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Systematic review

Mindfulness, cognitive behavioural and behaviour-based therapy for natural and treatment-induced menopausal symptoms: a systematic review and meta-analysis

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Background During menopause women experience vasomotor and psychosexual symptoms that cannot entirely be alleviated with hormone replacement therapy (HRT). Besides, HRT is contraindicated after breast cancer.

Objectives To review the evidence on the effectiveness of psychological interventions in reducing symptoms associated with menopause in natural or treatment-induced menopausal women.

Search strategy Medline/Pubmed, PsycINFO, EMBASE and AMED were searched until June 2017.

Selection criteria Randomised controlled trials (RCTs) concerning natural or treatment-induced menopause, investigating mindfulness or (cognitive-)behaviour-based therapy were selected. Main outcomes were frequency of hot flushes, hot flush bother experienced, other menopausal symptoms and sexual functioning.

Data collection and analysis Study selection and data extraction were performed by two independent researchers. A meta-analysis was performed to calculate the standardised mean difference (SMD).

Main results Twelve RCTs were included. Short-term (<20 weeks) effects of psychological interventions in comparison to no treatment or control were observed for hot flush bother (SMD −0.63, 95% CI −0.80 to −0.46, $P < 0.001$, $I^2 = 0\%$) and menopausal symptoms (SMD −0.34, 95% CI −0.52 to −0.15, $P < 0.001$, $I^2 = 0\%$). Medium-term (≥20 weeks) effects were observed for hot flush bother (SMD −0.49, 95% CI −0.80 to −0.19, $P = 0.002$, $I^2 = 63\%$). In the subgroup treatment-induced menopause, consisting of exclusively breast cancer populations, as well as in the subgroup natural menopause, hot flush bother was reduced by psychological interventions. Too few studies reported on sexual functioning to perform a meta-analysis.

Conclusions Psychological interventions reduced hot flush bother in the short and medium-term and menopausal symptoms in the short-term. These results are especially relevant for breast cancer survivors in whom HRT is contraindicated. There was a lack of studies reporting on the influence on sexual functioning.

Keywords Behavioural therapy, cognitive behavioural therapy, menopause, mindfulness, sexual functioning, vasomotor symptoms.

Tweetable abstract Systematic review: psychological interventions reduce bother by hot flushes in the short- and medium-term.

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Introduction

Menopause can occur either naturally or can be induced by treatments such as pelvic radiation, oophorectomy, endocrine therapy or chemotherapy.[1,2]

CMG van Driel and AS Stuursma contributed equally to the manuscript.

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Menopausal symptoms are experienced frequently with up to 85% of menopausal women reporting vasomotor symptoms (i.e. hot flushes and night sweats), up to 60% reporting vaginal discomfort (i.e. vaginal dryness and/or dyspareunia), and up to 87% reporting sexual dysfunction (e.g. lack of sexual desire and difficulty reaching orgasm).[3–5] Moreover, women who experience treatment-induced menopause report more severe symptom levels than women experiencing natural menopause.[6,7]

To reduce the aforementioned symptoms, hormone replacement therapy (HRT) is currently the most effective option.[8,9] However, the use of HRT in postmenopausal women is associated with increased breast cancer risk and contraindicated in breast cancer survivors.[10,11] Furthermore, HRT only partially relieves symptoms, symptom levels remain higher than in premenopausal women and especially sexual discomfort is not alleviated.[12] Therefore, safe nonhormonal alternatives to HRT are needed, in particular for breast cancer survivors such as young *BRCA1/2* mutation carriers after breast cancer and risk-reducing salpingo-oophorectomy.

Nonhormonal options to decrease the frequency and bother of hot flushes include stress-reducing psychological interventions such as cognitive behavioural therapy (CBT), behavioural therapy (BT) and mindfulness-based therapies (MBT).[13] The possible mechanism of action of these interventions is that they reduce stress. Stress is thought to lower the threshold for heat dissipation responses[14,15] and therefore can potentiate a hot flush.[16] It is proposed that CBT, BT and MBT diminish this trigger by reducing stress, so reducing the frequency of hot flushes. An additional mechanism of action of the above-mentioned interventions might be that by modifying cognitive appraisals of hot flushes, the bother caused by hot flushes can be decreased.[13]

Several large randomised controlled trials (RCTs) that were recently published have investigated the effect of CBT, MBT and BT on hot flushes and other menopausal symptoms.[17–20] The aim of this systematic review and meta-analysis is to add a quantitative examination of the existing evidence on the effectiveness of psychological interventions in reducing symptoms associated with menopause in women with natural or treatment-induced menopause.

Methods

The conduct and reporting of this systematic literature review and meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[21] First, studies were screened for eligibility based on their titles and abstract. Full texts of possibly eligible studies were retrieved after the initial screening for more detailed evaluation. Second, two review authors (CD and AS) independently performed a final selection of studies, assessed the risk of bias and extracted data from the full-text papers using a prespecified form. The following data were extracted with the use of these forms: population (e.g. sample size, natural or treatment-induced menopause), intervention (e.g. type of intervention, duration, length of programme), control group, co-interventions and outcomes (e.g. frequency and bother of hot flushes, menopausal symptoms, sexual functioning and adverse effects). Of the outcomes, the time-points of measurement and results such as means and measure of variance were extracted.

Menopausal symptoms were defined as the combined level of burden from a broad range of symptoms related to menopause such as psychosocial symptoms (e.g. irritability, forgetfulness), physical symptoms (e.g. joint pain, headaches), genital symptoms (e.g. dryness, itching), sexual dysfunction and vasomotor symptoms.

Electronic databases that were searched are Medline/Pubmed, EMBASE, PsycINFO and AMED. Other search methods used were reference checking of selected studies and of existing reviews on adjacent topics. Search terms of the electronic literature search are provided in the (Table S1). The initial search was conducted in February 2016 and an updated search was performed in June 2017.

Risk of bias was assessed with the risk of bias tool from the Cochrane collaboration,[22] see (Table S2). Disagreements on inclusion of studies, extracted data or risk of bias assessments was solved by consensus between the two review authors (CD and AS). If consensus was not reached the other authors were consulted (GB, MS and MM). The protocol of this systematic literature review and meta-analysis is registered in the PROSPERO database (CRD42016038135).

Eligibility criteria

Studies considered eligible were RCTs with a published full text in English evaluating the effect of CBT, BT or MBT on either naturally occurring or treatment-induced hot flushes, menopausal symptoms or sexual functioning compared with a waiting list or with 'care as usual' (e.g. lifestyle advice, breast cancer follow up). Menopause did not have to be formally established (e.g. by amenorrhea >12 months or laboratory tests), but could be based on patient-reported signs and symptoms of menopause. The intervention could either consist of group or individual therapy and could be a general programme or could be specifically tailored to symptoms associated with menopause. Only patient-reported outcomes were included.

Studies were excluded if interventions were limited to yoga, hypnosis, exercise, meditation, awareness training or breathing techniques as a stand-alone therapy, because these interventions were either not based on a stress-

reducing mechanism of action or were not based on widely used protocolled standards. Studies were also excluded if there was no face-to-face therapeutic contact with a therapist or trainer during the study (e.g. web-based interventions). Use of HRT in the intervention and/or control group was allowed. However, studies that specifically aimed to use HRT as the control condition were excluded. Lastly, studies were excluded if the outcomes were physical measures (e.g. sternal skin conductance) only. The rationale behind favouring patient-reported outcomes over physical measures was that patient-reported hot flush frequency could be more closely related to actual inconvenience caused by hot flushes as patient-reported hot flush frequency measures the perceptual aspect, whereas physical measures assess the physiological aspect of the hot flush construct.[23] Therefore we deemed patient-reported outcomes to be of more interest for clinical practice.

Statistical analysis

The following outcomes were considered at short-term (<20 weeks after randomisation) and at medium-term (≥20 weeks after randomisation): frequency and bother of hot flushes, menopausal symptoms and sexual functioning. A random effects meta-analysis using inverse variance method was performed. Using mean end points and standard deviations (SDs), per study a standardised mean difference (SMD) with a 95% CI was calculated for all outcomes. Effect size was defined as small (0.2), medium (0.5) or large (0.8).[24] Heterogeneity was assessed per outcome with I^2, chi-square test and P-value. Funnel plots were made to assess publication bias. Asymmetrical funnel plots indicate a higher risk of publication bias.[22] Asymmetry was assessed using Egger's test, which was interpreted using a cut-off value of 0.10.[25] As the effect of the interventions could differ for treatment-induced and natural menopausal symptoms, a subgroup analysis was performed for natural menopause versus treatment-induced menopause when two or more studies were available per subgroup for an outcome. All analyses were performed using Review manager (RevMan version 5.3.5.).

Results

Selection of studies

A flow diagram of the study selection is shown in Figure 1. Based on the title and abstract screening, 24 records were eligible for full-text assessment, of which 12 records did not meet the eligibility criteria. So, the final number of included studies in the qualitative synthesis was 12. Of the included studies, ten studies could be included in the main quantitative synthesis (meta-analysis), as two studies only reported medians because of possible skewness of the data.[26,27] An overview of studies reporting medians compared with studies in the main meta-analysis is shown in Figure 2.

Characteristics of included studies

The total size of study population per study varied from 16 to 214 women (Table 1). The combined sample size of all studies consisting of participants in the control and intervention groups was 1016 women. Six of the 12 included studies involved women whose symptoms were treatment-induced, all of which concerned breast cancer survivors.[17,19,26–29] Three studies investigated the effect of MBT,[19,28,30] five studies investigated CBT[17,18,29,31,32] and four studies investigated BT.[20,26,27,33] All studies, except three had a waiting list control group.[27,29,33] One study had a 'care as usual' control group,[29] which consisted of breast cancer survivors during follow up with lifestyle advice on coping with hot flushes by a nurse specialist. The second study had a population of women experiencing natural menopause and had an active control group. The placebo activity in this case was individual leisure reading.[33] The third study was conducted in breast cancer survivors and had an attention control group. The attention consisted of a general discussion of menopausal complaints with a nurse.[27]

To measure hot flush frequency, the frequency subscale of the hot flush rating scale (HFRS scale) or similar diaries were used. Hot flush bother was most often measured by the HFRS subscale that measures bother by hot flushes (problem-rating, distress and interference). Menopausal symptoms were measured using the Functional Assessment of Cancer Therapy – Endocrine Therapy Scale (FACT-ES) and the Menopausal Quality of life scale (MENQOL). Both questionnaires contain psychosocial, physical, vaginal, sexual and vasomotor items. Sexual activity was measured by the habit subscale of the Sexual Activity Questionnaire (SAQ) and sexual behaviour subscale of the Women's Health Questionnaire (WHQ). An overview of the reported results of the main outcomes is given in the (Table S3).

Assessment of risk of bias

A high risk of performance bias was present for all studies, because blinding of CBT-, BT- and MBT-based interventions is not feasible (see Table S4). Consequently, the risk of detection bias was high because outcomes were patient-reported.

Meta-analysis of overall effect

A statistically significant benefit from psychological interventions was seen on short-term hot flush bother (SMD −0.63, 95% CI −0.80 to −0.46, $P < 0.001$), short-term menopausal symptoms (SMD −0.34, 95% CI −0.52 to −0.15, $P < 0.001$) and medium-term hot flush bother (SMD −0.49, 95% CI −0.80 to −0.19, $P = 0.002$)

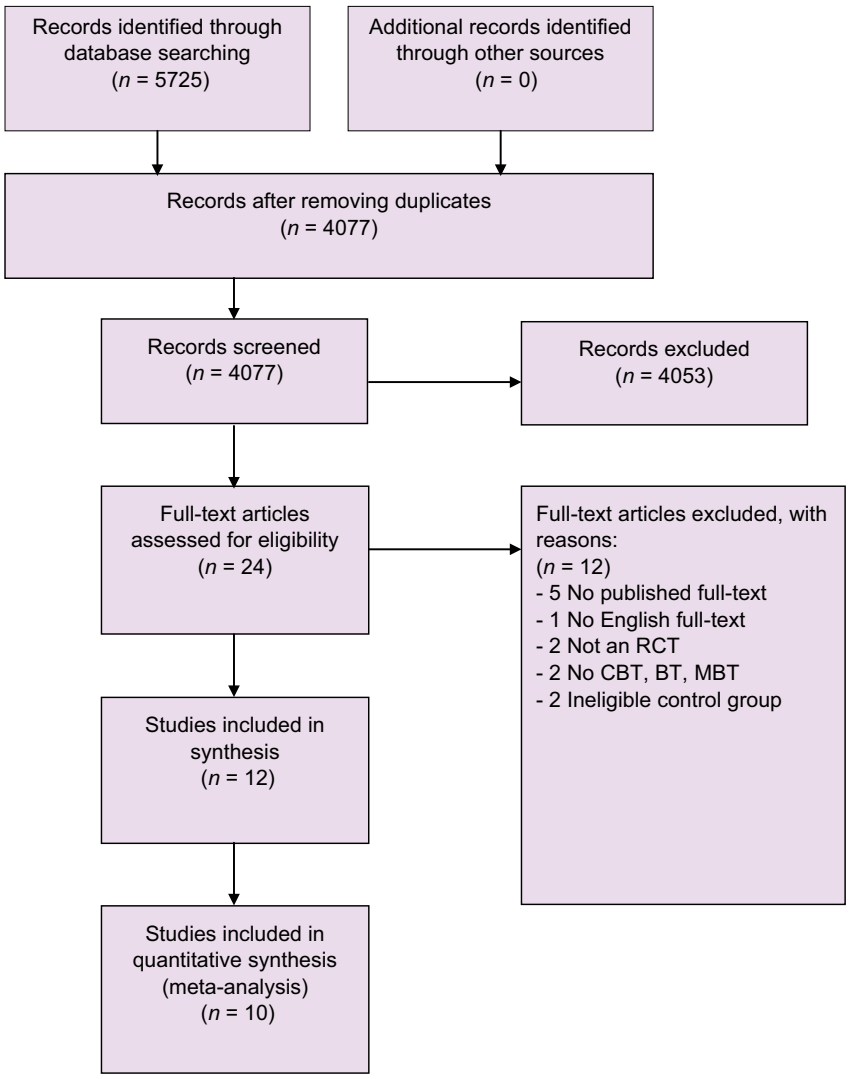

Figure 1. Flow diagram of study selection.

(Table 2). No statistically significant benefit from psychological interventions was seen on short-term hot flush frequency (SMD −0.41, 95% CI −0.83 to 0.01, $P = 0.05$) or medium-term hot flush frequency (SMD −0.21, 95% CI −0.89 to 0.26, $P = 0.29$). Heterogeneity was high for most outcomes. A meta-analysis of sexual functioning was not feasible because only two studies reported on this outcome.[17,20] An overview of the exact data entered into the main meta-analysis is shown in the (Table S5).

Publication bias

The Egger test result was >0.10 for all studies, indicating no proof of statistically significant publication bias. However the funnel plots showed some asymmetry, indicating that this result could be due to a limited number of studies per outcome (see Figure S1).

Subgroup analysis

A beneficial effect of psychological interventions was seen on short-term hot flush bother in the subgroup treatment-induced menopause (SMD −0.47, 95% CI −0.69 to −0.25, $P < 0.001$) as well as in the subgroup natural menopause (SMD −0.85, 95% CI: −1.11 to −0.59, $P < 0.001$) (see Figure S2). Benefit of psychological interventions was also seen on medium-term hot flush bother for both the natural menopause subgroup (SMD −0.77, 95% CI −1.16 to −0.39, $P < 0.001$) as well as in the treatment-induced menopause subgroup (SMD −0.32, 95% CI −0.64 to 0.00, $P = 0.05$).

Adverse effects

Four studies reported on adverse effects of CBT, MBT and BT and did not encounter any adverse effects.[18,20,28,29]

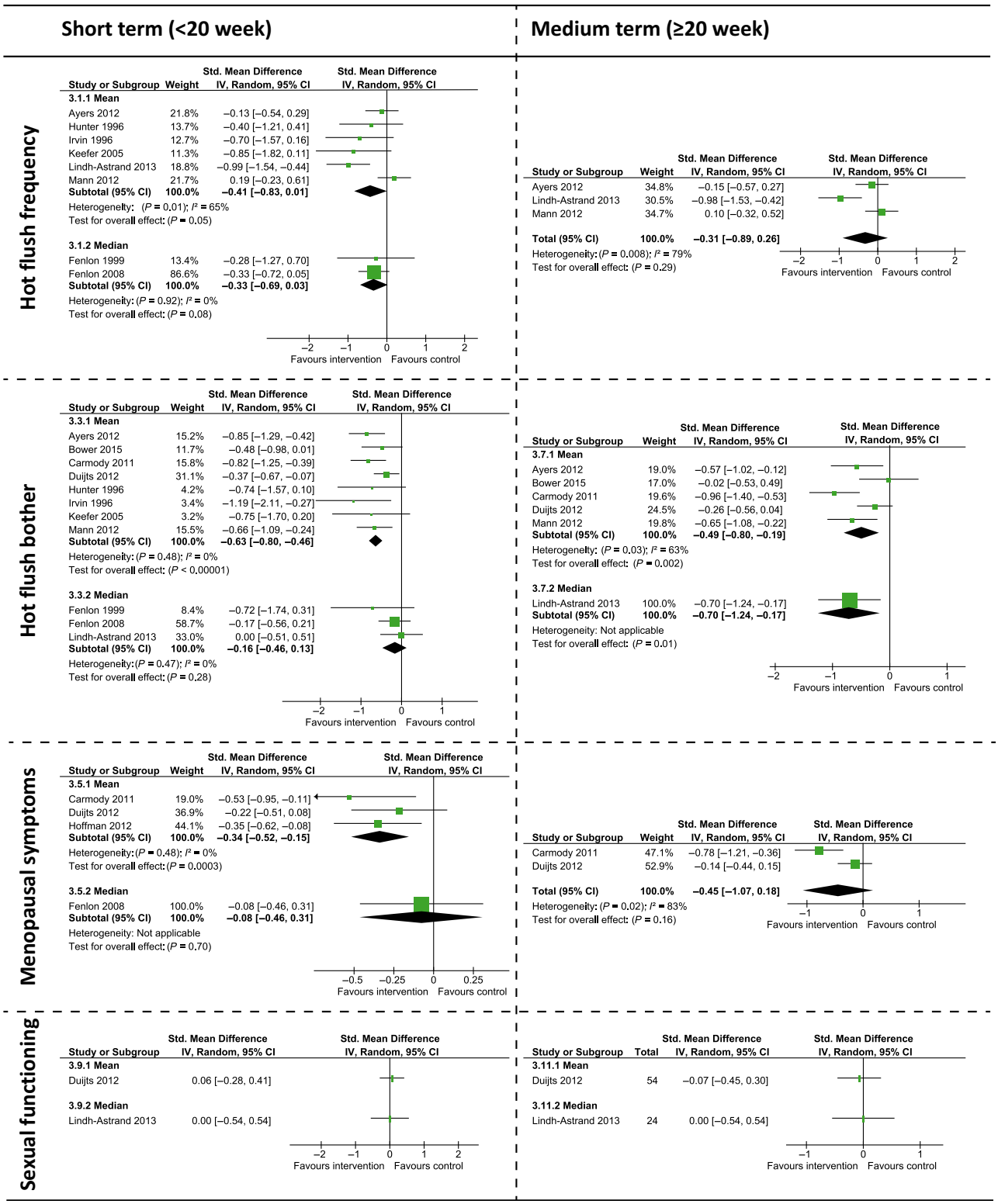

Figure 2. Forrest plot of hot flush frequency, hot flush bother, menopausal symptoms and sexual functioning for both short-term (<20 weeks) and medium-term (≥20 weeks) results, split for mean and median outcomes. CI, confidence interval; IV, inverse variance; SD, standard deviation; Std, standardized.

Table 1. Table of study characteristics

Study author, year, study design, country	Population largest *N* analysed, population type, mean age	Intervention Type, Group or individual, program length, population tailored or general	Comparison	Outcomes measured concept, scale
Mindfulness-based intervention				
Bower et al., (2015)[19] RCT	65, BC survivors Mean age: 47	MAP, Group 6 × 2 h, weekly Tailored	WLC	F/NS severity
Hoffman et al., (2012)[28] RCT	214, BC survivors Mean age: 50	MBSR, Group 8 × 2 h, weekly + 2 h General	WCL	Menopausal symptoms
Carmody et al., (2011)[30] RCT	92, peri/post-menopausal Mean age: 53	MBSR, Group 8 × 2.5 h, weekly General	WCL	HF bother HF intensity Menopausal symptoms
Cognitive behavioural therapy-based interventions				
Duijts et al., (2012)[17] RCT	173, BC survivors Mean age: 48	CBT, Group 6 × 1.5 h, weekly Tailored	WLC	Menopausal symptoms HF/NS bother sex. freq. change
Ayers et al., (2012)[18] RCT	129, peri/post-menopausal mean age: 53	CBT, Group 4 × 2 h, weekly Tailored	WLC	HF/NS problem rating HF/NS frequency
Mann et al., (2012)[29] RCT	88, BC survivors mean age: 54	CBT, Group 6 × 1.5 h, weekly Tailored	CAU (BCFU)	HF/NS problem rating HF/NS frequency
Keefer et al., (2005)[31] RCT	19, perimenopausal Mean age: 51	CBT, Group 8 × 1.5 h, weekly Tailored	WLC	HF frequency/2 weeks HF/NS problem rating
Hunter et al., (1996)[32] RCT	24, menopausal Mean age: 52	CBT, Individual 4 × 1 h/6–8 weeks Tailored	WLC	HF/NS problem rating HF/NS frequency
Behavioural therapy-based interventions				
Lindh-Åstrand et al., (2013)[20] RCT	59, post-menopausal Mean age 54.9	BT, Group 10 × 1 h/12 weeks Tailored	WLC	HF frequency/24 h VM symptoms and sexual behaviour
Fenlon et al., (2008)[27] RCT	104, BC survivors Median age: 55	BT, individual 1 × 1 h General	Att. C	HF frequency/week HF severity HF/NS problem rating Menopausal symptoms
Fenlon et al., (1999)[26] RCT	16, BC survivors Mean age: 48	BT, Individual 2 weekly. General	WLC	HF frequency/24 h HF/NS problem rating
Irvin et al., (1996)[33] RCT	33, post-menopausal Mean age 50.8	BT, Individual 1 × 1 h General	Act. C	HF frequency/24 h HF intensity

Act. C, active control group; Att. C, attention control group; BC, breast cancer; BT, behavioural therapy (relaxation); CAU, care as usual; CBT, cognitive behavioural therapy; HF, hot flush; MAP, mindfulness awareness programme; MBSR, mindfulness-based stress reduction; NS, night sweats; VM, vasomotor.

Discussion

Main findings

A small to moderate reduction of short- and medium-term hot flush bother and short-term menopausal symptoms by psychological interventions (i.e. CBT, BT and MBT) was found in the meta-analysis. Hot flush frequency however, was not statistically significantly reduced by psychological interventions. Furthermore, the short- and medium-term hot flush bother was reduced by psychological interventions in the breast cancer survivor subgroup and the natural menopause subgroup. However, medium-term hot flush

Table 2. Meta-analysis for hot flush frequency, hot flush bother and menopausal symptoms (short- and medium-term)

Outcome	No. of studies	*N* total	SMD (95% CI)	*P* (overall effect)	I^2 **/chi-square/*P* (heterogeneity)
Short-term (<20 weeks)					
HF frequency	6	300	−0.41 (−0.83 to 0.01)	0.05	65%/14.19/0.01
HF bother	7	568	−0.63 to 0.80 to −0.46)	<0.001*	0%/6.49/0.48
Menopausal symptoms	3	474	−0.34 (−0.52 to −0.15)	<0.001*	0%/1.46/0.48
Medium-term (≥20 weeks)					
HF frequency	3	234	−0.31 (−0.89 to 0.26)	0.29	79%/9.55/0.008
HF bother	5	486	−0.49 (−0.80 to −0.19)	0.002*	63%/10.75/0.03
Menopausal symptoms	2	264	−0.45 (−1.07 to 0.18)	0.16	83%/5.82/0.02

HF, hot flushes.
*Statistically significant (<0.05).
**Low: 0–24%, moderate: 25–49%, substantial: 50–74%, significant 75–100%.[22]

bother reduction was bordering on statistical significance in the breast cancer survivor subgroup. No adverse effects caused by psychological interventions were reported.

Strengths and limitations

This systematic literature review and meta-analysis is the first to investigate and quantify the efficacy of CBT, BT and MBT on menopausal symptoms in both naturally occurring and treatment-induced menopause in survivors of breast cancer with inclusion of recently published studies and novel mindfulness interventions. Furthermore, a large number of RCTs were included and subgroup analyses were possible for natural and treatment-induced subgroups for most outcomes. An important aspect of this systematic literature review and meta-analysis is that only patient-reported outcomes were included, which reflect the actual inconvenience caused by hot flushes.[23] A high level of heterogeneity was found in the meta-analysis, probably because of the differences in populations (natural versus treatment-induced) and possibly due to differences between interventions (e.g. type, duration). The level of heterogeneity was not of great concern because the aim of this systematic literature review and meta-analysis was to answer the wider question about the effectiveness of psychological interventions as a whole, as they are all based on the similar principal of stressor impact reduction, in all menopausal women regardless of cause. Other limitations were the fact that some of the included RCTs were small (i.e. five of the twelve studies consisted of <60 participants in total) and possible presence of publication bias.

Interpretation

Hot flush bother versus hot flush frequency

As reduction of hot flush bother was greater than the reduction of hot flush frequency it could be that the main mechanism of action of psychological interventions is to modify cognitive appraisal of hot flushes, thereby increasing coping skills to reduce the impact of hot flushes.[13] In the general population, women who report a low frequency of hot flushes can still experience substantial bother by hot flushes and vice versa.[34] Frequency of hot flushes has been identified as being associated with bother by hot flushes.[34] However, they were not interchangeable as other factors such as affect, symptom sensitivity, general health and sleep problems are also associated with the level of bother by hot flushes.[34] So, reduction of bother by hot flushes might be the most appropriate measure of improved quality of life in women suffering from vasomotor symptoms.[34,35]

Effectiveness in breast cancer survivors

Psychological interventions could be a valid strategy to reduce hot flush bother in breast cancer survivors. This is an important finding of the meta-analysis as breast cancer survivors are contraindicated to use HRT, but report more frequent, more severe, more distressing and a longer duration of hot flushes compared with age-matched controls or naturally menopausal women.[6,36–38]

Lack of long-term outcomes

No studies reported on long-term (≥52 weeks) outcomes. The effect of a booster session on maintaining the effect of the intervention warrants further investigation. This could not be evaluated properly in the meta-analysis because only two studies incorporated a booster session and did so within the short-term period.[17,27]

Lack of sexual outcomes

Only two of the 12 included studies reported on sexual outcomes.[17,20] The lack of sexual outcomes in current research stands in stark contrast to the fact that sexual functioning is shown to be severely impaired during menopause with 76% of menopausal women reporting sexual dysfunction.[5,39–41] A recent one-armed pilot study aimed at

improving sexual functioning in women with surgical menopause investigated the effect of an intervention combining MBT and sexual health education and found statistically significant improvement of sexual functioning.[42] This suggest that psychological therapy could be an effective intervention for improving sexual functioning in menopause. Indeed, a review by Al-Azzawi et al. concludes that nonpharmacological approaches, including psychological therapy, should be the first step in treating postmenopausal sexual dysfunction, before moving on to pharmacological options.[43]

Other causes of treatment-induced menopause

Lastly, breast cancer treatment was the only cause for treatment-induced menopause that was investigated in the included studies. However, there are more causes for treatment-induced menopause such as risk-reducing salpingo-oophorectomy in women with high risk for ovarian cancer (e.g. *BRCA1/2* mutation carriers). Risk-reducing salpingo-oophorectomy in *BRCA1/2* mutation carriers has become a widely applied procedure causing early surgical menopause.[44–47] Next to an increased risk for developing ovarian cancer, *BRCA1/2* mutation carriers also have an increased risk of developing breast cancer.[48–52] About one-third of *BRCA1/2* mutation carriers who experience surgical menopause have had breast cancer and therefore have a contraindication for using HRT.[53] This signifies the need for a safe, nonhormonal alternative for alleviating menopausal symptoms in groups with different causes of treatment-induced menopause.

Conclusion

The need for nonhormonal alternatives to HRT has been firmly established following the publication of the Women' Health Initiative[10] and considering the contraindication of HRT in breast cancer survivors. The results of this review suggest that psychological interventions could be a safe and effective treatment that reduces bother by hot flushes in all women experiencing symptoms associated with menopause, including breast cancer survivors. These findings support healthcare providers in offering psychological interventions to women who suffer from hot flushes and menopausal complaints, especially for women who will not be using HRT.

However, larger trials with a longer follow-up time are needed to confirm the (long-term) effectiveness of psychological therapies. Furthermore, RCTs investigating the comparative effectiveness of CBT, BT and MBT are needed, as studies on this topic are scarce.

The staggering lack of sexual outcomes in current research in conjunction with the fact that sexual functioning is severely impacted during menopause, emphasises that future research should focus on the effect of psychological interventions on sexual outcomes.

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Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

All authors (CvD, AS, MS, MM and GdB) were involved in the design and execution of the trial, analysis of the data and writing of the paper. CvD and AS contributed equally as first authors of the manuscript.

Details of ethical approval

For this study, no approval was required from a medical ethics committee as no experiments were done on human beings.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Funnel plots for short and medium term hot flush frequency, hot flush bother and menopausal symptoms including Egger test results.

Figure S2. Forest plot of short-term hot flush bother (subgroups natural versus treatment-induced menopausal symptoms).

Table S1. Search terms.

Table S2. Domains and scoring of Cochrane risk of bias tool[22]

Table S3. Outcomes and results per outcome type.

Table S4. Risk of bias assessment as measured with the risk of bias tool from the Cochrane collaboration.

Table S5. Transformed outcomes and results per outcome type as used in the meta-analysis. ■

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