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Complete List of Authors:	Sundgaard Lund, Kamma; University of Copenhagen, Section of General Practice, Department of Public Health Siersma, Volkert; University of Copenhagen, The Research Unit for General Practice Brodersen, John; University of Copenhagen, Centre of Research & Education in General Practice Primary Health Care Research Unit, Zealand Region Waldorff, Frans; Research Unit for General Practice, University of Southern Denmark
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Authors' names	Kamma Sundgaard Lund (KSL), Volkert Dirk Siersma (VS), John Brodersen (JB), Frans Boch Waldorff (FBW)
Authors' names, positions and address	Kamma Sundgaard Lund, MD (**Corresponding author**) Section of General Practice, Department of Public Health, University of Copenhagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: kaml@sund.ku.dk Mobil: +45 22 99 38 82 Volkert Dirk Siersma, Statistician (PhD) The Research Unit of General Practice and Section of General Practice, Department of Public Health, University of Copenhagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: siersma@sund.ku.dk John Brodersen, Professor (GP, MD, PhD) Primary Health Care Research Unit, Region Zealand, Alleen 15, 4180 Sorø, Denmark, and Section of General Practice, Department of Public Health, University of Copenahagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: jobr@sund.ku.dk Frans Boch Waldorff, Professor (GP, MD, PhD), The Research Unit for General Practice, Department of Public Health, University of Southern Denmark J.B: Winsløws vej 9, 5000 Odense, Denmark Email: fwaldorff@health.sdu.dk
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ABSTRACT

Objective:

To investigate the efficacy of a standardised brief acupuncture approach for women with moderate-to-severe menopausal symptoms.

Design:

Randomised and controlled, with 1:1 computer-generated allocation to the intervention group or the control group. The assessor and the statistician were blinded.

Setting:

Nine Danish primary care practices.

Participants:

We recruited 70 women with moderate-to-severe menopausal symptoms and nine general practitioners with accredited education in acupuncture.

Intervention:

The acupuncture style used in this study was western medical acupuncture with a standardised approach in the predefined acupuncture points CV-3, CV-4, LR-8, SP-6, and SP-9. The intervention group received one treatment for five consecutive weeks. The control group was offered treatment after six weeks.

Main outcome measures:

Outcomes were the differences between the randomisation groups in changes to mean scores using the scales in the MenoScores questionnaire, measured from baseline to week six. The primary outcome was the hot flushes scale; the secondary outcomes were the other scales in the questionnaire. All analyses were based on intention-to-treat analysis.

Results:

36 participants received the intervention and 34 were in the control group. The acupuncture intervention significantly decreased hot flushes (Δ -1.52 (95% CI (-2.19 to -0.85)); p<0.0001), day-and-night-sweats (Δ -1.21 (95% CI (-2.03 to -0.38)); p=0.0042), general sweating (Δ -0.86 (95% CI (-1.48 to -0.24)); p=0.0066), and menopausal-specific sleeping problems (Δ -1.61 (95% CI (-2.39 to -0.84)); p<0.0001) compared to the control group at the six-week follow-up. The pattern of decreased hot flushes was already apparent three weeks into the study. Mild potential adverse effects were reported by four participants.

Conclusion:

This standardised and brief acupuncture treatment produced a fast and clinically relevant reduction in hot flushes, day-and-night sweats, general sweating, and menopausal-specific sleeping problems in women with moderate-to-severe menopausal symptoms during the six-week intervention. No severe adverse effects were reported.

Trial registration:

ClinicalTrials.gov NCT02746497.

ARTICLE SUMMARY

Strengths and limitations of this study:

- This study has high methodological quality, allocation concealment, adequate power, a validated outcome measure, sufficient and transparent reporting leading to high external validity.
- The study had high participants adherence supporting that the intervention was manageable and well tolerated.
- Since the intervention was pragmatic, standardised and brief the applicability of the findings is high and might have a good chance of being implemented which could lead to new treatment options for menopausal women.
- At present no sufficient acupuncture placebo comparator exist which is a major limitation in acupuncture studies, this study included.

INTRODUCTION

Experience of menopausal symptoms is very common and has been shown to affect quality of life, health status, work productivity, and use of health services (1-3). The majority of women experience menopause in their early fifties (4) and have menopausal symptoms for four to five years on average (4-7). The most prominent symptom of menopause is hot flushes which affects around 75% of menopausal women (5, 6, 8) and is reported as very distressing by 10-20% (5). Other reported menopausal symptoms are night sweats, emotional vulnerability, sleep disturbances, fatigue, cognitive changes, joint pain, vaginal dryness, and loss of sexual desire (4, 5, 9).

Hormone therapy (HT) relieves menopausal symptoms (10, 11) but long-term HT is associated with an increased risk of breast cancer and thromboembolic disorders (11-14). Hence, many menopausal women avoid HT. Non-hormonal-based treatments such as clonidine, gabapentin, and antidepressants may also reduce menopausal symptoms. However, these drugs have frequent adverse effects such as sleep disturbance, dizziness, nausea, fatigue, dry mouth, and constipation (4, 5, 8, 15, 16). Non-pharmaceutical treatments, e.g. relaxation, exercise, herbal remedies, and diets containing phytoestrogens have been suggested, although there is a lack of knowledge about dose, duration, and, for herbal remedies and phytoestrogens, drug interactions and adverse effects. There is currently no convincing evidence of any beneficial effect from these treatments (4, 8, 15-17).

Several studies have demonstrated the effects of acupuncture on menopausal symptoms (15, 18-20), but they have been criticised for methodological limitations, e.g. poor design, inadequate sample size, inadequate control or placebo groups, absence of standardised protocols, and a lack of data on adverse effects (18, 19). Furthermore, due to different methods and a lack of validation of some outcome measures, comparison of results is difficult (18, 19). Therefore, further high-quality randomised acupuncture trials are needed (18, 19). Although the use of acupuncture differs between countries, it is sought by many patients (21-24) and practiced by a substantial number of physicians, especially general practitioners (GPs) (22, 25-27). If a clinically relevant effect on menopausal symptoms from acupuncture is demonstrated, this treatment may be considered for implementation in primary healthcare, leading to new options for menopausal women who cannot or do not wish to use HT.

We hypothesised that a brief and standardised acupuncture treatment could reduce moderate-to-severe menopausal symptoms and, in particular, it could have a clinically relevant effect in the reduction of hot flushes. Therefore, the objective of this study was to investigate the efficacy of a standardised brief acupuncture approach for women with

moderate-to-severe menopausal symptoms; primarily the efficacy on hot flushes measured as change from baseline to week six.

METHOD

Trial design:

The study was a randomised controlled trial (RCT) with a 1:1 allocation to the intervention or the control group. A detailed description of the methods used in the present study are found in the published protocol (28).

Settings and acupuncturists:

The study took place in nine primary care practices in both urban and rural settings. The acupuncturists were nine GPs and all but one were educated in acupuncture by the Danish Society for Evidence-based Acupuncture (DSEA) or the Danish Medical Acupuncture Society (DMAS). One GP had acupuncture training in Sri Lanka before DSEA and DMAS were formed. Participating GPs had, on average, 153 hours of acupuncture education (range 80 to 300), and had practiced acupuncture for 14 years (range 4 to 38).

The first author (KSL) held an individual meeting with each of the GP acupuncturists and provided them with the study protocol, an overview of the predefined acupuncture points, and a written manual with precise instructions for treatment. KSL asked the GP acupuncturists to behave neutrally and to provide only the specified acupuncture treatment and no other treatment or counselling. A two-and-a-half hour refresher course on the predefined acupuncture points and techniques was offered, and four GPs attended this course.

Participants:

Women were recruited through local newspapers, general practices close to the participating GP acupuncturist, the DSEA, and the DMAS. Recruitment took place between late September 2016 and mid December 2016.

Inclusion criteria: women aged 40-65 years with moderate-to-severe hot flushes (score ≥4 on a validated scale measuring hot flushes (MenoScores questionnaire, Appendix 1), intact cognitive function, and a valid e-mail address. Before enrolment participants gave written informed consent. *Exclusion criteria*: women who had had a hysterectomy and/or bilateral oophorectomy; women whose alcohol consumption exceeded 21 drinks per week; who used prescribed sleeping pills and/or prescribed sedatives; who had previously been diagnosed with breast, endometrial, cervical, or ovarian cancer; who had been diagnosed with other severe cancer disease within the past 5 years; who had heart valve disease; who were insulin dependent and/or had poorly controlled diabetes mellitus; who were diagnosed with thyroid disease; who were under investigation for serious disease e.g. cancer; who had received acupuncture treatment within the past 6 months; who had been pregnant or had been breast-feeding within the past two years; who were participating in another trial or had participated in another trial in the two weeks before screening for eligibility; who within the past four weeks had used one or more of the following treatments: systemic HT, hormonal intrauterine device, antidepressants and/or antiepileptics; who had received other medical treatment for hot flushes (e.g. clonidine), herbal remedies/alternative treatments for menopausal symptom, or corticosteroids (the use of inhaled steroids was not an exclusion criterion).

Enrolled participants were provided with oral and written information about the study (29). Participation was voluntary and there was no payment for taking part. Participants could withdraw their consent at any time. The first author carried out assessment of eligibility, obtained informed consent, and collected baseline characteristic data.

Intervention:

All participants were offered one treatment per week for five weeks by a GP acupuncturist in their local area. The intervention group received their treatment in the first five weeks after enrolment in the study. At present, no validated acupuncture placebo comparator exists (30, 31) and we decided to use a control group instead. The control group received their treatment after six weeks. Hence, this RCT is evaluated over a six-week study period (Appendix 2. Time schedule). The acupuncture style we used was western medical acupuncture, (WMA) (31, 32), with a standardised approach and predefined acupuncture points (Table 1 and Appendix 3), based on reports from experienced western medical acupuncturists (33).

A complete acupuncture session should not last more than 15 minutes, including insertion of needles, retention time, removal of needles, and documentation. Disposable sterile (Plandent) needles, size 0,30 x 30 mm, were inserted perpendicularly and rotated manually for a few seconds to elicit "de-qi" (needle sensation, a feeling of heaviness around the acupuncture point) (32). The predefined points were CV-3, CV-4, LR-8, SP-6, SP-9 (Table 1). A total of eight points was used, as LR-8, SP-6 and SP-9 were given bilaterally. Needle retention time was 10 minutes.

After each treatment, the GP acupuncturist completed a documentation scheme with the date, documentation for insertion of each of the needles, and whether "de-qi" was obtained. After the final treatment, the completed documentation was sent to the first author.

TABLE 1. Acupuncture points and location

CV-3	Anterior midline, 1 cun* proximal to the symphysis. Insertion depth; perpendicularly 0.5-1 cm.
CV-4	Anterior midline, 1 cun proximal to CV-3 and 3 cun inferior to the umbilicus. Insertion depth; perpendicularly 0.5-1 cm.
LR-8	Medial side of the knee, in the depression anterior/medial to the tendons of semimembranosus and the semitendinosus muscles, at the medial end of the popliteal crease. Insertion depth; perpendicularly 1.5-2 cm.
SP-9	Under the medial condyle of tibia in a depression between the posterior tibia and m. gastrocnemius. Insertion depth; perpendicularly 2-3 cm.
SP-6	3 cun proximal to the prominent part of the medial malleoli, on the medial and posterior border of the tibia. Insertion depth; perpendicularly 1-3 cm.

*A cun is an acupuncture measurement unit. 1 cun corresponds to the width of the study subject's thumb.

Outcome:

The study's outcomes were the differences between the randomisation groups in the mean change over the six-week study period measured in the scales of the MenoScores Questionnaire (MSQ). The MSQ is a content-specific patient-reported outcome measure (PROM) with high content validity and adequate psychometric properties measuring bothersome menopausal symptoms. The MSQ encompasses 11 scales and one single item (51 items in total), measuring

different menopausal domains of bothersome symptoms (Appendix 1). The MSQ scales are constructed such that higher scores denote more bothersome symptoms.

The primary outcome was the hot flushes (HF) scale, secondary outcomes were the remaining MSQ scales: day-and-night sweats (DNS), general sweating (GS), menopausal-specific sleeping problems (MSSP), emotional symptoms (EM), memory changes (MEM), skin and hair symptoms (SH), physical symptoms (PHY), abdominal symptoms (ABD), urinary and vaginal symptoms (URIN), sexual symptoms (SEX), and the single item tiredness (TR).

Of these MSQ scales, the HF, DNS, GS, and MSSP scales are most related to menopause, while the other MSQ scales are more related to general aging or other life events [Measuring bothersome menopausal symptoms: development and validation of the MenoScores Questionnaire. In review: Health and Quality of Life Outcomes]

Assessments and follow-up:

All participants received the MSQ by e-mail in study weeks zero, three, six, eight, eleven, and twenty-six (Appendix 2). Week zero (before randomisation), week three (intermediate assessment), and week six (final assessment) are reported in the present manuscript. In the period when participants were receiving acupuncture treatment, we asked them to complete the MSQ 1-2 days before the third treatment and one week after the fifth and last treatment (Appendix 2). Participants completed and returned the MSQ electronically. Reminders were sent within 1-2 days, if the participant did not return a completed MSQ within the scheduled time. Additionally, participants in the intervention group were asked about adverse effects at the three- and six-week follow-up. After the final treatment we asked the intervention group if, in general, they had experienced a beneficial effect from the acupuncture treatment.

Sample size:

The necessary sample size for the RCT was determined from reports on the primary outcome HF and the two secondary outcome DNS and MSSP in the MSQ validation study [in review, as previously described]. We considered a reduction in a scale score as clinically relevant if it corresponded to a reduction from “a lot” to “quite a bit” on a global item regarding whether the respondent was bothered by menopausal symptoms. In the MSQ validation study, women who were bothered “a lot” had a mean score of 4.98 on the HF scale, and women who were bothered “quite a bit” had a

mean score of 3.48 on the HF scale. Both groups with a standard deviation (SD) around 1.4. To detect such a reduction on the HF scale with 90% power, 5% level of significance, and accounting for 20% dropouts, we needed to include 48 participants (24 participants in each group). To achieve a similar power on the DNS and MSSP scales, we needed 56 and 68 participants, respectively.

Randomisation:

The allocation sequence was computer generated using SAS software (v 9.4, SAS institute, Cary, NC, USA) and kept by a person independent of the project organisation (affiliated to the Centre for Health Economic Research, University of Southern Denmark). After enrolment, the independent person allocated the participants to one of the two randomisation groups. The participants were subsequently referred to the acupuncturist. This process ensured that allocation could not be guessed or later changed, thereby securing allocation concealment. Randomisation was done in blocks, with random block sizes, and stratified by age and level of symptoms (experiencing hot flushes "quite a bit" or "a lot").

Statistical methods:

We compared the primary and secondary outcomes between the randomisation groups using Wald tests in linear mixed models including a subject-random effect. The comparisons were adjusted for stratification in the randomisation: age and level of symptoms. To assess the randomisation within these linear models, comparisons of the outcomes at baseline were performed. Covariates at baseline were compared between randomisation groups with t-tests (continuous covariates) or chi-squared tests (categorical covariates). Analyses were performed as intention-to-treat analyses. Four or more treatments were considered adequate adherence. The statistical significance was assessed controlling for the false discovery rate at 5%. SAS v9.4 was used for the analyses.

Blinding:

Statistician and outcome assessors were blinded until all analyses were completed. Participants and acupuncturist were not blinded.

Patient involvement:

In the development of the research question, and in the design of the study, the development and content validity of the outcome measure (MSQ) was ensured by qualitative interviews with women who experienced bothersome menopausal symptoms [in review, as previously described]. During this process, the relevance of this present study was also confirmed. Patients were not involved in the recruitment or conduction of the study. The burden of intervention was not assessed by the participants. When results are published they will be disseminated to the Danish College of General Practitioners, the DSEA, the DMAS, the project research homepage (29), local newspaper and Danish women's lifestyle magazines.

RESULTS

We interviewed 207 women for eligibility, of which 70 met the inclusion criteria and were enrolled over a three-month period: we allocated 36 participants to the intervention group, and 34 to the control group. The number of participants treated by a single acupuncturist ranged from minimum one to maximum 16 (including the delayed treatment of the control group). No statistically significant differences in baseline characteristics between the randomisation groups were identified (Table 2). Four participants dropped out: one in the intervention group and three in the control group (Figure 1). The MSQ response rate was 100% for all remaining participants at all assessments points. The adherence to treatment was very high: 34 out of 36 received all five planned acupuncture treatments, and one received four out of five treatments. We collected primary data between October 2016 and February 2017.

TABLE 2. Baseline characteristics for each group of women	Control (n=34)	Intervention (n=36)	p-value
Age (years), *mean (SD)*	54.1 (4.9)	55.3 (4.0)	0,2613
Age, *n (%)*			0,4783
40-55 years	13 (38.2)	17 (47.2)	
56-65 years	21 (61.8)	19 (52.8)	
Employment, *n (%)*			0,9999
Employed	31 (91.2)	32 (88.9)	

Unemployed	3 (8.8)	4 (11.1)	
Education, *n (%)*			0,5858
Vocational	8 (23.5)	8 (22.2)	
Short (<3 years)	4 (11.8)	3 (8.3)	
Long (≥3 years)	16 (47.1)	22 (61.1)	
Other	6 (17.7)	3 (8.3)	
Household, *n (%)*			0,1993
Living alone	1 (2.9)	5 (13.9)	
Living with others	33 (97.1)	31 (86.1)	
Physical activity, *n (%)*			0,3384
No physical activity	7 (20.6)	3 (8.3)	
1-3 times per week	20 (58.8)	23 (63.9)	
≥4 times per week	7 (20.6)	10 (27.8)	
Smoking, *n (%)*			0,9999
Yes	1 (2.9)	2 (5.6)	
No	33 (97.1)	34 (94.4)	
Alcohol, *n (%)*			0,0067
No alcohol	1 (2.9)	8 (22.2)	
≤14 units per week	29 (85.3)	19 (52.8)	
>14 units per week	4 (11.8)	9 (25.0)	
BMI (kg/m^2), *mean (SD)*	25.5 (5.2)	24.9 (3.2)	0,5645
Menstruation in the last year, *n (%)*			0,4171
Yes	7 (20.6)	11 (30.6)	
No	27 (79.4)	25 (69.4)	
Number of births, *n (%)*			0,7805
None	3 (8.8)	2 (5.6)	
One	5 (14.7)	8 (22.2)	
Two	20 (58.8)	18 (50.0)	
More than two	6 (17.7)	8 (22.2)	
Incontinentia, *n (%)*			0,4471
No	13 (38.2)	10 (27.8)	
Yes	21 (61.8)	26 (72.2)	
Chronic disease, *n (%)*			0,5427
Yes	5 (14.7)	8 (22.2)	
No	29 (85.3)	28 (77.8)	
Previous experience with alternative treatment, *n (%)*			0,7871
No	8 (23.5)	10 (27.8)	
Yes	26 (76.5)	26 (72.2)	
Duration of hot flushes (years), *mean (SD)*	3.41 (2.74)	4.59 (3.96)	0,1513
Hot Flushes, *n (%)*			0,2316
HF=4	20 (58.8)	15 (41.7)	
HF>4	14 (41.2)	21 (58.3)	

FIGURE 1. Trial flow

The analyses of the observed raw scores demonstrated generally lower means in the intervention group compared to the control group when followed up. Statistical significance was found in the HF, DNS, GS and MSSP scales at week six. This tendency was already apparent at week three although only significant in the HF scale (Appendix 4).

The developments in the MSQ scales across the two randomisation groups over the study period are presented in Figures 2 and 3.

FIGURE 2: Development of the HF, DNS, GS, and MSSP scales over the study period

FIGURE 3: Development of the remaining (EM, MEM, SH, PHY, ABD, URIN, SEX) MSQ scales and the single item over the study period.

Primary outcome:

The intervention group was significantly less bothered by hot flushes at six weeks: Δ -1.52 (95% CI (-2.19 to -0.85); p<0.0001). This difference was also statistically significant at three weeks: Δ -1.38 (95% CI (-2.05 to -0.71); p<0.0001. (Table 3).

Secondary outcomes:

Statistically significant differences were identified at six weeks in the following secondary outcomes: DNS: Δ -1.21 (95% CI (-2.03 to -0.38); p=0.0042); GS: Δ -0.86 (95% CI (-1.48 to -0.24) p=0.0066); and MSSP: Δ -1.61 (95% CI (-2.39 to -0.84); p<0.0001). (Table 3).

TABLE 3. Differences in means, primary, and secondary outcomes

(Differences in mean scores between the randomisation groups at each of the follow-up time points)

	Week 0 (baseline)[1]		Week 3[2]		Week 6[2]	
	Δ (95%CI)	p-value	Δ (95%CI)	p-value	Δ (95%CI)	p-value
Hot flushes (HF)	0.07 0(-0.59; 0.72)	0.8384	-1.38 (-2.05; -0.71)	<.0001*	-1.52 (-2.19; -0.85)	<.0001*
Day-and-night sweats (DNS)	-0.02 (-0.83; 0.78)	0.9545	-0.98 (-1.80; -0.16)	0.0191	-1.21 (-2.03;-0.38)	0.0042*
General sweating (GS)	0.05 (-0.55; 0.66)	0.8620	-0.53 (-1.14; 0.09)	0.0926	-0.86 (-1.48; -0.24)	0.0066*
Menopausal-specific sleeping problems (MSSP)	0.23 (-0.53; 0.98)	0.5583	-0.67 (-1.44; 0.10)	0.0878	-1.61 (-2.39; -0.84)	<.0001*
Emotional symptoms (EM)	1.05 (-1.44; 3.54)	0.4081	-2.12 (-4.64; 0.40)	0.0996	-2.30 (-4.82; 0.23)	0.0747
Memory changes (MEM)	-0.18 (-0.76; 0.41)	0.5515	-0.64 (-1.23; -0.04)	0.0356	-0.38 (-0.97; 0.22)	0.2139
Physical symptoms (PHY)	0.09 (-1.43; 1.60)	0.9111	-1.20 (-2.74; 0.33)	0.1235	-1.61 (-3.14; -0.07)	0.0408
Urinary and vaginal symptoms (URIN)	0.82 (0.10; 1.53)	0.0251	0.37 (-0.35; 1.10)	0.3129	0.02 (-0.71; 0.75)	0.9500
Abdominal symptoms (ABD)	0.10 (-0.58; 0.77)	0.7808	-0.21 (-0.89; 0.48)	0.5559	-0.61 (-1.30; 0.08)	0.0829
Skin and hair symptoms (SH)	0.35 (-0.69; 1.39)	0.5113	-1.07 (-2.13; -0.02)	0.0467	-1.17 (-2.23; -0.10)	0.0315
Sexual symptoms (SEX)	-0.15 (-1.00; 0.69)	0.7228	-0.91 (-1.76; -0.06)	0.0369	-0.30 (-1.16; 0.55)	0.4818
Tiredness (TR)	0.10 (-0.32; 0.53)	0.6307	-0.23 (-0.67; 0.20)	0.2886	-0.36 (-0,51; 0.36)	0.1100

[1]Difference in mean score of intervention relative to control adjusted for stratification factors (age and level of symptoms ("quite a bit" or "a lot" HF))

[2]Difference in mean score of intervention relative to control, beyond the difference already present at Week 0 (baseline), adjusted for stratification factors (age and level of symptoms ("quite a bit" or "a lot" HF))

*Significant at a 0.0069 level to control for the false discovery rate at 0.05

Negative values Δ = fewer symptoms in the intervention group

In the intervention group, 80% of participants reported a general beneficial treatment effect after six weeks.

Harms:

No serious harms were reported in the intervention group. Four participants reported mild potential adverse effects: one experienced tiredness and headache after treatment; another experienced more hot flushes in some of the weeks, but

reported this to be associated with increased stress in her personal and professional life; one had to urinate more frequently; and one experienced tingling in the leg where the needle had been placed.

DISCUSSION

Principal findings:

The standardised acupuncture treatment used in the present study reduced the HF, DNS, GS and MSSP scales after five weekly treatments, and the HF scale was reduced after two acupuncture treatments. The intervention did not significantly reduce the remaining MSQ scales, but we did also not expect to see this because this study was underpowered regarding these scales. Additionally, since significant reductions were exclusively found in the scales most related to the menopause, our findings emphasise that the intervention was targeted to menopausal symptoms and are not an artefact of general care. The acupuncture treatment was well tolerated: one participant dropped out and only four participants reported mild potential adverse effects. No serious harms were reported.

Strengths and weaknesses of the study:

The intervention period was relatively brief. However, it served to test a pragmatic, standardised, and brief acupuncture approach manageable by both GPs and participants. Therefore, the suitability of the treatment outlined in this study in day-to-day primary care is high. The study had very high participant adherence: only four out of 70 participants dropped out. The remaining participants fulfilled the criteria for adequate treatment adherence, and had a 100% MSQ response rate, demonstrating that the intervention was well tolerated. The fact that the control group was also offered treatment after six weeks probably contributed to the high adherence rate. Finally, all participants were offered the same intervention, and co-interventions for menopausal symptoms were not allowed in the study period, thereby reducing the risk of performance bias.

Another strength in this study was the use of a condition-specific PROM (MSQ) with high content validity and adequate psychometric properties ensuring high construct validity of the study measurements. Moreover, data from the MSQ validation study was used to generate the power calculation based on relevant clinical effects which ensured adequate sample size. We did not use a physiological measurement e.g. skin conductance or temperature (which would probably have been technically difficult) because we believe PROMs are the most appropriate method to obtain

information on participants' own perception of their symptoms (34). The recall time frame in this study was one week which reduced the risk of recall bias.

The lack of a sufficient acupuncture placebo comparator is a major limitation in acupuncture studies, including this study. In WMA theories, sham (placebo) acupuncture is not perceived as inactive but rather another, although less effective, form of needling (30, 31). Furthermore, a meta-analysis concluded that non-specific effects associated with sham acupuncture are often moderately large and might be larger than other placebo interventions (35). An important weakness of the present study is that the identified positive effects from acupuncture treatment could be caused by a placebo effect and not a specific physiological effect of needling. However, our aim was not to distinguish between specific and non-specific effects of needling, but to investigate the impact of acupuncture versus no treatment. We found that the acupuncture treatment used in this study had an important clinical effect. If we ignore these findings, due to a lack of knowledge about possible specific effects of acupuncture, women with moderate-to-severe menopausal symptoms could miss out on a low cost and effective treatment with only minor potential adverse effects.

One final limitation was that blinding of acupuncturists and participants in this study design was not possible. However, we secured blinding of the statistician and outcome assessors until all analyses were completed.

Comparison with other studies:

Some previous studies have demonstrated real acupuncture to be significantly superior to sham acupuncture (36-38). However, a Cochrane review from 2013 regarding acupuncture for menopausal hot flushes, found no significant differences between real acupuncture compared to sham, but a beneficial effect of acupuncture compared to no treatment, and that acupuncture was inferior to HT. The evidence was in general of poor quality, and further high quality studies were recommended (18). Results from two recent studies, one comparing real acupuncture with sham (39) and one comparing acupuncture with no treatment (40), confirm the findings reported in the Cochrane review.

The present study demonstrates that acupuncture is significantly superior to no treatment. Our study was based on WMA theories while most previous studies were based on traditional Chinese medicine (TCM) theories and diagnoses (18, 21, 36-44) involving the concepts of yin/yang and circulation of qi (31, 32). Most previous studies had longer intervention periods and/or more treatment sessions (21, 37-48) and several studies used individualised treatment with variation in the selection of acupuncture points (21, 38, 40, 41, 44). Tailored treatments might be a truer reflection of the actual clinical context. However, in an RCT, we believe that treatment should be standardised so that the

intervention can be replicated. Some studies differ from this study by including patients treated for breast cancer (36, 37, 42, 43), which makes it difficult to compare results. Some studies allowed other co-interventions (e.g. adjuvant anti-hormone therapy, cystostaticum, clonidine, antidepressants, HT, or other alternative remedies) (21, 36, 37, 39, 40, 42) which might affect outcomes. Finally, some studies assessed other relevant secondary outcomes such as quality of life, hot flush interference, sleep quality, and one study also assessed plasma oestradiol. Most studies used self-reported outcomes but in several of them the validation of the outcome measures was lacking, unclear, or not reported (36, 37, 42, 43). We did not use a quality of life measure, because we did not find a Rasch validated quality of life instrument for our target group. The MSQ validation ensured that all aspects considered important by menopausal women themselves were covered by the MSQ scales. We would expect that a reduction in the HF, DNS, GS, and MSSP scales may ultimately have a positive indirect impact on a menopausal woman's overall sense of well-being and quality of life. To our knowledge, this study is the only one to use a PROM that is condition-specific with high-content validity and psychometrically Rasch validated.

Meaning of the study: possible explanations and implications for clinicians and policymakers

The lack of a proper acupuncture placebo comparator has major implications for conducting and interpreting acupuncture studies. Therefore, we need to continue the discussion about what level of evidence should be accepted as sufficient for a treatment to be considered effective. This is particularly the case when we cannot accurately explain the underlying mechanism behind the treatment, nor determine how much of the effect is caused by placebo. In addition, it is important to note that in the present study the intervention was targeted at menopausal symptoms, and subsequently demonstrated a targeted effect, not an improvement across all symptoms. We also need to take the balance between benefits and harms into consideration. There is strong evidence that acupuncture for menopausal symptoms is without serious harms. Thus, requirements for evidence of the efficacy of acupuncture treatment might be less rigorous. On the contrary, acupuncture treatment in a private setting (i.e. outside a publicly funded health care system) might involve considerable personal expense and opportunity costs.

We consider the intervention in this study to be low cost, both to the individual and to the health system, but this needs to be further investigated and included in a discussion of value-based healthcare (49).

Future research:

The long-term effect, the characteristics of women who benefit from acupuncture treatment, cost-effectiveness, the underlying mechanism of needling, and the impact of placebo need further investigation.

CONCLUSION

A standardized acupuncture treatment gives women suffering from moderate-to-severe menopausal symptoms a clinically relevant reduction in hot flushes, day-and-night sweats, general sweating, and menopausal-specific sleeping problems. Acupuncture for menopausal symptoms is a realistic option for women who cannot or do not wish to use HT. Women seeking acupuncture treatment for menopausal symptoms should be informed of the current evidence, and its limitations, so they can integrate this with personal preferences and values in their decision-making. This study has high methodological quality, adequate power, a validated outcome measure, and sufficient reporting leading to high validity of the study and findings. Furthermore, this study use a pragmatic, standardised, and brief intervention which leads to findings that may have a higher chance of being implemented and thereby are more likely to lead to new treatment options for menopausal women.

OTHER INFORMATION

Acknowledgements:

We would like to thank the doctors and women who took part in this study, Palle Rosted, and DSEA for inspiration and counselling.

Registration:

ClinicalTrials.gov NCT02746497.

Ethical approval:

Approvals from the Committees on Health Research Ethics (H-16016365), the Committee of Multipractice Studies in General Practice (MPU 08-2016) and the Danish Data Protection Agency (SUND-2016-24) were obtained before

enrolment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (ICH GCP).

Protocol:

Please refer to (28) for full trial protocol.

Funding:

The Idella Foundation, the University of Copenhagen, the Research Foundation of General Practice including the Foundation of Multipractice Studies. The funders had no role in study design, collection, analysis, and interpretation of data, in writing of the article or decision to submit for publication. None of the authors are financially influenced by the funders.

Competing interests:

All authors have completed the ICMJE uniform disclosure form and declare no support from any organisation for the submitted work, no financial relationship with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could have appeared to have influenced the submitted work.

Contributor and guarantor information:

FBW conceived the idea. All authors took part in the design and planning of the study. KSL conducted the study supported by all authors. KSL drafted the manuscripts and all authors revised the entire manuscript critically and approved the final version for publication. The statistics was carried out by VS. FBW is guarantor for the study.

Data access:

All authors had access to and take responsibility for the data and analyses. Relevant anonymised data can be available on reasonable request.

Transparency declaration:

The corresponding author affirms, on behalf of all authors, that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

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Figure 1. Trial flow (ACOM study)

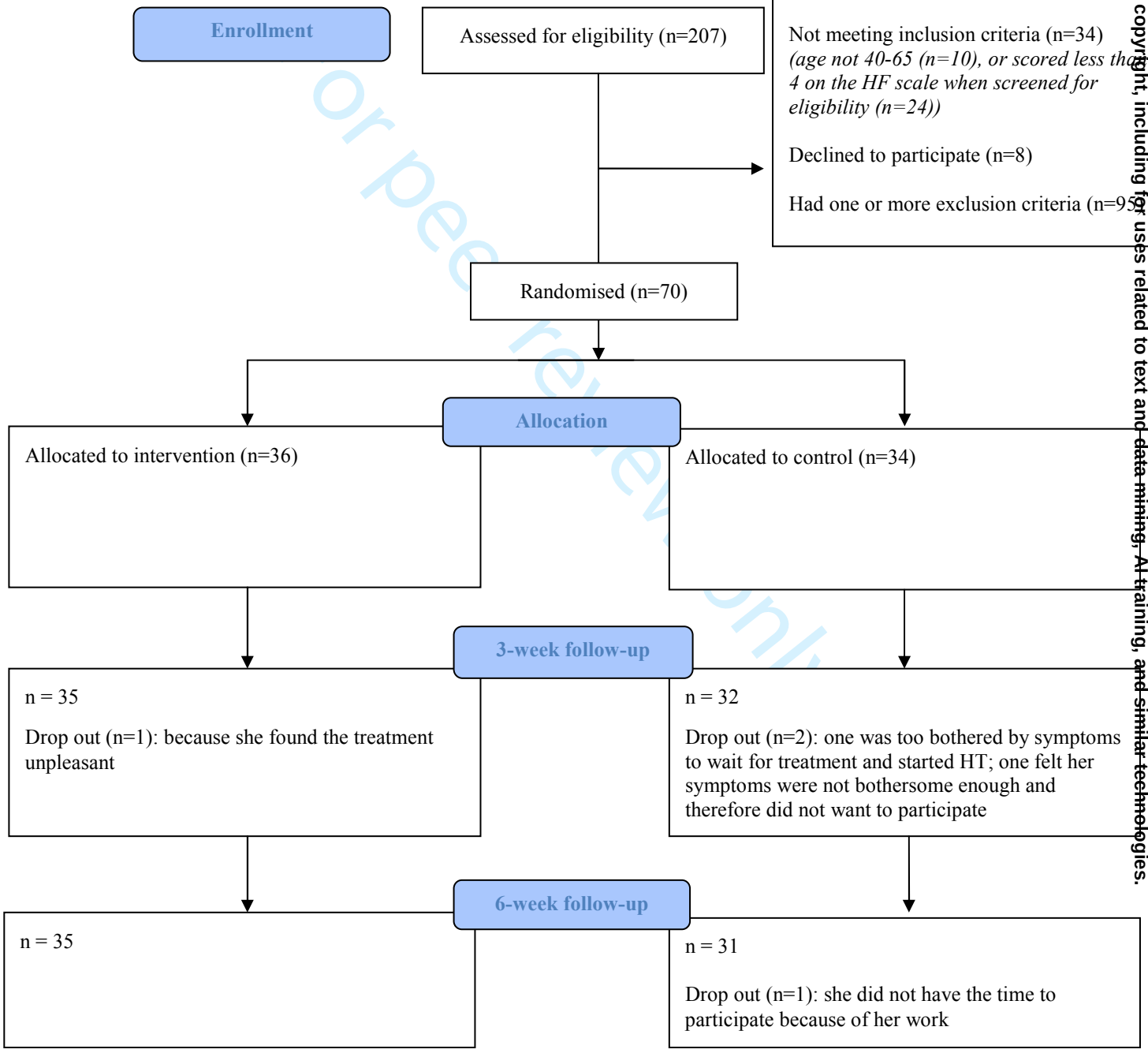


Figure 2: Development of the HF, DNS, GS, and MSSP scales over the study period

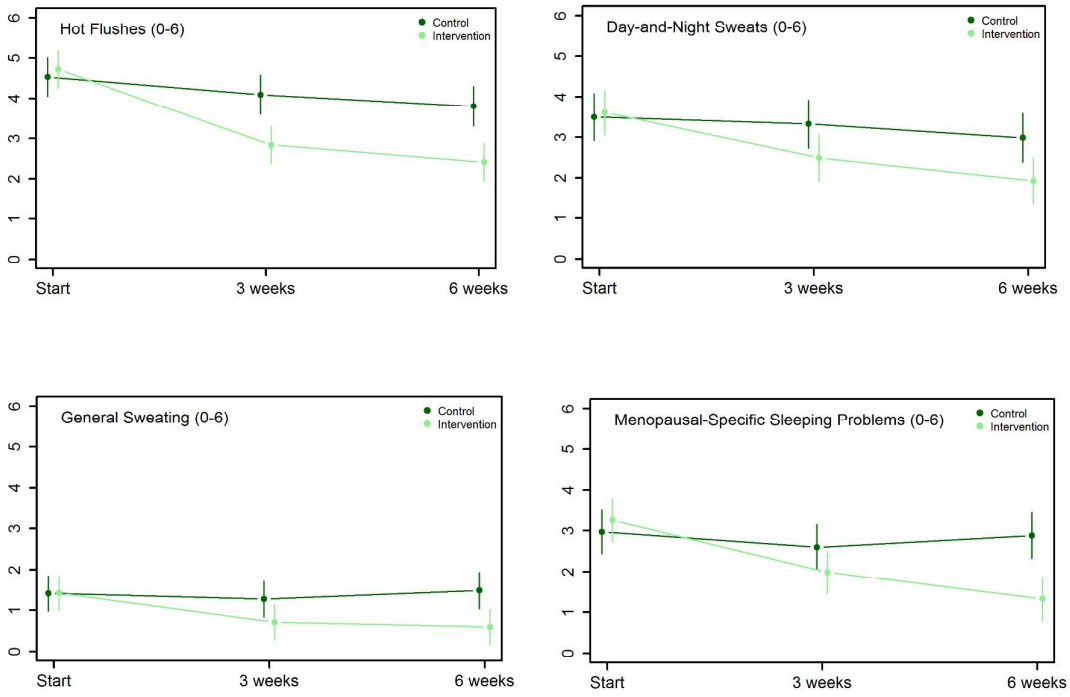
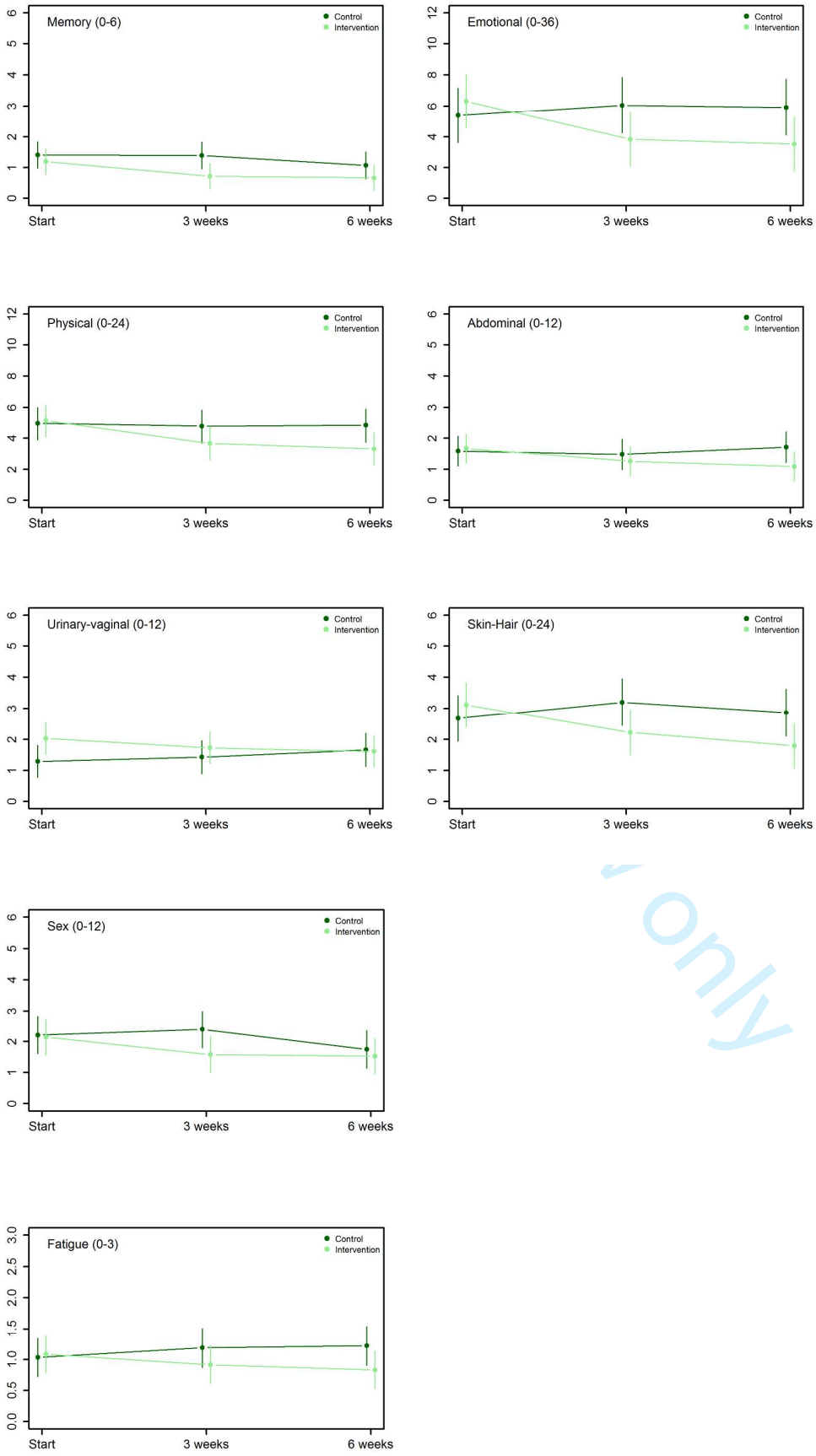


Figure 3. Development of the remaining MSQ scales and single item over the study period



Appendix 1: Outcome measure, The MenoScores Questionnaires (MSQ)

Outcome	MSQ (11 scales and 1 single item, in total 51 items)	Number of items	Scale score*
Primary outcome	Hot flushes (HF)	2	0-6
Secondary outcomes	Day and night sweats (DNS)	2	0-6
	General sweating (GS)	2	0-6
	Menopausal-specific sleeping problems (MSSP)	2	0-6
	Emotional (EM)	12	0-36
	Memory (MEM)	2	0-6
	Skin-hair (SH)	8	0-16
	Physical (PHY)	8	0-24
	Abdominal (ABD)	4	0-8
	Urinary and vaginal (URIN)	4	0-12
	Sexual (SEX)	4	0-8
	Single item about tiredness	1	0-3
After last acupuncture treatment	MSQ plus one item asking about the general effect		
* A higher scores denote more symptoms			

Appendix 2: Time schedule: Enrolment, interventions, and assessments.

STUDY PERIOD														
	Enrolment	**Allocation**	**Post allocation**											**Long term**
TIMEPOINT	***-t1***	**0**	***W*1***	***W2***	***W3***	***W4***	***W5***	***W6***	***W7***	***W8***	***W9***	***W10***	***W11***	***W26***
ENROLMENT:														
Eligibility screen	x													
Informed consent	x													
Eligibility screening questionnaire	x													
Allocation		x												
INTERVENTIONS:														
Intervention			x	x	x	x	x							
Control								x	x	x	x	x		
ASSESSMENTS**:**														
Eligibility screening questionnaire incl. HF scale	x													
Baseline data	x													
MSQ		x**			x			x***		x			x	x

*W1= Study week 1, W2 = Study week 2 and so on.

** MSQ is completed before allocation and first treatment.

*** Intervention group complete MSQ one week after final treatment (week 6). Control group complete MSQ before first treatment (week 6).

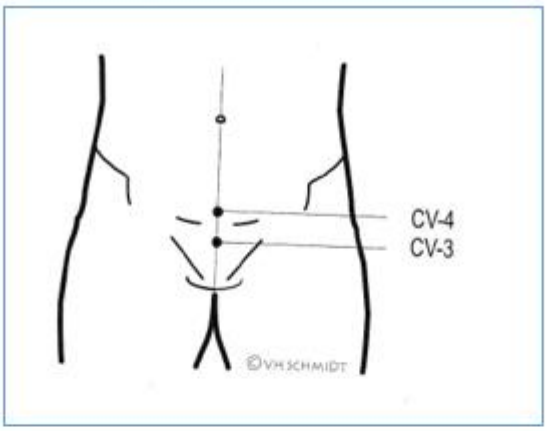
MSQ = MenoScores Questionnaire. HF scale = Hot flushes scale from MSQ.

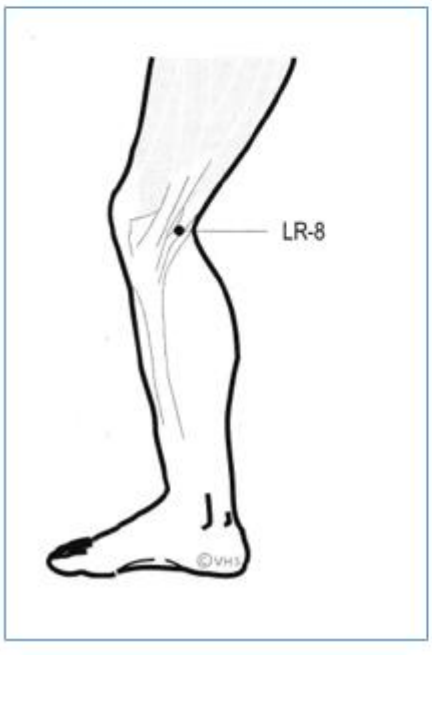
**** Intermediate assessment at week 3. Main comparison of primary outcome at week 6 before "cross-over". Assessment of legacy effect at week 11. Assessment of long-term effect at week 26.

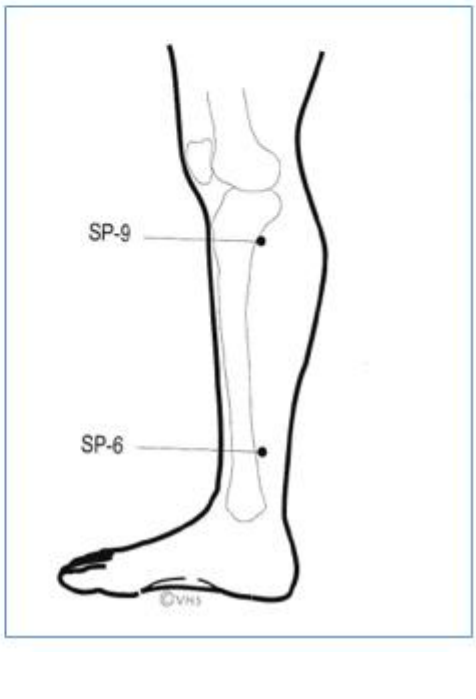
Appendix 3

Drawings are from the book "Akupunktur – på naturvidenskabeligt grundlag".

Permission to reproduce the drawings is given by the publisher Klim, and the book's author Palle Rosted







Appendix 4. Observed reduction in mean scores in the two randomisation groups at baseline and each of the follow-up time points

	Week 0					Week 3					Week 6				
	Control		Intervention			Control		Intervention			Control		Intervention		
	Mean (SD)	n	Mean (SD)	n	p-value	Mean (SD)	n	Mean (SD)	n	p-value	Mean (SD)	n	Mean (SD)	n	p-value
HF	4.53 (0.90)	34	4.72 (0.85)	36	0,3592	4.09 (1.30)	32	2.86 (1.59)	35	0,0009	3.84 (1.64)	31	2.43 (1.40)	35	0,0004
DNS	3.50 (1.56)	34	3.61 (1.95)	36	0,7925	3.34 (1.70)	32	2.51 (1.56)	35	0,0419	3.26 (1.91)	31	1.94 (1.55)	35	0,0120
GS	1.41 (1.43)	34	1.42 (1.25)	36	0,9879	1.28 (1.53)	32	0.71 (0.93)	35	0,0755	1.48 (1.69)	31	0.60 (0.81)	35	0,0112
MSSP	2.97 (1.40)	34	3.25 (1.30)	36	0,3906	2.59 (1.78)	32	2.00 (1.51)	35	0,1478	2.84 (1.82)	31	1.34 (1.47)	35	0,0003
EM	5.38 (5.22)	34	6.31 (6.11)	36	0,4983	5.94 (5.65)	32	3.80 (4.21)	35	0,0867	5.39 (5.69)	31	3.49 (4.67)	35	0,1281
MEM	1.41 (1.44)	34	1.19 (1.31)	36	0,5110	1.41 (1.54)	32	0.71 (1.10)	35	0,0406	1.10 (1.42)	31	0.66 (1.14)	35	0,1743
PHY	4.94 (3.56)	34	5.11 (4.03)	36	0,8521	4.78 (2.83)	32	3.66 (3.40)	35	0,1444	4.84 (3.72)	31	3.31 (2.78)	35	0,0672
URIN	1.29 (1.27)	34	2.03 (1.80)	36	0,0518	1.41 (1.41)	32	1.74 (1.87)	35	0,4061	1.81 (1.65)	31	1.63 (1.52)	35	0,9682
ABD	1.59 (1.67)	34	1.67 (1.49)	36	0,8370	1.50 (1.48)	32	1.26 (1.15)	35	0,4589	1.68 (1.99)	31	1.09 (1.22)	35	0,1581
SH	2.68 (2.07)	34	3.11 (2.59)	36	0,4400	3.28 (2.41)	32	2.26 (2.25)	35	0,0781	2.94 (2.62)	31	1.83 (1.64)	35	0,0480
SEX	2.23 (1.92)	26	2.19 (1.55)	27	0,9248	2.48 (1.85)	25	1.58 (1.58)	26	0,0676	1.91 (1.73)	23	1.54 (1.55)	28	0,8757
TR	1.03 (1.03)	34	1.08 (0.84)	36	0,8117	1.19 (0.97)	32	0.91 (1.02)	35	0,2620	1.19 (1.14)	31	0.83 (0.89)	35	0,1560

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Abstract p. 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract p. 1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p. 1
	2b	Specific objectives or hypotheses	p. 2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p. 2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	none
Participants	4a	Eligibility criteria for participants	p. 3
	4b	Settings and locations where the data were collected	p. 2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	p. 3 and 4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p. 4 and 5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	none
Sample size	7a	How sample size was determined	p. 5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p. 5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p. 5 and 6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p. 5 and 6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p. 5 and 6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p. 6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p. 6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p. 6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p. 7 and figure 1.
	13b	For each group, losses and exclusions after randomisation, together with reasons	p. 7 and figure 1.
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p. 3 and 7
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	p. 6 (ITT)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	p. 7 and 8, table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Figure 2. and 3., Appendix 4.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p. 8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p. 9 and 10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p. 9 and 12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p. 11 and 12
Other information			
Registration	23	Registration number and name of trial registry	Abstract and manus p. 12
Protocol	24	Where the full trial protocol can be accessed, if available	Reference 28, p. 12
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p. 12 and 13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Summary points

Without a complete published description of interventions, clinicians and patients cannot reliably implement effective interventions

The quality of description of interventions in publications, regardless of type of intervention, is remarkably poor

The Template for Intervention Description and Replication (TIDieR) checklist and guide has been developed to improve the completeness of reporting, and ultimately the replicability, of interventions

TIDieR can be used by authors to structure reports of their interventions, by reviewers and editors to assess completeness of descriptions, and by readers who want to use the information

Tables

Table 1| **Items included in the Template for Intervention Description and Replication (TIDieR) checklist: information to include when describing an intervention. Full version of checklist provides space for authors and reviewers to give location of the information (see appendix 3)**

Item No	Item
Brief name	
1	Provide the name or a phrase that describes the intervention Page 1
Why	
2	Describe any rationale, theory, or goal of the elements essential to the intervention Page 1
What	
3	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL) Page 2 and 3, reference 29
4	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities Page 3 and 4
Who provided	
5	For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given Page 2
How	
6	Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group Page 2,3 and 4
Where	
7	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features Page 2
When and How Much	
8	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose Page 3 and 4
Tailoring	
9	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how Page 3 and 4
Modifications	
10*	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how) Not applicable
How well	
11	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them Page 6 and 7
12*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned Page 7,8 and 9

*If checklist is completed for a protocol, these items are not relevant to protocol and cannot be described until study is complete.

BMJ Open

Efficacy of a standardised acupuncture approach for women with bothersome menopausal symptoms: a pragmatic randomised study in primary care (the ACOM study)

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Efficacy of a standardised acupuncture approach for women with bothersome menopausal symptoms: a pragmatic randomised study in primary care (the ACOM study)

Title	Efficacy of a standardised acupuncture approach for women with bothersome menopausal symptoms: a pragmatic randomised study in primary care (the ACOM study)
Authors' names	Kamma Sundgaard Lund (KSL), Volkert Siersma (VS), John Brodersen (JB), Frans Boch Waldorff (FBW)
	Kamma Sundgaard Lund, MD (**Corresponding author**)

Authors' names, positions and address	Section of General Practice, Department of Public Health, University of Copenhagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: kaml@sund.ku.dk Mobil: +45 22 99 38 82 Volkert Siersma, Statistician (PhD) The Research Unit of General Practice and Section of General Practice, Department of Public Health, University of Copenhagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: siersma@sund.ku.dk John Brodersen, Professor (GP, MD, PhD) Primary Health Care Research Unit, Region Zealand, Alleen 15, 4180 Sorø, Denmark, and Section of General Practice, Department of Public Health, University of Copenahagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: jobr@sund.ku.dk Frans Boch Waldorff, Professor (GP, MD, PhD), The Research Unit for General Practice, Department of Public Health, University of Southern Denmark J.B: Winsløws vej 9, 5000 Odense, Denmark Email: fwaldorff@health.sdu.dk
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ABSTRACT

Objective:

To investigate the efficacy of a standardised brief acupuncture approach for women with moderate-to-severe menopausal symptoms.

Design:

Randomised and controlled, with 1:1 allocation to the intervention group or the control group. The assessor and the statistician were blinded.

Setting:

Nine Danish primary care practices.

Participants:

70 women with moderate-to-severe menopausal symptoms and nine general practitioners with accredited education in acupuncture.

Intervention:

The acupuncture style was western medical with a standardised approach in the predefined acupuncture points CV-3, CV-4, LR-8, SP-6, and SP-9. The intervention group received one treatment for five consecutive weeks. The control group was offered treatment after six weeks.

Main outcome measures:

Outcomes were the differences between the randomisation groups in changes to mean scores using the scales in the MenoScores questionnaire, measured from baseline to week six. The primary outcome was the hot flushes scale; the secondary outcomes were the other scales in the questionnaire. All analyses were based on intention-to-treat analysis.

Results:

36 participants received the intervention and 34 were in the control group. Four participants dropped out before week six. The acupuncture intervention significantly decreased hot flushes: Δ -1.6 (95% CI (-2.3 to -0.8); p<0.0001), day-and-night-sweats: Δ -1.2 (95% CI (-2.0 to -0.4); p=0.0056), general sweating: Δ -0.9 (95% CI (-1.6 to -0.2); p=0.0086), menopausal-specific sleeping problems: Δ -1.8 (95% CI (-2.7 to -1.0); p<0.0001), emotional symptoms: Δ -3.4 (95% CI (-5.3 to -1.4); p=0.0008); physical symptoms: Δ -1.7 (95% CI (-3 to -0.4); p=0.010) and skin and hair symptoms: Δ -1.5 (95% CI (-2.5 to -0.6); p=0.0021) compared to the control group at the six-week follow-up. The pattern of decrease in hot flushes, emotional symptoms, skin and hair symptoms was already apparent three weeks into the study. Mild potential adverse effects were reported by four participants but no severe adverse effects were reported.

Trial registration:

ClinicalTrials.gov NCT02746497.

ARTICLE SUMMARY

Strengths and limitations of this study:

- This study has high methodological quality, allocation concealment, adequate power, a validated outcome measure, sufficient and transparent reporting leading to high external validity.
- The study had high participants adherence supporting that the intervention was manageable and well tolerated.
- Since the intervention was pragmatic, standardised and brief the applicability of the findings is high and might have a good chance of being implemented which could lead to new treatment options for menopausal women.
- At present no sufficient acupuncture placebo comparator exist which is a major limitation in acupuncture studies, this study included.

INTRODUCTION

Experience of menopausal symptoms is very common and has been shown to affect quality of life, health status, work productivity, and use of health services (1-3). The majority of women experience menopause in their early fifties (4) and have menopausal symptoms for four to five years on average (4-7). The most prominent symptom of menopause is hot flushes which affects around 75% of menopausal women (5, 6, 8) and is reported as very distressing by 10-20% (5). Other reported menopausal symptoms are night sweats, emotional vulnerability, sleep disturbances, fatigue, cognitive changes, joint pain, vaginal dryness, and loss of sexual desire (4, 5, 9).

Hormone therapy (HT) relieves menopausal symptoms (10, 11) but long-term HT is associated with an increased risk of breast cancer and thromboembolic disorders (11-14). Hence, many menopausal women avoid HT. Non-hormonal-based treatments such as clonidine, gabapentin, and antidepressants may also reduce menopausal symptoms. However, these drugs have frequent adverse effects such as sleep disturbance, dizziness, nausea, fatigue, dry mouth, and constipation (4, 5, 8, 15, 16). Non-pharmaceutical treatments, e.g. relaxation, exercise, herbal remedies, and diets containing phytoestrogens have been suggested, although there is a lack of knowledge about dose, duration, and, for herbal remedies and phytoestrogens, drug interactions and adverse effects. There is currently no convincing evidence of any beneficial effect from these treatments (4, 8, 15-17).

Several studies have demonstrated the effects of acupuncture on menopausal symptoms (15, 18-20), but they have been criticised for methodological limitations, e.g. poor design, inadequate sample size, inadequate control or placebo groups, absence of standardised protocols, and a lack of data on adverse effects (18, 19). Furthermore, due to different methods and a lack of validation of some outcome measures, comparison of results is difficult (18, 19). Therefore, further high-quality randomised acupuncture trials are needed (18, 19). Although the use of acupuncture differs between countries, it is sought by many patients (21-24) and practiced by a substantial number of physicians, especially general practitioners (GPs) (22, 25-27). If a clinically relevant effect on menopausal symptoms from acupuncture is demonstrated, this treatment may be considered for implementation in primary healthcare, leading to new options for menopausal women who cannot or do not wish to use HT.

We hypothesised that a brief and standardised acupuncture treatment could reduce moderate-to-severe menopausal symptoms and, in particular, it could have a clinically relevant effect in the reduction of hot flushes. Therefore, the objective of this study was to investigate the efficacy of a standardised brief acupuncture approach for women with

moderate-to-severe menopausal symptoms; primarily the efficacy on hot flushes measured as change from baseline to week six.

METHOD

Trial design:

The study was a randomised controlled trial (RCT) with a 1:1 allocation to the intervention or the control group. A detailed description of the methods used in the present study are found in the published protocol (28).

Settings and acupuncturists:

The study took place in nine primary care practices in both urban and rural settings. The acupuncturists were nine GPs and all but one were educated in acupuncture by the Danish Society for Evidence-based Acupuncture (DSEA) or the Danish Medical Acupuncture Society (DMAS). One GP had acupuncture training in Sri Lanka before DSEA and DMAS were formed. Participating GPs had, on average, 153 hours of acupuncture education (range 80 to 300), and had practiced acupuncture for 14 years (range 4 to 38).

The first author (KSL) held an individual meeting with each of the GP acupuncturists and provided them with the study protocol, an overview of the predefined acupuncture points, and a written manual with precise instructions for treatment. KSL asked the GP acupuncturists to behave neutrally and to provide only the specified acupuncture treatment and no other treatment or counselling. A two-and-a-half hour refresher course on the predefined acupuncture points and techniques was offered, and four GPs attended this course.

Participants:

Women were recruited through local newspapers, general practices close to the participating GP acupuncturist, the DSEA, and the DMAS. Recruitment took place between late September 2016 and mid December 2016.

Inclusion criteria: women aged 40-65 years with moderate-to-severe hot flushes (score ≥4 on a validated scale measuring hot flushes (MenoScores questionnaire (29) and Appendix 1), intact cognitive function, and a valid e-mail address. Before enrolment participants gave written informed consent. *Exclusion criteria*: women who had had a hysterectomy and/or bilateral oophorectomy; women whose alcohol consumption exceeded 21 drinks per week; who used prescribed sleeping pills and/or prescribed sedatives; who had previously been diagnosed with breast, endometrial, cervical, or ovarian cancer; who had been diagnosed with other severe cancer disease within the past 5 years; who had heart valve disease; who were insulin dependent and/or had poorly controlled diabetes mellitus; who were diagnosed with thyroid disease; who were under investigation for serious disease e.g. cancer; who had received acupuncture treatment within the past 6 months; who had been pregnant or had been breast-feeding within the past two years; who were participating in another trial or had participated in another trial in the two weeks before screening for eligibility; who within the past four weeks had used one or more of the following treatments: systemic HT, hormonal intrauterine device, antidepressants and/or antiepileptics; who had received other medical treatment for hot flushes (e.g. clonidine), herbal remedies/alternative treatments for menopausal symptom, or corticosteroids (the use of inhaled steroids was not an exclusion criterion).

Enrolled participants were provided with oral and written information about the study (30). Participation was voluntary and there was no payment for taking part. Participants could withdraw their consent at any time. The first author carried out assessment of eligibility, obtained informed consent, and collected baseline characteristic data.

Intervention:

All participants were offered one treatment per week for five weeks by a GP acupuncturist in their local area. The intervention group received their treatment in the first five weeks after enrolment in the study. At present, no validated acupuncture placebo comparator exists (31, 32) and we decided to use a control group instead. The control group received their treatment after six weeks. Hence, this RCT is evaluated over a six-week study period (Appendix 2. Time schedule). No other treatment (medicine or alternative remedies) for menopausal symptoms was allowed in any of the groups beginning four weeks prior to enrolment until study week 11. The acupuncture style we used was western medical acupuncture, (WMA) (32, 33), with a standardised approach and predefined acupuncture points (Table 1 and Appendix 3), based on reports from experienced western medical acupuncturists (34).

A complete acupuncture session should not last more than 15 minutes, including insertion of needles, retention time, removal of needles, and documentation. Disposable sterile (Plandent) needles, size 0,30 x 30 mm, were inserted perpendicularly and rotated manually for a few seconds to elicit "de-qi" (needle sensation, a feeling of heaviness around the acupuncture point) (33). The predefined points were CV-3, CV-4, LR-8, SP-6, SP-9 (Table 1). A total of eight points was used, as LR-8, SP-6 and SP-9 were given bilaterally. Needle retention time was 10 minutes.

After each treatment, the GP acupuncturist completed a documentation scheme with the date, documentation for insertion of each of the needles, and whether "de-qi" was obtained. After the final treatment, the completed documentation was sent to the first author.

TABLE 1. Acupuncture points and location

CV-3	Anterior midline, 1 cun* proximal to the symphysis. Insertion depth; perpendicularly 0.5-1 cm.
CV-4	Anterior midline, 1 cun proximal to CV-3 and 3 cun inferior to the umbilicus. Insertion depth; perpendicularly 0.5-1 cm.
LR-8	Medial side of the knee, in the depression anterior/medial to the tendons of semimembranosus and the semitendinosus muscles, at the medial end of the popliteal crease. Insertion depth; perpendicularly 1.5-2 cm.
SP-9	Under the medial condyle of tibia in a depression between the posterior tibia and m. gastrocnemius. Insertion depth; perpendicularly 2-3 cm.
SP-6	3 cun proximal to the prominent part of the medial malleoli, on the medial and posterior border of the tibia. Insertion depth; perpendicularly 1-3 cm.

*A cun is an acupuncture measurement unit. 1 cun corresponds to the width of the study subject's thumb.

Outcome:

The study's outcomes were the differences between the randomisation groups in the mean change over the six-week study period measured in the scales of the MenoScores Questionnaire (MSQ) (29). The MSQ is a content-specific patient-reported outcome measure (PROM) with high content validity and adequate psychometric properties measuring bothersome menopausal symptoms. The MSQ encompasses 11 scales and one single item (51 items in total), measuring

different menopausal domains of bothersome symptoms (Appendix 1). The MSQ scales are constructed such that higher scores denote more bothersome symptoms.

The primary outcome was the hot flushes (HF) scale, secondary outcomes were the remaining MSQ scales: day-and-night sweats (DNS), general sweating (GS), menopausal-specific sleeping problems (MSSP), emotional symptoms (EM), memory changes (MEM), skin and hair symptoms (SH), physical symptoms (PHY), abdominal symptoms (ABD), urinary and vaginal symptoms (URIN), sexual symptoms (SEX), and the single item tiredness (TR).

Of these MSQ scales, the HF, DNS, GS, and MSSP scales are most related to menopause, while the other MSQ scales are more related to general aging or other life events (29).

Assessments and follow-up:

All participants received the MSQ by e-mail in study weeks zero, three, six, eight, eleven, and twenty-six (Appendix 2). Week zero (before randomisation), week three (intermediate assessment), and week six (final assessment) are reported in the present manuscript. In the period when participants were receiving acupuncture treatment, we asked them to complete the MSQ 1-2 days before the third treatment and one week after the fifth and last treatment (Appendix 2). Participants completed and returned the MSQ electronically. Reminders were sent within 1-2 days, if the participant did not return a completed MSQ within the scheduled time. Additionally, participants in the intervention group were asked about adverse effects at the three- and six-week follow-up. After the final treatment we asked the intervention group if, in general, they had experienced a beneficial effect from the acupuncture treatment.

Sample size:

The necessary sample size for the RCT was determined from reports on the primary outcome HF and the two secondary outcome DNS and MSSP in the MSQ validation study (29). We considered a reduction in a scale score as clinically relevant if it corresponded to a reduction from “a lot” to “quite a bit” on a global item regarding whether the respondent was bothered by menopausal symptoms. In the MSQ validation study, women who were bothered “a lot” had a mean score of 4.98 on the HF scale, and women who were bothered “quite a bit” had a mean score of 3.48 on the HF scale. Both groups with a standard deviation (SD) around 1.4. To detect such a reduction on the HF scale with 90% power,

5% level of significance, and accounting for 20% dropouts, we needed to include 48 participants (24 participants in each group). To achieve a similar power on the DNS and MSSP scales, we needed 56 and 68 participants, respectively.

Randomisation:

The allocation sequence was computer generated using SAS software (v 9.4, SAS institute, Cary, NC, USA) and kept by a person independent of the project organisation (affiliated to the Centre for Health Economic Research, University of Southern Denmark). After enrolment, the independent person allocated the participants to one of the two randomisation groups. The participants were subsequently referred to the acupuncturist. This process ensured that allocation could not be guessed or later changed, thereby securing allocation concealment. Randomisation was done in blocks, with random block sizes, and stratified by age (aged 40-55 or 56-65 years) and level of symptoms (experiencing hot flushes "quite a bit" or "a lot").

Statistical methods:

For each of the primary and secondary outcomes, the up to three assessments for each woman were modelled with a linear mixed model with a level for each time point for each randomisation group; the inherent correlation between observations on the same woman was accounted for by the inclusion of a subject-random effect. The effect of the intervention was estimated at week 3 and week 6 by the mean difference of the outcome beyond the difference already present at baseline and assessed by the appropriate Wald test in the model. The model additionally included as covariates the dichotomisations used in the stratification of the randomisation: age and level of symptoms. Four or more treatments were considered adequate adherence. The statistical significance was assessed controlling for the false discovery rate at 5% with the method of Benjamini and Hochberg (35). SAS v9.4 was used for the analyses.

Blinding:

Statistician and outcome assessors were blinded until all analyses were completed. Participants and acupuncturist were not blinded.

Patient involvement:

In the development of the research question, and in the design of the study, the development and content validity of the outcome measure (MSQ) was ensured by qualitative interviews with women who experienced bothersome menopausal symptoms (29). During this process, the relevance of this present study was also confirmed. Patients were not involved in the recruitment or conduction of the study. The burden of intervention was not assessed by the participants. When results are published they will be disseminated to the Danish College of General Practitioners, the DSEA, the DMAS, the project research homepage (30), local newspaper and Danish women's lifestyle magazines.

RESULTS

We interviewed 207 women for eligibility, of which 70 met the inclusion criteria and were enrolled over a three-month period: we allocated 36 participants to the intervention group, and 34 to the control group. The number of participants treated by a single acupuncturist ranged from minimum one to maximum 16 (including the delayed treatment of the control group). No markedly differences in baseline characteristics between the randomisation groups were identified (Table 2). Inspection of the residuals of the models did not reveal serious variance heterogeneity. Inspection of Cook's D did not reveal subjects that were particularly influential to the results. Four participants dropped out: one in the intervention group and three in the control group (Figure 1). The MSQ response rate was 100% for all remaining participants at all assessments points. The adherence to treatment was very high: 34 out of 36 received all five planned acupuncture treatments, and one received four out of five treatments. We collected primary data between October 2016 and February 2017.

TABLE 2. Baseline characteristics for each group of women	Control (n=34)	Intervention (n=36)
Age (years), *mean (SD)*	54.1 (5)	55.3 (4)
Age, *n (%)*		
40-55 years	13 (38)	17 (47)
56-65 years	21 (62)	19 (53)
Employment, *n (%)*		

Employed	31 (91)	32 (89)
Unemployed	3 (9)	4 (11)
Education, *n (%)*		
Vocational	8 (24)	8 (22)
Short (<3 years)	4 (12)	3 (8)
Long (≥3 years)	16 (47)	22 (61)
Other	6 (18)	3 (8)
Household, *n (%)*		
Living alone	1 (3)	5 (14)
Living with others	33 (97)	31 (86)
Physical activity, *n (%)*		
No physical activity	7 (21)	3 (8)
1-3 times per week	20 (59)	23 (64)
≥4 times per week	7 (21)	10 (28)
Smoking, *n (%)*		
Yes	1 (3)	2 (6)
No	33 (97)	34 (94)
Alcohol, *n (%)*		
No alcohol	1 (3)	8 (22)
≤14 units per week	29 (85)	19 (53)
>14 units per week	4 (12)	9 (25)
BMI (kg/m^2), *mean (SD)*	25.5 (5)	24.9 (3)
Menstruation in the last year, *n (%)*		
Yes	7 (21)	11 (31)
No	27 (79)	25 (69)
Number of births, *n (%)*		
None	3 (9)	2 (6)
One	5 (15)	8 (22)
Two	20 (59)	18 (50)
More than two	6 (18)	8 (22)
Incontinentia, *n (%)*		
No	13 (38)	10 (28)
Yes	21 (62)	26 (72)
Chronic disease, *n (%)*		
Yes	5 (15)	8 (22)
No	29 (85)	28 (78)
Previous experience with alternative treatment, *n (%)*		
No	8 (24)	10 (28)
Yes	26 (77)	26 (72)
Duration of hot flushes (years), *mean (SD)*	3.41 (3)	4.59 (4)
Hot Flushes, *n (%)*		
HF=4	20 (59)	15 (42)
HF>4	14 (41)	21 (58)

FIGURE 1. Trial flow

The analyses of the observed raw scores demonstrated generally lower means in the intervention group compared to the control group when followed up (Appendix 4).

The developments in the MSQ scales across the two randomisation groups over the study period are presented in Figures 2 and 3.

FIGURE 2: Development of the HF, DNS, GS, and MSSP scales over the study period

FIGURE 3: Development of the remaining (EM, MEM, SH, PHY, ABD, URIN, SEX) MSQ scales and the single item over the study period.

Primary outcome:

The intervention group was significantly less bothered by hot flushes at six weeks: Δ -1.6 (95% CI (-2.3 to -0.8); p<0.0001). This difference was also statistically significant at three weeks: Δ -1.5 (95% CI (-2.2 to -0.7); p=0.0002). (Table 3).

Secondary outcomes:

Statistically significant differences were identified at six weeks in the following secondary outcomes: DNS: Δ -1.2 (95% CI (-2.0 to -0.4); p=0.0056); GS: Δ -0.9 (95% CI (-1.6 to -0.2) p=0.0086); MSSP: Δ -1.8 (95% CI (-2.7 to -1.0); p<0.0001); EM: Δ -3.4 (95% CI (-5.3 to -1.4); p=0.0008); PHY: Δ -1.7 (95% CI (-3 to -0.4); p=0.010) and SH Δ -1.5 (95% CI (-2.5 to -0.6); p=0.0021) (Table 3). This difference was also statistically significant at three weeks in EM: Δ -3.2 (95% CI (-5.1 to -1.2); p=0.0015) and SH: Δ -1.4 (95% CI (-2.4 to -0.5); p=0.0036) (Table 3).

Table 3: Differences in means, primary and secondary outcomes

Differences in mean scores between the randomization groups at each of the follow-up time points.

	Week 0 (baseline)[1]	Week 3[2]		Week 6[2]	
	Δ (95%CI)	Δ (95%CI)	p-value	Δ (95%CI)	p-value
Hot flushes (HF)	0.1 (-0.6; 0.7)	-1.5 (-2.2; -0.7)	0.0002*	-1.6 (-2.3; -0.8)	<.0001*
Day-and-night sweats (DNS)	0.0 (-0.9; 0.8)	-1 (-1.8; -0.1)	0.024	-1.2 (-2.0;-0.4)	0.0056*
General sweating (GS)	0.0 (-0.6; 0.6)	-0.6 (-1.3; 0.1)	0.091	-0.9 (-1.6; -0.2)	0.0086*
Menopausal-specific sleeping problems (MSSP)	0.2 (-0.5; 1)	-0.9 (-1.7;- 0.1)	0.033	-1.8 (-2.7; -1.0)	<.0001*
Emotional symptoms (EM)	1.0 (-1.5; 3.5)	-3.2 (-5.1; -1.2)	0.0015*	-3.4 (-5.3; -1.4)	0.0008*
Memory changes (MEM)	-0.2 (-0.8; 0.4)	-0.5 (-1.0; 0.1)	0.11	-0.2 (-0.8; 0.1)	0.49
Physical symptoms (PHY)	0.1 (-1.5; 1.6)	-1.3 (-2.6;- 0.0)	0.049	-1.7 (-3; -0.4)	0.010*
Urinary and vaginal symptoms (URIN)	0.8 (0.1; 1.5)	-0.4 (-1.1; 0.3)	0.21	-0.8 (-1.5; -0.1)	0.025
Abdominal symptoms (ABD)	0.1 (-0.6; 0.8)	-0.3 (-1; 0.4)	0.38	-0.7 (-1.4; 0.0)	0.042
Skin and hair symptoms (SH)	0.3 (-0.7; 1.4)	-1.4 (-2.4; -0.5)	0.0036*	-1.5 (-2.5; -0.6)	0.0021*
sexual symptoms (SEX)	-0.2 (-1; 0.7)	-0.7 (-1.4; -0.1)	0.032	-0.3 (-0.8; 0.5)	0.69
Tiredness (TR)	0.1 (-0.3; 0.5)	-0.3 (-0.8; 0.1)	0.15	-0.5 (-0.9; 0.0)	0.049

[1]Difference in mean score of intervention relative to control, adjusted for stratification factors (age and level of symptoms ("quite a bit" or "a lot" HF))

[2]Difference in mean score of intervention relative control beyond the difference already present at Week 0 (baseline), adjusted for stratification factors (age and level of symptoms ("quite a bit" or "a lot" HF))

*Significant at a 0.01 level to control for the false discovery rate at 0.05

Negative values Δ = less symptoms in the intervention group

In the intervention group, 80% of participants reported a general beneficial treatment effect after six weeks.

Harms and adverse events:

No serious harms or adverse events were reported in the intervention group. Four participants reported mild potential adverse effects: one experienced tiredness and headache after treatment; another experienced more hot flushes in some of the weeks, but reported this to be associated with increased stress in her personal and professional life; one had to urinate more frequently; and one experienced tingling in the leg where the needle had been placed.

Beside the four participants who reported mild potential adverse effects one participant dropped out because she found the needling unpleasant (Figure 1). However, this was not unexpected as acupuncture needling in some cases is experienced as a bit unpleasant (needles are inserted into the body which might be a bit unpleasant).

DISCUSSION

Principal findings:

The standardised acupuncture treatment used in the present study reduced the HF, DNS, GS, MSSP, EM, PHY and SH scales after five weekly treatments, and the HF, EM and SH scales was reduced after two acupuncture treatments. The intervention did not significantly reduce the remaining MSQ scales, but we did also not expect to see this because this study was underpowered regarding these scales. Additionally, since significant reductions were only found in some of the scales, our findings emphasise that the intervention was targeted to menopausal symptoms and are not an artefact of general care. The acupuncture treatment was well tolerated: one participant dropped out and only four participants reported mild potential adverse effects. No serious harms were reported.

Strengths and weaknesses of the study:

The intervention period was relatively brief. However, it served to test a pragmatic, standardised, and brief acupuncture approach manageable by both GPs and participants. Therefore, the suitability of the treatment outlined in this study in day-to-day primary care is high. The study had very high participant adherence: only four out of 70 participants dropped out. The remaining participants fulfilled the criteria for adequate treatment adherence, and had a 100% MSQ response

rate, demonstrating that the intervention was well tolerated. The fact that the control group was also offered treatment after six weeks probably contributed to the high adherence rate. Finally, all participants were offered the same intervention, and co-interventions for menopausal symptoms were not allowed in the study period, thereby reducing the risk of performance bias.

Another strength in this study was the use of a condition-specific PROM (MSQ) with high content validity and adequate psychometric properties ensuring high construct validity of the study measurements. Moreover, data from the MSQ validation study (29) was used to generate the power calculation based on relevant clinical effects which ensured adequate sample size. We did not use a physiological measurement e.g. skin conductance or temperature (which would probably have been technically difficult) because we believe PROMs are the most appropriate method to obtain information on participants' own perception of their symptoms (36). The recall time frame in this study was one week which reduced the risk of recall bias.

The placebo effect plays an important role in all interventional studies and is influenced by expectations and beliefs. All GPs were certified acupuncturists and although they were instructed to behave neutrally, their beliefs in acupuncture could have affected their interaction with the participants and possibly have intensified a placebo effect. However, correct acupuncture techniques requires extensive training and using GPs without such training would have been wrong and misleading. In addition, all participants were volunteers with presumably expectations of a beneficial effect. This might have enhanced the placebo effect in the intervention group and could have caused a nocebo effect in the control group. However, we did not see such deterioration in the control group. In fact, the control group showed a trend of improvement, in particular in the HF scale, which may be explained by a regression to the mean. The lack of a sufficient acupuncture placebo comparator is a major limitation in acupuncture studies, including this study. In WMA theories, sham (placebo) acupuncture is not perceived as inactive but rather another, although less effective, form of needling (31, 32). Furthermore, a meta-analysis concluded that non-specific effects associated with sham acupuncture are often moderately large and might be larger than other placebo interventions (37). If sham is not inactive, a study testing sham versus real acupuncture is not a placebo controlled study but rather a study testing two different types of acupuncture. Therefore, we decided to investigate the impact of acupuncture versus no treatment. An important weakness of the present study is that the identified positive effects from acupuncture treatment could be caused by a placebo effect and not a specific physiological effect of needling. However, our aim was not to distinguish between specific and non-specific effects of needling, but to investigate the impact of acupuncture versus no treatment. We

found that the acupuncture treatment used in this study had an important clinical effect. If we ignore these findings, due to a lack of knowledge about possible specific effects of acupuncture, women with moderate-to-severe menopausal symptoms could miss out on a low cost and effective treatment with only minor potential adverse effects.

One final limitation was that blinding of acupuncturists and participants in this study design was not possible. However, we secured blinding of the statistician and outcome assessors until all analyses were completed.

Comparison with other studies:

Some previous studies have demonstrated real acupuncture to be significantly superior to sham acupuncture (38-40). However, a Cochrane review from 2013 regarding acupuncture for menopausal hot flushes, found no significant differences between real acupuncture compared to sham, but a beneficial effect of acupuncture compared to no treatment, and that acupuncture was inferior to HT. The evidence was in general of poor quality, and further high quality studies were recommended (18). Results from two recent studies, one comparing real acupuncture with sham (41) and one comparing acupuncture with no treatment (42), confirm the findings reported in the Cochrane review.

The present study demonstrates that acupuncture is significantly superior to no treatment. Our study was based on WMA theories while most previous studies were based on traditional Chinese medicine (TCM) theories and diagnoses (18, 21, 38-46) involving the concepts of yin/yang and circulation of qi (32, 33). Most previous studies had longer intervention periods and/or more treatment sessions (21, 39-50) and several studies used individualised treatment with variation in the selection of acupuncture points (21, 40, 42, 43, 46). Tailored treatments might be a truer reflection of the actual clinical context. However, in an RCT, we believe that treatment should be standardised so that the intervention can be replicated. Some studies differ from this study by including patients treated for breast cancer (38, 39, 44, 45), which makes it difficult to compare results. In contrary to our study, some studies allowed other co-interventions (e.g. adjuvant anti-hormone therapy, cystostaticum, clonidine, antidepressants, HT, or other alternative remedies) (21, 38, 39, 41, 42, 44) which might have affected their outcomes. Finally, some studies assessed other relevant secondary outcomes such as quality of life, hot flush interference, sleep quality, and one study also assessed plasma oestradiol. Most studies used self-reported outcomes but in several of them the validation of the outcome measures was lacking, unclear, or not reported (38, 39, 44, 45). We did not use a quality of life measure, because we did not find a Rasch validated quality of life instrument for our target group. The MSQ validation ensured that all aspects considered important by menopausal women themselves were covered by the MSQ scales. We would expect that a

reduction in the HF, DNS, GS, MSSP, EM, PHY and SH scales may ultimately have a positive indirect impact on a menopausal woman's overall sense of well-being and quality of life. To our knowledge, this study is the only one to use a PROM that is condition-specific with high-content validity and psychometrically Rasch validated.

Meaning of the study: possible explanations and implications for clinicians and policymakers:

The lack of a proper acupuncture placebo comparator has major implications for conducting and interpreting acupuncture studies. Therefore, we need to continue the discussion about what level of evidence should be accepted as sufficient for a treatment to be considered effective. This is particularly the case when we cannot accurately explain the underlying mechanism behind the treatment, nor determine how much of the effect is caused by placebo. In addition, it is important to note that in the present study the intervention was targeted at menopausal symptoms, and subsequently demonstrated a targeted effect, not an improvement across all symptoms. We also need to take the balance between benefits and harms into consideration. There is strong evidence that acupuncture for menopausal symptoms is without serious harms. Thus, requirements for evidence of the efficacy of acupuncture treatment might be less rigorous. On the contrary, acupuncture treatment in a private setting (i.e. outside a publicly funded health care system) might involve considerable personal expense and opportunity costs.

We consider the intervention in this study to be low cost, both to the individual and to the health system, but this needs to be further investigated and included in a discussion of value-based healthcare (51).

Future research:

The long-term effect, the characteristics of women who benefit from acupuncture treatment, cost-effectiveness, the underlying mechanism of needling, and the impact of placebo need further investigation.

CONCLUSION

A standardized acupuncture treatment gives women suffering from moderate-to-severe menopausal symptoms a clinically relevant reduction in hot flushes, day-and-night sweats, general sweating, menopausal-specific sleeping problems, emotional symptoms, physical symptoms and skin and hair symptoms. Acupuncture for menopausal

symptoms is a realistic option for women who cannot or do not wish to use HT. Women seeking acupuncture treatment for menopausal symptoms should be informed of the current evidence, and its limitations, so they can integrate this with personal preferences and values in their decision-making. This study has high methodological quality, adequate power, a validated outcome measure, and sufficient reporting leading to high validity of the study and findings. Furthermore, this study use a pragmatic, standardised, and brief intervention which leads to findings that may have a higher chance of being implemented and thereby are more likely to lead to new treatment options for menopausal women.

OTHER INFORMATION

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Registration:

ClinicalTrials.gov NCT02746497.

Ethical approval:

Approvals from the Committees on Health Research Ethics (H-16016365), the Committee of Multipractice Studies in General Practice (MPU 08-2016) and the Danish Data Protection Agency (SUND-2016-24) were obtained before enrolment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (ICH GCP).

Protocol:

Please refer to (28) for full trial protocol.

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Competing interests:

All authors have completed the ICMJE uniform disclosure form and declare no support from any organisation for the submitted work, no financial relationship with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could have appeared to have influenced the submitted work.

Contributor and guarantor information:

Frans Boch Waldorff (FBW) conceived the idea. Frans Boch Waldroff (FBW), Volkert Seirsma (VS), John Brodersen (JB) and Kamma Sundgaard Lund (KSL) all took part in the design and planning of the study. Kamma Sundgaard Lund conducted the study supported by Frans Boch Waldroff, Volkert Seirsma and John Brodersen. Kamma Sundgaard Lund drafted the manuscripts and Frans Boch Waldroff, Volkert Seirsma and John Brodersen revised the entire manuscript critically and approved the final version for publication. The statistics was carried out by Volkert Siersma. Frans Boch Waldorff is guarantor for the study.

Data access:

All authors had access to and take responsibility for the data and analyses. Relevant anonymised data can be available on reasonable request.

Transparency declaration:

The corresponding author affirms, on behalf of all authors, that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

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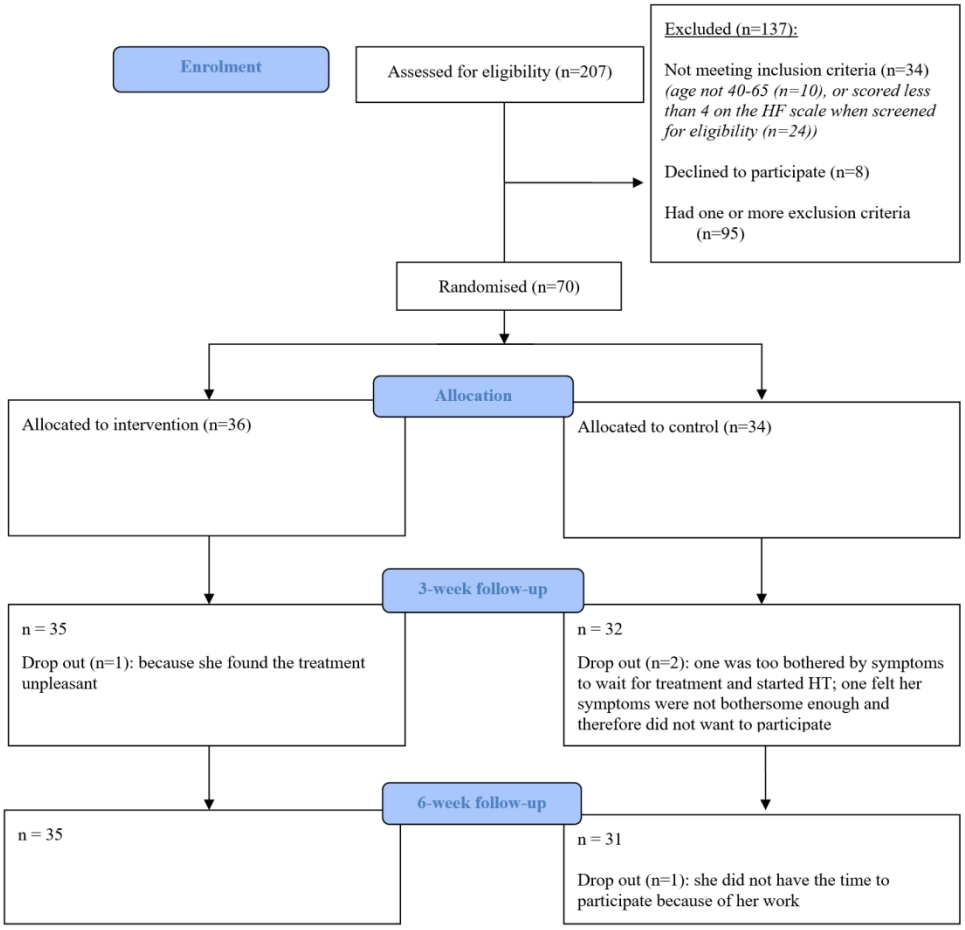

Figure 1. Trial Flow

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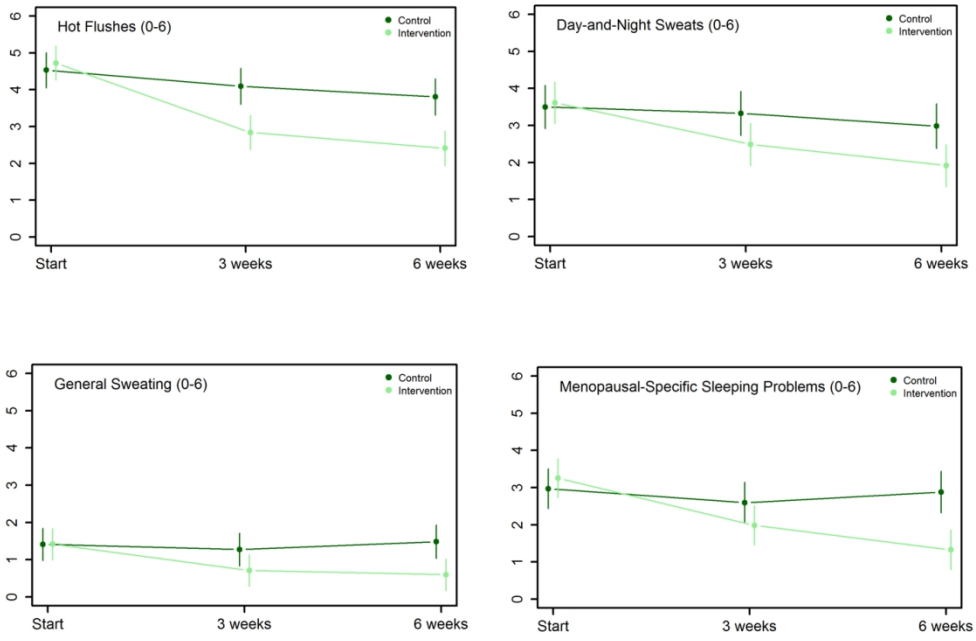


Figure 2. Development of the HF, DNS, GS, and MSSP scales over the study period. The error bars denote the 95% confidence interval of the estimate of the outcome means for each randomization group for each time point.

123x95mm (300 x 300 DPI)

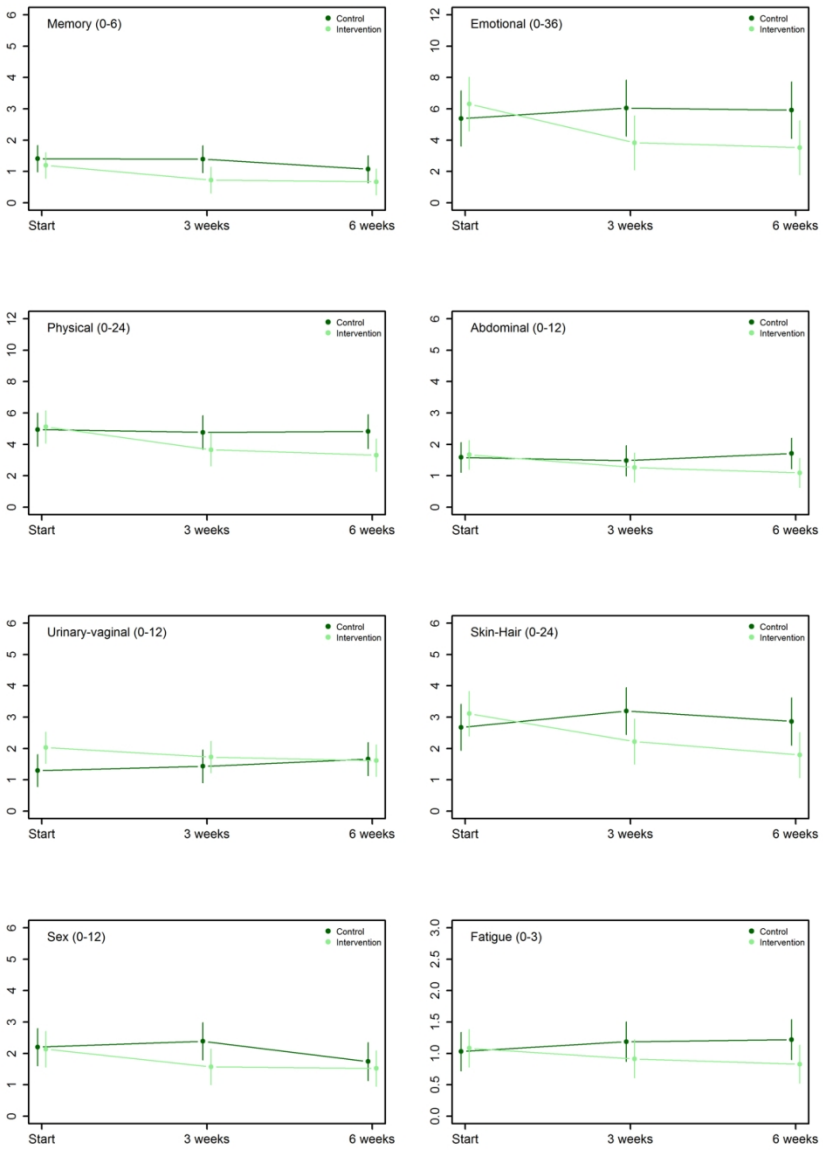


Figure 3. Development of the remaining (EM, MEM, SH, PHY, ABD, URIN, SEX) MSQ scales and the single item over the study period.
The error bars denote the 95% confidence interval of the estimate of the outcome means for each randomization group for each time point.

101x142mm (300 x 300 DPI)

Appendix 1: Outcome measure, The MenoScores Questionnaires (MSQ)

Outcome	MSQ (11 scales and 1 single item, in total 51 items)	Number of items	Scale score*
Primary outcome	Hot flushes (HF)	2	0-6
Secondary outcomes	Day and night sweats (DNS)	2	0-6
	General sweating (GS)	2	0-6
	Menopausal-specific sleeping problems (MSSP)	2	0-6
	Emotional (EM)	12	0-36
	Memory (MEM)	2	0-6
	Skin-hair (SH)	8	0-16
	Physical (PHY)	8	0-24
	Abdominal (ABD)	4	0-8
	Urinary and vaginal (URIN)	4	0-12
	Sexual (SEX)	4	0-8
	Single item about tiredness	1	0-3
After last acupuncture treatment	MSQ plus one item asking about the general effect		
* A higher scores denote more symptoms			

Appendix 2: Time schedule: Enrolment, interventions, and assessments.

STUDY PERIOD														
	Enrolment	**Allocation**	**Post allocation**											**Long term**
TIMEPOINT	***-t_1***	**0**	***W*1***	***W2***	***W3***	***W4***	***W5***	***W6***	***W7***	***W8***	***W9***	***W10***	***W11***	***W26***
ENROLMENT:														
Eligibility screen	x													
Informed consent	x													
Eligibility screening questionnaire	x													
Allocation		x												
INTERVENTIONS:														
Intervention			x	x	x	x	x							
Control								x	x	x	x	x		
ASSESSMENTS**:**														
Eligibility screening questionnaire incl. HF scale	x													
Baseline data	x													
MSQ		x**			x			x***		x			x	x

*W1= Study week 1, W2 = Study week 2 and so on.

** MSQ is completed before allocation and first treatment.

*** Intervention group complete MSQ one week after final treatment (week 6). Control group complete MSQ before first treatment (week 6).

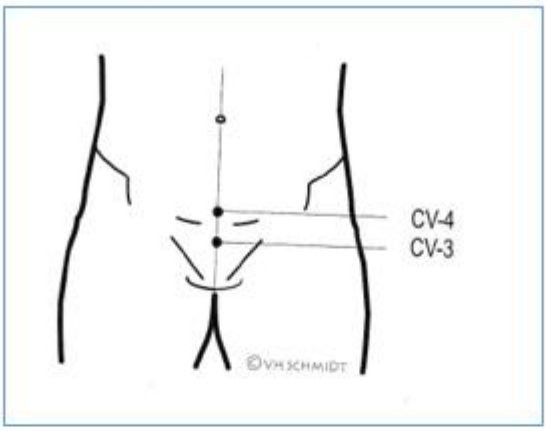
MSQ = MenoScores Questionnaire. HF scale = Hot flushes scale from MSQ.

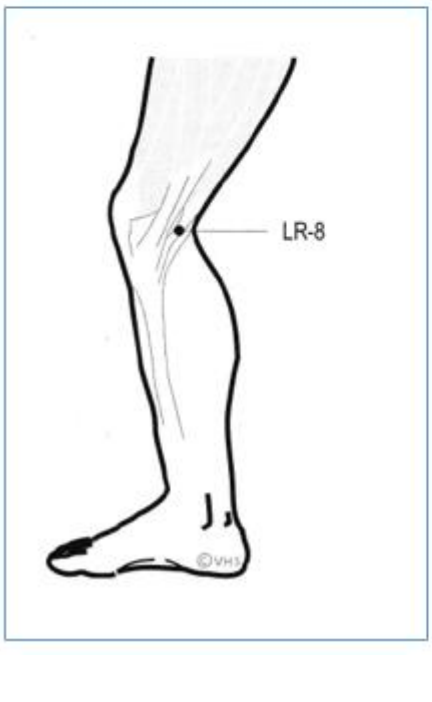
**** Intermediate assessment at week 3. Main comparison of primary outcome at week 6 before "cross-over". Assessment of legacy effect at week 11. Assessment of long-term effect at week 26.

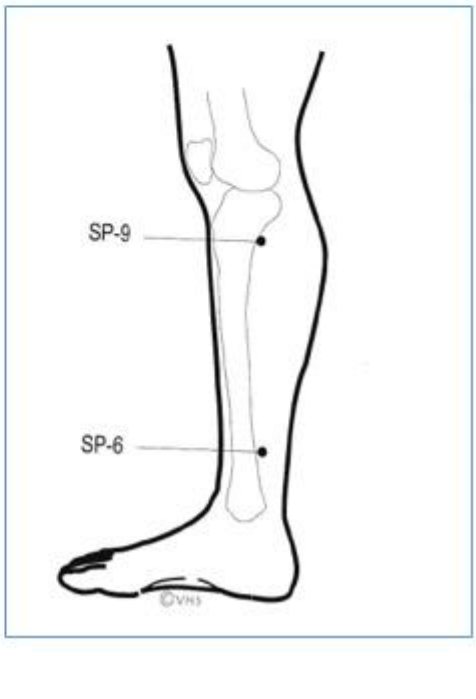
Appendix 3

Drawings are from the book "Akupunktur – på naturvidenskabeligt grundlag".

Permission to reproduce the drawings is given by the publisher Klim, and the book's author Palle Rosted







Appendix 4. Observed reduction in mean scores in the two randomization groups at baseline and each of the follow-up time points

	Week 0				Week 3				Week 6			
	Control		Intervention		Control		Intervention		Control		Intervention	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
HF	4.53 (0.90)	34	4.72 (0.85)	36	4.09 (1.30)	32	2.86 (1.59)	35	3.68 (1.64)	31	2.43 (1.40)	35
DNS	3.50 (1.56)	34	3.61 (1.95)	36	3.34 (1.70)	32	2.51 (1.56)	35	3.03 (1.91)	31	1.94 (1.55)	35
GS	1.41 (1.43)	34	1.42 (1.25)	36	1.28 (1.53)	32	0.71 (0.93)	35	1.45 (1.69)	31	0.60 (0.81)	35
MSSP	2.97 (1.40)	34	3.25 (1.30)	36	2.59 (1.78)	32	2.00 (1.51)	35	2.90 (1.82)	31	1.34 (1.47)	35
EM	5.38 (5.22)	34	6.31 (6.11)	36	5.94 (5.65)	32	3.80 (4.21)	35	5.45 (5.69)	31	3.49 (4.67)	35
MEM	1.41 (1.44)	34	1.19 (1.31)	36	1.41 (1.54)	32	0.71 (1.10)	35	1.10 (1.42)	31	0.66 (1.14)	35
PHY	4.94 (3.56)	34	5.11 (4.03)	36	4.78 (2.83)	32	3.66 (3.40)	35	4.84 (3.72)	31	3.31 (2.78)	35
URIN	1.29 (1.27)	34	2.03 (1.80)	36	1.41 (1.41)	32	1.74 (1.87)	35	1.61 (1.65)	31	1.63 (1.52)	35
ABD	1.59 (1.67)	34	1.67 (1.49)	36	1.50 (1.48)	32	1.26 (1.15)	35	1.68 (1.99)	31	1.09 (1.22)	35
SH	2.68 (2.07)	34	3.11 (2.59)	36	3.28 (2.41)	32	2.26 (2.25)	35	2.94 (2.62)	31	1.83 (1.64)	35
SEX	2.23 (1.92)	26	2.19 (1.55)	27	2.48 (1.85)	25	1.58 (1.58)	26	1.61 (1.73)	23	1.54 (1.55)	28
TR	1.03 (1.03)	34	1.08 (0.84)	36	1.19 (0.97)	32	0.91 (1.02)	35	1.19 (1.14)	31	0.83 (0.89)	35

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Abstract p. 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract p. 1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p. 1
	2b	Specific objectives or hypotheses	p. 2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p. 2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	none
Participants	4a	Eligibility criteria for participants	p. 3
	4b	Settings and locations where the data were collected	p. 2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	p. 3 and 4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p. 4 and 5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	none
Sample size	7a	How sample size was determined	p. 5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p. 5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p. 5 and 6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p. 5 and 6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p. 5 and 6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p. 6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p. 6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p. 6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p. 7 and figure 1.
	13b	For each group, losses and exclusions after randomisation, together with reasons	p. 7 and figure 1.
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p. 3 and 7
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	p. 6 (ITT)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	p. 7 and 8, table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Figure 2. and 3., Appendix 4.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p. 8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p. 9 and 10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p. 9 and 12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p. 11 and 12
Other information			
Registration	23	Registration number and name of trial registry	Abstract and manus p. 12
Protocol	24	Where the full trial protocol can be accessed, if available	Reference 28, p. 12
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p. 12 and 13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Summary points

Without a complete published description of interventions, clinicians and patients cannot reliably implement effective interventions

The quality of description of interventions in publications, regardless of type of intervention, is remarkably poor

The Template for Intervention Description and Replication (TIDieR) checklist and guide has been developed to improve the completeness of reporting, and ultimately the replicability, of interventions

TIDieR can be used by authors to structure reports of their interventions, by reviewers and editors to assess completeness of descriptions, and by readers who want to use the information

Tables

Table 1| **Items included in the Template for Intervention Description and Replication (TIDieR) checklist: information to include when describing an intervention. Full version of checklist provides space for authors and reviewers to give location of the information (see appendix 3)**

Item No	Item
Brief name	
1	Provide the name or a phrase that describes the intervention Page 1
Why	
2	Describe any rationale, theory, or goal of the elements essential to the intervention Page 1
What	
3	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL) Page 2 and 3, reference 29
4	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities Page 3 and 4
Who provided	
5	For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given Page 2
How	
6	Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group Page 2,3 and 4
Where	
7	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features Page 2
When and How Much	
8	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose Page 3 and 4
Tailoring	
9	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how Page 3 and 4
Modifications	
10*	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how) Not applicable
How well	
11	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them Page 6 and 7
12*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned Page 7,8 and 9

*If checklist is completed for a protocol, these items are not relevant to protocol and cannot be described until study is complete.

BMJ Open

Efficacy of a standardised acupuncture approach for women with bothersome menopausal symptoms: a pragmatic randomised study in primary care (the ACOM study)

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Efficacy of a standardised acupuncture approach for women with bothersome menopausal symptoms: a pragmatic randomised study in primary care (the ACOM study)

Title	Efficacy of a standardised acupuncture approach for women with bothersome menopausal symptoms: a pragmatic randomised study in primary care (the ACOM study)
Authors' names	Kamma Sundgaard Lund (KSL), Volkert Siersma (VS), John Brodersen (JB), Frans Boch Waldorff (FBW)
Authors' names, positions and address	Kamma Sundgaard Lund, MD, PhD (**Corresponding author**) Section of General Practice, Department of Public Health, University of Copenhagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: kaml@sund.ku.dk Mobil: +45 22 99 38 82 Volkert Siersma, Statistician (PhD) The Research Unit of General Practice and Section of General Practice, Department of Public Health, University of Copenhagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: siersma@sund.ku.dk John Brodersen, Professor (GP, MD, PhD) Primary Health Care Research Unit, Region Zealand, Alleen 15, 4180 Sorø, Denmark, and Section of General Practice, Department of Public Health, University of Copenahagen Øster Farimagsgade 5, Q P.O. Box 2099, 1014 Copenhagen K, Denmark Email: jobr@sund.ku.dk Frans Boch Waldorff, Professor (GP, MD, PhD), The Research Unit for General Practice, Department of Public Health, University of Southern Denmark J.B: Winsløws vej 9, 5000 Odense, Denmark Email: fwaldorff@health.sdu.dk
Word count (excluding title page, abstract, foodnotes, references, figures and tables)	4344

ABSTRACT

Objective:

To investigate the efficacy of a standardised brief acupuncture approach for women with moderate-to-severe menopausal symptoms.

Design:

Randomised and controlled, with 1:1 allocation to the intervention group or the control group. The assessor and the statistician were blinded.

Setting:

Nine Danish primary care practices.

Participants:

70 women with moderate-to-severe menopausal symptoms and nine general practitioners with accredited education in acupuncture.

Intervention:

The acupuncture style was western medical with a standardised approach in the predefined acupuncture points CV-3, CV-4, LR-8, SP-6, and SP-9. The intervention group received one treatment for five consecutive weeks. The control group was offered treatment after six weeks.

Main outcome measures:

Outcomes were the differences between the randomisation groups in changes to mean scores using the scales in the MenoScores questionnaire, measured from baseline to week six. The primary outcome was the hot flushes scale; the secondary outcomes were the other scales in the questionnaire. All analyses were based on intention-to-treat analysis.

Results:

36 participants received the intervention and 34 were in the control group. Four participants dropped out before week six. The acupuncture intervention significantly decreased hot flushes: Δ -1.6 (95% CI (-2.3 to -0.8); p<0.0001), day-and-night-sweats: Δ -1.2 (95% CI (-2.0 to -0.4); p=0.0056), general sweating: Δ -0.9 (95% CI (-1.6 to -0.2); p=0.0086), menopausal-specific sleeping problems: Δ -1.8 (95% CI (-2.7 to -1.0); p<0.0001), emotional symptoms: Δ -3.4 (95% CI (-5.3 to -1.4); p=0.0008); physical symptoms: Δ -1.7 (95% CI (-3 to -0.4); p=0.010) and skin and hair symptoms: Δ -1.5 (95% CI (-2.5 to -0.6); p=0.0021) compared to the control group at the six-week follow-up. The pattern of decrease in hot flushes, emotional symptoms, skin and hair symptoms was already apparent three weeks into the study. Mild potential adverse effects were reported by four participants but no severe adverse effects were reported.

Trial registration:

ClinicalTrials.gov NCT02746497.

ARTICLE SUMMARY

Strengths and limitations of this study:

- This study has high methodological quality, allocation concealment, adequate power, a validated outcome measure, sufficient and transparent reporting leading to high external validity.
- The study had high participants adherence supporting that the intervention was manageable and well tolerated.
- Since the intervention was pragmatic, standardised and brief the applicability of the findings is high and might have a good chance of being implemented which could lead to new treatment options for menopausal women.
- At present no sufficient acupuncture placebo comparator exist which is a major limitation in acupuncture studies, this study included.

INTRODUCTION

Experience of menopausal symptoms is very common and has been shown to affect quality of life, health status, work productivity, and use of health services (1-3). The majority of women experience menopause in their early fifties (4) and have menopausal symptoms for four to five years on average (4-7). The most prominent symptom of menopause is hot flushes which affects around 75% of menopausal women (5, 6, 8) and is reported as very distressing by 10-20% (5). Other reported menopausal symptoms are night sweats, emotional vulnerability, sleep disturbances, fatigue, cognitive changes, joint pain, vaginal dryness, and loss of sexual desire (4, 5, 9).

Hormone therapy (HT) relieves menopausal symptoms (10, 11) but long-term HT is associated with an increased risk of breast cancer and thromboembolic disorders (11-14). Hence, many menopausal women avoid HT. Non-hormonal-based treatments such as clonidine, gabapentin, and antidepressants may also reduce menopausal symptoms. However, these drugs have frequent adverse effects such as sleep disturbance, dizziness, nausea, fatigue, dry mouth, and constipation (4, 5, 8, 15, 16). Non-pharmaceutical treatments, e.g. relaxation, exercise, herbal remedies, and diets containing phytoestrogens have been suggested, although there is a lack of knowledge about dose, duration, and, for herbal remedies and phytoestrogens, drug interactions and adverse effects. There is currently no convincing evidence of any beneficial effect from these treatments (4, 8, 15-17).

Several studies have demonstrated the effects of acupuncture on menopausal symptoms (15, 18-20), but they have been criticised for methodological limitations, e.g. poor design, inadequate sample size, inadequate control or placebo groups, absence of standardised protocols, and a lack of data on adverse effects (18, 19). Furthermore, due to different methods and a lack of validation of some outcome measures, comparison of results is difficult (18, 19). Therefore, further high-quality randomised acupuncture trials are needed (18, 19). Although the use of acupuncture differs between countries, it is sought by many patients (21-24) and practiced by a substantial number of physicians, especially general practitioners (GPs) (22, 25-27). If a clinically relevant effect on menopausal symptoms from acupuncture is demonstrated, this treatment may be considered for implementation in primary healthcare, leading to new options for menopausal women who cannot or do not wish to use HT.

We hypothesised that a brief and standardised acupuncture treatment could reduce moderate-to-severe menopausal symptoms and, in particular, it could have a clinically relevant effect in the reduction of hot flushes. Therefore, the objective of this study was to investigate the efficacy of a standardised brief acupuncture approach for women with

moderate-to-severe menopausal symptoms; primarily the efficacy on hot flushes measured as change from baseline to week six.

METHOD

Trial design:

The study was a randomised controlled trial (RCT) with a 1:1 allocation to the intervention or the control group. A detailed description of the methods used in the present study are found in the published protocol (28).

Settings and acupuncturists:

The study took place in nine primary care practices in both urban and rural settings. The acupuncturists were nine GPs and all but one were educated in acupuncture by the Danish Society for Evidence-based Acupuncture (DSEA) or the Danish Medical Acupuncture Society (DMAS). One GP had acupuncture training in Sri Lanka before DSEA and DMAS were formed. Participating GPs had, on average, 153 hours of acupuncture education (range 80 to 300), and had practiced acupuncture for 14 years (range 4 to 38).

The first author (KSL) held an individual meeting with each of the GP acupuncturists and provided them with the study protocol, an overview of the predefined acupuncture points, and a written manual with precise instructions for treatment. KSL asked the GP acupuncturists to behave neutrally and to provide only the specified acupuncture treatment and no other treatment or counselling. A two-and-a-half hour refresher course on the predefined acupuncture points and techniques was offered, and four GPs attended this course.

Participants:

Women were recruited through local newspapers, general practices close to the participating GP acupuncturist, the DSEA, and the DMAS. Recruitment took place between late September 2016 and mid December 2016.

Inclusion criteria: women aged 40-65 years with moderate-to-severe hot flushes (score ≥4 on a validated scale measuring hot flushes (MenoScores questionnaire (29) and Appendix 1), intact cognitive function, and a valid e-mail address. Before enrolment participants gave written informed consent. *Exclusion criteria*: women who had had a hysterectomy and/or bilateral oophorectomy; women whose alcohol consumption exceeded 21 drinks per week; who used prescribed sleeping pills and/or prescribed sedatives; who had previously been diagnosed with breast, endometrial, cervical, or ovarian cancer; who had been diagnosed with other severe cancer disease within the past 5 years; who had heart valve disease; who were insulin dependent and/or had poorly controlled diabetes mellitus; who were diagnosed with thyroid disease; who were under investigation for serious disease e.g. cancer; who had received acupuncture treatment within the past 6 months; who had been pregnant or had been breast-feeding within the past two years; who were participating in another trial or had participated in another trial in the two weeks before screening for eligibility; who within the past four weeks had used one or more of the following treatments: systemic HT, hormonal intrauterine device, antidepressants and/or antiepileptics; who had received other medical treatment for hot flushes (e.g. clonidine), herbal remedies/alternative treatments for menopausal symptom, or corticosteroids (the use of inhaled steroids was not an exclusion criterion).

Enrolled participants were provided with oral and written information about the study (30). Participation was voluntary and there was no payment for taking part. Participants could withdraw their consent at any time. The first author carried out assessment of eligibility, obtained informed consent, and collected baseline characteristic data.

Intervention:

All participants were offered one treatment per week for five weeks by a GP acupuncturist in their local area. The intervention group received their treatment in the first five weeks after enrolment in the study. At present, no validated acupuncture placebo comparator exists (31, 32) and we decided to use a control group instead. The control group received their treatment after six weeks. Hence, this RCT is evaluated over a six-week study period (Appendix 2. Time schedule). No other treatment (medicine or alternative remedies) for menopausal symptoms was allowed in any of the groups beginning four weeks prior to enrolment until study week 11. The acupuncture style we used was western medical acupuncture, (WMA) (32, 33), with a standardised approach and predefined acupuncture points (Table 1 and Appendix 3), based on reports from experienced western medical acupuncturists (34).

A complete acupuncture session should not last more than 15 minutes, including insertion of needles, retention time, removal of needles, and documentation. Disposable sterile (Plandent) needles, size 0,30 x 30 mm, were inserted perpendicularly and rotated manually for a few seconds to elicit "de-qi" (needle sensation, a feeling of heaviness around the acupuncture point) (33). The predefined points were CV-3, CV-4, LR-8, SP-6, SP-9 (Table 1). A total of eight points was used, as LR-8, SP-6 and SP-9 were given bilaterally. Needle retention time was 10 minutes.

After each treatment, the GP acupuncturist completed a documentation scheme with the date, documentation for insertion of each of the needles, and whether "de-qi" was obtained. After the final treatment, the completed documentation was sent to the first author.

TABLE 1. Acupuncture points and location

CV-3	Anterior midline, 1 cun* proximal to the symphysis. Insertion depth; perpendicularly 0.5-1 cm.
CV-4	Anterior midline, 1 cun proximal to CV-3 and 3 cun inferior to the umbilicus. Insertion depth; perpendicularly 0.5-1 cm.
LR-8	Medial side of the knee, in the depression anterior/medial to the tendons of semimembranosus and the semitendinosus muscles, at the medial end of the popliteal crease. Insertion depth; perpendicularly 1.5-2 cm.
SP-9	Under the medial condyle of tibia in a depression between the posterior tibia and m. gastrocnemius. Insertion depth; perpendicularly 2-3 cm.
SP-6	3 cun proximal to the prominent part of the medial malleoli, on the medial and posterior border of the tibia. Insertion depth; perpendicularly 1-3 cm.

*A cun is an acupuncture measurement unit. 1 cun corresponds to the width of the study subject's thumb.

Outcome:

The study's outcomes were the differences between the randomisation groups in the mean change over the six-week study period measured in the scales of the MenoScores Questionnaire (MSQ) (29). The MSQ is a content-specific patient-reported outcome measure (PROM) with high content validity and adequate psychometric properties measuring bothersome menopausal symptoms. The MSQ encompasses 11 scales and one single item (51 items in total), measuring

different menopausal domains of bothersome symptoms (Appendix 1). The MSQ scales are constructed such that higher scores denote more bothersome symptoms.

The primary outcome was the hot flushes (HF) scale, secondary outcomes were the remaining MSQ scales: day-and-night sweats (DNS), general sweating (GS), menopausal-specific sleeping problems (MSSP), emotional symptoms (EM), memory changes (MEM), skin and hair symptoms (SH), physical symptoms (PHY), abdominal symptoms (ABD), urinary and vaginal symptoms (URIN), sexual symptoms (SEX), and the single item tiredness (TR).

Of these MSQ scales, the HF, DNS, GS, and MSSP scales are most related to menopause, while the other MSQ scales are more related to general aging or other life events (29).

Assessments and follow-up:

All participants received the MSQ by e-mail in study weeks zero, three, six, eight, eleven, and twenty-six (Appendix 2). Week zero (before randomisation), week three (intermediate assessment), and week six (final assessment) are reported in the present manuscript. In the period when participants were receiving acupuncture treatment, we asked them to complete the MSQ 1-2 days before the third treatment and one week after the fifth and last treatment (Appendix 2). Participants completed and returned the MSQ electronically. Reminders were sent within 1-2 days, if the participant did not return a completed MSQ within the scheduled time. Additionally, participants in the intervention group were asked about adverse effects at the three- and six-week follow-up. After the final treatment we asked the intervention group if, in general, they had experienced a beneficial effect from the acupuncture treatment.

Sample size:

The necessary sample size for the RCT was determined from reports on the primary outcome HF and the two secondary outcome DNS and MSSP in the MSQ validation study (29). We considered a reduction in a scale score as clinically relevant if it corresponded to a reduction from “a lot” to “quite a bit” on a global item regarding whether the respondent was bothered by menopausal symptoms. In the MSQ validation study, women who were bothered “a lot” had a mean score of 4.98 on the HF scale, and women who were bothered “quite a bit” had a mean score of 3.48 on the HF scale. Both groups with a standard deviation (SD) around 1.4. To detect such a reduction on the HF scale with 90% power, 5%

level of significance, and accounting for 20% dropouts, we needed to include 48 participants (24 participants in each group). To achieve a similar power on the DNS and MSSP scales, we needed 56 and 68 participants, respectively.

Randomisation:

The allocation sequence was computer generated using SAS software (v 9.4, SAS institute, Cary, NC, USA) and kept by a person independent of the project organisation (affiliated to the Centre for Health Economic Research, University of Southern Denmark). After enrolment, the independent person allocated the participants to one of the two randomisation groups. The participants were subsequently referred to the acupuncturist. This process ensured that allocation could not be guessed or later changed, thereby securing allocation concealment. Randomisation was done in blocks, with random block sizes, and stratified by age (aged 40-55 or 56-65 years) and level of symptoms (experiencing hot flushes "quite a bit" or "a lot").

Statistical methods:

For each of the primary and secondary outcomes, the up to three assessments for each woman were modelled with a linear mixed model with a level for each time point for each randomisation group; the inherent correlation between observations on the same woman was accounted for by the inclusion of a subject-random effect. The effect of the intervention was estimated at week 3 and week 6 by the mean difference of the outcome beyond the difference already present at baseline and assessed by the appropriate Wald test in the model. The model additionally included as covariates the dichotomisations used in the stratification of the randomisation: age and level of symptoms. The analysis was done intention to treat. Four or more treatments were considered adequate adherence.

All outcomes were Rasch validated which implies sufficiency, i.e. the sum-score carries all information of the measurement. Therefore, a score on one of scales of 4 is more than a score of 3, etc. This justifies the use of the scores of the scales as continuously valued outcome variables in our analyses. A check of the assumptions of the linear regression analyses, aided by the Central Limit Theorem, justifies the comparison of the untransformed mean difference in scores and the use of the asymptotic Wald t-tests. Finally, the mixed model approach constitutes a first line defence against differential dropout.

The statistical significance was assessed controlling for the false discovery rate at 5% with the method of Benjamini and Hochberg (35). SAS v9.4 was used for the analyses.

Blinding:

Statistician and outcome assessors were blinded until all analyses were completed. Participants and acupuncturist were not blinded.

Patient involvement:

In the development of the research question, and in the design of the study, the development and content validity of the outcome measure (MSQ) was ensured by qualitative interviews with women who experienced bothersome menopausal symptoms (29). During this process, the relevance of this present study was also confirmed. Patients were not involved in the recruitment or conduction of the study. The burden of intervention was not assessed by the participants. When results are published they will be disseminated to the Danish College of General Practitioners, the DSEA, the DMAS, the project research homepage (30), local newspaper and Danish women's lifestyle magazines.

RESULTS

We interviewed 207 women for eligibility, of which 70 met the inclusion criteria and were enrolled over a three-month period: we allocated 36 participants to the intervention group, and 34 to the control group. The number of participants treated by a single acupuncturist ranged from minimum one to maximum 16 (including the delayed treatment of the control group). No markedly differences in baseline characteristics between the randomisation groups were identified (Table 2). Inspection of the residuals of the models did not reveal serious variance heterogeneity. Inspection of Cook's D did not reveal subjects that were particularly influential to the results. Four participants dropped out: one in the intervention group and three in the control group (Figure 1). The MSQ response rate was 100% for all remaining participants at all assessments points. The adherence to treatment was very high: 34 out of 36 received all five planned

acupuncture treatments, and one received four out of five treatments. We collected primary data between October 2016 and February 2017.

TABLE 2. Baseline characteristics for each group of women	Control (n=34)	Intervention (n=36)
Age (years), *mean (SD)*	54.1 (5)	55.3 (4)
Age, *n (%)*		
40-55 years	13 (38)	17 (47)
56-65 years	21 (62)	19 (53)
Employment, *n (%)*		
Employed	31 (91)	32 (89)
Unemployed	3 (9)	4 (11)
Education, *n (%)*		
Vocational	8 (24)	8 (22)
Short (<3 years)	4 (12)	3 (8)
Long (≥3 years)	16 (47)	22 (61)
Other	6 (18)	3 (8)
Household, *n (%)*		
Living alone	1 (3)	5 (14)
Living with others	33 (97)	31 (86)
Physical activity, *n (%)*		
No physical activity	7 (21)	3 (8)
1-3 times per week	20 (59)	23 (64)
≥4 times per week	7 (21)	10 (28)
Smoking, *n (%)*		
Yes	1 (3)	2 (6)
No	33 (97)	34 (94)
Alcohol, *n (%)*		
No alcohol	1 (3)	8 (22)
≤14 units per week	29 (85)	19 (53)
>14 units per week	4 (12)	9 (25)
BMI (kg/m^2), *mean (SD)*	25.5 (5)	24.9 (3)
Menstruation in the last year, *n (%)*		
Yes	7 (21)	11 (31)
No	27 (79)	25 (69)
Number of births, *n (%)*		
None	3 (9)	2 (6)
One	5 (15)	8 (22)
Two	20 (59)	18 (50)
More than two	6 (18)	8 (22)

Incontinentia, *n (%)*		
No	13 (38)	10 (28)
Yes	21 (62)	26 (72)
Chronic disease, *n (%)*		
Yes	5 (15)	8 (22)
No	29 (85)	28 (78)
Previous experience with alternative treatment, *n (%)*		
No	8 (24)	10 (28)
Yes	26 (77)	26 (72)
Duration of hot flushes (years), *mean (SD)*	3.41 (3)	4.59 (4)
Hot Flushes, *n (%)*		
HF=4	20 (59)	15 (42)
HF>4	14 (41)	21 (58)

FIGURE 1. Trial flow

The analyses of the observed raw scores demonstrated generally lower means in the intervention group compared to the control group when followed up (Appendix 4).

The developments in the MSQ scales across the two randomisation groups over the study period are presented in Figures 2 and 3.

FIGURE 2: Development of the HF, DNS, GS, and MSSP scales over the study period

FIGURE 3: Development of the remaining (EM, MEM, SH, PHY, ABD, URIN, SEX) MSQ scales and the single item over the study period.

Primary outcome:

The intervention group was significantly less bothered by hot flushes at six weeks: Δ -1.6 (95% CI (-2.3 to -0.8); p<0.0001). This difference was also statistically significant at three weeks: Δ -1.5 (95% CI (-2.2 to -0.7); p=0.0002). (Table 3).

Secondary outcomes:

Statistically significant differences were identified at six weeks in the following secondary outcomes: DNS: Δ -1.2 (95% CI (-2.0 to -0.4); p=0.0056); GS: Δ -0.9 (95% CI (-1.6 to -0.2) p=0.0086); MSSP: Δ -1.8 (95% CI (-2.7 to -1.0); p<0.0001); EM: Δ -3.4 (95% CI (-5.3 to -1.4); p=0.0008); PHY: Δ -1.7 (95% CI (-3 to -0.4); p=0.010) and SH Δ -1.5 (95% CI (-2.5 to -0.6); p=0.0021) (Table 3). This difference was also statistically significant at three weeks in EM: Δ -3.2 (95% CI (-5.1 to -1.2); p=0.0015) and SH: Δ -1.4 (95% CI (-2.4 to -0.5); p=0.0036) (Table 3).

Table 3: Differences in means, primary and secondary outcomes

Differences in mean scores between the randomization groups at each of the follow-up time points.

	Week 0 (baseline)[1]	Week 3[2]		Week 6[2]	
	Δ (95%CI)	Δ (95%CI)	p-value	Δ (95%CI)	p-value
Hot flushes (HF)	0.1 (-0.6; 0.7)	-1.5 (-2.2; -0.7)	0.0002*	-1.6 (-2.3; -0.8)	<.0001*
Day-and-night sweats (DNS)	0.0 (-0.9; 0.8)	-1 (-1.8; -0.1)	0.024	-1.2 (-2.0;-0.4)	0.0056*
General sweating (GS)	0.0 (-0.6; 0.6)	-0.6 (-1.3; 0.1)	0.091	-0.9 (-1.6; -0.2)	0.0086*
Menopausal-specific sleeping problems (MSSP)	0.2 (-0.5; 1)	-0.9 (-1.7;- 0.1)	0.033	-1.8 (-2.7; -1.0)	<.0001*
Emotional symptoms (EM)	1.0 (-1.5; 3.5)	-3.2 (-5.1; -1.2)	0.0015*	-3.4 (-5.3; -1.4)	0.0008*
Memory changes (MEM)	-0.2 (-0.8; 0.4)	-0.5 (-1.0; 0.1)	0.11	-0.2 (-0.8; 0.1)	0.49
Physical symptoms (PHY)	0.1 (-1.5; 1.6)	-1.3 (-2.6;- 0.0)	0.049	-1.7 (-3; -0.4)	0.010*
Urinary and vaginal symptoms (URIN)	0.8 (0.1; 1.5)	-0.4 (-1.1; 0.3)	0.21	-0.8 (-1.5; -0.1)	0.025
Abdominal symptoms (ABD)	0.1 (-0.6; 0.8)	-0.3 (-1; 0.4)	0.38	-0.7 (-1.4; 0.0)	0.042
Skin and hair symptoms (SH)	0.3 (-0.7; 1.4)	-1.4 (-2.4; -0.5)	0.0036*	-1.5 (-2.5; -0.6)	0.0021*
sexual symptoms (SEX)	-0.2 (-1; 0.7)	-0.7 (-1.4; -0.1)	0.032	-0.3 (-0.8; 0.5)	0.69
Tiredness (TR)	0.1 (-0.3; 0.5)	-0.3 (-0.8; 0.1)	0.15	-0.5 (-0.9; 0.0)	0.049

[1]Difference in mean score of intervention relative to control, adjusted for stratification factors (age and level of symptoms ("quite a bit" or "a lot" HF))

[2]Difference in mean score of intervention relative control beyond the difference already present at Week 0 (baseline), adjusted for stratification factors (age and level of symptoms ("quite a bit" or "a lot" HF))

*Significant at a 0.01 level to control for the false discovery rate at 0.05

Negative values Δ = less symptoms in the intervention group

In the intervention group, 80% of participants reported a general beneficial treatment effect after six weeks.

Harms and adverse events:

No serious harms or adverse events were reported in the intervention group. Four participants reported mild potential adverse effects: one experienced tiredness and headache after treatment; another experienced more hot flushes in some of the weeks, but reported this to be associated with increased stress in her personal and professional life; one had to urinate more frequently; and one experienced tingling in the leg where the needle had been placed.

Beside the four participants who reported mild potential adverse effects one participant dropped out because she found the needling unpleasant (Figure 1). However, this was not unexpected as acupuncture needling in some cases is experienced as a bit unpleasant (needles are inserted into the body which might be a bit unpleasant).

DISCUSSION

Principal findings:

The standardised acupuncture treatment used in the present study reduced the HF, DNS, GS, MSSP, EM, PHY and SH scales after five weekly treatments, and the HF, EM and SH scales was reduced after two acupuncture treatments. The intervention did not significantly reduce the remaining MSQ scales, but we did also not expect to see this because this study was underpowered regarding these scales. Additionally, since significant reductions were only found in some of the scales, our findings emphasise that the intervention was targeted to menopausal symptoms and are not an artefact of general care. The acupuncture treatment was well tolerated: one participant dropped out and only four participants reported mild potential adverse effects. No serious harms were reported.

Strengths and weaknesses of the study:

The intervention period was relatively brief. However, it served to test a pragmatic, standardised, and brief acupuncture approach manageable by both GPs and participants. Therefore, the suitability of the treatment outlined in this study in day-to-day primary care is high. The study had very high participant adherence: only four out of 70 participants dropped out. The remaining participants fulfilled the criteria for adequate treatment adherence, and had a 100% MSQ response

rate, demonstrating that the intervention was well tolerated. The fact that the control group was also offered treatment after six weeks probably contributed to the high adherence rate. Finally, all participants were offered the same intervention, and co-interventions for menopausal symptoms were not allowed in the study period, thereby reducing the risk of performance bias. Not all menopausal women need or request treatment and we believe this acupuncture intervention is most relevant to women who experience moderate-to-severe menopausal symptoms. We wanted to avoid outcomes confounded by co-factors such as severe illness, other medications or co-interventions and since the study took place in primary care the participants should reflect healthy women attending their GP requesting treatment for menopausal symptoms. We believe the participants are representative of such women and that our standardized and pragmatic intervention could easily be transferred to most clinical settings.

Another strength in this study was the use of a condition-specific PROM (MSQ) with high content validity and adequate psychometric properties ensuring high construct validity of the study measurements. Moreover, data from the MSQ validation study (29) was used to generate the power calculation based on relevant clinical effects which ensured adequate sample size. We did not use a physiological measurement e.g. skin conductance or temperature (which would probably have been technically difficult) because we believe PROMs are the most appropriate method to obtain information on participants' own perception of their symptoms (36). The recall time frame in this study was one week which reduced the risk of recall bias.

The placebo effect plays an important role in all interventional studies and is influenced by expectations and beliefs. All GPs were certified acupuncturists and although they were instructed to behave neutrally, their beliefs in acupuncture could have affected their interaction with the participants and possibly have intensified a placebo effect. However, correct acupuncture techniques requires extensive training and using GPs without such training would have been wrong and misleading. In addition, all participants were volunteers with presumably expectations of a beneficial effect. This might have enhanced the placebo effect in the intervention group and could have caused a nocebo effect in the control group. However, we did not see such deterioration in the control group. In fact, the control group showed a trend of improvement, in particular in the HF scale, which may be explained by a regression to the mean. The lack of a sufficient acupuncture placebo comparator is a major limitation in acupuncture studies, including this study. In WMA theories, sham (placebo) acupuncture is not perceived as inactive but rather another, although less effective, form of needling (31, 32). Furthermore, a meta-analysis concluded that non-specific effects associated with sham acupuncture are often moderately large and might be larger than other placebo interventions (37). If sham is not inactive, a study testing sham versus real acupuncture

is not a placebo controlled study but rather a study testing two different types of acupuncture. Therefore, we decided to investigate the impact of acupuncture versus no treatment. An important weakness of the present study is that the identified positive effects from acupuncture treatment could be caused by a placebo effect and not a specific physiological effect of needling. However, our aim was not to distinguish between specific and non-specific effects of needling, but to investigate the impact of acupuncture versus no treatment. We found that the acupuncture treatment used in this study had an important clinical effect. If we ignore these findings, due to a lack of knowledge about possible specific effects of acupuncture, women with moderate-to-severe menopausal symptoms could miss out on a low cost and effective treatment with only minor potential adverse effects.

One final limitation was that blinding of acupuncturists and participants in this study design was not possible. However, we secured blinding of the statistician and outcome assessors until all analyses were completed.

Comparison with other studies:

Some previous studies have demonstrated real acupuncture to be significantly superior to sham acupuncture (38-40). However, a Cochrane review from 2013 regarding acupuncture for menopausal hot flushes, found no significant differences between real acupuncture compared to sham, but a beneficial effect of acupuncture compared to no treatment, and that acupuncture was inferior to HT. The evidence was in general of poor quality, and further high quality studies were recommended (18). Results from two recent studies, one comparing real acupuncture with sham (41) and one comparing acupuncture with no treatment (42), confirm the findings reported in the Cochrane review.

The present study demonstrates that acupuncture is significantly superior to no treatment. Our study was based on WMA theories while most previous studies were based on traditional Chinese medicine (TCM) theories and diagnoses (18, 21, 38-46) involving the concepts of yin/yang and circulation of qi (32, 33). Most previous studies had longer intervention periods and/or more treatment sessions (21, 39-50) and several studies used individualised treatment with variation in the selection of acupuncture points (21, 40, 42, 43, 46). Tailored treatments might be a truer reflection of the actual clinical context. However, in an RCT, we believe that treatment should be standardised so that the intervention can be replicated. Some studies differ from this study by including patients treated for breast cancer (38, 39, 44, 45), which makes it difficult to compare results. In contrary to our study, some studies allowed other co-interventions (e.g. adjuvant anti-hormone therapy, cystostaticum, clonidine, antidepressants, HT, or other alternative remedies) (21, 38, 39, 41, 42, 44) which might have affected their outcomes. Finally, some studies assessed other relevant secondary outcomes such as quality of life,

hot flush interference, sleep quality, and one study also assessed plasma oestradiol. Most studies used self-reported outcomes but in several of them the validation of the outcome measures was lacking, unclear, or not reported (38, 39, 44, 45). We did not use a quality of life measure, because we did not find a Rasch validated quality of life instrument for our target group. The MSQ validation ensured that all aspects considered important by menopausal women themselves were covered by the MSQ scales. We would expect that a reduction in the HF, DNS, GS, MSSP, EM, PHY and SH scales may ultimately have a positive indirect impact on a menopausal woman's overall sense of well-being and quality of life. To our knowledge, this study is the only one to use a PROM that is condition-specific with high-content validity and psychometrically Rasch validated.

Meaning of the study: possible explanations and implications for clinicians and policymakers:

The lack of a proper acupuncture placebo comparator has major implications for conducting and interpreting acupuncture studies. Therefore, we need to continue the discussion about what level of evidence should be accepted as sufficient for a treatment to be considered effective. This is particularly the case when we cannot accurately explain the underlying mechanism behind the treatment, nor determine how much of the effect is caused by placebo. In addition, it is important to note that in the present study the intervention was targeted at menopausal symptoms, and subsequently demonstrated a targeted effect, not an improvement across all symptoms. We also need to take the balance between benefits and harms into consideration. There is strong evidence that acupuncture for menopausal symptoms is without serious harms. Thus, requirements for evidence of the efficacy of acupuncture treatment might be less rigorous. On the contrary, acupuncture treatment in a private setting (i.e. outside a publicly funded health care system) might involve considerable personal expense and opportunity costs.

We consider the intervention in this study to be low cost, both to the individual and to the health system, but this needs to be further investigated and included in a discussion of value-based healthcare (51).

Future research:

The long-term effect, the characteristics of women who benefit from acupuncture treatment, cost-effectiveness, the underlying mechanism of needling, and the impact of placebo need further investigation.

CONCLUSION

A standardized acupuncture treatment gives women suffering from moderate-to-severe menopausal symptoms a clinically relevant reduction in hot flushes, day-and-night sweats, general sweating, menopausal-specific sleeping problems, emotional symptoms, physical symptoms and skin and hair symptoms. Acupuncture for menopausal symptoms is a realistic option for women who cannot or do not wish to use HT. Women seeking acupuncture treatment for menopausal symptoms should be informed of the current evidence, and its limitations, so they can integrate this with personal preferences and values in their decision-making. This study has high methodological quality, adequate power, a validated outcome measure, and sufficient reporting leading to high validity of the study and findings. Furthermore, this study use a pragmatic, standardised, and brief intervention which leads to findings that may have a higher chance of being implemented and thereby are more likely to lead to new treatment options for menopausal women.

OTHER INFORMATION

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Registration:

ClinicalTrials.gov NCT02746497.

Ethical approval:

Approvals from the Committees on Health Research Ethics (H-16016365), the Committee of Multipractice Studies in General Practice (MPU 08-2016) and the Danish Data Protection Agency (SUND-2016-24) were obtained before enrolment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (ICH GCP).

Protocol:

Please refer to (28) for full trial protocol.

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Competing interests:

All authors have completed the ICMJE uniform disclosure form and declare no support from any organisation for the submitted work, no financial relationship with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could have appeared to have influenced the submitted work.

Contributor and guarantor information:

Frans Boch Waldorff (FBW) conceived the idea. Frans Boch Waldroff (FBW), Volkert Seirsma (VS), John Brodersen (JB) and Kamma Sundgaard Lund (KSL) all took part in the design and planning of the study. Kamma Sundgaard Lund conducted the study supported by Frans Boch Waldroff, Volkert Seirsma and John Brodersen. Kamma Sundgaard Lund drafted the manuscripts and Frans Boch Waldroff, Volkert Seirsma and John Brodersen revised the entire manuscript critically and approved the final version for publication. The statistics was carried out by Volkert Siersma. Frans Boch Waldorff is guarantor for the study.

Data access:

All authors had access to and take responsibility for the data and analyses. Relevant and only anonymised data (PROM scores) can be available for research on reasonable request (kaml@sund.ku.dk). Data will be saved for 5 years.

The protocol was published in march 2017.

Transparency declaration:

The corresponding author affirms, on behalf of all authors, that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

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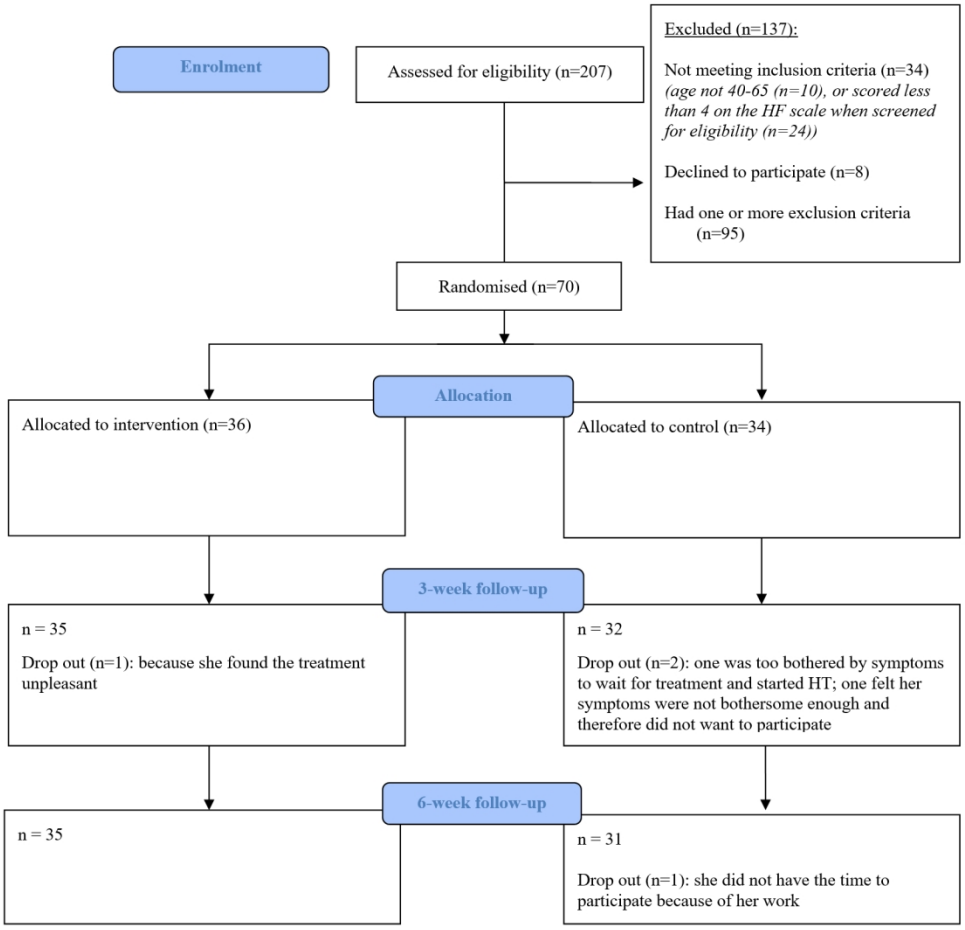

Figure 1. Trial Flow

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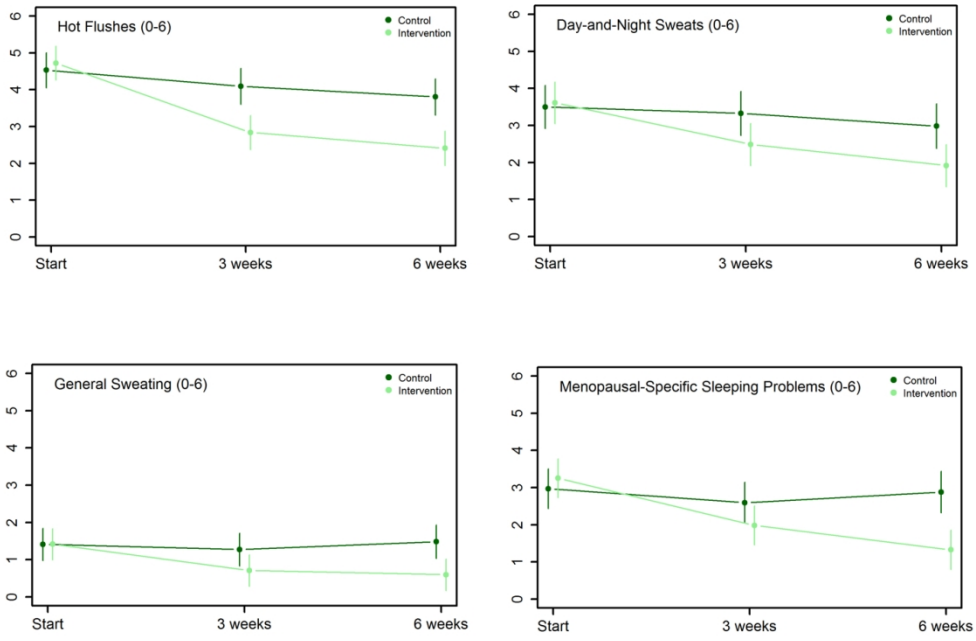


Figure 2. Development of the HF, DNS, GS, and MSSP scales over the study period. The error bars denote the 95% confidence interval of the estimate of the outcome means for each randomization group for each time point.

123x95mm (300 x 300 DPI)

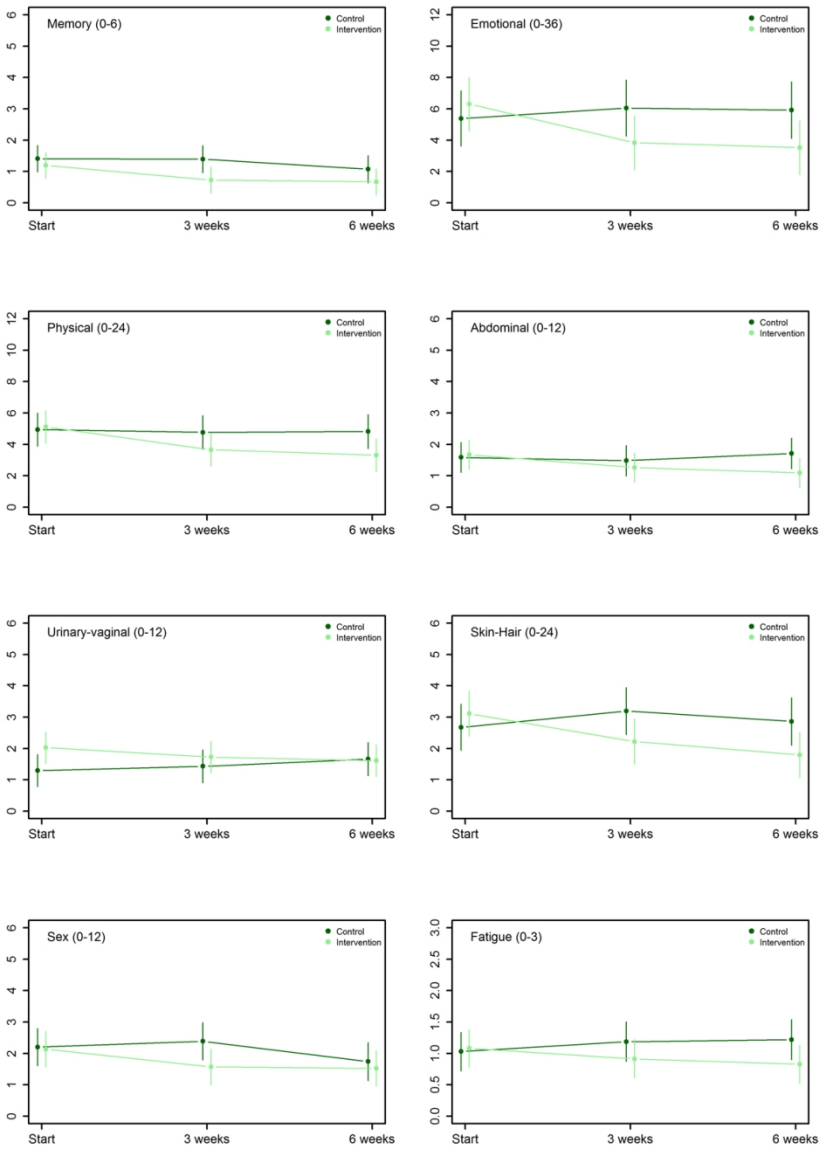


Figure 3. Development of the remaining (EM, MEM, SH, PHY, ABD, URIN, SEX) MSQ scales and the single item over the study period.
The error bars denote the 95% confidence interval of the estimate of the outcome means for each randomization group for each time point.

101x142mm (300 x 300 DPI)

Appendix 1: Outcome measure, The MenoScores Questionnaires (MSQ)

Outcome	MSQ (11 scales and 1 single item, in total 51 items)	Number of items	Scale score*
Primary outcome	Hot flushes (HF)	2	0-6
Secondary outcomes	Day and night sweats (DNS)	2	0-6
	General sweating (GS)	2	0-6
	Menopausal-specific sleeping problems (MSSP)	2	0-6
	Emotional (EM)	12	0-36
	Memory (MEM)	2	0-6
	Skin-hair (SH)	8	0-16
	Physical (PHY)	8	0-24
	Abdominal (ABD)	4	0-8
	Urinary and vaginal (URIN)	4	0-12
	Sexual (SEX)	4	0-8
	Single item about tiredness	1	0-3
After last acupuncture treatment	MSQ plus one item asking about the general effect		
* A higher scores denote more symptoms			

Appendix 2: Time schedule: Enrolment, interventions, and assessments.

STUDY PERIOD														
	Enrolment	**Allocation**	**Post allocation**											**Long term**
TIMEPOINT	***-t₁***	**0**	***W*1***	***W2***	***W3***	***W4***	***W5***	***W6***	***W7***	***W8***	***W9***	***W10***	***W11***	***W26***
ENROLMENT:														
Eligibility screen	x													
Informed consent	x													
Eligibility screening questionnaire	x													
Allocation		x												
INTERVENTIONS:														
Intervention			x	x	x	x	x							
Control								x	x	x	x	x		
ASSESSMENTS**:**														
Eligibility screening questionnaire incl. HF scale	x													
Baseline data	x													
MSQ		x**			x			x***		x			x	x

*W1= Study week 1, W2 = Study week 2 and so on.

** MSQ is completed before allocation and first treatment.

*** Intervention group complete MSQ one week after final treatment (week 6). Control group complete MSQ before first treatment (week 6).

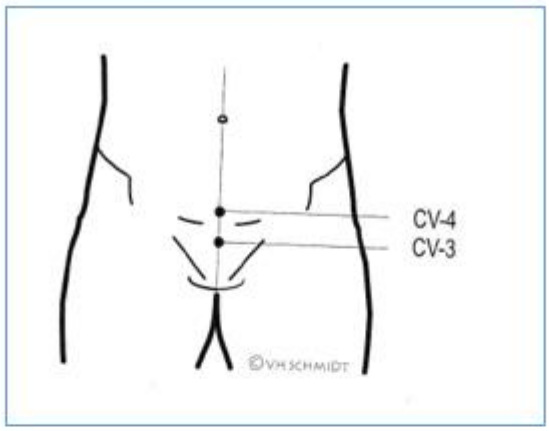
MSQ = MenoScores Questionnaire. HF scale = Hot flushes scale from MSQ.

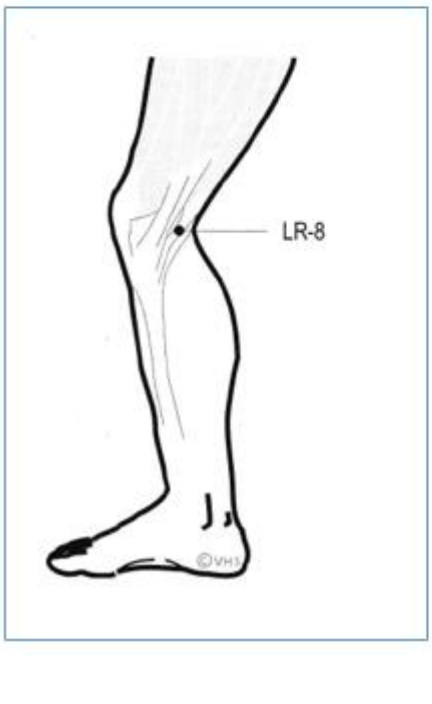
**** Intermediate assessment at week 3. Main comparison of primary outcome at week 6 before "cross-over". Assessment of legacy effect at week 11. Assessment of long-term effect at week 26.

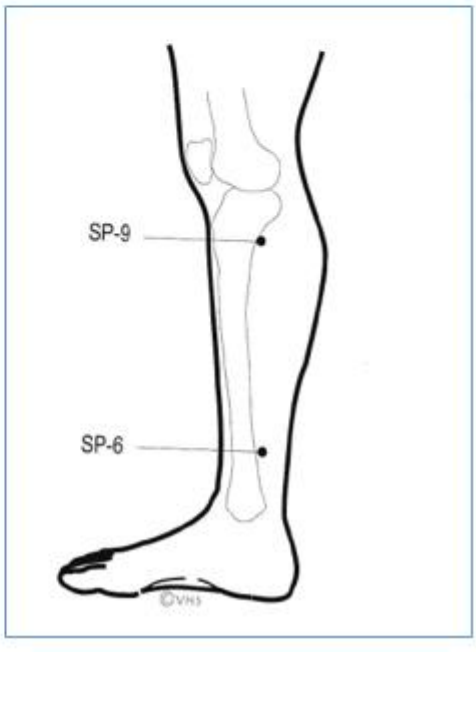
Appendix 3

Drawings are from the book "Akupunktur – på naturvidenskabeligt grundlag".

Permission to reproduce the drawings is given by the publisher Klim, and the book's author Palle Rosted







Appendix 4. Observed reduction in mean scores in the two randomization groups at baseline and each of the follow-up time points

	Week 0				Week 3				Week 6			
	Control		Intervention		Control		Intervention		Control		Intervention	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
HF	4.53 (0.90)	34	4.72 (0.85)	36	4.09 (1.30)	32	2.86 (1.59)	35	3.68 (1.64)	31	2.43 (1.40)	35
DNS	3.50 (1.56)	34	3.61 (1.95)	36	3.34 (1.70)	32	2.51 (1.56)	35	3.03 (1.91)	31	1.94 (1.55)	35
GS	1.41 (1.43)	34	1.42 (1.25)	36	1.28 (1.53)	32	0.71 (0.93)	35	1.41 (1.69)	31	0.60 (0.81)	35
MSSP	2.97 (1.40)	34	3.25 (1.30)	36	2.59 (1.78)	32	2.00 (1.51)	35	2.99 (1.82)	31	1.34 (1.47)	35
EM	5.38 (5.22)	34	6.31 (6.11)	36	5.94 (5.65)	32	3.80 (4.21)	35	5.77 (5.69)	31	3.49 (4.67)	35
MEM	1.41 (1.44)	34	1.19 (1.31)	36	1.41 (1.54)	32	0.71 (1.10)	35	1.10 (1.42)	31	0.66 (1.14)	35
PHY	4.94 (3.56)	34	5.11 (4.03)	36	4.78 (2.83)	32	3.66 (3.40)	35	4.84 (3.72)	31	3.31 (2.78)	35
URIN	1.29 (1.27)	34	2.03 (1.80)	36	1.41 (1.41)	32	1.74 (1.87)	35	1.61 (1.65)	31	1.63 (1.52)	35
ABD	1.59 (1.67)	34	1.67 (1.49)	36	1.50 (1.48)	32	1.26 (1.15)	35	1.68 (1.99)	31	1.09 (1.22)	35
SH	2.68 (2.07)	34	3.11 (2.59)	36	3.28 (2.41)	32	2.26 (2.25)	35	2.94 (2.62)	31	1.83 (1.64)	35
SEX	2.23 (1.92)	26	2.19 (1.55)	27	2.48 (1.85)	25	1.58 (1.58)	26	1.61 (1.73)	23	1.54 (1.55)	28
TR	1.03 (1.03)	34	1.08 (0.84)	36	1.19 (0.97)	32	0.91 (1.02)	35	1.19 (1.14)	31	0.83 (0.89)	35

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Abstract p. 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract p. 1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p. 1
	2b	Specific objectives or hypotheses	p. 2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p. 2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	none
Participants	4a	Eligibility criteria for participants	p. 3
	4b	Settings and locations where the data were collected	p. 2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	p. 3 and 4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p. 4 and 5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	none
Sample size	7a	How sample size was determined	p. 5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p. 5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p. 5 and 6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p. 5 and 6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p. 5 and 6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p. 6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p. 6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p. 6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p. 7 and figure 1.
	13b	For each group, losses and exclusions after randomisation, together with reasons	p. 7 and figure 1.
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p. 3 and 7
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	p. 6 (ITT)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	p. 7 and 8, table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Figure 2. and 3., Appendix 4.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p. 8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p. 9 and 10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p. 9 and 12
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p. 11 and 12
Other information			
Registration	23	Registration number and name of trial registry	Abstract and manus p. 12
Protocol	24	Where the full trial protocol can be accessed, if available	Reference 28, p. 12
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p. 12 and 13

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Summary points

Without a complete published description of interventions, clinicians and patients cannot reliably implement effective interventions

The quality of description of interventions in publications, regardless of type of intervention, is remarkably poor

The Template for Intervention Description and Replication (TIDieR) checklist and guide has been developed to improve the completeness of reporting, and ultimately the replicability, of interventions

TIDieR can be used by authors to structure reports of their interventions, by reviewers and editors to assess completeness of descriptions, and by readers who want to use the information

Tables

Table 1| **Items included in the Template for Intervention Description and Replication (TIDieR) checklist: information to include when describing an intervention. Full version of checklist provides space for authors and reviewers to give location of the information (see appendix 3)**

Item No	Item
Brief name	
1	Provide the name or a phrase that describes the intervention Page 1
Why	
2	Describe any rationale, theory, or goal of the elements essential to the intervention Page 1
What	
3	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL) Page 2 and 3, reference 29
4	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities Page 3 and 4
Who provided	
5	For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given Page 2
How	
6	Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group Page 2,3 and 4
Where	
7	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features Page 2
When and How Much	
8	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose Page 3 and 4
Tailoring	
9	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how Page 3 and 4
Modifications	
10*	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how) Not applicable
How well	
11	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them Page 6 and 7
12*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned Page 7,8 and 9

*If checklist is completed for a protocol, these items are not relevant to protocol and cannot be described until study is complete.