Effects of acupuncture on menopause-related symptoms
The baseline values and the mean differences at each time point for the total and three subscale scores of the MRS are presented in table 5. Significant imbalances were observed at the screening and baseline measurements in the MRS total score and the psychological and somatic subscale scores (p=0.0007, 0.0026 and 0.0048 at screening.
and 0.0024, 0.0033 and 0.0145 at baseline, respectively), showing significantly higher scores (worse symptoms) in the real acupuncture group than in the sham acupuncture group. When data was analysed by initially planned statistical methods (i.e., a two-sample t test or Wilcoxon rank sum test), it showed some beneficial effects of acupuncture.

### Table 3  Baseline characteristics of the randomised sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active AT (n=27)</th>
<th>Sham AT (n=27)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.4±3.2</td>
<td>52.5±3.5</td>
<td>0.0255</td>
</tr>
<tr>
<td>Height</td>
<td>158.2±3.7</td>
<td>155.0±4.6</td>
<td>0.0066</td>
</tr>
<tr>
<td>Weight</td>
<td>58.5±9.3</td>
<td>56.1±6.7</td>
<td>0.2845</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.3±3.2</td>
<td>23.4±3.1</td>
<td>0.9250</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perimenopausal</td>
<td>15</td>
<td>9</td>
<td>0.1003</td>
</tr>
<tr>
<td>Postmenopausal*</td>
<td>12</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Duration of amenorrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of dysmenorrhea</td>
<td>15</td>
<td>17</td>
<td>0.5796</td>
</tr>
<tr>
<td>Use of hormone replacement therapy</td>
<td>2</td>
<td>3</td>
<td>1.0000</td>
</tr>
<tr>
<td>Previous experience of acupuncture</td>
<td>4</td>
<td>6</td>
<td>0.4835</td>
</tr>
<tr>
<td>Hot flush score</td>
<td>9.7±1.5</td>
<td>13.1±2.4</td>
<td>0.2452</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD or number where appropriate. AT: acupuncture.

*Two surgical postmenopausal women in treatment group and three in control group were included.

### Table 4  Primary outcome, hot flush scores

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Baseline</th>
<th>Post-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week −4</td>
<td>Week 0</td>
<td>Week 7</td>
<td>Week 11</td>
</tr>
<tr>
<td>Hot flush scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Real</td>
<td>18.5±24.1</td>
<td>10.0±8.1</td>
<td>−6.4±5.2</td>
<td>−8.0±7.9</td>
</tr>
<tr>
<td>Sham</td>
<td>14.2±10.6</td>
<td>11.7±12.6</td>
<td>−5.6±9.2</td>
<td>−7.5±9.6</td>
</tr>
<tr>
<td>Percentage changes in hot flush scores (0–100)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Real</td>
<td>NA</td>
<td>NA</td>
<td>−65.1±32.7</td>
<td>−71.9±35.0</td>
</tr>
<tr>
<td>Sham</td>
<td>NA</td>
<td>NA</td>
<td>−41.2±50.5</td>
<td>−65.7±37.2</td>
</tr>
<tr>
<td>Hot flush frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Real</td>
<td>6.5±7.3</td>
<td>4.7±3.2</td>
<td>−2.3±2.1</td>
<td>−3.2±2.9</td>
</tr>
<tr>
<td>Sham</td>
<td>6.5±4.5</td>
<td>5.4±4.2</td>
<td>−2.1±3.3</td>
<td>−3.2±3.4</td>
</tr>
<tr>
<td>Hot flush severity (0–10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Real</td>
<td>2.6±0.6</td>
<td>2.0±0.5</td>
<td>−1.0±0.9</td>
<td>−1.1±0.9</td>
</tr>
<tr>
<td>Sham</td>
<td>2.2±0.8</td>
<td>1.8±0.6</td>
<td>−0.4±0.6</td>
<td>−0.7±0.8</td>
</tr>
</tbody>
</table>

p Value calculated by comparing changes of relevant scores for hot flushes between real and sham acupuncture from baseline (week 0).

NA, not applicable.

### Table 5  Secondary outcome, MRS scores

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Baseline</th>
<th>Post-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week −4*</td>
<td>Week 0*</td>
<td>Week 7†</td>
<td>Week 11†</td>
</tr>
<tr>
<td>Real acupuncture (n=27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22.8±6.3</td>
<td>20.4±7.5</td>
<td>−7.3±6.7</td>
<td>−9.2±7.9</td>
</tr>
<tr>
<td>Psychological</td>
<td>9.0±3.0</td>
<td>8.2±3.8</td>
<td>−3.1±3.5</td>
<td>−3.8±4.2</td>
</tr>
<tr>
<td>Somatic</td>
<td>8.3±2.0</td>
<td>7.4±2.6</td>
<td>−2.6±1.9</td>
<td>−3.4±2.5</td>
</tr>
<tr>
<td>Urogenital</td>
<td>5.3±2.7</td>
<td>4.7±2.7</td>
<td>−1.4±2.5</td>
<td>−1.9±2.6</td>
</tr>
<tr>
<td>Sham acupuncture (n=27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16.9±5.6</td>
<td>14.5±5.9</td>
<td>−3.8±6.7</td>
<td>−5.7±7.0</td>
</tr>
<tr>
<td>Psychological</td>
<td>6.0±3.2</td>
<td>5.0±2.7</td>
<td>−1.1±3.1</td>
<td>−1.5±3.0</td>
</tr>
<tr>
<td>Somatic</td>
<td>6.6±2.3</td>
<td>5.7±2.4</td>
<td>−1.3±2.5</td>
<td>−2.4±2.8</td>
</tr>
<tr>
<td>Urogenital</td>
<td>4.3±2.8</td>
<td>3.7±2.5</td>
<td>−1.3±2.4</td>
<td>−1.6±2.4</td>
</tr>
</tbody>
</table>

*Values in these columns present those of the measured at each time point.

†p Value calculated by comparing baseline values of total and subscale scores of MRS between real and sham acupuncture (analysis of covariance).

‡p Value calculated by comparing changes of total and subscale scores of MRS at each time point from baseline (two-sample t test).

§p Value calculated by comparing changes of total and subscale scores of MRS between real and sham acupuncture from baseline (analysis of covariance).

MRS, Menopause Rating Scale.
tecture. After 11 sessions of acupuncture treatments, the total and urogenital subscale scores of the MRS showed no significant differences between the real and sham acupuncture groups at any time point, whereas the psychological and somatic subscale scores at week 7 and the psychological subscale scores at week 15 showed statistically significant between-group differences (p value 0.0439, 0.0331 and 0.0256, respectively). Given the notable imbalance of the screening and baseline values in a total and psychological subscale which are likely to increase risk of bias, data were re-analysed by analysis of covariance with the baseline values as covariates to consider baseline imbalance of MRS scores although they were not planned in the study protocol. Analysis of covariance found no significant between-group difference of total and three subscale MRS scores at week 7 and 15 (table 5).

Effects of acupuncture on sexual hormones
The mean baseline value of oestradiol (pg/ml), FSH (mIU/ml) and LH (mIU/ml) were 34.9±45.8, 65.8±55.2 and 30.4±15.4 in the real acupuncture group and 52.0±74.4, 72.8±85.8 and 37.9 in the sham acupuncture group, respectively, showing no significant differences between groups (p=0.5589, 0.4734 and 0.0882, respectively). At post-treatment measurement, the mean change of oestradiol, FSH and LH was 18.0±54.7, −8.7±20.9 and −3.9±15.5 in the real acupuncture group and −21.2±77.7, 3.5±22.1 and −0.6±14.0 in the sham acupuncture group, respectively, showing no significant differences between the groups (p=0.0749, 0.0992 and 0.9588, respectively).

Blinding test
At the end of the post-treatment follow-up, we asked participants who completed the 11 sessions of real or sham acupuncture to describe their perception of whether they were treated with real or sham acupuncture treatment. Of the 25 participants in the sham acupuncture group, 17 (74%) reported their perception that they likely received real acupuncture and six reported they were assigned to sham acupuncture group while two of the 25 participants in the real acupuncture group mentioned that they felt that they were assigned to the sham acupuncture group, 21 reported they were in the real acupuncture group. Five participants (two participants in real acupuncture group and three in sham acupuncture group) did not answer the questionnaires.

Adverse events
Minimal bleeding and subsequent bruising at the needling points were observed in one person in the sham acupuncture group. Other than that, no adverse events were observed.

DISCUSSION
In this study, real acupuncture treatments failed to show significant differences in hot flush scores and frequencies compared to sham acupuncture, whereas hot flush severity scores were significantly lower in the real acupuncture group than the sham acupuncture group at week 7 but not week 15. The psychological subscale scores at weeks 7 and 15 and the somatic subscale scores at week 7 in the MRS showed statistically significant differences compared to the sham group at an initial analysis; however, subsequent analysis of covariance showed no significant difference when baseline imbalances in the total, psychological and somatic subscale scores of MRS were taken into account in the analysis. Sex hormones (FSH, LH and oestradiol) showed no significant intergroup differences, suggesting no hormonal effects of acupuncture in relation to menopausal hot flushes in this study, although the post-treatment elevation of 18.0 pg/ml of oestradiol in real acupuncture group and reduction of 21.2 pg/ml of those in sham acupuncture group compared to baseline value were observed at week 7.

This trial found up to 72% and 65% within-group reductions in the hot flush scores from baseline with real and sham acupuncture, respectively. In terms of hot flush severity, significant improvements were observed in the real acupuncture group compared to the sham acupuncture group (48% vs 22% reduction at week 7 from baseline), as seen in previous studies. These results suggest a promising role of acupuncture for hot flushes. However, non-specific effects from the high expectation of participants, which we did not measure, and the unintended sensory stimulation of sham acupuncture, which may have resulted in similar neurophysiological effects, might have played substantial roles in these observed effects. Previous research has suggested that acupuncture might not have point-specific effects, which contradicts to traditional acupuncture theory. This hypothesis could be one important explanation for our observed beneficial effects in both groups, and should be further investigated. Far-infrared irradiation on the lower abdomen as adjuncts of acupuncture in both groups might also have played a role. Thus, we could not exclude other effects of far-infrared irradiation for our results showing beneficial effects in both groups. An improvement during the non-treatment run-in period was found to be a predictor of the placebo response for menopausal symptoms in a phytotherapy RCT. This trial also showed a tendency of reduced hot flushes during the run-in period, which indicated that the placebo effect could have influenced the study results.

The suggested mechanisms of hot flushes include the alteration of the levels of neuropeptides (endorphin and serotonin) induced by oestrogen withdrawal resulting in thermoregulatory dysfunction due to a narrowed thermoneutral zone and the triggering of a heat loss response (ie, hot flushes and sweating) by even a normal increase in the core body temperature. The calcitonin gene-related protein (CGRP) is a vasodilator and may mediate these vasomotor symptoms. Based on this hypothesis, previous studies have measured the urinary excretion of CGRP after acupuncture, showing a significant decrease of urine CGRP in one study but not in two other studies. The true mechanisms of the effect of acupuncture for hot flushes needs to be elucidated by further research.
We used acupuncture points selected by four clinical experts who have practiced traditional Korean medicine in gynaecology over 10 years. The seven points used in this study were HT7, HT8, LI4, ST36, PC6, SP6 and CV4, which partially corresponded to the core eight points (LU7, SP6, HT6, KI6, KI7, CV4, LR5 and LI4) in the largest acupuncture trial for hot flushes (ACUFLASH study) in Norway.16 Three acupuncture points (LI4, SP6 and CV4) in our study were also used in the ACUFLASH study, although one point (PC6) was not used in the ACUFLASH study and also not selected by the Delphi-consensus by international practitioners.38 This divergence in the acupuncture points used between the different studies might be due to different ‘schools’, training courses and clinical contexts in different countries.39 Whether these differences might produce different outcomes remains unknown. It would be interesting to explore whether the different clinical contexts in the different countries are associated with different clinical decision-making (ie, contents of consultation during the diagnostic process, points selected for treatment, frequency of treatment and the total number of sessions that are acceptable to both the practitioners and patients), different symptom manifestations and different treatment outcomes in terms of acupuncture treatment of hot flushes.

One may argue that employing additional usual care arm would have made this study more informative, since both efficacy from comparing sham acupuncture and effectiveness from comparing usual care could have been measured in the same study population. However, we placed our research question to measure efficacy of real acupuncture compared to sham intervention in controlled context, whereas evaluating overall effectiveness compared to usual care to reflect a real-world clinical practice needs more pragmatic study-condition. Thus, we decided not to combine two different research questions in this study design. Overall effectiveness of acupuncture compared to usual care was addressed in another study which showed beneficial effects of acupuncture for 2-month study periods.17

The limitations of this study include the relatively short period of observation (less than 6 months) and baseline imbalances of patient characteristics and MRS scores, although we employed an analysis of covariance method to adjust observed baseline imbalances of MRS scores, which was not planned in protocol. Standardised acupuncture points and restricted consultation/interaction between the practitioner and participants might diminish the external validity of the results in this study. Only one traditional Korean medicine doctor conducted the whole acupuncture sessions in both the real and sham acupuncture groups. Thus, the practitioners’ different attitudes to the different groups (if present) might have affected the treatment procedure and outcomes, although we attempted to minimise those effects by extensively controlled research settings and found no evidence of protocol violations. Using only subjective outcomes relying on participant self-report might not be an optimal method for measuring hot flush activities, although the currently available objective measure of hot flushes (ie, sternal skin conductance monitors) only provides information about hot flush frequency and requires more study on the suitability of its long-term use in ambulatory settings.39 Two participants in real acupuncture group and one in sham group were excluded from outcome analysis, since they lacked essential baseline outcome values for intention-to-treat analysis with last-observation carried forward method. This can increase risk of bias because all randomised patients were not analysed.

We attempted to minimise effects of natural remission of hot flushes for our results by preceding a 4-week run-in period, which was the most available length in our given study circumstance and resources. However, we could not completely exclude those effects from our observed results since natural remission still could occur during the study period. Lastly, the number of participants in this study was similar or relatively small compared to those in other sham-controlled acupuncture RCTs for hot flushes which showed no significant between-group differences,31 32 although sample size was calculated using the result of a previous Korean RCT.38 Thus, we still could not exclude the possibility that this study was underpowered to detect meaningful efficacy of real acupuncture for hot flushes.

CONCLUSION
Compared to sham acupuncture, 11 sessions of real acupuncture over 7 weeks were not effective for reducing measures of hot flushes, except for hot flush severity. Future acupuncture RCTs should properly address the limitations and difficulties encountered in this study of employing the sham-acupuncture control group.

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