

# Effects of applied relaxation on vasomotor symptoms in postmenopausal women: a randomized controlled trial

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## Abstract

**Objective:** This work aimed to study the efficacy of group therapy with applied relaxation on vasomotor symptoms and health-related quality of life in postmenopausal women.

**Methods:** In this open, randomized controlled trial, 60 healthy postmenopausal women with at least seven moderate to severe hot flashes per 24 hours were randomized to either group therapy with applied relaxation (n = 33) or untreated control group (n = 27) for 12 weeks. A follow-up visit was scheduled 3 months after the end of therapy or participation in the control group. Salivary cortisol was measured three times during a 6-month period. Hot flashes were recorded in self-registered diaries, and health-related quality of life was assessed with the Women's Health Questionnaire.

**Results:** The number of hot flashes decreased by 5.0 per 24 hours in the applied relaxation group compared with 1.9 in the control group on the 12th week ( $P < 0.001$ ) and still remained at the same level at the 3-month follow-up ( $P < 0.001$ ). Health-related quality of life for vasomotor symptoms, sleep, and memory improved significantly on the 12th week measurement in the applied relaxation group compared with the control group. Salivary cortisol concentration was lowered markedly in the applied relaxation group on a single measurement but was otherwise mainly stable in both groups.

**Conclusions:** Applied relaxation can be used to treat vasomotor symptoms in healthy postmenopausal women.

**Key Words:** Randomized controlled trial – Menopause – Hot flashes – Applied relaxation – Health-related quality of life – Salivary cortisol.

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Women's health-related quality of life (HRQoL) during climacteric is dependent on the interaction of different factors, including physical, social, cultural, and personal characteristics<sup>1-4</sup> and ability to cope with stress.<sup>5</sup> Approximately 70% of women in Europe and North America experience hot flashes and night sweats during menopause, and 15% to 20% of these women describe these as troublesome mainly because of discomfort, social embarrassment, and sleep disturbances.<sup>6-8</sup>

Many women may not use hormone therapy (HT) because of adverse effects and contraindications. At present, prescription of HT has been significantly reduced owing to revised national and international treatment guidelines.<sup>9,10</sup> These new guidelines have made healthcare providers and women, in general, more cautious, as demonstrated by this large reduction in the prescription of HT.<sup>11,12</sup>

Different alternatives to HT for alleviation of vasomotor symptoms are described in the literature. These include pharmacological treatments,<sup>13</sup> different types of natural remedies,<sup>14,15</sup> acupuncture,<sup>16,17</sup> lifestyle changes, and mind-body therapies.<sup>18</sup>

Innes et al<sup>18</sup> presented a systematic review of mind-body therapies for menopausal symptoms. The review consists of 21 articles representing 18 clinical trials from six countries that met the inclusion criteria, including 12 randomized controlled trials (N = 719), 1 nonrandomized controlled trial (N = 58), and 5 uncontrolled trials (N = 105). Nine trials found that breath-based and other relaxation therapies showed promising results for alleviating vasomotor and other menopausal symptoms. Most of the studies reviewed had methodological or other limitations, complicating interpretation of findings. Further studies of these techniques will contribute to our understanding of their limitations and potentials.

Applied relaxation (AR) is a technique based on cognitive-behavioral therapy (CBT) using coping mechanisms and conditioning.<sup>19</sup> The method is frequently used within psychiatry to treat phobia, panic disorders, anxiety, and depression.<sup>19</sup> AR focuses on muscle relaxation, where breathing is used for the conditioning of relaxation. The goal is to reach rapid relaxation through right breathing in situations with bothersome symptoms (ie, hot flashes). A previous study with healthy postmenopausal women showed promising results on hot flash frequency, with an average decrease of more than 70%.<sup>20</sup> The effect persisted 3 months after therapy, and psychological well-being significantly improved probably owing to better sleep and

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diminished vasomotor symptoms. Similar results were seen in a group of women with breast cancer and vasomotor symptoms.<sup>21</sup> The level of evidence was, however, low in both studies owing to the study design. Although the studies were randomized and controlled, there was no group of women without treatment.

The factors underlying how alternative treatment works and the mechanisms underlying improvements in symptoms are not fully understood.

Many studies show that women with vasomotor symptoms report sleep disturbances.<sup>22,23</sup> If sleep is interrupted many times during nighttime, which is the reality in many women with vasomotor symptoms, the human stress system may be activated.<sup>24</sup> An important part of the human stress system is the hypothalamic-pituitary-adrenal (HPA) axis. Activation of the HPA axis is initiated by the secretion of corticotrophin-releasing hormone, which in turn induces cortisol secretion from the adrenal cortex. Cortisol is a potent stress hormone regulated by the hypothalamic-pituitary axis with a specific secretion pattern. The HPA axis, besides responding to short-term stressors under resting conditions, follows a circadian rhythm, with a morning peak of cortisol as a response to awakening and with lower activity during the day and night until the early morning when HPA activity slowly increases before awakening.<sup>25</sup> Cortisol excretion differs between men and women of different ages. The method of analyzing salivary cortisol excretion is often used to measure different types of stress reactions.<sup>26-28</sup> Menopausal symptoms may be seen as stressors. Women who, in addition, sleep restlessly and are stressed from their symptoms may have a cortisol excretion profile different from that of otherwise asymptomatic women. One could expect women with disturbed sleep owing to nighttime flashes not to reach the normal morning peak of cortisol as a response to awakening.

We suggested that we could follow the biological effect of AR by sampling cortisol as a marker of vasomotor symptoms-induced stress.

Cortisol in saliva reflects the free, biologically active fraction of cortisol in the serum, and the concentration is therefore independent of the concentration of the binding protein in plasma.<sup>29</sup> The sampling is noninvasive and painless and can be implemented in the home (<http://www.salimetrics.com>).

The objectives of the study were to compare the frequency of moderate to severe vasomotor symptoms between postmenopausal women treated with AR and an untreated control group (CG) and to investigate if HRQoL significantly improved in the treatment group (AR group) compared with the CG. Another objective was to measure salivary cortisol excretion three times in 24 hours in the treatment group before, during, and 3 months after treatment with AR and to compare these results with those from the CG.

## METHODS

### Participants

Postmenopausal women with hot flashes were invited to participate in this open randomized controlled study through advertisements in a local newspaper. Enrollment took place in one gynecological outpatient university-based clinic in Sweden

between January 2007 and September 2010. The eligibility criteria were as follows: (a) postmenopausal women (at least 12 mo since the last menstrual bleeding occurred or, in previously hysterectomized women, serum follicle-stimulating hormone level categorized as postmenopausal according to references in a local laboratory); (b) seven or more moderate to severe hot flashes per 24 hours or 50 or more hot flashes per week according to a 2-week screening diary; (c) ability to understand and speak Swedish; and (d) freely given informed consent forms. The exclusion criteria were as follows: (a) unstable thyroid disease or other metabolic diseases; (b) treatment of menopause-related symptoms with HT or other complementary or alternative treatments; (c) treatment with psychopharmacological drugs and/or sedatives; (d) untreated psychiatric disease; (e) frequent exercise ( $\geq 2$  h of high-intensity activities per week). All eligible women were offered medical examination and gynecological examination, including vaginal ultrasound, before inclusion in the study.

The trial was conducted in accordance with the Declaration of Helsinki.<sup>30</sup> Approval of the Regional Ethics Review Board in Linköping was received before the start of the study. All women received oral and written information about the study. A written informed consent form was obtained from all study participants before inclusion.

### Intervention

Eligible women were randomized to either AR, which required participation in 10 group sessions during a period of 12 weeks, or to participation in an untreated CG. The therapist (E.N.) met the women assigned to AR in a group consisting of six to eight women. The women were told to practice each component at home daily.

The weekly sessions based on a scheme from Ost,<sup>19</sup> as we have previously described,<sup>20</sup> lasted for 60 minutes each. During the first session, the women in the AR group were given a lecture about menopause and theories of AR mechanisms and how AR may be applied in vasomotor symptoms. The group was given a rationale for applying AR as a coping technique for handling sudden unanticipated symptoms by quickly calming down and thus gaining control of the situation. The women assigned to the CG were told that, apart from continuing the daily registration of hot flashes, they were to act as an untreated CG using none of the following: hormonal treatment, other alternative medications, and natural remedies for hot flashes (not even acupuncture, mind-body therapies, or intensive physical activity). After 6 months of participation in the CG, they were offered the AR program.

### Outcomes

The primary endpoint was the average number of moderate and severe hot flashes per 24 hours recorded in self-registered diaries on the 12th week in the AR group compared with the CG. The secondary variable was the average number of moderate and severe hot flashes per 24 hours after the 3-month follow-up and in the subgroup of women in the AR group who were defined as responders. Responders were defined as women with a 50% or higher reduction in hot flashes from baseline to the

12th week and at 3 months after “end of treatment.” Moreover, the total scores in the Women’s Health Questionnaire (WHQ), as measured on the 12th week and after the 3-month follow-up, were recorded.

The third endpoint was to follow the secretion of cortisol in all women to determine if the daily pattern of excretion would change within the AR group compared with the CG.

Adverse events were documented by using open-ended questions at each contact.

### Measurements of study variables

#### Hot flashes

Paper-and-pencil hot flash diary was used to assess hot flash frequency during the 2-week screening period and during 12 weeks in the AR group or the CG. Both groups had a 3-month follow-up, with hot flash registration in the diary at 1 week per month. Severity was subjectively estimated on a scale consisting of the following: (1) mild hot flashes (hot flash without sweating, not bothersome); (2) moderate hot flashes (bothersome hot flash and sweating, but without interruption of daily/nightly activity); or (3) severe hot flashes (bothersome hot flash and sweating, with interruption of daily/nightly activity). The women were told to register twice daily (ie, in the morning, the women should register all hot flashes that occurred in the night; in the evening just before bedtime, they were told to register all hot flashes that occurred during daytime). The women were encouraged to register continuously during the day.

The baseline average number and severity of flashes per 24 hours were calculated from the 2-week screening period, and the 12th week figure was calculated as an average of the 7 days of the 12th week. Data from the diaries were missing in four women on the 12th week (three women in the AR group and one woman in the CG) and in three women at the 3-month follow-up (two women in the AR group and one woman in the CG). In addition, nine women (eight women in the AR group and one woman in the CG) did not complete every recording during the 12th week, and a carry-forward procedure was used (ie, registrations on the 11th week were carried forward to replace missing values on the 12th week). No data were missing at the 3-month follow-up.

#### Health-related quality of life

HRQoL was assessed using the WHQ at baseline; on the 12th week in the AR group and the CG, respectively; and at the 3-month follow-up. The questionnaire was used as a self-administered instrument validated and used to assess middle-aged women’s physiological and emotional health. It has been widely used in multinational clinical trials and has high internal reliability (Cronbach’s  $\alpha = 0.70-0.84$ ) and test-retest reliability (Cronbach’s  $\alpha = 0.78-0.96$ ).<sup>31</sup>

The WHQ has been validated for Swedish conditions<sup>32</sup> and contains 36 items assessing nine subscales (depressed mood, anxiety/fear, vasomotor symptoms, sleep problems, somatic symptoms, menstrual symptoms, sexual behavior, memory/concentration, and attractiveness). Each item is rated on a four-point scale to reflect frequency (yes, definitely; yes, sometimes; no, not much; no, not at all) and reduced to a binary

option ranging between 0 and 1. The subscales are summarized and divided by the number of items for each subscale. The value 0 is the most positive option, and the value 1 is the most negative option.<sup>33</sup> The WHQ is sensitive to change, and a meaningful clinically significant change on the subscales<sup>34</sup> is suggested as a difference of 0.10 to 0.20.<sup>33</sup>

In total, 4 (2%) of 180 questionnaires were missing.

#### Salivary cortisol

Before collecting their saliva, the women were instructed not to eat, drink, or smoke later than 60 minutes before sampling. For women working nighttime, the instruction was to collect the sample on a “free day.” Brushing of teeth was not allowed for 60 minutes before sample collection to minimize the risk of blood contamination. The women were not allowed to perform physical exercise within 30 minutes before sample collection and were instructed to rest (preferably lying down) for at least 30 minutes.

Saliva was collected with Salimetrics Oral Swab (<http://www.salimetrics.com>) three times during a 24-hour period: at awakening, 30 minutes after awakening, and at bedtime. The procedure was repeated by all women three times during the study: at baseline, on the 12th week, and after the 3-month follow-up (end of the study). The analyses were performed at the laboratory of the Linköping University Hospital according to the recommendations of the manufacturer. All samples were analyzed in one batch after the end of the study. A commercial enzyme immunoassay kit designed for the analysis of salivary cortisol was used (<http://www.salimetrics.com>). The measurable range was 0.3 to 82 nmol/L. Calibrations and quality control in two different levels were performed at the beginning and at the end of each assay. The coefficient of variation was below 6%.

#### Adverse events

At every follow-up contact, all women were given open-ended questions on whether any adverse events had occurred since the last visit.

#### Randomization

An independent statistician prepared a computer-generated randomization list. The randomization process was unknown to the study team. In total, at least 60 women were planned for randomization to either the AR group or the CG.

If the inclusion and exclusion criteria were met, a sealed opaque envelope was opened in consecutive order by the investigator together with the women.

#### Statistical methods

Sample size assumption was based on the assumption that using AR for vasomotor symptoms would reduce both the severity and the frequency of hot flashes by at least 50% from baseline. Standard deviation was estimated to be one hot flash per 24 hours. To obtain a power of 80%, we would need 20 women per group to detect a significant difference between groups ( $P < 0.05$ , two-sided test).

The study was also designed to analyze variation in 24-hour salivary cortisol levels and a possible relation to hot flashes.

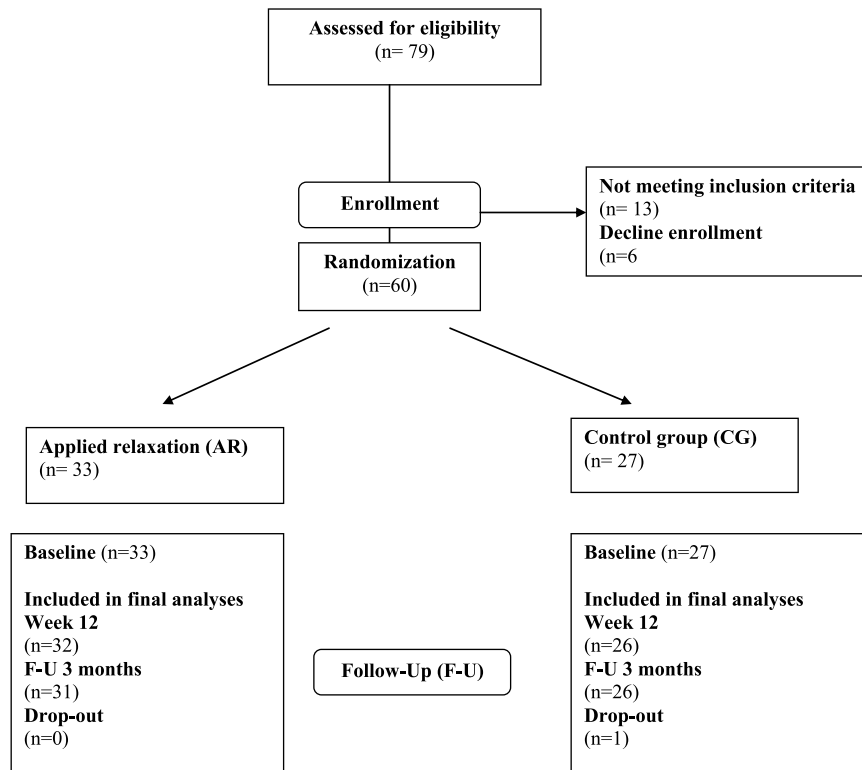


FIG. 1. Recruitment and flow of women included in the final analyses of the study. AR, applied relaxation; CG, control group.

Because there have been no previous studies in this area and to compensate for dropouts, we estimated that we would need approximately 50% more women for this analysis and thus decided to include about 30 women in each group.

Data were analyzed according to “intention to treat” (ie, including all women who fulfilled the inclusion criteria, had no exclusion criteria, initiated their treatment or control arm according to randomization, and had at least one hot flash measurement registered).

Baseline and demographic data were described as mean (SD). To compare differences between the two groups, we used Student’s *t* test for hot flashes and Mann-Whitney *U* test for analysis of differences in the change of scores in the WHQ. Repeated-measures analysis of variance was used to compare hot flashes per 24 hours between the two groups from baseline to the 3-month follow-up.

Descriptive statistics were used to analyze salivary cortisol in each studied group, and Mann-Whitney *U* test was used for measurements between groups.

$P < 0.05$  (two-sided) was considered significant. Data analyses were performed by Statistica from Stat Soft, standard version 9. All statistical analyses were performed with assistance from an independent statistician.

## RESULTS

Of the 79 women screened for eligibility, 60 women were randomized to either the AR group ( $n = 33$ ) or the untreated CG ( $n = 27$ ; Fig. 1). Six women declined enrollment, three

women started HT or other treatment of vasomotor symptoms, and three women declined because of personal reasons.

All women in the AR group continued the 12-week program, but two women did not fulfill the requirement of keeping the weekly diaries and the WHQ at the 3-month follow-up. In the CG, one woman discontinued prematurely after the baseline visit because of health-related problems.

No significant differences in demographic variables or clinical characteristics were found between the two groups at baseline (Table 1). Only one woman was a nighttime worker (included in the AR group), five women were retired, and the remaining women were part or full daytime workers.

### Hot flashes

The two groups did not differ in moderate and severe hot flash frequency per 24 hours at baseline. There was a statistically

TABLE 1. Baseline demographic and clinical characteristics of participating women

	AR group		Untreated CG		<i>P</i> <sup>a</sup>
	Mean (SD)	n	Mean (SD)	n	
Age at inclusion, y	54.0 (5.7)	33	56.0 (5.1)	27	NS
Months since menopause	58.7 (82.8)	25	58.3 (56.6)	25	NS
Body mass index, kg/m <sup>2</sup>	25.8 (4.3)	33	25.3 (3.0)	27	NS
Number of hot flashes/24 h	9.1 (2.8)	33	9.7 (2.6)	27	NS

AR, applied relaxation; CG, control group; NS, not significant.  
<sup>a</sup>Student’s *t* test.



significant difference in the frequency of moderate and severe hot flashes between the two groups on the 12th week ( $P < 0.001$ ) and at the 3-month follow-up ( $P < 0.001$ ; Table 2). Repeated-measures analysis of variance showed that moderate and severe hot flash frequency significantly decreased over time in the AR group compared with the CG ( $F[2,106] = 12.99$ ,  $P < 0.001$ ; Fig. 2).

In addition, the reduction in hot flashes in the AR group was 55% from baseline to the 12th week and 52% at the 3-month follow-up compared with a reduction of 20% and 18%, respectively in the CG.

In an analysis of the subgroup of women in the AR group defined as responders ( $n = 14$ ), the mean reduction in hot flashes was 67% (range, 51%-83%) on the 12th week and 75% (range, 50%-96%) at the 3-month follow-up. In the CG, 2 of 26 women had a reduction in hot flashes of more than 50%.

**Health-related quality of life**

There were no differences in WHQ scores between the two groups at baseline. The median baseline scores and the changes in eight of the dimensions after 12 weeks and 3 months are shown in Table 3. The dimension for menstrual symptoms was not analyzed because all women were postmenopausal. After 12 weeks, memory/concentration ( $P < 0.05$ ), vasomotor symptoms ( $P < 0.05$ ), and sleep ( $P < 0.05$ ) dimension scores in the WHQ were statistically significantly improved in women randomized to the AR group compared with the CG (Table 3). A clinically significant change within each domain of the WHQ has been proposed to be a difference of at least 0.10 to 0.20.<sup>31,32</sup> The changes in the above-mentioned domains were even higher (0.14-0.50) in the AR group, whereas the CG had no significant changes at all according to the WHQ. Moreover, at 3 months, there were significant differences in the dimensions for somatic symptoms ( $P < 0.05$ ), memory/concentration ( $P < 0.01$ ), sleep ( $P < 0.01$ ), and anxiety ( $P < 0.05$ ) between the AR group and the CG. In addition, there were statistically significant improvements in the dimension for vasomotor symptoms for the women defined as responders ( $n = 14$ ) in the AR group compared with nonresponders ( $n = 18$ ).

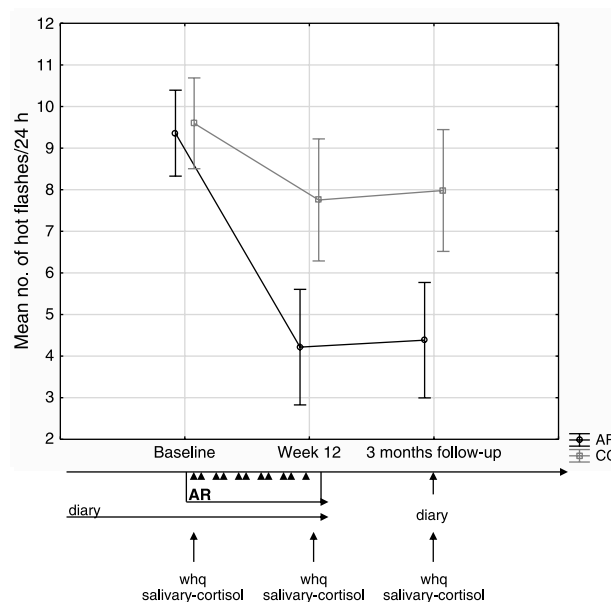
**Salivary cortisol**

There was no difference in the daily secretion of salivary cortisol between the two studied groups at baseline. Women participating in the study had a normal diurnal pattern of cortisol. The baseline median morning value in the AR group was 8.4 nmol/L, and the baseline median morning value in the CG

**TABLE 2.** Number of moderate and severe hot flashes per 24 hours between the AR group and the untreated CG

	AR group		CG		<i>P</i> <sup>a</sup>
	Mean (SD)	n	Mean (SD)	n	
Hot flash frequency per 24 h					
Baseline	9.1 (2.8)	33	9.7 (2.6)	27	NS
12th wk	4.1 (3.3)	32	7.8 (4.1)	26	<0.001
3-mo follow-up	4.4 (3.5)	31	8.0 (3.8)	26	<0.001

AR, applied relaxation; CG, control group; NS, not significant.  
<sup>a</sup>Student's *t* test.



**FIG. 2.** Mean (SD) number of moderate and severe hot flashes per 24 hours registered by women in two randomization groups (at baseline, at 12 wk, and after 3 mo of follow-up). AR, applied relaxation; CG, control group; WHQ, Women's Health Questionnaire.

was 8.8 nmol/L. The baseline median evening value for the AR group was 1.4 nmol/L, and that for the CG median evening value was 1.1 nmol/L. There was no significant difference between the groups at baseline.

A significantly lower value for morning secretion was observed only once; this lower value was observed in the AR group at the 3-month follow-up, as measured with the Mann-Whitney *U* test ( $P < 0.05$ ). The median value for the AR group at this time was 7.1 versus CG 9.9 nmol/L.

**Adverse events**

No woman discontinued treatment because of adverse effects.

**DISCUSSION**

The main finding is that AR can be accepted as a well-functioning treatment of vasomotor symptoms in otherwise healthy postmenopausal women. The results show that both moderate to severe vasomotor symptoms and HRQoL significantly improved in women using AR compared with untreated women. All improvements in the AR group remained 3 months after program completion.

Almost all women attended the weekly program and registered the daily practice of AR in their diaries. Once women had become accustomed to practising AR, they were able to relax without actively noting this. Women begin to breathe deeply a few times without being aware of this change in breathing. The purpose of this method is to make this change in breathing a habit and something that the women are no longer aware of. If they succeed, it becomes impossible to measure the exact frequency of practising AR.

**TABLE 3.** WHQ scores at baseline and the median changes from baseline to 12th weeks and from baseline to the 3-month follow-up

WHQ dimensions	AR group		CG		P <sup>a</sup>
	Median (IQR; 25 to 75)	n	Median (IQR; 25 to 75)	n	
Depressed mood					
Baseline	0.00 (0.00 to 0.21)	32	0.14 (0.00 to 0.29)	27	NS
Change from baseline to 12 wk	0.00 (−0.07 to 0.14)	32	0.00 (−0.14 to 0.00)	26	NS
Change from baseline to follow-up	0.00 (0.00 to 0.14)	30	0.00 (−0.14 to 0.00)	26	NS
Somatic symptoms					
Baseline	0.29 (0.14 to 0.43)	33	0.29 (0.14 to 0.43)	27	NS
Change from baseline to 12 wk	−0.14 (−0.29 to 0.00)	32	0.00 (−0.14 to 0.00)	26	NS
Change from baseline to follow-up	−0.14 (−0.29 to 0.00)	30	0.00 (−0.14 to 0.14)	26	<0.05
Memory/concentration					
Baseline	0.33 (0.00 to 0.33)	33	0.33 (0.00 to 0.67)	27	NS
Change from baseline to 12 wk	0.00 (−0.33 to 0.00)	33	0.00 (−0.33 to 0.33)	26	<0.05
Change from baseline to follow-up	0.00 (−0.33 to 0.00)	31	0.00 (−0.33 to 0.33)	26	<0.01
Vasomotor symptoms					
Baseline	1.00 (1.00 to 1.00)	33	1.00 (1.00 to 1.00)	27	NS
Change from baseline to 12 wk	0.00 (−0.50 to 0.00)	33	0.00 (0.00 to 0.00)	26	<0.05
Change from baseline to follow-up	−0.50 (−1.00 to 0.00)	31	0.00 (0.00 to 0.00)	26	NS
Anxiety/fear					
Baseline	0.00 (0.00 to 0.25)	33	0.00 (0.00 to 0.25)	27	NS
Change from baseline to 12 wk	0.00 (−0.25 to 0.00)	33	0.00 (0.00 to 0.25)	26	NS
Change from baseline to follow-up	0.00 (−0.25 to 0.00)	31	0.00 (0.00 to 0.25)	26	<0.05
Sleep problems					
Baseline	0.67 (0.33 to 0.67)	33	0.33 (0.00 to 0.67)	27	NS
Change from baseline to 12 wk	−0.33 (−0.67 to 0.00)	32	0.00 (−0.33 to 0.00)	26	<0.05
Change from baseline to follow-up	−0.33 (−0.67 to 0.00)	31	0.00 (0.00 to 0.33)	26	<0.01
Attractiveness					
Baseline	0.00 (0.00 to 0.50)	33	0.50 (0.00 to 0.50)	27	NS
Change from baseline to 12 wk	0.00 (0.00 to 0.00)	33	0.00 (0.00 to 0.50)	26	NS
Change from baseline to follow-up	0.00 (0.00 to 0.50)	31	0.00 (0.00 to 0.50)	26	NS
Sexual behavior					
Baseline	0.33 (0.00 to 0.67)	31	0.33 (0.00 to 0.33)	24	NS
Change from baseline to 12 wk	0.00 (0.00 to 0.00)	30	0.00 (0.00 to 0.33)	23	NS
Change from baseline to follow-up	0.00 (−0.33 to 0.00)	29	0.00 (0.00 to 0.17)	24	NS

Values of scores vary between 0 (“good health status”) and 1 (“poor health status”).

WHQ, Women’s Health Questionnaire; AR, applied relaxation; CG, control group; IQR, interquartile range; NS, not significant.

<sup>a</sup>Mann-Whitney *U* test for comparison between groups.

The primary study variable was a subjective estimation of the number and severity of hot flashes. This method has been used in several studies and is considered to be a valid and reliable method.<sup>35,36</sup>

The minimal clinically important reduction in hot flashes is suggested to be approximately 50%.<sup>37</sup> This study showed that the treatment group of 33 women had a 55% reduction in moderate to severe vasomotor symptoms. When analyzing women with higher than 50% reduction, we found a group of 14 women with a significant mean reduction in hot flashes: 67% on the 12th week and 76% at the 3-month follow-up. These findings are similar to our previous results<sup>20,21</sup> in which we randomized women to different treatments, but note that there was no untreated CG then, so the presence of a CG is a strength of this study. In a recent randomized study by Ayers et al of women who participated in group CBT or self-help CBT, a significantly reduced hot flash/night sweat problem rating was observed 6 weeks after randomization compared with women randomized to a no-treatment CG. The total hot flash frequency was reduced by 40%, 36%, and 23%, respectively, in the group CBT, self-help CBT, and no-treated CG (not significant) at the end of the study.<sup>38</sup> Our study showed results in line with Ayers et al and demonstrated even stronger effects for AR (“CBT-like-therapy”).

The results for women defined as responders lead us to ask if it is possible that some women are particularly well suited for this type of treatment and some others simply are not. The fact that the women were recruited through advertisements could possibly have an impact on the generalizability of the results. Mechanisms, perceptions of hot flashes, and ways to manage sweats and hot flashes are probably different for different women. There are possible relationships between biological, cognitive-behavioral, and environmental factors influencing hot flashes<sup>8</sup>; thus, for some women, “CBT-like-therapy” may not be suitable.

HRQoL is an important factor to study when introducing “new” treatments. A clinically significant change within each domain of the WHQ is a difference of approximately 0.10 to 0.20.<sup>31,32</sup> In our study, the median changes in the above-mentioned domains were even higher (0.14–0.50) in the AR group, whereas the CG had no significant changes at all according to the WHQ. This is probably an effect of diminished vasomotor symptoms, which improve sleep and secondary memory and concentration. In general, the women themselves believed that they are in better somatic health. The study of Ayers et al<sup>38</sup> showed similar significant improvements in some of the WHQ dimensions (somatic symptoms, anxiety/fears, and memory/concentration) when they compared group CBT and an

untreated CG. Thus, Ayers et al did not find any significant improvements in the dimensions for sleep and vasomotor symptoms.

Several studies have found group differences in basal cortisol to be dependent on the time of day.<sup>34,39-41</sup> For example, concerning chronic stress, cortisol relationship that is dependent on the time of day has been found. It is clear that sampling several times during the day yields a more thorough picture of basal HPA activity than sampling at one single point. In this study, almost all women were used (five women retired, and only one woman was a nighttime worker), which means that the group was homogenous in that perspective. Salivary cortisol was lower in the AR group in one single measurement but remained generally unchanged. The reasons for the generally constant level of salivary cortisol may be the following: first, the women had normal salivary cortisol levels at baseline and showed no high morning levels as a secondary measurement of chronic stress. Second, learning AR may not affect the excretion of diurnal salivary cortisol even if women feel better and their symptoms are reduced. Third, night awakenings were maybe not as many to influence the HPA axis at baseline. Probably mechanisms other than cortisol and HPA are involved, which can explain the improved well-being and diminished vasomotor symptoms in this study.

No adverse physical or psychological effects were reported during the study period, which means that this type of treatment probably is harmless and may be one important reason for the compliance being so high in the AR group. This is consistent with other studies using mind-body therapies.<sup>18</sup> Multiple randomized placebo-controlled trials have been performed to test antidepressant treatment of vasomotor symptoms. The effect of antidepressants on vasomotor symptoms (measured as the number of hot flashes) is usually, at best, up to 50%. The dropout rates for reported studies of antidepressants for vasomotor symptoms are, however, remarkably high because of adverse effects.<sup>42-46</sup> According to these findings, AR is safe and compares well with studies on antidepressants.

## CONCLUSIONS

AR can be suggested as an appropriate and safe alternative therapy for reducing moderate to severe hot flashes in healthy postmenopausal women. Furthermore, AR improves HRQoL.

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