



# Internet-based cognitive behavioral therapy aimed at alleviating treatment-induced menopausal symptoms in breast cancer survivors: Moderators and mediators of treatment effects

Vera Atema<sup>a</sup>, Marieke van Leeuwen<sup>a</sup>, Jacobien M. Kieffer<sup>a</sup>, Hester S.A. Oldenburg<sup>b</sup>, Marc van Beurden<sup>c</sup>, Myra S. Hunter<sup>d</sup>, Neil K. Aaronson<sup>a,\*</sup>

<sup>a</sup> Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

<sup>b</sup> Department of Surgical Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

<sup>c</sup> Department of Gynecology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

<sup>d</sup> Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, United Kingdom

## ARTICLE INFO

### Keywords:

Menopause  
Hot flushes  
Breast cancer  
Moderation  
Mediation  
Randomized controlled trial

## ABSTRACT

**Objectives:** Results from our recently conducted randomized controlled trial (RCT) indicated that Internet-based cognitive behavioral therapy (iCBT), with or without therapist support, is effective in reducing the perceived impact of hot flushes and night sweats (HF/NS) and overall levels of menopausal symptoms in breast cancer survivors with treatment-induced menopausal symptoms.

**Study design:** We used data of 235 women and compared the iCBT groups combined (n = 156) with the control group (n = 79). Bootstrapped multiple regression analyses with interaction terms (group x potential moderator) or indirect effects (mediation pathway) were conducted.

**Main outcome measures:** Reductions in perceived impact of HF/NS and overall levels of menopausal symptoms.

**Results:** Women with lower levels of education benefited most from the iCBT. Age, time since diagnosis, current endocrine treatment, oophorectomy, frequency of HF/NS, and psychological distress did not moderate the treatment effects. Factors that mediated treatment effects were the development of healthier beliefs about experiencing hot flushes in a social context, about the impact of night sweats on sleep and daily functioning, and about the ability to control and cope with hot flushes. The acquisition of behavioral coping strategies and decreased psychological distress did not mediate treatment effects.

**Conclusion:** The results suggest that women with lower levels of education may benefit most from the current iCBT program, with or without therapist support. The development of healthier HF/NS beliefs contribute significantly to the observed positive effect of iCBT on the burden of menopausal symptoms.

**Clinical trial information:** NCT02672189.

## 1. Introduction

Many young breast cancer (BC) survivors are confronted with menopausal symptoms caused by their BC treatment [1]. The most prevalent and disruptive menopausal symptoms are hot flushes and night sweats (HF/NS) which negatively affect health-related quality of life (HRQOL), and can result in women discontinuing their endocrine treatment [2–5]. A cognitive behavioral therapy (CBT) program was developed by Hunter and colleagues to help women cope with these HF/NS [6,7]. Four randomized controlled trials (RCTs) have provided evidence of the efficacy of this program, delivered in groups or in self-

help or guided self-help format, in reducing the perceived impact of HF/NS in healthy women (MENOS2 trial, MENOS@work trial) [8,9] and in BC survivors (MENOS1 trial and EVA trial) [10,11]. To increase compliance in the Dutch setting [11] we translated the program into an Internet-based format [12]. We recently evaluated this Internet-based CBT program (iCBT) in an RCT and found that both guided and self-managed versions significantly improved the perceived impact of HF/NS, overall levels of menopausal symptoms, sleep quality, and the frequency of HF/NS when compared to a waiting-list control group [13]. Moreover, the level of compliance was much higher compared to that observed in the earlier, group-based trial [11].

\* Corresponding author at: Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands.

E-mail address: [n.aaronson@nki.nl](mailto:n.aaronson@nki.nl) (N.K. Aaronson).

<https://doi.org/10.1016/j.maturitas.2019.09.007>

Received 15 July 2019; Received in revised form 11 September 2019; Accepted 16 September 2019

0378-5122/ © 2019 Elsevier B.V. All rights reserved.

Because individuals may differ in their response to interventions, it is important to gain insight into characteristics that moderate treatment effects, and thus identify those who will benefit most from an intervention [14]. Two studies have investigated the potential moderators and mediators of the positive effects of the CBT program in the MENOS1 and 2 trials. Although Norton et al. [15] did not identify any demographic or psychosocial moderators in their study among healthy women with menopausal symptoms, Chilcot et al. [16] found that BC survivors who did not undergo chemotherapy, who had higher levels of psychological distress at baseline, and who were non-white benefited most from the CBT. Other studies have identified additional moderators of the effects of psychosocial interventions [17–19]. For example, a meta-analysis using individual cancer patient data from 22 RCTs found that younger patients and patients who had undergone chemotherapy and/or surgery benefited most from psychosocial interventions [17]. Results from two other RCTs evaluating the efficacy of CBT for chronic pain or iCBT for sleep problems reported that more highly educated patients benefited most from the interventions [18,19].

Understanding the therapeutic change mechanisms responsible for treatment effects (i.e. mediators) provides valuable information for theory testing and further refinement of an intervention [14]. The proposed change mechanisms of our iCBT for women with menopausal symptoms reflect the general change mechanisms of CBT, i.e. changing maladaptive beliefs (cognitions) and behaviors. More specifically, our iCBT program targets three types of negative beliefs: the belief that hot flushes are embarrassing and that others will judge you when you experience hot flushes in a social context, the belief that you cannot influence the extent to which night sweats impact negatively on sleep and daily functioning and the belief that you are unable to cope or control hot flushes [20]. Additionally, the iCBT teaches two behavioral strategies: 1) ways to accept, ignore and/or use humor to cope with hot flushes (positive coping behavior) and 2) ways to remain in social situations even in the presence of HF/NS (avoidance behavior) [21,22]. The iCBT also aims to reduce psychological distress, as psychological distress negatively affects the perception and the frequency of hot flushes [22]. Chilcot et al. [16] found that, among BC survivors, changing all three unhelpful beliefs about HF/NS, improving sleep, and decreasing psychological distress mediated the treatment effects of CBT on HF/NS. Norton and colleagues [15] replicated these findings, in part, reporting that changes in beliefs about coping and control over hot flushes, and about the impact of night sweats on sleep and daily functioning, mediated improvements in HF/NS following CBT. In both studies, the beliefs that one is able to control and cope effectively with hot flushes was identified as the main mediator of the treatment effects [15,16].

The objective of the current study was to determine which of the hypothesized variables actually moderate and mediate the effects of our iCBT program among BC survivors who have experienced treatment-induced menopausal symptoms.

## 2. Methods

### 2.1. Research design and study sample

A detailed description of the design of the RCT has been reported elsewhere [23]. Briefly, from 2015 to 2017, we conducted an RCT to evaluate the efficacy of iCBT, with and without therapist support, in reducing treatment-induced menopausal symptom burden in BC survivors. Patients were recruited from 12 hospitals in the Netherlands. Following provision of the informed consent and completion of a baseline questionnaire (T0), 254 patients were randomized to guided iCBT, self-managed iCBT, or a waiting-list (control group).

Women randomized to either of the two interventions had access to a six-week iCBT program. A strong emphasis was placed on HF/NS, but other related problems were also addressed (e.g. sleep, stress). The level of literacy for the program was set at B1, making it comprehensible for

at least 80% of the population [24]. Women in the guided iCBT group received an additional telephone intake and weekly online feedback from a therapist. Participants allocated to the control group received usual care, which did not involve any form of care aimed at coping with menopausal symptoms.

Follow-up assessments were at 10 weeks (short-term, T1) and 24 weeks post-randomization (longer-term, T2). All institutional review boards of the participating centers approved the study. Data from 235 women (156 in the intervention groups and 79 patients in the control group) who completed all assessments were used for the current analysis.

### 2.2. Measures

Patient sociodemographic and clinical characteristics were assessed at baseline and included, among others, age, educational level and type of BC treatment.

#### 2.2.1. Outcome variables

The perceived impact of HF/NS was assessed by the problem rating of the Hot Flush Rating Scale (HFRS) [25]. Additionally, the overall levels of menopausal symptoms was assessed with the Functional Assessment of Cancer Treatment-Endocrine Symptoms questionnaire (FACT-ES) [26].

#### 2.2.2. Potential moderators

The choice of potential moderators was based on, but not limited to previous literature [15–19] and included age, education, time since diagnosis, current endocrine treatment, past oophorectomy, baseline frequency of hot flushes and night sweats as assessed by the HFRS frequency subscales [25], and baseline levels of psychological distress as assessed by the Hospital Anxiety and Depression Scale (HADS) [27].

#### 2.2.3. Potential mediators

The choice of potential mediators was based on the cognitive model of Hunter et al. and related studies [15,16,22]. The HF/NS Beliefs and Behavior Scale – Short Form was used to assess HF/NS beliefs and behaviors, organized into three belief subscales and two behavior subscales. It includes items from the Hot Flush Beliefs Scale [20] and the Hot Flush Behavior Scale [21] and is included in a Supplementary File. Psychological distress was assessed with the HADS [27].

### 2.3. Statistical analyses

Scale scores were calculated according to published scoring algorithms. Missing values were replaced by the average score of the completed items if at least 50% of the items in that scale were completed. Since the observed differences in the efficacy of the guided and self-managed iCBT groups were relatively small, and to increase statistical power, these groups were combined for the analyses [13].

We used the PROCESS Macro developed by Hayes [28] to conduct path analyses in which ordinary least squares regression-based models are constructed. A bootstrapping method was used to calculate 99% confidence intervals of the conditional effect in the moderation model and the indirect effect in the mediation model.

For the moderation analyses, a regression-based model was constructed for each potential moderator separately in order to estimate the conditional (interaction) effect. Each model included the change score (T0-T2) for perceived impact of HF/NS or for overall levels of menopausal symptoms as the dependent variable, the main effects of group (intervention versus control) and moderator, and a group by moderator interaction effect. Variables that significantly moderated the relationship between group allocation and change in perceived impact of HF/NS or overall levels of menopausal symptoms were adjusted for in the mediation analysis.

Prior to the mediation analysis, we used Student's t-tests to examine

**Table 1**  
Sociodemographic, clinical and menopause-related characteristics.

	All patients (n = 235)		iCBT patients <sup>a</sup> (n = 156)		Control patients (n = 79)	
Age, mean years (SD)	47.50	(5.36)	47.70	(5.24)	47.02	(5.61)
Education, N (%)						
High school & vocational education	128	(54.5%)	85	(54.5%)	43	(54.4%)
College/university	107	(45.5%)	71	(45.5%)	36	(45.6%)
Time since diagnosis, mean years (SD)	3.10	(1.39)	3.13	(1.42)	3.04	(1.35)
Chemotherapy						
Endocrine therapy: current use, N (%)	193	(82.1%)	128	(82.1%)	65	(82.3%)
Oophorectomy, N (%)	43	(18.3%)	28	(17.9%)	15	(19.0%)
Chemotherapy N (%)	221	(94.0)	148	(94.9)	73	(92.4)
Prescribed medication for HF/NS	26	(11.1)	15	(9.6)	11	(13.9)
Hot flush frequency per week, mean (SD)	50.22	(39.02)	51.78	(40.33)	47.14	(36.36)
Night sweats frequency per week, mean (SD)	18.07	(13.38)	18.02	(13.02)	18.16	(14.15)
Perceived impact of HF/NS, mean (SD) <sup>b</sup>	4.87	(1.86)	4.97	(1.81)	4.67	(1.94)
Overall levels of menopausal symptoms, mean (SD) <sup>c</sup>	50.67	(8.72)	50.96	(9.01)	50.12	(8.15)

Abbreviations: n, number; SD, standard deviation.

<sup>a</sup> 'iCBT patients' include all women allocated to the guided or self-managed iCBT group.

<sup>b</sup> Score range: 0–10, with higher scores reflecting a higher perceived impact of HF/NS.

<sup>c</sup> Score range: 0–72, with higher scores reflecting less overall levels of menopausal symptoms.

whether changes between baseline to short-term follow-up (T0-T1) in HF/NS beliefs and behaviors and psychological distress were significantly different between the intervention and the control group. Subsequently, regression-based models were constructed to estimate the indirect effect of each potential mediator separately. Each model included the change score (T0-T2) of perceived impact of HF/NS or overall levels of menopausal symptoms as the dependent variable, the change score between T0-T1 of the potential mediator and group. We calculated partially standardized effects, which express the indirect effect relative to the standard deviation of the dependent variable [28].

All analyses were conducted in SPSS version 22.

### 3. Results

#### 3.1. Sample characteristics

Sociodemographic, clinical and menopause-related characteristics of the study sample are shown in Table 1. The mean age of the women was 47.5 years (standard deviation (SD) = 5.4) and 46% had completed college or university. The average time since BC diagnosis was 3.1 years (SD = 1.4) and the majority had received chemotherapy (94%) and was still undergoing endocrine treatment (82%). At baseline, women experienced, on average, 50.2 hot flushes (SD = 39.0) and 18.1 night sweats (SD = 13.4) per week. The mean baseline problem rating score was 4.9 (SD = 1.9) for HF/NS, and 50.7 (SD = 8.7) for overall levels of menopausal symptoms. All baseline characteristics were balanced across groups.

#### 3.2. Moderation analyses

Results of the interaction analyses are shown in Table 2. Only educational level significantly moderated the relationship between group allocation and changes in perceived impact of HF/NS ((interaction effect (estimate) = 1.38, 99%CI = 0.05 to 2.71)). That is, patients who completed secondary or vocational education showed a significantly greater decrease in perceived impact of HF/NS (unstandardized regression coefficient ( $B = -1.49$ , 99%CI =  $-2.39$  to  $-0.59$ ) compared to women who completed college or university ( $B = -0.11$ , 99%CI =  $-1.10$  to  $0.84$ ) (See Fig. 1). We did not observe any moderating effects of age, time since diagnosis, current endocrine treatment, past oophorectomy, frequency of hot flushes or night sweats, and psychological distress.

#### 3.3. Mediation analyses

Patients in the iCBT groups reported significantly greater improvement (T0-T1) on all three belief scales, i.e. beliefs about hot flushes in a social context (mean difference = 0.35, 99%CI = 0.02 to 0.67), beliefs about night sweats and sleep (mean difference = 0.38, 99%CI = 0.02 to 0.73), and beliefs about coping/control (mean difference =  $-0.54$ , 99%CI =  $-0.87$  to  $-0.22$ ) compared to the control group. Patients allocated to the iCBT groups also reported significantly greater improvement (T0-T1) in effective coping behavior (mean difference = 0.45, 99%CI =  $-0.76$  to  $-0.14$ ) as compared to the control group (Table 3). No significant group differences were observed for avoidance behavior or psychological distress.

Results from the mediation analyses (Table 4) indicated that changes in beliefs about hot flushes in a social context and beliefs about coping/control significantly mediated the relationship between group allocation and changes in perceived impact of HF/NS ((partially standardized indirect effect (estimate) = 0.10, 99%CI = 0.01 to 0.24; estimate = 0.19, 99%CI = 0.07 to 0.39, respectively)) and between group allocation and changes in menopausal symptoms (estimate = 0.07, 99%CI = 0.00 to 0.19; estimate = 0.17, 99%CI = 0.04 to 0.35, respectively). This indicates that the development of healthier beliefs about hot flushes in a social context and beliefs about one's ability to control and cope effectively with hot flushes contribute to lower perceived impact of HF/NS and reduced menopausal symptom burden in the iCBT groups. Beliefs about coping/control had the largest mediating effect in the individual mediation models. That is, improvement in beliefs about one's ability to cope effectively with hot flushes accounted for the largest percentage (43%) of the total treatment effect for perceived impact of HF/NS and overall levels of menopausal symptoms.

We found that changes in beliefs about night sweats and sleep also mediated the relationship between group allocation and changes in perceived impact of HF/NS (estimate = 0.09, 99%CI =  $-0.2$  to  $-0.01$ ), indicating that the development of healthier beliefs about one's ability to reduce the impact of night sweats on sleep and daily functioning contribute to a lower perceived impact of HF/NS in the iCBT groups. We did not find any mediating effects of changes in positive coping behavior, avoidance behavior, or psychological distress.

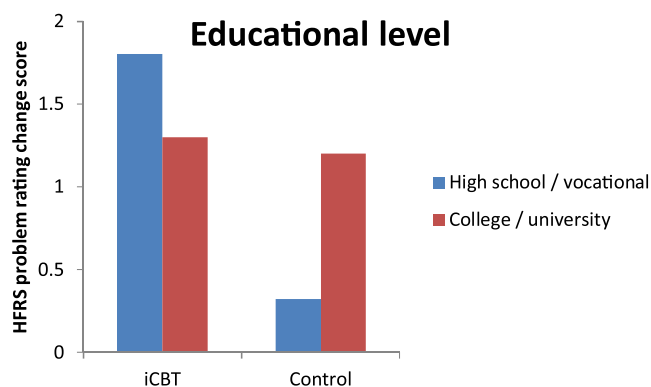
We conducted additional analyses correcting for potential confounding effects of educational level. These analyses did not alter the results as reported above (data not shown).

**Table 2**  
Interaction effects of potential moderator variables with treatment group on longer-term follow-up changes in perceived impact of HF/NS (HFRS problem rating scale) and overall levels of menopausal symptoms (FACT-ES).

Potential Moderator	Perceived impact of HF/NS			Overall levels of menopausal symptoms		
	Estimate	(99% CI)	p	Estimate	(99% CI)	p-value
Age	-0.06	(-0.18-0.07)	0.22	0.22	(-0.23-0.67)	0.20
Educational level (high school/ vocational <sup>a</sup> vs college/ university)	<b>1.38</b>	(0.05-2.71)	<b>&lt; 0.01</b>	-4.84	(-9.74-0.06)	0.01
Time since diagnosis (< 3 years <sup>a</sup> vs ≥ 3 years)	0.14	(-1.21-1.49)	0.79	1.69	(-3.23-6.61)	0.37
Current endocrine treatment (no <sup>a</sup> vs yes)	-0.16	(-1.92-1.60)	0.82	1.23	(-2.75-5.20)	0.54
Oophorectomy (no <sup>a</sup> vs yes)	0.17	(-1.57-1.90)	0.80	-0.63	(-7.01-5.76)	0.80
Hot flush frequency	0.01	(-0.02-0.02)	0.44	-0.01	(-0.07-0.06)	0.75
Night sweats frequency	-0.03	(-0.08-0.02)	0.10	0.15	(0.02-0.33)	0.03
Psychological distress	0	(-0.11-0.10)	0.95	0.12	(-0.25-0.50)	0.40

Note: Bold font indicates significant moderation effect at p < 0.01.

<sup>a</sup> indicates reference category.



**Fig. 1.** Improvements from baseline to longer-term follow up in perceived impact of HF/NS (HFRS problem rating scale), stratified by educational level. Note: Higher scores indicate greater improvement (scale range 0–10). Abbreviations: HFRS, Hot Flush Rating Scale.

**4. Discussion**

The aim of the current study was to identify patient characteristics that moderate, and therapeutic change mechanisms that mediate the beneficial effects of iCBT on treatment-induced menopausal symptoms in BC survivors [13]. Our results indicate that women with a high school or vocational training degree in the iCBT group improved more in perceived impact of HF/NS than their counterparts in the control group, whereas this was not the case for women with a college or university degree. Women with a higher educational level in the control group improved to almost the same extent as their counterparts in the intervention group. This contrasts with findings from previous studies that either reported no moderating effect of education or the opposite effect (i.e. more highly educated women benefiting most) [15–19]. A possible explanation for our finding is that more highly educated women who were allocated to the control group may have sought alternative sources of information or strategies for dealing with their menopausal symptoms, whereas the less well educated women in the control group may have been less likely to do so [29]. Another possibility is that our iCBT program was designed to be understandable for women with all levels of education, and thus the language used in the iCBT was quite basic. It may be that more highly educated women could

**Table 3**  
Between-group changes in mean change from baseline to short-term follow -up scores on potential mediators of treatment effects.

Potential mediator	T0			T1			Between-group difference T0-T1		
	N	Mean	(SD)	N	Mean	(SD)	Mean change	(SE)	p-value
Beliefs about hot flushes in a social context <sup>a</sup>									
All intervention patients	156	1.91	(1.18)	154	1.21	(1.12)	0.35	(0.13)	<b>&lt; 0.01</b>
Control group	79	1.84	(1.27)	79	1.49	(1.19)			
Beliefs about night sweats and sleep <sup>a</sup>									
All intervention patients	156	1.09	(1.09)	154	1.70	(1.03)	0.38	(0.12)	<b>&lt; 0.01</b>
Control group	78	1.06	(1.06)	79	2.01	(0.99)			
Beliefs about coping/control <sup>b</sup>									
All intervention patients	156	3.02	(0.97)	154	3.81	(0.86)	-0.54	(0.13)	<b>&lt; 0.001</b>
Control group	79	3.14	(1.08)	79	3.38	(0.95)			
Positive coping behavior <sup>b</sup>									
All intervention patients	156	3.42	(0.94)	153	3.89	(0.73)	-0.45	(0.11)	<b>&lt; 0.001</b>
Control group	79	3.60	(0.86)	79	3.62	(0.84)			
Avoidance behavior <sup>a</sup>									
All intervention patients	156	0.79	(0.89)	153	0.59	(0.84)	0.17	(0.10)	0.08
Control group	79	0.79	(0.89)	79	0.76	(0.97)			
Psychological distress <sup>c</sup>									
All intervention patients	156	11.16	(6.94)	156	6.39	(0.52)	1.00	(0.63)	0.11
Control group	79	11.17	(6.43)	79	6.50	(0.73)			

Note: bold font indicates significant between group differences at p < 0.01.

Abbreviations: N, number; SD, standard deviation, T0, baseline assessment; T1, short-term follow-up assessment.

<sup>a</sup> scale range: 0–5, higher scores reflect more negative beliefs and behaviors.

<sup>b</sup> scale range: 0–5, higher scores reflect more positive beliefs and behaviors.

<sup>c</sup> scale range: 0–42, higher scores reflect more psychological distress.

**Table 4**

Indirect effects of potential mediators of treatment effects on baseline to longer-term follow-up changes in perceived impact of HF/NS (HFRS problem rating scale) and overall levels of menopausal symptoms (FACT-ES).

	Perceived impact of HF/NS			Overall levels of menopausal symptoms		
	Estimate	(99% CI)	% of total effect explained by mediator	Estimate	(99% CI)	% of total effect explained by mediator
Total treatment effect <sup>a</sup>	−0.85	(0.34–1.37)		2.73	(0.26–5.20)	
Indirect effect of treatment through beliefs and behaviors <sup>b</sup>						
Beliefs about hot flushes in a social context	−0.10	(−0.23–0.01)	22.7	0.07	(0.00–0.19)	18.5
Beliefs about night sweats and sleep	−0.09	(−0.21–0.01)	19.0	0.05	(−0.02–0.17)	13.0
Beliefs about coping/control	−0.19	(−0.37–0.06)	43.1	0.17	(0.06–0.34)	42.5
Positive coping behavior	−0.06	(−0.20–0.04)	14.3	0.08	(−0.01–0.21)	21.7
Avoidance behavior	−0.01	(−0.07–0.06)	1.3	0.01	(−0.04–0.08)	3.6
Psychological distress	−0.02	(−0.10–0.01)	5.1	0.05	(−0.03–0.16)	12.7

Note: Bold font indicates significant mediation effects at  $p < 0.01$ .

<sup>a</sup> Unstandardized estimate for treatment effect, unadjusted for mediators.

<sup>b</sup> Partially standardized estimates of the indirect effect of treatment (intervention versus control) on the perceived impact of HF/NS and overall levels of menopausal symptoms through the mediator.

have benefited from a more sophisticated approach to the provision of information and behavioral strategies. This suggests that a more tailored version of the program that takes the educational level of participants into consideration may be more effective [29]. Although Chilcot et al reported that baseline psychological distress moderated the effect of CBT on HF/NS, Norton et al did not observe such an effect [15,16]. This was also the case in our study. The fact that we did not observe a moderating effect of baseline psychological distress may be due to the fact that the women who participated in our study reported low levels of distress at baseline.

In line with the MENOS trials, the iCBT resulted in healthier HF/NS beliefs and behaviors [15,16]. Our findings indicate that changes in beliefs about feelings of embarrassment or feeling judged by others when experiencing hot flushes in a social context, beliefs about one's ability to influence the extent to which night sweats negatively impact sleep and daily functioning, and beliefs about one's ability to control and cope effectively with hot flushes mediated the positive effect observed on the perceived impact of HF/NS. The development of healthier beliefs about experiencing hot flushes in a social context and beliefs about one's ability to cope effectively with hot flushes also contributed to the positive intervention effect found on overall menopausal symptom burden as assessed by the FACT-ES. This suggests that, although our iCBT program was primarily targeted at the development of healthier beliefs and behaviors in relation to HF/NS, the changes in the beliefs also had a salutary effect on a broader range of menopausal symptoms.

Although a positive trend was observed, changes in psychological distress were not found to significantly mediate the observed positive effects of the iCBT program on the perceived impact of HF/NS or overall menopausal symptoms. The MENOS trials yielded mixed findings [15,16]. In our study, the decrease in distress was very similar between the intervention and control groups. This decrease in distress was anticipated in the intervention groups, but not in the control group. We would note that, for all groups, both baseline and follow-up distress scores were in the normal range. This reflects the fact that we excluded women from the study who were judged as being highly distressed during the screening interview. In line with previous studies, we did not find a significant mediating effect of positive coping behaviors [15,16]. However, a positive trend suggests that the development of a healthier coping style could have contributed to the treatment effects. Although the iCBT program had a positive effect on both coping beliefs and behavior, it appears that the primary mediating effect was via the beliefs about being able to cope with HF/NS. These findings also suggest that, in contact with patients, healthcare professionals should stress that the impact of HF/NS can be influenced and should inform women about

effective coping strategies.

Although the study of Chilcot et al. [16] reported that sleep mediated the effect of CBT on the perceived impact of HF/NS, we chose not to include sleep in our analyses because we considered the causal directionality to be questionable. That is, it is just as plausible, or even more plausible that improving the experience of night sweats has a positive impact on sleep than vice versa.

Several limitations of the current study should be noted. First, the sample size was not specifically powered to detect small effects. We endorse recommendations that have been made to conduct meta-analyses based on individualized patient data (IPD) derived from several RCTs in order to increase power and replicate previous findings [17,30]. Second, although we believe we have included the most important potential moderating and mediating variables, we do not presume to have been exhaustive. For example, our study was not suitable for replicating the moderating effect of chemotherapy as observed by Chilcot and colleagues [16], since 94% of the women in our sample had received chemotherapy. This study also had several notable strengths. This included the RCT design, multicenter participation and the high questionnaire completion rate.

In conclusion, our findings indicate that BC survivors with a high school/vocational training degree benefited most from the iCBT program for treatment-induced HF/NS, and that the positive effects of the iCBT program on the perceived impact of HF/NS and overall menopausal symptom burden were mediated by the development of healthier HF/NS beliefs. This suggests that the iCBT program should be tailored to the educational level of women, and that more effort be devoted to strengthening the behavioral component of the program.

## Contributors

Vera Atema contributed to conception and design, collection and assembly of data, and data analysis and interpretation.

Marieke van Leeuwen contributed to conception and design, and data analysis and interpretation.

Jacobien M. Kieffer contributed to conception and design, and data analysis and interpretation.

Hester S.A. Oldenburg contributed to conception and design.

Marc van Beurden contributed to conception and design.

Myra S. Hunter contributed to conception and design.

Neil K. Aaronson contributed to conception and design, and data analysis and interpretation.

All authors participated in the writing of the manuscript and saw and approved the final version.

## Conflict of Interest

Myra S. Hunter has books available via Routledge and Boom publishers.

All other authors declare they have no competing interests.

## Funding

This work was supported by the Dutch Cancer Society (grant no. NKI 2014-6788) and the Netherlands Cancer Institute.

## Ethical approval

All institutional review boards of the participating centers approved the study. All participants provided informed consent.

## Provenance and peer review

This article has undergone peer review.

## Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.maturitas.2019.09.007>.

## References

- N.E. Avis, S. Crawford, J. Manuel, Psychosocial problems among younger women with breast cancer, *Psychooncology* 13 (5) (2004) 295–308.
- J.S. Carpenter, M.A. Andrykowski, Menopausal symptoms in breast cancer survivors, *Oncol. Nurs. Forum* 26 (8) (1999) 1311–1317.
- P. Gupta, D.W. Sturdee, S.L. Palin, K. Majumder, R. Fear, T. Marshall, I. Paterson, Menopausal symptoms in women treated for breast cancer: the prevalence and severity of symptoms and their perceived effects on quality of life, *Climacteric* 9 (1) (2006) 49–58.
- Z. Moon, M.S. Hunter, R. Moss-Morris, L.D. Hughes, Factors related to the experience of menopausal symptoms in women prescribed tamoxifen, *J. Psychosom. Obstet. Gynaecol.* (2016) 1–10.
- C.C. Murphy, L.K. Bartholomew, M.Y. Carpentier, S.M. Bluethmann, S.W. Vernon, Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review, *Breast Cancer Res. Treat.* 134 (2) (2012) 459–478.
- M.S. Hunter, K.L.M. Liao, Evaluation of a four-session cognitive-behavioural intervention for menopausal hot flushes, *Br. J. Health Psychol.* 1 (1996) 113–125.
- M.S. Hunter, S. Coventry, H. Hamed, I. Fentiman, E.A. Grunfeld, Evaluation of a group cognitive behavioural intervention for women suffering from menopausal symptoms following breast cancer treatment, *Psychooncology* 18 (5) (2009) 560–563.
- B. Ayers, M. Smith, J. Hellier, E. Mann, M.S. Hunter, Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial, *Menopause* 19 (7) (2012) 749–759.
- C. Hardy, A. Griffiths, S. Norton, M.S. Hunter, Self-help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@Work): a multicenter randomized controlled trial, *Menopause* 25 (5) (2018) 508–519.
- E. Mann, M.J. Smith, J. Hellier, J.A. Balabanovic, H. Hamed, E.A. Grunfeld, M.S. Hunter, Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial, *Lancet Oncol.* 13 (3) (2012) 309–318.
- S.F.A. Duijts, M. Van Beurden, H.S.A. Oldenburg, M.S. Hunter, J.M. Kieffer, M.M. Stuiver, M.A. Gerritsma, M.B.E. Menke-Pluymers, P.W. Plaisir, H. Rijna, A.M.F. Lopes Cardozo, G.J. Timmers, S. Van der Meij, H. Van der Veen, N. Bijker, L.M. De Widt-Levert, M.M. Geenen, G. Heuff, E.J. Van Dulken, E. Boven, N.K. Aaronson, Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized controlled multicenter trial, *J. Clin. Oncol.* 30 (33) (2012) 4124–4133.
- V. Atema, M. van Leeuwen, H.S.A. Oldenburg, M. van Beurden, M.S. Hunter, N.K. Aaronson, An Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: results of a pilot study, *Menopause* 24 (7) (2017) 762–767.
- V. Atema, M. van Leeuwen, J.M. Kieffer, H.S.A. Oldenburg, M. van Beurden, M.A. Gerritsma, M.A. Kuenen, P.W. Plaisier, A.M.F. Lopes Cardozo, Y.E.A. van Riet, G. Heuff, H. Rijna, S. van der Meij, E.M. Noorda, G.J. Timmers, B.C. Vrouwenraets, M. Bollen, H. van der Veen, N. Bijker, M.S. Hunter, N.K. Aaronson, Efficacy of internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors: results of a randomized controlled trial, *J. Clin. Oncol.* (2019) Jco1800655.
- H.C. Kraemer, G.T. Wilson, C.G. Fairburn, W.S. Agras, Mediators and moderators of treatment effects in randomized clinical trials, *Arch. Gen. Psychiatry* 59 (10) (2002) 877–883.
- S. Norton, J. Chilcot, M.S. Hunter, Cognitive-behavior therapy for menopausal symptoms (hot flushes and night sweats): moderators and mediators of treatment effects, *Menopause* 21 (6) (2014) 574–578.
- J. Chilcot, S. Norton, M.S. Hunter, Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: who benefits and how does it work? *Maturitas* 78 (1) (2014) 56–61.
- J. Kalter, I.M. Verdonck-de Leeuw, M.G. Sweegers, N.K. Aaronson, P.B. Jacobsen, R.U. Newton, K.S. Courneya, J.F. Aitken, J. Armes, C. Arving, L.J. Boersma, A.M.J. Braamse, Y. Brandberg, S.K. Chambers, J. Dekker, K. Ell, R.J. Ferguson, M.F.M. Gielissen, B. Glimelius, M.M. Goedendorp, K.D. Graves, S.P. Heiney, R. Horne, M.S. Hunter, B. Johansson, M.L. Kimman, H. Knoop, K. Meneses, L.L. Northouse, H.S. Oldenburg, J.B. Prins, J. Savard, M. van Beurden, S.W. van den Berg, J. Brug, L.M. Buffart, Effects and moderators of psychosocial interventions on quality of life, and emotional and social function in patients with cancer: an individual patient data meta-analysis of 22 RCTs, *Psychooncology* 27 (4) (2018) 1150–1161.
- J.E. Broderick, F.J. Keefe, S. Schneider, D.U. Junghaenel, P. Bruckenthal, J.E. Schwartz, A.T. Kaell, D.S. Caldwell, D. McKee, E. Gould, Cognitive behavioral therapy for chronic pain is effective, but for whom? *Pain* 157 (9) (2016) 2115–2123.
- N. Vincent, K. Walsh, S. Lewycky, Determinants of success for computerized cognitive behavior therapy: examination of an insomnia program, *Behav. Sleep Med.* 11 (5) (2013) 328–342.
- M.J. Rendall, L.M. Simonds, M.S. Hunter, The hot flush beliefs scale: a tool for assessing thoughts and beliefs associated with the experience of menopausal hot flushes and night sweats, *Maturitas* 60 (2) (2008) 158–169.
- M.S. Hunter, B. Ayers, M. Smith, The hot flush behavior scale: a measure of behavioral reactions to menopausal hot flushes and night sweats, *Menopause* 18 (11) (2011) 1178–1183.
- M.S. Hunter, E. Mann, A cognitive model of menopausal hot flushes and night sweats, *J. Psychosom. Res.* 69 (5) (2010) 491–501.
- V. Atema, M. van Leeuwen, H.S. Oldenburg, V. Retel, M. van Beurden, M.S. Hunter, N.K. Aaronson, Design of a randomized controlled trial of Internet-based cognitive behavioral therapy for treatment-induced menopausal symptoms in breast cancer survivors, *BMC Cancer* 16 (1) (2016) 920.
- Common European Framework of Reference for Languages: Learning, Teaching, Assessment, (2018) <https://rm.coe.int/cefr-companion-volume-with-new-descriptors-2018/1680787989>.
- M.S. Hunter, K.L.M. Liao, A psychological analysis of menopausal hot flushes, *Br. J. Clin. Psychol.* 34 (1995) 589–599.
- L.J. Fallowfield, S.K. Leaity, A. Howell, S. Benson, D. Cella, Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B, *Breast Cancer Res. Treat.* 55 (2) (1999) 189–199.
- A.S. Zigmund, R.P. Snaith, The hospital anxiety and depression scale, *Acta Psychiatr. Scand.* 67 (6) (1983) 361–370.
- A.F. Hayes, Introduction to Mediation, Moderation, and Conditional Process Analysis: a Regression-based Approach, The Guilford Press, New York, 2018.
- D.R. Longo, Understanding health information, communication, and information seeking of patients and consumers: a comprehensive and integrated model, *Health expectations* 8 (3) (2005) 189–194.
- R.D. Riley, P.C. Lambert, G. Abo-Zaid, Meta-analysis of individual participant data: rationale, conduct, and reporting, *BMJ* 340 (2010) c221.