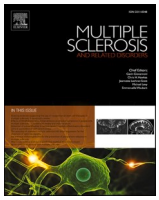
Multiple Sclerosis and Related Disorders 67 (2022) 104098

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Original article

Menopausal symptoms and hormone therapy in women with multiple sclerosis: A baseline-controlled study☆

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ARTICLE INFO

Keywords:
Menopause
Hormone therapy
Multiple sclerosis
Vasomotor symptoms
Depression
Sleep

ABSTRACT

Background: Depression, sleep disturbances, and cognitive difficulties impair the quality of life in people with multiple sclerosis (MS). Similar symptoms are also frequent during the menopausal transition. In clinical practice, it is important to consider the multifactorial causes of these overlapping symptoms and the potential benefits of menopausal hormone therapy (MHT). The objective of this study was to evaluate vasomotor symptoms (VMS), mood, sleep, and cognition of menopausal women with and without MS at baseline and during one year of MHT.

Methods: In this prospective baseline-controlled study, peri- and early postmenopausal participants with (n=14) and without (n=13) MS received MHT containing 1 or 2 mg of estradiol and cyclical 10 mg dydrogesterone for one year. VMS frequency, depressive symptoms (measured by Beck Depression Inventory), insomnia severity (Insomnia Severity Index), and cognitive performance (Paced Auditory Serial Addition Test; PASAT, Symbol Digit Modalities Test; SDMT) were evaluated at baseline and at 3 and 12 months of treatment. Differences in the outcome measures between groups at baseline were assessed using the Mann-Whitney U test. Changes during follow-up compared to baseline within groups were evaluated by Wilcoxon Signed Ranks Test. $P < 0.05$ was considered for statistical significance. MS activity was monitored by clinical assessment and brain MRI at baseline and at 12 months.

Results: Depressive symptoms were more common in MS group, while vasomotor and insomnia symptoms were equally common. During follow-up with MHT, VMS frequency decreased in both groups. Depressive symptoms decreased at 3 months ($p = 0.031$ with MS; $p = 0.024$ without MS) and the reduction was sustained at 12 months ($p = 0.017$; $p = 0.042$, respectively). Alleviation in insomnia symptoms was seen in participants without MS at 3 months ($p = 0.029$) and in those participants with MS suffering insomnia at baseline ($p = 0.016$ at 3 months; $p = 0.047$ at 12 months). Both groups improved their performance in PASAT, but no significant change was observed in SDMT. MS activity at baseline was mainly stable, and no increase in activity was detected during MHT.

Conclusion: Improvements in vasomotor, depressive, and insomnia symptoms observed during one year of MHT are encouraging and suggest that larger placebo-controlled studies of MHT in women with MS are warranted. Cognitive implications were inconclusive because the findings in PASAT likely result from practice effect. MHT did not show any adverse effect on MS activity and increasing safety data will hopefully facilitate patient recruitment for future studies.

1. Introduction

Women with multiple sclerosis (MS) undergo the menopausal transition decades after the disease onset (McGinley et al., 2021) at the age when the conversion from relapsing-remitting MS to disease progression usually leads to an accumulation and worsening of MS

☆ European Union Drug Regulating Authorities Clinical Trials Database number: 2014-005129-10

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https://doi.org/10.1016/j.msard.2022.104098
Received 5 April 2022; Received in revised form 20 July 2022; Accepted 7 August 2022
Available online 8 August 2022

symptoms (Musella et al., 2018). Many invisible symptoms in MS overlap with the common menopausal symptoms, such as depression, insomnia, and cognitive difficulties (Bove et al., 2021; Monteleone et al., 2018). In clinical practice, it is often challenging to determine the source of these symptoms, but given that they are among determinators of quality of life (QOL) in MS (Gil-González et al., 2020), holistic care is crucial.

In the general population, menopausal hormone therapy (MHT) is the most effective treatment for common menopausal symptoms (Al-Safi and Santoro, 2014). Less information is available on the effects in MS (Midaglia et al., 2020). Women with MS have reported both positive and neutral responses to MHT (Bove et al., 2016b, 2015; Holmqvist et al., 2006; Smith and Studd, 1992). In a recent randomized placebo-controlled trial an 8-week treatment with combination of bazedoxifene and conjugated estrogen was well-tolerated in MS (Bove et al., 2022). No consistent association between menopause, MHT use, and disability accumulation has been found (Baroncini et al., 2019; Bove et al., 2016a; Kopp et al., 2022; Ladeira et al., 2018). In the Nurses' Health Study, MHT was associated with a better physical QOL in postmenopausal women with MS, although causal relationship could not be assessed (Bove et al., 2016c).

The purpose of this open-label baseline-controlled study was to compare the frequency of common menopausal symptoms in peri- and early postmenopausal women with or without MS and to evaluate these symptoms, tolerability, and MS disease activity during one year of MHT containing 1 or 2 mg of estradiol combined with cyclical 10 mg of dydrogesterone (Femoston®).

2. Material and methods

The ethical approval was obtained from the Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital in Finland, and all participants provided a written, informed consent.

2.1. Study population

The recruitment took place from August 2015 to September 2017. An invitation letter was sent directly to 60 targeted age women with MS treated in the Neurology Outpatient Clinic of Tampere University Hospital. Sixteen (27%) women responded and 11 (18%) were enrolled based on a screening questionnaire regarding their MS, medical history, and menopausal state. A shorter announcement was released through email posting and social media of the local and national MS organizations. Altogether, 34 contacts were received and nine (26%) were enrolled based on the screening questionnaire. The enrollment was stopped when 20 eligible women were identified. Fifteen age-matched women without MS were recruited from the staff of Tampere University and Tampere University Hospital by email and other information platforms of the institutions.

Menopausal state at baseline was confirmed by a gynecologist (author H.T. or K.A.), based on symptoms, clinical and ultrasound examination, and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol levels. Participants with FSH higher than 30 IU/l were classified as postmenopausal. Exclusion criteria included malignant, autoimmune, and neurodegenerative diseases other than MS, contraindication for MHT, and ongoing systemic hormonal therapy or contraception except hormonal devices. Other medications as needed were allowed at baseline and during the follow-up.

Inclusion criteria in the MS group were a confirmed diagnosis of initially relapsing-remitting MS by McDonald criteria 2010 (Polman et al., 2011) and mild to moderate disability by the Expanded Disability Status Scale (EDSS) score < 6 (Meyer-Moock et al., 2014), assessed by a neurologist (author L.J). MS demographics were collected from medical records. Disease-modifying therapy (DMT) with interferon β-preparations, glatiramer acetate, teriflunomide, and dimethyl fumarate was allowed if started at least three months before the baseline visit and used steadily over the study.

2.2. Study protocol and intervention

The included procedures for baseline and 3- and 12-month follow-up visits are shown in the flow chart in Fig. 1.

After the baseline visit, all eligible participants started per oral MHT including either 1 or 2 mg of estradiol combined with cyclic 10 mg dydrogesterone (Femoston®), approved in Europe for estrogen deficiency symptoms in menopausal women (Stevenson et al., 2013). The dosage of estradiol based on the menopausal phase and symptoms.

MS activity was monitored by clinical assessment and a 1.5 Tesla brain magnetic resonance imaging (MRI) at baseline and at 12 months. The MRI protocol included T1- and T2-weighted, fluid attenuation inversion recovery (FLAIR), diffusion-weighted imaging, and gadolinium (Gd) enhanced T1-weighted sequences. The neuroradiologist analyzed the scans. The volumes of FLAIR white matter hyperintensities were quantified using a fully automated MSmetrix software (icometrix, Leuven, Belgium). The exact method is described elsewhere (Jain et al., 2015).

2.3. Symptom assessment

At baseline and follow-up visits all participants were asked to evaluate the frequency (almost daily, weekly, monthly, or seldom/never) of their vasomotor symptoms (VMS), including hot flashes and night sweats.

Depressive symptoms were evaluated with the Finnish version of the 21-item Beck Depression Inventory (BDI) which is a widely used self-report screening tool for depressive symptoms. The maximum score is 63 and the recommended cut-off point of 10 for depressive mood was used to classify participants as depressed (Beck et al., 1988).

The Insomnia Severity Index (ISI) is a 7-item self-report measure to assess insomnia symptoms and treatment response in clinical research (Morin et al., 2011). The total score ranges from 0 to 28 and a higher score suggests more severe insomnia. A cut-off score of 8 was used for insomnia.

Cognitive assessments included Paced Auditory Serial Addition Test (PASAT) with 3.0 seconds interstimulus time and written form of Symbol Digit Modalities Test (SDMT). Both tests are commonly used to assess the cognitive performance of people with MS, especially information processing speed (Benedict et al., 2017; Tombaugh, 2006).

2.4. Power calculation and statistical analyses

The required sample size was calculated for the change in PASAT performance. According to some studies, 20% change in PASAT has been considered as clinically meaningful change (Meyer-Moock et al., 2014). With mean scores of 45/60 that would be 9 points. Barker-Collo et al. (2013) have reported a standard deviation (SD) of 12.17 for mean PASAT change in relapsing-remitting MS. When comparing the changes in PASAT between groups, with an α-error of 0.05 and a β-error of 0.2, the required sample size would be 30 per group. Because our study population is more homogenous considering age, sex, and MS disease severity, the SD was assumed smaller. With a SD of 9.0, the required sample size is 17 per group. Therefore, the aim was 20 participants per group.

Data were summarized as mean (SD) or median (interquartile range, IQR) for continuous variables and frequency (percentage) for categorical variables. Bivariate assessments of differences in demographic factors and outcome measures between study groups at baseline were conducted using the Mann-Whitney U test for continuous variables and Fisher's Exact Test for categorical variables. Wilcoxon Signed Ranks Test was used to test the statistical difference in the outcome measures within groups at 3 and 12 months compared to baseline. Nonparametric and exact tests were used because of the small sample size and non-normally

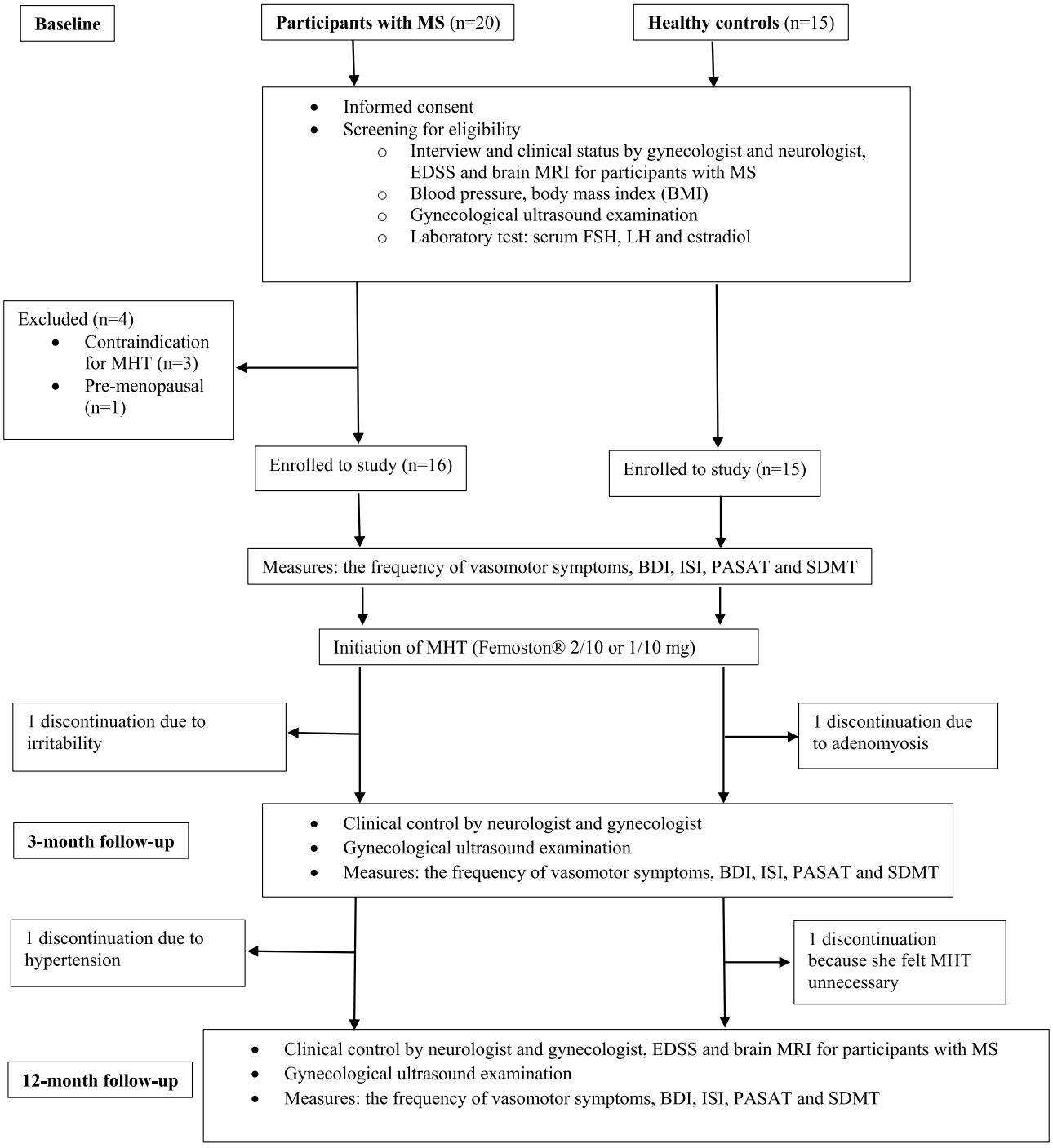

Fig. 1. Flow chart of study protocol and progression.
Abbreviations: MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MHT, menopausal hormone therapy; BDI, Beck Depression Inventory; ISI, Insomnia Severity Index; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test.

distributed data. Correlation between variables was calculated with Spearman's correlation coefficient. Analyses were conducted with SPSS Statistics software version 26.0 and $p < 0.05$ was considered for statistical significance.

3. Results

3.1. Demographics and clinical characteristics

Four out of 20 participants with MS (pwMS) were excluded at baseline because of pre-menopausal status or a contraindication to MHT. Fourteen pwMS and 13 participants without MS (healthy controls, HC) completed the follow-up and were included in the final analysis (Fig. 1). Their baseline demographics, clinical characteristics, and estradiol dosages are summarized in Table 1. PwMS were statistically significantly less educated and had a lower employment rate than HC. Differences in menopausal status and estradiol dosing were not statistically significant. Within the first four months of follow-up, the gynecologist decreased the estradiol dose from 2 to 1 mg in three pwMS and one HC because of common side-effects (headache, breast tenderness,

Table 1
Baseline demographics and clinical characteristics of the participants.

Characteristic	Participants with MS (n = 14)	Healthy controls (n = 13)	p-value [1]
Age (y), Mean (range; SD)	52.1 (48-54; 2.0)	50.5 (46-58; 3.5)	0.15
BMI (kg/m^2), Mean (range; SD)	27.1 (18.0-41.2; 6.0)	27.1 (22.8-33.5; 3.1)	0.58
Current smokers, n (%)	2 (14%)	1 (8%)	1.0
Pregnancies, Mean (range; SD)	1.9 (0-6; 1.7)	2.2 (0-4; 1.1)	0.25
Married/cohabiting, n (%)	11 (79%)	10 (77%)	0.34
Education in years, Mean (range; SD)	12.3 (6-17; 2.8)	14.7 (9-23; 3.1)	0.028
Employment status, n (%)			0.016
Employed	8 (57%)	13 (100%)	
Unemployed	1 (7%)	0	
On disability pension	5 (36%)	0	
FSH (IU/l), Mean (range; SD)	67.3 (3.10-148.2; 38.0)	40.0 (2.8-108.2; 37.4)	0.085
Postmenopausal (FSH > 30 IU/l), n (%)	11 (79%)	6 (46%)	0.12
The dosage of the estradiol, n (%) [2]			0.21
1 mg	3 (21%)	5 (38%)	
2 mg	11 (79%)	8 (62%)	
MS type, n (%)			
Relapsing-remitting	10 (71%)		
Secondary progressive	4 (29%)		
Disease duration in years, Mean (range; SD)	16.9 (6-34; 8.3)		
EDSS, Median (interquartile range)	3.0 (2.5-4.5)		
Disease-modifying therapy, n			
interferon beta	2		
glatiramer acetate	2		
dimethyl fumarate	1		
none	9		

MS, multiple sclerosis; BMI, body mass index; FSH, follicle-stimulating hormone; EDSS, Expanded Disability Status Scale; SD, standard deviation; IQR, interquartile range.
[1] Level of significance: $p < 0.05$
[2] The dosage used most of the follow-up time

peripheral edema) and in one pwMS the lack of efficacy led to dose escalation.

Three pwMS had a previous depression diagnosis, and they were all treated with a stable dose of selective serotonin reuptake inhibitor (SSRI) before study onset and over the follow-up. One pwMS used venlafaxine on a stable dose for fatigue symptoms. None of the HC had been diagnosed with depression but one had a stable clomipramine treatment for panic disorder.

At baseline, the inflammatory activity of MS was mainly stable. PwMS had been relapse-free for at least six months and only one had a Gd-enhancing lesion in brain MRI. The median EDSS was 3.0 corresponding moderate disability. During the follow-up, EDSS scores remained stable in nine (64 %), increased by 2 points in one (7%) and decreased by 0.5-1 points in four (29%) pwMS. One pwMS experienced a mild, transient episode of new symptoms that was adjudicated as a clinical relapse by the neurologist, but no relapse treatment was provided and there was no new MRI lesion on subsequent testing. None of the pwMS had Gd-enhancing lesions at 12-month follow-up MRI. The increase in FLAIR-lesions volumes was nonsignificant (Table 2). Because of technical issues, volumetric analysis was unsuccessful in three scans.

One pwMS did not return the BDI at baseline and another returned neither BDI nor ISI at 12 months. Only completed data from all time points were included in the statistical analysis.

Table 2
The absolute and percentage change in outcome measures, EDSS and brain MRI findings during the 12-month follow-up. Data are presented as median (interquartile range) except for MRI findings as mean (standard deviation).

Outcome	Participants with MS (n = 14)	Healthy controls (n = 13)
BDI		
Baseline	11.0 * (4.25-20.25)	4.0 (2.5-8.0)
12 months	5.5 (2.25-8.75)	3.0 (1.0-4.5)
%-change	-50.0%	-25.0%
p value [1]	**0.017**	**0.042**
ISI		
Baseline	10.0 * (3.5-16.0)	6.0 (4.5-9.5)
12 months	8.0 * (2.0-12.5)	3.0 (1.0-7.0)
%-change	-20.0%	-50.0%
p value [1]	0.050	0.13
PASAT		
Baseline	42.0 (36.0-51.25)	48.0 (44.5-51.0)
12 months	50.0 (39.75-52.5)	52.0 (42.5-53.0)
%-change	+19.0%	+8.3%
p value [1]	**0.002**	0.10
SDMT		
Baseline	41.0 (36.5-44.0)	45.0 (41.5-53.0)
12 months	42.5 (38.25-48.25)	51.0 (38.0-54.0)
%-change	+3.7%	+13.3%
p value [1]	0.33	0.46
EDSS		
Baseline	3.0 (2.5-4.5)	
12 months	3.0 (2.5-4.5)	
%-change	0.0%	
p value [1]	0.56	
Volume of FLAIR-lesions (ml, n=10)		
Baseline	15.5 (12.7)	
12 months	16.5 (10.2)	
%-change	+6,5%	
p value [1]	0.16	
No. of participants with Gd-enhancing lesions		
Baseline	1	
12 months	0	

BDI, Becks Depression Inventory; ISI, Insomnia Severity Index; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modalities Test; EDSS, Expanded Disability Status Scale; FLAIR, fluid attenuation inversion recovery
[1] The significance of the change compared to baseline (Wilcoxon Signed Ranks Test); $p < 0.05$ was considered statistically significant
* Above the cut-off score (BDI $\geq$ 10 and ISI $\geq$ 8)

3.2. Symptom severity at baseline and over the follow-up

3.2.1. Vasomotor symptoms

At baseline, five pwMS (36%) and five HC (39%) reported daily hot flashes but at 3- and 12-month follow-up visits, none of the participants reported them more often than once a week. The number of participants suffering from night sweats every night reduced in pwMS from seven (50%) at baseline to two (14%) at 3 months and one (7%) at 12 months and in HC from six (46%) to zero (0%) at both follow-up visits.

3.2.2. Depressive symptoms

At baseline, pwMS reported more depressive symptoms than HC ($p = 0.040$). Both groups demonstrated a significant decrease in depressive symptoms at 3 months and the decrease was sustained at 12 months (Fig. 2, Table 2).

Seven pwMS (58%) were classified as depressed (BDI $\geq$ 10) at baseline. Their median scores decreased from 18.0 (IQR: 12-22) to 6.0 (IQR: 5-14) at 3 months ($p = 0.016$) and the decrease persisted at 12 months (median 6.0, IQR: 5-15; $p = 0.031$) when only two (17%) pwMS were classified as depressed. Two HC (15%) were classified as depressed at baseline, and during the follow-up their scores decreased from 18 to 15 and from 10 to 3. No anti-depressive treatments were started or stopped during the study.

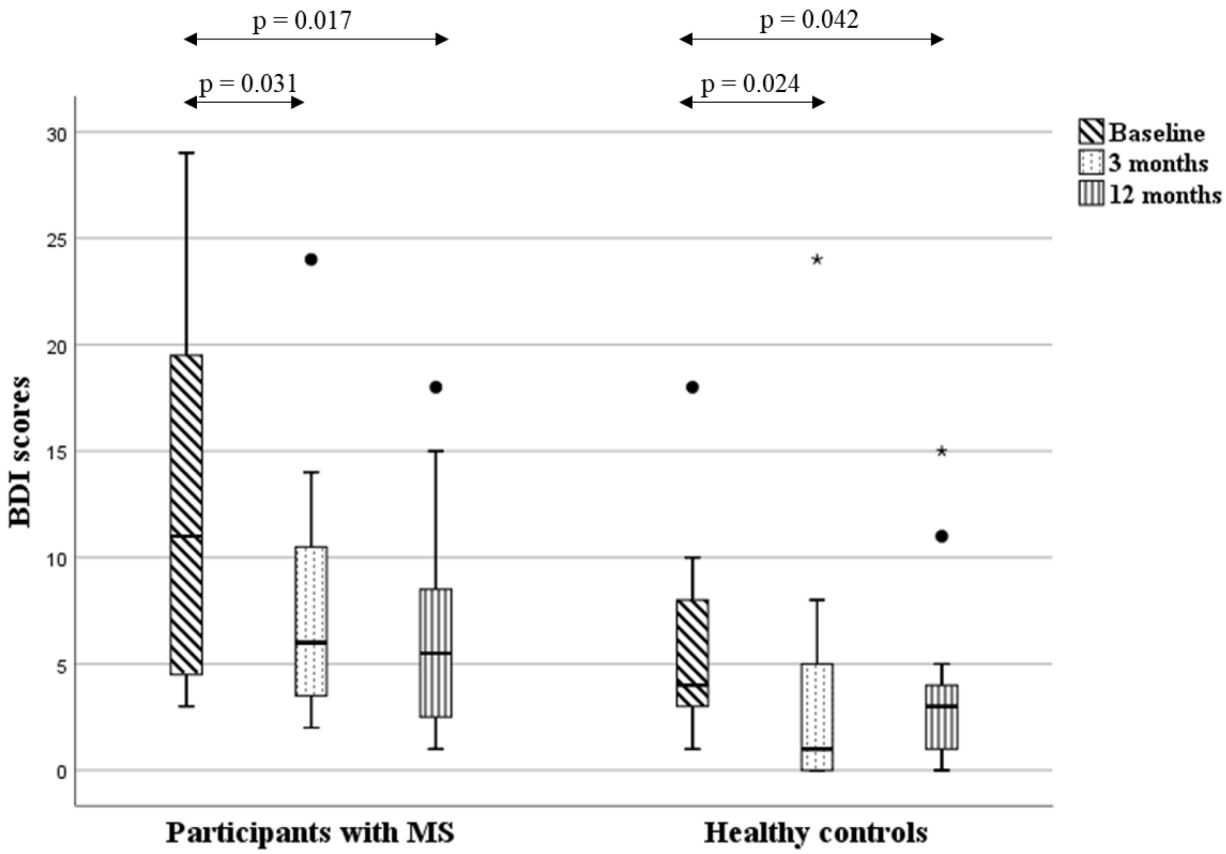

Fig. 2. Boxplot showing median, interquartile range, minimum and maximum of BDI scores in participants with MS and healthy controls. Potential outliers are indicated by dots and extreme values by asterisks.

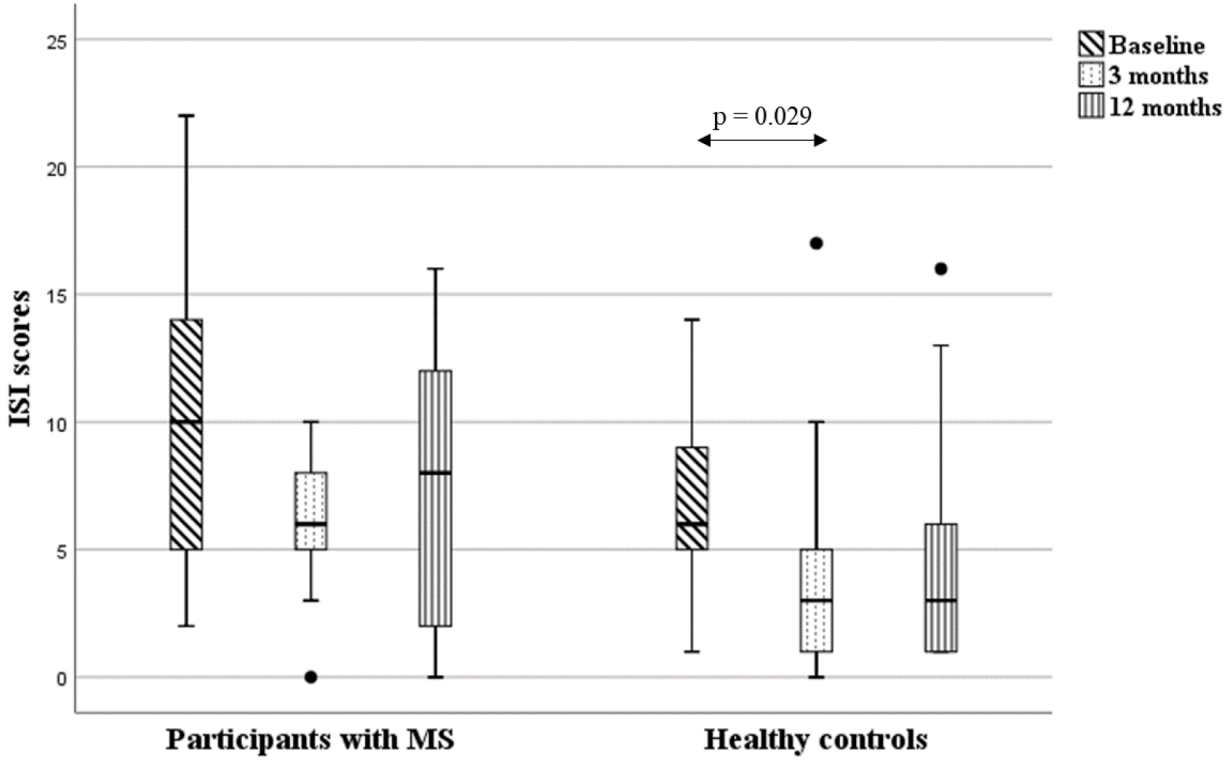

Fig. 3. Boxplot showing median, interquartile range, minimum and maximum of ISI scores in participants with MS and healthy controls. Potential outliers are indicated by dots.

3.2.3. Insomnia symptoms

At baseline, pwMS reported more insomnia symptoms than HC, but the difference was not statistically significant ($p = 0.29$). Symptoms decreased in both groups but a statistically significant change in ISI scores was reached only in HC at three months ($p = 0.029$; Fig. 3, Table 2).

Seven pwMS (54%) and six HC (42%) scored 8 or more at baseline, indicating insomnia. In this subgroup of pwMS, the median ISI scores decreased from 14 (IQR: 13-20) to 6 (IQR: 5-10) at three months ($p = 0.016$) and increased again to 10 (IQR 8-13) at 12 months ($p = 0.047$, compared to baseline). HC above the cut-off score also demonstrated a decrease in median scores from 9.5 (IQR: 8.75-13.25) to 6 (IQR: 3-11.75) at three months and increase to 6.5 (IQR: 1-13.75) in 12 months but these findings did not reach statistical significance.

There was no significant difference in baseline insomnia symptoms or in their change between those who had night sweats at baseline every night and those who had them less frequently. The change in insomnia symptoms did not correlate with the change in depressive symptoms.

3.2.4. Cognitive performance

The baseline median scores in PASAT and SDMT were lower among pwMS than HC, but the difference was statistically significant only in SDMT ($p = 0.043$, Table 2). In PASAT, pwMS improved at all time points, but statistical significance was reached only at 12 months (Fig. 4a). HC improved at three months but no more at 12 months. In SDMT, there was no statistically significant change at 3 or 12 months in either group (Fig. 4b).

In HC, the decrease in insomnia symptoms correlated with improvement in PASAT ($r = -0.59$; $p = 0.035$). Otherwise, the changes in depressive or insomnia symptoms did not significantly correlate with the changes in cognitive tests.

4. Discussion

In this preliminary study, we compared menopausal symptoms between women with and without MS and monitored the symptoms, tolerability, and MS activity over one year of MHT. The baseline depressive symptoms were more common in women with MS, while vasomotor symptoms and sleep disturbances showed similar rates. During MHT, vasomotor and depressive symptoms decreased already at three months in both groups, and the decrease was sustained at 12 months. A minor relief was seen in insomnia but the changes in cognitive performance were inconclusive.

Safety concerns were raised by many women contacted during the recruitment period of the present study. The same issue was the major enrollment barrier for women with MS in the MHT trial by Bove et al. (2022). We observed no serious or unexpected adverse effects over the one-year follow-up period. Compared to stable baseline activity of MS, no sign of increased activity during MHT was detected corroborating the findings of previous studies (Bove et al., 2022, 2016a; Kopp et al., 2022). This is an important piece of safety information for future larger studies, although the potential increased risk of disability progression with prolonged (>5 years) use of hormones observed in the Danish cohort study should be considered (Kopp et al., 2022).

MHT might improve the well-being of menopausal women with MS by alleviating vasomotor, depressive, and insomnia symptoms. However, our findings are observational, and in the future the efficacy of MHT should be evaluated in a placebo-controlled design. The rate of placebo improvement in VMS has ranged from 20% up to 60% (Freeman et al., 2015) and high rates have also been shown in depression and insomnia (Kirsch, 2019; Yeung et al., 2018). A placebo group was not included in this preliminary study as a larger cohort is needed to distinguish between treatment and placebo responses. Baseline-controlled design, in which participants' status on therapy is compared with status before therapy, was chosen here also because of the considerable individual differences in MS and menopausal transition. The potential baseline differences between the treatment and placebo groups could have complicated the interpretation of results and the control of confounders.

Common hallmarks of menopause are vasomotor symptoms. Hot flashes and night sweats affect about 75% of women in the general population and are often the most bothersome symptoms of menopause (Monteleone et al., 2018). Physiological events prior to hot flashes have shown core body temperature increase and during the flash skin blood flow and temperature increase lasting from minutes to an hour (Freedman, 2014). In MS, environmental- or exercise-induced rise in body temperature causes transient exacerbation in neurological symptoms known as Uhthoff's phenomenon (Jain et al., 2020). Women with MS have also reported temporary worsening of existing MS symptoms triggered by hot flashes (Bove et al., 2016b), and it would be warranted to evaluate whether the MHT could stabilize the symptoms.

Sleep disturbances are a common feature in both MS and perimenopause (Baker et al., 2018; Sakkas et al., 2019). At the baseline of this study, 54% of participants with MS and 42% of participants without MS reported insomnia symptoms, although severe symptoms were rare. Sleep complaints or their change were not associated with night sweats or depressive symptoms, which corroborates the findings of Geiger et al. (2019). Night sweats certainly affect sleep quality in menopause, and in several previous studies MHT has reduced sleep complaints mainly in women with concomitant VMS (Gava et al., 2019). Nevertheless, other aspects including many medical and psychosocial factors, circadian rhythm alterations, and underlying sleep disorders, such as obstructive sleep apnea or restless legs syndrome (Baker et al., 2018), should be considered when assessing insomnia in the menopausal population.

The lifetime risk for depression in MS is two to five times higher compared to the general population (Feinstein et al., 2014), shown also in our data where depressive symptoms were far more common in participants with MS (58% vs. 15%). The menopausal transition could be a particularly vulnerable time for depression in MS given that fluctuating estradiol level itself increases the depression risk (Gordon and Girdler, 2014). Moreover, in menopause many women with MS face the conversion to disease progression and thereby new physical and psychosocial implications of MS (Tutuncu et al., 2013). In the general population, estrogen therapy has shown antidepressant effects in perimenopausal women (Maki et al., 2018). A significant decrease in depressive symptoms during MHT in the present study suggests that further placebo-controlled studies are warranted also in MS. Depression substantially adds to the burden of MS and even relates to mortality (Feinstein et al., 2014). Our findings indicate the importance of screening for depressive symptoms in menopausal women with MS. When needed, accurate diagnostics and evaluation of the contributing factors should be made, and the benefits and risks of treatment choices should be discussed.

The effect of MHT on cognition in the general population has been controversial. In the KEEPS–Cognitive and Affective Study, four years of MHT did not alter the cognition in recently menopausal women (Gleason et al., 2015) and the change in global brain volumes measured three years after exposure to MHT was not significantly different from placebo-treated women (Kantarci et al., 2018). Potential benefits in other studies seem to be limited to recently menopausal women (Hogervorst et al., 2022). Later or in prolonged use, the effect may even be harmful (Maki, 2013). Our hypothesis of the possible favorable effects of MHT on cognition in MS is based on some preliminary data that estrogen, in estriol treatment or in combined oral contraceptives, may improve cognitive functioning in women with MS (De Giglio et al., 2017; Voskuhl et al., 2016). However, improvements seen here in PASAT are likely a consequence of practice effect. In a cognitively intact population, the greatest improvement is usually seen in the first retest (Tombaugh, 2006) but among people with MS improvement up to the fourth administration has been reported (Rosti-Otajärvi et al., 2008).

The strength of our data includes the narrow age group and short duration of menopause before the intervention in both groups. All

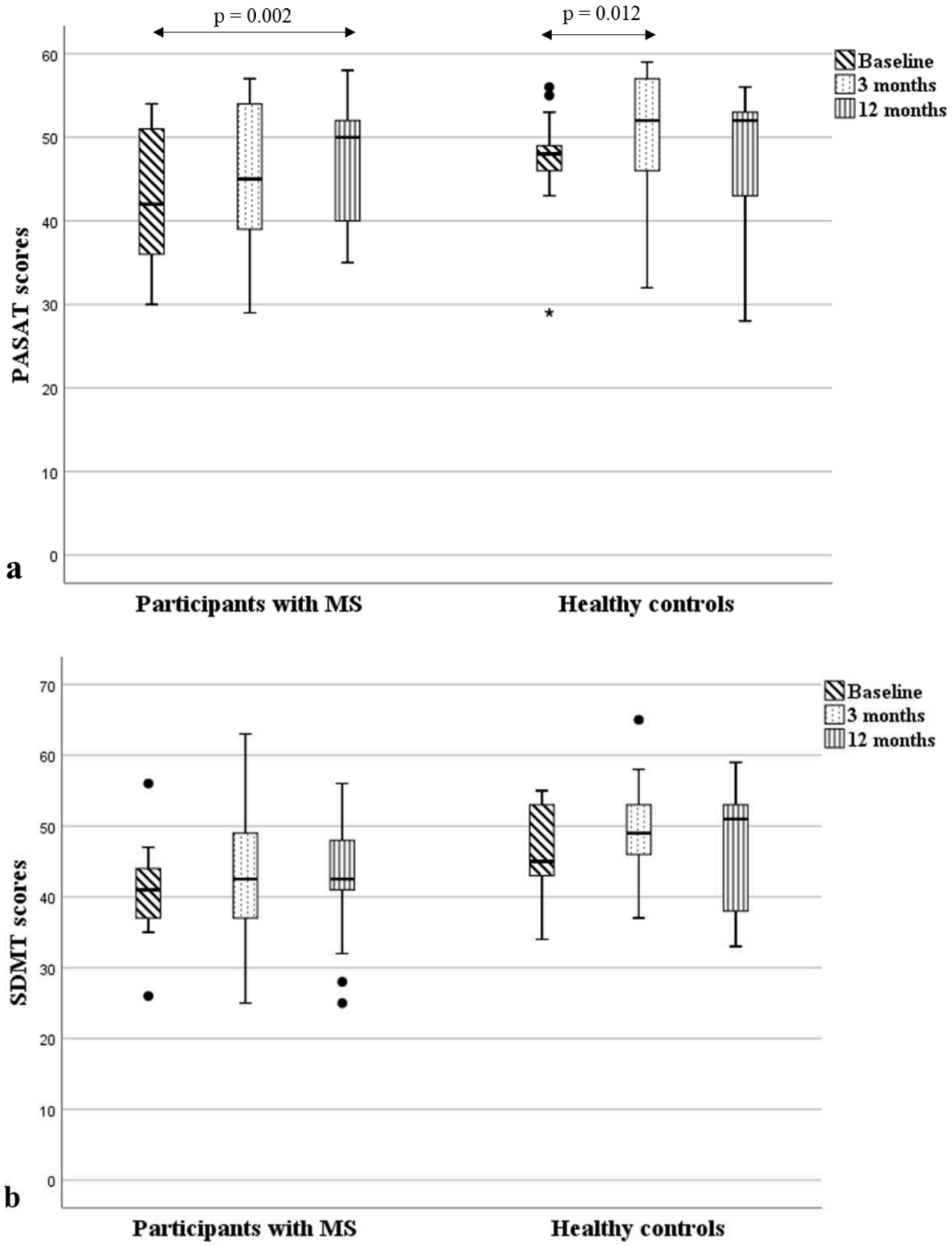

Fig. 4. Boxplot showing median, interquartile range, minimum and maximum of (a) PASAT and (b) SDMT scores in participants with MS and healthy controls. Potential outliers are indicated by dots and extreme values by asterisks.

participants used the same route of estrogen administration and the same progestin and treatment regimen. Disease activity in MS was stable controlled by MRI and clinical assessments. Thus, temporal changes in test performance caused by the fluctuation in disease activity may be considered negligible.

The main limitations in our data concern the small sample size and the absence of placebo group as discussed earlier. We are not able to separate MHT effect from placebo effect or statistical artefacts like regression to the mean phenomenon. Some spontaneous recovery may occur as depressive symptoms tend to fluctuate, and VMS will resolve over time. However, the improvement in VMS seen already at three months is unlikely caused by the natural course of symptoms alone, as the median duration of VMS in longitudinal studies has been 5-10 years (Al-Safi and Santoro, 2014). Participants with MS had lower socioeconomic status, which, in addition to MS, may explain the higher prevalence of depressive symptoms (Timur and Şahin, 2010). They were also more often classified as postmenopausal which may be explained by slightly older age in the MS group. This difference was not statistically significant but may influence the comparability of the results. In future larger studies, accurate staging of menopause according to a consensus guideline developed by the Stages of Reproductive Aging Workshop (STRAW) should be considered (Harlow et al., 2012). Finally, because of stable disease activity, moderate disability, and exclusion of the high efficacy DMTs, these findings may not be generalizable to women with higher disability or more active MS.

5. Conclusions

In clinical practice, many common and bothering symptoms are shared between MS and menopause raising further challenges for the management of MS. During one year of MHT, we observed a substantial relief of vasomotor and depressive symptoms and minor relief in insomnia symptoms. As the symptoms were common, this may considerably improve the well-being of menopausal women with MS. MHT, as used here, did not show any adverse effect on MS activity. Although these preliminary results should be interpreted with caution, the findings are encouraging and suggest that larger randomized placebo-controlled studies should be conducted. Increasing safety data will hopefully facilitate recruitment for future studies. Our findings do not raise concerns that MHT, a treatment with proven efficacy against VMS and with updated guidelines for use (de Villiers et al., 2016), should be avoided in a holistic treatment plan for women with MS.

Role of Funding Source

This work was supported by the State Research Funding of the Expert Responsibility area of Tampere University Hospital and a grant from Novartis to Tampere University for the MRI imaging.

The funding sources were not involved in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Ethical approval

The ethical approval of the Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital for this study was obtained (code R15006M) and all participants provided written, informed consent.

CRediT authorship contribution statement

Laura Juutinen: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft. **Katja Ahinko:** Investigation, Formal analysis, Writing – review & editing. **Helena Tinkanen:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Eija Rosti-Otajärvi:** Formal analysis, Writing – review & editing. **Marja-Liisa Sumelahti:** Conceptualization, Methodology, Formal analysis, Project administration, Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

The authors thank Professor Tomi Mikkola (Helsinki University Hospital) for the menopausal symptom questionnaire and statistician Mika Helminen (Tampere University Hospital) for assistance in statistical analysis. We thank research coordinator Anne Simi (Tampere University Hospital) and all study participants for their effort.

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