

Resistance training for hot flashes in postmenopausal women: A randomised controlled trial

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ABSTRACT

Objectives: To investigate the effect of 15 weeks of resistance training on the frequency of moderate to severe hot flashes in postmenopausal women.

Study design: Postmenopausal women with at least 4 moderate or severe hot flashes or night sweats per day were randomized to a 15-week resistance training intervention or unchanged physical activity. Participants did not exercise regularly at baseline and had not used any therapy for hot flashes two months prior to study entry. The resistance training was performed three times per week and the program contained 8 exercises performed with 8–12 repetitions in 2 sets. Loads were set individually from eight-repetition maximum-strength tests and increased progressively.

Main outcome measures: The primary outcome was change in mean moderate or severe hot flashes per day from baseline to week 15, assessed with symptom diaries. Secondary outcomes included change in hot flush score and time spent on physical activity.

Results: Between November 19, 2013, and October 26, 2016, 65 women were enrolled; 58 completed the trial and were included in the analyses. The mean age was 55 and the mean number of moderate or severe hot flashes per day at baseline was 7.1; there were no baseline differences between groups. The frequency of hot flashes decreased more in the intervention group than in the control group (mean difference -2.7 , 95% CI -4.2 to -1.3). The mean percentage change was -43.6% (-56.0 to -31.3) in the intervention group and -2.0% (-16.4 – 12.4) in the control group.

Conclusion: A 15-week resistance-training program decreased the frequency of moderate and severe hot flashes among postmenopausal women and could be an effective and safe treatment option to alleviate vasomotor symptoms.

1. Introduction

Most women experience hot flashes (HF) and night sweats (vasomotor symptoms) around menopause that may impair quality of life (QoL) [1]. Although oestrogen therapy with or without a progestogen (HT) is an effective treatment, its use was restricted after reports associating HT with breast cancer and cardiovascular events [2]. Pharmacological options are few and not as effective as HT [3]. Many women use alternative treatments like vitamin supplements, natural remedies or relaxation to get relief from HF [4]. Evidently, there is a gap between the need for an effective treatment and the treatment options available.

Exercise has been suggested as a low-risk treatment of HF, but evidence is still inconclusive [5]. Some observational studies linked regular physical activity to fewer or milder HF [6–10], others found no association [11,12]. Evidence from intervention studies is of low quality [5]. Previous studies focused on aerobic or low-intensity exercise, with no or moderate effect on HF [13]. Low compliance to exercise, high dropout and lack of outcome data could explain part of the low treatment effect.

The World Health Organization recommends resistance training twice weekly to all adults [14]. It is especially important in postmenopausal women where decreases in muscle strength, bone mineral density, and basal metabolic rate are accelerated. Resistance training

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appears to counteract the decrease in those areas, as well as improve other health-related outcomes [15,16]. β -endorphin released during exercise has been suggested to stabilize thermoregulation but the concentration of β -endorphin in cerebrospinal fluid decreases after menopause [17]. In theory, resistance training may decrease HF by induction of central β -endorphin production through activation of large muscle groups, which would be a much-needed addition to the few existing treatment options.

We aimed to investigate the effect of standardised resistance training on HF in postmenopausal women. We hypothesized that 15 weeks of resistance training would decrease moderate and severe HF more than in a control group receiving no intervention.

2. Methods

2.1. Study design

This was an open, parallel-group randomised controlled trial, with a published protocol [18]. Participants were randomized to a 15-week resistance training-intervention or a non-treated control group (1:1 allocation). All participants completed a baseline two-week HF diary and thereafter daily during the 15-week study. At baseline we allowed a maximum of 225 min physical activity/week of any intensity (including maximum 75 min at moderate-vigorous intensity) [14], based on screening interviews.

2.2. Study population

Postmenopausal women (≥ 12 months amenorrhea), ≥ 45 years old with at least four moderate to severe HF/day over a two-week screening period were included. Women with amenorrhea due to hysterectomy or an intrauterine device were defined as postmenopausal if follicle-stimulating hormone levels were > 20 mIU/ml at baseline. We excluded women who used medical therapy, including HT or natural preparations for HF during the past two months. Antidepressants were allowed if the dose was stable and treatment unrelated to HF. Further exclusion criteria were: blood pressure $> 160/100$ mmHg, capillary haemoglobin < 110 g/l, any unstable medical condition or physical inability to participate in resistance training.

Participants were recruited through advertisements in local newspapers and posters displayed at the University Hospital. Women eligible after telephone screening were invited to a visit at the outpatient clinic of Gynaecology including information about the study, written informed consent, checking of eligibility criteria and collection of clinical baseline data (Fig. 1). Those who were eligible received a two-week diary to register HF and physical activity. The final assessment of eligibility and randomization was done during a second visit based on the number of HF registered in the diary.

At a third visit after 15 weeks measurements were repeated. Inclusion started November 2013 and ended October 2016.

2.3. Randomization and sample size

An independent statistician created the allocation sequence using a computer-based random number generator (Stata 13.1, StataCorp LP, Texas, USA). Group allocation was concealed in opaque, sealed and sequentially numbered envelopes stored in a locked location handled by a research nurse. When a new participant was included, the investigator opened the envelope next in turn in the presence of the participant.

The sample size calculation was based on results from a pilot study including the first 16 participants in the present trial. Forty participants were needed to detect a 50% difference in moderate and severe HF with 80% power and an expected dropout rate of 20%. A 50% decrease in HF has been considered a clinically significant change for women [19]. The goal was set to include 60 participants to increase the power of secondary outcome variables. However, we included all eligible women

who responded to the last advertisement in September 2016, resulting in 65 included women.

2.4. Intervention

The 15-week training program performed three times/week contained six exercises in seated resistance machines and two body-weight exercises; chest press, leg press, seated row, leg curl, latissimus dorsi pull-down, leg extension, crunches and back raises [20].

The seated exercises were performed with 8–12 repetitions in two sets with two minutes' rest between sets. Body-weight exercises were performed until exhaustion in two sets (approximately 20 repetitions/set). Loads were set to correspond to 8–12 repetition maximum (RM) [21] after individual testing by a physiotherapist (HL). To minimize the risk of injury, participants trained at 15–20 RM with 15–20 repetitions/set during the first three weeks. Training sessions were preceded by 7–10 min warm-up and finished with dynamic and static stretching. Participants exercised independently at a local gym three times/week, with one session/week in the presence of the physiotherapist who gradually increased loads. Attendance was logged via the gym's electronic card system and participants documented exercises, loads and repetitions in a personal log-book.

Participants in the control group were instructed not to change their physical activity habits during 15 weeks and to avoid any other treatment for HF. After 15 weeks, they were offered a free four-month membership at the gym and an individual resistance-training introduction.

2.5. Outcome assessment

The primary outcome was change in frequency of moderate and severe HF from baseline to week 15. Participants daily noted the number of mild, moderate and severe HF in diaries, as well as minutes spent on physical activity. To minimize missing data, they sent their diary to the research nurse every fourth week, and were contacted if a diary was missing. Secondary outcomes included change in HF score and the correlation between change in HF frequency and change in minutes spent on physical activity. All women completed a validated questionnaire to assess physical activity (International Physical Activity Questionnaire; IPAQ) at baseline and week 15 [22].

The participants registered health issues in their HF diaries, including new medications, and were asked about health problems at the week-15 visit. The physiotherapist reported health problems impeding exercise and registered any adverse events during the training sessions.

Participants who completed a mean of \geq two resistance-training sessions/week were defined as compliant, excluding missed sessions due to illness. We assessed compliance by combining logs from the gym's electronic card system with data from the gym log books. If a participant missed training sessions due to illness (noted in the HF diary or adverse events log), that week was excluded from the evaluation of compliance (maximum three weeks exclusion was permitted).

2.6. Statistical analyses

All eligible randomised participants who did not withdraw from the trial and provided more than only baseline data were included in the intention-to-treat analyses for the primary outcome. Baseline characteristics were visualized using means and standard deviations, or medians and interquartile ranges if non-normally distributed. Outcome assessors were blinded when performing the statistical analysis on the primary outcome, and $p < 0.05$ was considered statistically significant. All analyses were performed in IBM SPSS Statistics 24 (IBM, New York, USA).

2.6.1. Effect on hot flashes

Baseline values were calculated as the mean of moderate and severe

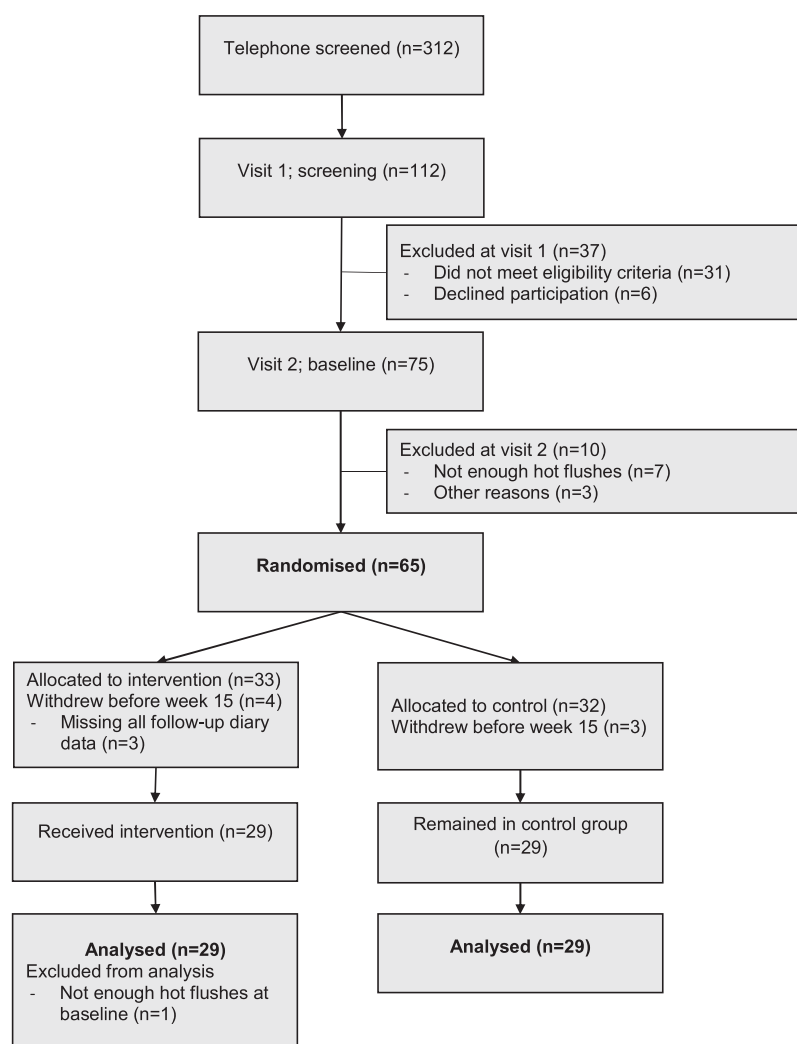


Fig. 1. Overview of the trial flow. All women completed a two-week hot flush screening diary between visit 1 and 2. Inclusion and randomisation were done during visit 2. Seven participants withdrew before the end of the 15-week study period. One participant was included despite too few hot flushes at baseline and was excluded from the analyses.

HF/24 h from the two-week screening diary. Post-intervention values were calculated similarly, using data from week 15 in the diaries. Analysis of covariance was used to compare mean moderate and severe HF at week 15 between the intervention group and the control group, adjusted for HF at baseline (Table 2). Mean absolute and percentage change from baseline to week 15 were calculated for the intervention and control groups separately and compared between the groups using student's t-test. Confidence intervals (95%) for the mean absolute and percentage change were calculated separately, and are presented in Table 2.

We calculated a HF score by multiplying the mean mild, moderate and severe HF/24 h by one (mild), two (moderate) or three (severe) respectively. The generated scores were added to provide a HF score for each participant at baseline and week 15 and the change was compared between the groups using student's t-test.

Mean moderate and severe HF/24 h were also calculated for week 3, 6, 9 and 12 and the change over time analysed using ANOVA for repeated measures for both groups separately. We also defined the proportion in each group that decreased by at least 50% in frequency of moderate and severe HF from baseline to week 15 and compared them using chi² test.

The influence of compliance was analysed by dichotomizing the intervention group into "compliant" or "non-compliant" based on our pre-specified definition. The mean change in HF frequency was

compared between the compliant and non-compliant groups, as well as between the compliant group and control group.

2.6.2. Resistance training and physical activity

Pearson correlation analysis was performed to evaluate the correlation between mean resistance training sessions/week and the change in frequency of moderate and severe HF in the intervention group.

Minutes spent on low-intensity and moderate- to vigorous intensity physical activity/week were extracted from the HF diaries and added to minutes spent on resistance training/week. Training sessions at the gym were standardized as lasting 45 min (standard program), or 60 min if the participant had noted extra exercises in their gym logbook. Paired comparisons from baseline to week 15 were performed for both groups using Wilcoxon signed rank test for related samples. Data from IPAQ were used to calculate metabolic equivalent (MET) minutes/week for both groups at baseline and at week 15, and the difference analysed by Mann-Witney-U test [23].

2.6.3. Missing data

If a participant had not completed the HF diary until the end of week 15 but registered ≥ 13 weeks, the last seven registered days were carried forward and used as week 15. If < 13 weeks were registered we used mean imputation to replace the missing value, using the mean value for week 15 from the participant's allocated group.

Table 1

Baseline characteristics of included participants. There were no significant differences between the groups in any of the variables. Hot flush severity was defined as follows: mild – sensation of heat without sweating; moderate – sensation of heat with sweating, able to continue activity; severe – sensation of heat with sweating and need to pause an ongoing activity, including waking up during the night. Hot flush score = the sum of mean hot flushes multiplied by severity (mild x 1, moderate x 2, severe x 3). Physical activity data in this table derived from the hot flush screening diary.

	Intervention group n = 29	Control group n = 29
	Mean (SD)	
Age at inclusion, years	55.2 (5.5)	55.4 (5.0)
Weight, kg	76.3 (12.0)	72.3 (11.5)
Body mass index, kg/m ²	28.2 (4.1)	26.7 (3.6)
Waist circumference, cm	92.2 (12.5)	88.8 (12.9)
	N (%)	
Smoker	1 (3.4)	1 (3.4)
	Median (IQR)	
Physical activity	115 (118.75)	160 (152.5)
Total physical activity, min/wk	83 (107.5)	120 (130.25)
Low intensity, min/wk	15 (35.0)	0 (48.8)
Moderate-vigorous intensity, min/wk		
	Mean (SD)	
Hot flushes/24 h		
Moderate	3.2 (1.5)	2.9 (1.7)
Severe	4.3 (3.4)	3.8 (2.6)
Moderate + Severe	7.5 (4.0)	6.6 (2.2)
Hot flush score	20.5 (11.6)	17.9 (6.4)

3. Results

Totally 312 women were telephone screened, 65 were randomised and 58 attended the week-15 visit (Fig. 1). One participant was mistakenly included despite too few HF at baseline and was excluded from the analyses. Among the eight participants who withdrew, seven did not provide more than baseline diary data and were not included in the analyses, which therefore contained 58 women (Table 1 shows baseline characteristics).

3.1. Effect on hot flushes

Moderate and severe HF decreased more in the intervention group than in the control group (mean difference -2.7 , 95% CI -4.2 to -1.3). The mean percentage decrease was -43.6% (-56.0 – -31.3) in the intervention group versus no change in the control group (Table 2). There was no significant difference between compliant and non-compliant participants. Moderate and severe HF decreased by at least 50% in 13/29 (44.8%) participants in the intervention group and 1/29 (3.4%) in the control group ($p < 0.001$). The longitudinal analysis showed that HF decreased significantly already after three weeks of resistance training, whereas the control group did not change (Fig. 2).

Table 2

Comparison of moderate and severe hot flushes at baseline and week 15 between intervention and control groups. Effect size calculated by ANCOVA adjusted for baseline values. The table also shows change in moderate and severe hot flushes and hot flush score from baseline to week 15. Hot flush score; the sum of mean hot flushes multiplied by severity (mild x 1, moderate x 2, severe x 3). Difference between change scores calculated by Student's t-test.

	Intervention group n = 29	Control group n = 29	Intervention vs control
Moderate + severe hot flushes, Mean (SD)			Mean difference (95% CI)
Baseline	7.5 (4.0)	6.6 (2.2)	
Week 15	4.4 (4.1)	6.5 (3.3)	-2.7 (-4.2 to -1.3)
Change in mean hot flushes/24 h, Mean (95% CI)			P for difference between groups
Percentage change	-43.6% (-56.0 – -31.3)	-2.0% (-16.4 – 12.4)	< 0.001
Absolute change	-3.1 (-4.3 – -1.9)	-0.2 (-1.1 – 0.8)	< 0.001
Change in hot flush score, Mean (95% CI)			
Percentage change	-44.3% (-56.5 – -32.1)	1.9% (-13.4 – 17.2)	< 0.001
Absolute change	-8.8 (-12.2 – -5.3)	0.1 (-2.5 – 2.7)	< 0.001

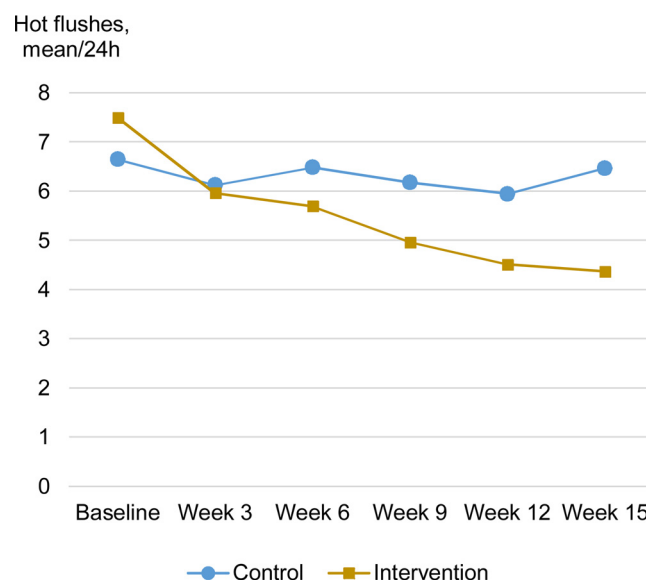


Fig. 2. Mean moderate and severe hot flushes/24 h registered in hot flush diaries during the trial by the control group and intervention group, respectively. The chart shows data from selected weeks. Control N = 29, Intervention N = 29.

3.2. Resistance training and physical activity

Participants in the intervention group completed a mean of 2.2 resistance training sessions/week and 62% were defined as compliant. There was no significant correlation between change in frequency of moderate and severe HF and mean completed training sessions/week, neither when analysed according to intention to treat nor per protocol.

3.2.1. Diary data

Median weekly time spent on physical activity of any intensity increased by 68 min in the intervention group (to 183 min at week 15, $p = 0.03$) whereas there was no difference in the control group (146 min at week 15, $p = 0.93$) without any correlation between change in minutes/week and change in mean HF/day in either group.

3.2.2. IPAQ data

Median MET minutes/week at baseline was 429 in the intervention group and 596 in the control group ($p = 0.37$) versus 1524 in the intervention group and 624 in the control group after 15 weeks (p for difference between groups = 0.02).

3.3. Missing data

Fourteen participants (10 controls, 4 in the intervention group) did

not complete the HF diaries until week 15. Of these, nine women (three in the intervention group) completed the diaries until week 13; two participants completed 12 weeks, two completed five weeks (one in the intervention group), and one completed four weeks. The significant differences between groups were not affected by whether the five participants who had registered < 13 weeks were excluded from the analyses or included using mean imputation. Regarding data from IPAQ, 8/29 in the intervention group and 5/29 in the control group had ticked “I don’t know” on one or several questions, meaning 45/58 IPAQ forms could be used to calculate MET minutes.

3.4. Adverse events

No serious adverse events were reported. Two participants were prevented from resistance training for one week, one due to knee pain after the first exercise session and another reported thigh pain after three weeks. In total, five participants in the control group and eleven in the intervention group reported mild muscle or joint pain at some point.

4. Discussion

Frequency of moderate and severe HF decreased by 44% in postmenopausal women randomised to 15 weeks of resistance training, whereas there was no significant change in the control group. Almost half of the intervention group reported a clinically significant decrease in HF of at least 50%. Two-thirds of the intervention group reached the compliance goal and performed resistance training at least two times/week.

Our findings differ from most previous studies on effects of exercise on menopausal HF that mostly have shown no or only modest effects [5]. Sternfeld and colleagues [24] found that vasomotor symptoms decreased to the same extent in women randomised to 12 weeks of aerobic exercise and women receiving no exercise intervention. Likewise, another study found similar decreases in HF with two aerobic exercise interventions as in untreated controls [13].

Release of endogenous opioids during exercise has been proposed to affect the thermoregulatory centre, diminishing HF [6]. If the exercise needs to be performed at a certain intensity to be effective, this could be a reason why most low-intensity interventions like walking or yoga have been found to have no effect [25–27]. A small intervention study compared 12 weeks of aerobic exercise to HT and found that HF decreased by almost 50% in women who continued to exercise for another three months after the original study period [28]. The resistance training in our study was performed with high loads which may have contributed to the clinically significant and rapid decrease in HF.

Previous studies have all tested variants of aerobic exercise, and the difference in outcomes could be explained by different physiological responses to resistance training and aerobic exercise. While aerobic exercise mainly increases VO_2 max and work capacity, resistance training leads to increased strength and muscle volume. Although both exercise modalities activate muscle groups, different muscle fibres are recruited as a response to the different demands during exercise, with more muscle fibres being activated during resistance training than aerobic exercise. However, it is not known whether resistance training affects the endogenous opioid system differently than aerobic exercise.

A strength with this study was the standardised exercise dose based on individual strength tests at baseline, i.e. everyone exercised at the same relative intensity. The same physiotherapist performed all tests and followed the participants. We used personal diaries, electronic logs, and a validated questionnaire to assess compliance and change in physical activity. The control group did not increase its physical activity and the increase in the intervention group consisted of resistance training. Thus, the exercise group received the intended intervention and there was no “spill-over” effect of the intervention to the control group. Previous studies reported high drop-out rates [28], low

compliance to the intervention [25], or have not reported compliance [26]. Incomplete outcome data has also been an issue, resulting in risk of bias and lower power in the analyses to detect changed HF. In this study compliance was good, and 89% of participants finished the trial.

On the other hand, there were missing data from 14 participants who did not complete the HF diaries until the end of week 15. Most with incomplete diaries belonged to the control group (10/14), which could increase the risk of bias in the results. The analysis could underestimate the decrease in the control group if HF decreased in both groups. However, the repeated measures ANOVA showed that HF in the control group only varied non-significantly between different time points and the differential missing data should not have affected our primary analysis to show a “false” larger effect.

Another limitation was the lack of a placebo/sham intervention in the control group. They could have received weekly support to mimic the regular contact with the physiotherapist. A Finnish trial that compared aerobic exercise to no treatment let all participants take part in lectures about physical activity to motivate them to stay in the trial [26]. A drawback with that option is that participants in the control group may become motivated to increase their physical activity, which defeats the purpose of the control group. Further limitations include our use of a self-reported measure to evaluate HF, although the number of HF registered in a diary correlate well with the number of flushes registered objectively [29].

The results of our trial may only be generalised to the studied group, i.e. healthy postmenopausal women. Further research is needed to investigate whether this is applicable to others suffering from HF, like breast and prostate cancer patients. It is also unknown whether different exercise regimes or modalities affect HF differently. A future study should include several exercise arms, with both aerobic and resistance training, to make direct comparisons possible.

5. Conclusion and implications

Resistance training was an effective and safe intervention to reduce hot flushes in postmenopausal women. This implicates that resistance training could be recommended to postmenopausal women and might relieve hot flushes, adding to other health effects.

Contributors

Emilia Berin contributed to validation, formal analysis, investigation, data curation, writing the original draft, reviewing and editing, and visualization.

Mats Hammar contributed to conceptualization, methodology, validation, investigation, reviewing and editing the manuscript, and funding acquisition.

Hanna Lindblom contributed to methodology, validation, investigation, and reviewing and editing the manuscript.

Lotta Lindh-Åstrand contributed to conceptualization, methodology, software, validation, formal analysis, investigation, reviewing and editing the manuscript, and funding acquisition.

Marie Rubér contributed to software, investigation, and reviewing and editing the manuscript.

Anna-Clara Spetz Holm contributed to conceptualization, methodology, validation, formal analysis, investigation, reviewing and editing the manuscript, funding acquisition, and project administration.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ministry of Education and Research. Grant applications are peer reviewed by expert panels within the area of research to assess the scientific quality and feasibility. The funding source was not involved in study design, data collection or preparation of the manuscript.

Ethical statement

We confirm that the submitted work has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. We confirm that the study has been conducted in line with the ethical principles set up in the Declaration of Helsinki. All participants received detailed oral and written information about the study before inclusion, and all gave written informed consent to participate.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

Individual participant data that underlie the results (text, tables, figures) will be available after deidentification to investigators whose proposed use of the data has been approved by an independent ethical review committee identified for the purpose. Data will be shared for the purpose of individual participant data meta-analysis. The study protocol may also be available upon request. Data will be available ten years following article publication by submitting a proposal to the corresponding author. After ten years data may still be available upon request, but cannot be guaranteed.

Ethical approval

The Regional Ethical Review Board in Linköping approved the trial protocol (ID: 2013/285-31). All participants gave oral and written informed consent to participate in the trial. We followed the principles set up by the World Medical Association in the Declaration of Helsinki and applicable standards of ICH-Good Clinical Practice.

CRediT authorship contribution statement

Emilia Berin: Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Mats Hammar:** Conceptualization, Methodology, Validation, Investigation, Writing - review & editing, Funding acquisition. **Hanna Lindblom:** Methodology, Validation, Investigation, Writing - review & editing. **Lotta Lindh-Åstrand:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - review & editing, Funding acquisition. **Marie Rubér:** Software, Investigation, Writing - review & editing. **Anna-Clara Spetz Holm:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - review & editing, Funding acquisition, Project administration.

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