Published in final edited form as:
Menopause. 2014 April ; 21(4): 403–409. doi:10.1097/GME.0b013e31829d4c4c.

Increased Hot Flash Severity and Related Interference in Perimenopausal HIV-infected Women

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Abstract

Objective—As women with HIV are living longer, more are entering the perimenopause. Prior studies suggest that HIV-infected women are more likely to have hot flashes than non-HIV-infected women. However, little is known regarding the severity and degree of interference that hot flashes have on daily function, mood, and quality of life in this population.

Methods—Perimenopausal HIV-infected and non-HIV-infected women matched by age, race, and menstrual patterns completed the Menopause Rating Scale (MRS) to assess hot flash severity and the Hot Flash Related Daily Interference Scale (HFRDIS). MRS and HFRDIS scores and subscores were compared between groups.

Results—33 HIV-infected and 33 non-HIV-infected women similar in age (47 (45,48) median (interquartile range) vs. 47 (46,49) yrs; race (64% vs. 52% non-white; *P*=0.32), and menstrual patterns (# periods in past year; 5 (4,9) vs. 6 (4,10); *P*=0.53) were studied. Perimenopausal HIV-infected women reported greater hot flash severity (HIV; 2 (1,3) vs. non-HIV: 1 (0,3); *P*=0.03), and hot flash-related interference (HFRDIS total score; 37 (10,60) vs. 6 (0,20); *P*=0.001).

Conclusions—Perimenopausal HIV-infected women experience greater hot flash severity and related interference compared to non-HIV-infected perimenopausal women. Increased distress secondary to hot flashes may reduce quality of life and negatively impact important health-promoting behaviors including adherence to antiretroviral therapy in HIV-infected women.

Keywords

HIV; Menopause; Hot Flashes; Menopause Symptoms; Quality of Life

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Data: Some of these data were presented at 22nd annual North American Menopause Society meeting held in September 2011 in Washington D.C., and the 20th annual Conference on Retroviruses and Opportunistic Infections held in March 2013 in Atlanta, GA.

Conflicts of Interest
For the remaining authors, no conflicts of interest were declared.

Introduction

Menopause is associated with a number of bothersome symptoms including hot flashes[1–3], and prior studies suggest these symptoms peak during the perimenopause [1,4]. Vasomotor symptoms or hot flashes are reported to be the most common symptom associated with menopause[5,6], and such symptoms are both burdensome and distressing. Hot flashes are also associated with increased anxiety and depressive symptoms during the early perimenopause [5,7,8]. A recent study among a large, racially diverse cohort of HIV-infected and non-infected pre, peri, and postmenopausal women showed that those experiencing persistent hot flashes were approximately 45% more likely to experience elevated depressive symptoms [4]. Collectively, menopausal symptoms negatively impact quality of life, relationships, and role performance [9].

As life span increases in HIV-infected women, more are entering the perimenopause. Prior studies suggest that HIV-infected women initiate menopause at a younger age than non-HIV-infected women[10–13], and consequently may encounter hot flashes and other related symptoms earlier. Of concern is that the burdensome nature of hot flashes coupled with depression and other co-morbidities commonly associated with HIV,[14,15] may further reduce quality of life in this population during the perimenopause. Collectively, these symptoms may negatively impact adherence to antiretroviral therapy (ART) [16] and increase the risk of developing an AIDS defining illness [17], as prior studies have shown that those with depression have poor adherence to ART [18,19].

Few clinical studies evaluating menopause symptoms among HIV-infected women have been conducted [11,13,20–22], and the majority have reported on prevalence of menopause symptoms verses degree of symptom severity or related interference. Two prior studies reported on hot flash prevalence among cohorts of pre, peri, and post-menopausal HIV-infected women, and found that postmenopausal HIV-infected women reported experiencing more hot flashes than the pre or perimenopausal women[13,21]. However, neither study included a non-HIV-infected comparison group. In contrast, studies by Ferreira et al.[22] and Miller et al.[20] compared the prevalence of menopause symptoms among pre, peri, and post-menopausal HIV-infected and non-HIV-infected women [20,22]. Ferreira et al.[22] found that 78% of Brazilian HIV-infected women reported vasomotor symptoms compared to 60% of non-HIV-infected women, though symptom prevalence was not reported with regard to specific menopause stage and data on symptom intensity were not available. Similarly, Miller et al.[20] evaluated the prevalence of menopause symptoms among a cohort specifically designed to recruit pre, peri, and postmenopausal HIV-infected and drug-using women and found that a greater number of HIV-infected women reported vasomotor symptoms (64% vs. 58%). However, while the prevalence of vasomotor symptoms is higher among women with HIV, to our knowledge, no prior study has evaluated whether hot flashes are more severe or have a greater negative impact on mood, relationships, social activities and quality of life in HIV-infected compared to non-HIV-infected women during the perimenopause. This information is important, as many HIV-infected women already experience impaired quality of life, and the negative influence of hot flashes may further impact well-being and participation in health promoting behaviors including adherence.

This investigation evaluated hot flash severity and interference among perimenopausal HIV-infected and non-HIV-infected women of similar age, race and menstrual patterns. We hypothesized that hot flashes would be more severe and interfere more with daily function in perimenopausal HIV-infected women than in perimenopausal non-HIV-infected women.

Methods

Study population and design

Sixty-six women, thirty-three HIV-infected women and thirty-three non-HIV-infected women, between 45–52 years of age were enrolled at the Massachusetts General Hospital (MGH) from June 2010 to May 2012 for a longitudinal evaluation of menopause symptoms and metabolic changes associated with the menopause transition. This paper reports baseline cross-sectional data on hot flash severity and burden among this cohort. Participants were recruited via advertisement at community AIDS service organizations, newspapers, outpatient clinics, and through a research participant registry comprised of individuals interested in receiving information on clinical trials. Interested participants completed a phone screen to determine eligibility. Women in both the HIV and control groups were required to be clinically perimenopausal, defined as the presence of 1 menstrual cycle greater than 60 days in length in the prior 6 months, or irregular menses in 2 or more cycles within the past 6 months [23]. Women were excluded if amenorrheic for 12 months or greater, had a hysterectomy or any active cancer, were pregnant or breast feeding in the past year, or were using hormone therapy of any kind in the past 6 months. The HIV-infected women were on a stable treatment regimen for at least 3 months, and were excluded if diagnosed with an opportunistic infection within the 3 months prior to study enrollment. A stratification algorithm was utilized for recruitment to ensure that the HIV-infected and non-HIV-infected women were similar. Women were recruited in blocks of 10 starting with the HIV-infected women and were stratified by age, race, and menstrual patterns (having greater than or less than 6 periods in the prior year). Similar numbers in each stratification block were recruited. Written and informed consent was obtained from all participants prior to enrollment, and this study was approved by and conducted in accordance with the guidelines for experimental investigation with human subjects mandated by the Partners Institutional Review Board at MGH.

Measurements

Eligible participants were seen at the Clinical Research Center at MGH. A comprehensive health history was obtained including assessment of menstruation history and menstrual patterns, medication use, including selective serotonin reuptake inhibitor (SSRI) use, and HIV-specific health characteristics.

To further characterize the population, serum estradiol and follicle stimulating hormone (FSH) levels were measured via Access Chemiluminescent Immunoassay (Beckman Coulter, Fullerton, California), and were not obtained on specific days of menstrual cycle phase. CD4 cell count was measured via flow cytometry (MultiTEST CD3 FITC/CD8 PE/CD45 PerCP/CD4 APC reagent, Becton Dickinson Biosciences, San Jose, California).

Questionnaires

Women were asked if they have experienced hot flashes in the past year and reported the number of days they had experienced hot flashes in the past 4 weeks. The Menopause Rating Scale (MRS) was then used to assess presence and severity of menopause symptoms[24,25]. The MRS is an 11-item questionnaire comprised of 3 symptom domains: somatic symptoms (e.g. hot flashes), psychological symptoms (e.g. depressive mood), and urogenital symptoms (e.g. vaginal dryness). Women were asked to report symptoms and degree of severity for each symptom (scale 0–4; none, mild, moderate, severe, extremely severe) experienced at this time. The total MRS score was computed by adding each individual item score (range 0; asymptomatic to 44; highest degree of complaint). Similar to others,[26–28] item 1 of the MRS was used to assess hot flash severity.

The Hot Flash Related Daily Interference Scale (HFRDIS), a 10-item questionnaire, was completed to determine the impact of hot flashes on daily activities and quality of life [29]. Women rated the degree of hot flash interference (during the past week) for each item on a scale from 0 (do not interfere) to 10 (completely interfere); and a higher total score indicates greater interference (score range 0–100). The total HFRDIS score as well as individual item scores are presented to demonstrate the degree of interference with each individual activity and quality of life.

Statistical Analysis

The Student's *t*-test was used to analyze normally distributed continuous variables with data presented as mean +/− standard deviation. The Wilcoxon rank-sum test was used to analyze non-normally distributed variables, with data presented as median (interquartile range; IQR). Categorical variables were analyzed using the Chi-square test and are presented as proportions. Hot flash severity (MRS item 1), overall menopause symptom severity (total MRS score) and hot flash interference (total HFRDIS scores) were compared between HIV-infected and non-HIV-infected women using linear regression models adjusting for characteristics that differed between groups including smoking and history of substance abuse. Models were further adjusted for hot flash frequency.

With 66 participants, the study was powered to detect a 0.7 SD difference between the groups, with power at 0.8 and a two-sided 0.05 significance level. All analyses were performed using SAS JMP statistics software (version 9.0; SAS Institute Inc., Cary, NC). Statistical significance was assumed if the *P*-value was less than or equal to 0.05.

Results

Study Population

A total of 66 women were enrolled (33 HIV-infected and 33 non-HIV-infected), and characteristics of the study population are presented in Table 1. Women were similar in age, race, and menstrual patterns. The median age of both groups was 47 years, and greater than half of the women were of diverse racial and ethnic backgrounds. More HIV-infected women were current smokers than were non-HIV-infected women (70% vs. 42%, *P*=0.03, Table 1) and a greater number of HIV-infected women reported having a history of substance use compared to the non-HIV-infected women (76% vs. 36%, *P*=0.001, Table 1). Few women were taking methadone, the prevalence of which did not differ between groups (Table 1). SSRI use was not different between groups (HIV-infected: 33% (11) vs. non-HIV-infected 18% (6), *P*=0.16).

All women had menstrual patterns consistent with perimenopause (number of menstrual periods in past year: HIV-infected 5 (4, 9), median (IQR) vs. non-HIV-infected 6 (4,10), *P*=0.53, Table 1). Ninety-four percent of the HIV-infected women compared to 85% of the non-HIV-infected women reported experiencing hot flashes in the past year (*P*=0.23). The median number of days with hot flashes during the 4 week time period preceding study entry was 8 days for the cohort overall. The median number of days during the past 4 weeks during which HIV-infected and non-infected women reported experiencing hot flashes was 12 (3,28) and 3 (0,18), *P*=0.10, with HIV-infected women more likely to have experienced hot flashes on at least 8 days in the past 4 weeks compared to the non-HIV-infected women (67% vs. 42%, *P*=0.048; Table 1). No difference in FSH or estradiol levels was observed between groups (Table 1).

Among the HIV-infected women, the mean duration of HIV infection was 14±6 years (Table 1). Ninety-one percent were receiving antiretroviral therapy, and the mean CD4 cell

count was 686±432 cells#/mm^3 (Table 1). Within the HIV-infected group, hot flash frequency did not correlate with CD4 cell count or duration of HIV.

Hot Flash Severity and Menopause Symptoms

The HIV-infected women experienced greater hot flash severity compared to the non-HIV-infected women (MRS item one: 2 (1, 3) verse 1 (0, 3), *P*=0.03, Table 2). Specifically, these findings indicate that HIV-infected women were experiencing moderate hot flash severity compared to mild hot flash severity experienced by the non-HIV-infected women (Table 2). The HIV-infected women also had higher total scores on the Menopause Rating Scale (MRS; 15±8 vs. 10±7, *P*=0.008), indicating worse menopause-related symptom severity overall (Table 2). HIV-infected women reported more sleep problems (MRS item three: 2 (1,3) vs. 2 (0,2), *P*=0.04) and psychological symptom severity including depressed mood, irritability, and anxiety (MRS items 4–6, $P \leq 0.05$ for all comparisons, Table 2). No significant difference in urogenitial symptoms including sexual problems (MRS item 8; *P*=0.25) and vaginal dryness (MRS item10; *P*=0.41) was observed between groups (Table 2). Within the HIV-infected group, hot flash severity did not correlate with CD4 cell count or duration of HIV.

Hot Flash Related Interference

The HIV-infected women in this study also reported greater interference of hot flashes with daily function compared to the non-HIV-infected women, as evidenced by significantly higher total scores on the HFRDIS (37 (10,60) vs. 6 (0,20), *P*=0.001, Table 3). Individual HFRDIS item analyses demonstrated that HIV-infected women experienced a greater degree of hot flash interference with all activities compared to the non-HIV-infected women (HFRDIS items 1–9, Table 3), including quality of life (HFRDIS item ten: 3 (0,7) vs. 0 (0,2), *P*=0.002). Within the HIV-infected group, hot flash interference did not correlate with CD4 cell count or duration of HIV.

Differences between HIV-infected and non-HIV-infected women for the total HFRDIS score, total MRS score, and MRS item 1 score remained generally significant after adjusting for differences in smoking status and substance abuse history (Tables 2 & 3). HIV status also remained significant for the total HFRDIS score and total MRS score, controlling for hot flash frequency. However, between group differences for hot flash severity (MRS item 1) were no longer significant controlling for hot flash frequency (Tables 2).

Discussion

Results of this study show that perimenopausal HIV-infected women experience greater hot flash severity and greater hot flash-related interference with daily activities and quality of life compared to well-matched perimenopausal non-HIV-infected women. Within the HIV-infected group, hot flash frequency, severity, and interference did not correlate with CD4 cell count or duration of HIV. Our findings suggest a greater burden of hot flashes among perimenopausal women who are infected with HIV, which may have important consequences for their quality of life, and potentially reduce their adherence to anti-retroviral therapy.

Early studies among HIV-infected peri and postmenopausal women demonstrated an association between HIV-specific characteristics and vasomotor symptoms. An investigation by Clark et. al [11] demonstrated that menopausal HIV-infected women with higher CD4 cell counts (>500 cells/mm^3) were more likely to report hot flashes. Similarly, Miller et al.[20] observed a reduction in the prevalence of menopause symptoms as CD4 cell count declined (<200 cells/mm^3) among HIV-infected non-ART users. While these studies show that hot

flash prevalence correlates with CD4 cell count, we did not observe this pattern for hot flash severity or interference in our sample, although few of our participants had a CD4 count below 200 cells/mm^3. We also did not observe a relationship of hot flash severity or interference to the duration of HIV. Possible explanations for greater hot flash severity in the HIV-infected population include the effects of ART or immunological dysfunction on estradiol metabolism or function, though our sample may have been too small to show these associations or perhaps a stronger relationship between HIV-related factors and symptom severity are seen among post-menopausal women, who have endured a longer duration of estrogen suppression.

Smoking and illicit substance use has been shown to influence the presence and/or severity of hot flashes in prior studies among non-HIV-infected women[30–32]. In a study among menopausal HIV-infected and non-HIV-infected drug using women, a higher prevalence of hot flashes was observed among the HIV-infected women[20]. While increased smoking rates and substance abuse history commonly seen in HIV-infected women might be thought to contribute to increased hot flash severity, our results were generally unaffected by adjustment for these differences between groups.

Previous research has demonstrated that HIV-infected women may enter menopause at an earlier age than non-HIV-infected women[10–13] and therefore may develop hot flashes at an earlier age, raising the possibility that our HIV-infected group reported greater hot flash severity and interference because they had experienced hot flashes for a longer duration. However, the age of our study participants is within the normal age range for perimenopause and we purposefully matched women in the groups with respect to not only age, but also number of menstrual periods in the prior year. Estradiol and FSH levels were not different between the groups, suggesting that the women were at similar stages of the perimenopausal transition with regard to age, menstrual patterns, and biological indices. We also did not observe differences in the use of SSRI, which have been shown to reduce hot flash severity in non-HIV-infected menopausal women[33]. Given these findings, further research is necessary to determine the mechanism of increased hot flash severity among HIV-infected perimenopausal women.

In addition to greater hot flash severity, HIV-infected women experienced greater interference of hot flashes on sleep, mood, relationships, daily activities and quality of life compared to the non-HIV-infected women. Although the HFRDIS has not been utilized previously in HIV-infected women, this instrument has been used in other populations of chronically ill women such as breast cancer survivors [34]. Similar to our findings, Carpenter et. al [34] demonstrated that breast cancer survivors (including those who were naturally post-menopausal) reported more severe hot flashes, and greater hot flash interference compared to healthy women [34]. Carpenter et. al also reported differences in hot flash related interference with overall quality of life among her cohort utilizing the HFRDIS quality of life item 10. Interestingly, HIV-infected women in our study reported a higher mean score for the overall quality of life item, indicating more interference than did the breast cancer survivors in Carpenter et. al's [34] study (HIV-infected women, N=33, HFRDIS item ten score: 3.48±3.27, mean/SD vs. breast cancer survivors, N=69, HFRDIS item ten score: 1.58±2.31), suggesting hot flashes may cause greater distress among perimenopausal HIV-infected women.

The HIV-infected women in this cohort also reported more severe sleep problems (difficulty falling asleep, sleeping through the night, waking up early), depressive symptoms, irritability, and anxiety compared to the non-HIV-infected women (MRS items 3–6). Consistent with this finding, the HIV-infected women experienced greater hot-flash related interference with sleep, mood, and concentration (HFRDIS items 4–6). Further studies are

needed to determine the association of hot flash severity and its relationship with sleep and mood among a larger group of perimenopausal HIV-infected women, specifically to identify HIV-related characteristics that may influence this relationship.

This study has limitations. Although the comparison groups are closely matched by demographics and menstrual patterns, there may be residual confounding by factors that were not measured. Perimenopause status was assessed cross-sectionally based on retrospective menstrual cycle pattern reporting rather than prospective monitoring or FSH criteria. Additionally, given that this study was designed to recruit perimenopausal women exclusively, study findings may be most relevant for HIV-infected women experiencing perimenopause, and not generalizable post-menopausal women. Recall bias may have influenced menopause symptom occurrence and menstrual patterns which were retrospectively assessed. However recall should not have differed between groups. Based on the findings of the present study, additional studies are needed to further investigate the effect of HIV-infection, immune function, and ART class/specific medications on vasomotor symptoms among a larger cohort of HIV-infected women.

Conclusions

In summary, HIV-infected women are living longer with their disease and more are now entering the perimenopause. Many HIV-infected individuals already experience reduced quality of life due to illness-related factors [35] and social stressors. Our data suggest that for perimenopausal HIV-infected women, there may be an additional burden of hot flashes on quality of life, which may destabilize an already precarious situation of wellness, abstinence from substances, and adherence to ART. These data highlight the need for clinicians to include a comprehensive review of hot flashes in their assessment of midlife HIV-infected women, as effective treatments are available that may reduce symptom burden and improve quality of life in this population.

Acknowledgments

Source of Funding: Funding for this project was provided by NIH K23 NR011833-01A1 to S.E.L., and support of the Nutrition Obesity Research Center at Harvard: P30-DK040561. This work was also conducted with support from Harvard Catalyst | The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award 8UL1TR000170-05 and financial contributions from Harvard University and its affiliated academic health care centers). The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health.

Unrelated to this project, Dr. Joffe reports board membership with Noven, consultancy (non-compensational) with Sunovion, and current research funding from Cephalon/Teva.

We would like to thank all of the women who participated in this study, and the nursing, bionutrition, and administrative staff of the MGH Clinical Research Center for their excellent care and dedication to our patients.

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Table 1

Characteristics of the Study Population

Demographic Characteristics	HIV + (N= 33)	HIV − (N= 33)	P-Value
Age (years)	47 (45,48)	47 (46,49)	0.06
% older than median split	33% (11)	45% (15)	0.31
Race: %(#)			
Non-White	64% (21)	52% (17)	0.32
Hispanic Ethnicity	15% (5)	12% (4)	0.72
Body Mass Index	28.6±6.5	28.7±5.6	0.98
Current Smoker % (#)	70% (23)	42% (14)	0.03*
History of Substance Abuse % (#)	76% (25)	36% (12)	0.001**
Current Methadone use % (#)	9% (3)	6% (2)	0.64
Current selective serotonin reuptake inhibitor (SSRI) use % (#)	33% (11)	18% (6)	0.16
Menopause-Related Clinical Characteristics			
Total Number of Periods in the Past Year	5 (4,9)	6 (4,10)	0.53
Experienced hot flashes 8 or more days in the past 4 weeks (range:0–28 days)†	67% (22)	42% (14)	0.048*
Follicle Stimulating Hormone (mIU/mL) ††	24 (8,53)	35 (15,63)	0.19
Estradiol (pg/mL) †††	60 (32, 206)	81 (44,154)	0.61
(pmol/L)	220 (118,756)	297 (162,565)	
HIV-Related Characteristics			
Duration of HIV (years)	14± 6	-	-
Currently taking Antiretroviral Therapy % (#)	91% (30)	-	-
Current NRTI use	91% (30)	-	-
Current NNRTI use	9% (3)	-	-
Current PI use	45% (15)	-	-
CD4 count (#/mm3)††††	686±432	-	-
Nadir CD4 count (#/mm3)†††††	199 (60,290)	-	-

Data are reported as % (N) for categorical variables, and for continuous variables, as mean/SD or median (IQR=interquartile range) for data that were not normally distributed.

*=P<0.05,

**=P<0.01.

†Median hot flash frequency split. Missing values are not included in the calculation: N=2,

†††Missing values not included in calculation: N=3,

††††Missing values not included in calculation: N=7,

†††††Missing values not included in calculation: N=3. PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor.

Table 2

Differences in Menopause Symptom and Hot Flash Severity in Perimenopausal HIV-Infected and Non-HIV-Infected Women

Menopause Rating Scale Score (MRS)†	**HIV + N= 33**	**HIV − N= 33**	**P-Value**
Total Menopause Rating Scale Score (MRS; range 0–44)	15±8	10±7	0.008**a,c
Individual MRS Item Responses (range 0–one, mild, moderate, severe extremely severe)			
MRS item 1: Hot Flashes	2 (1,3)	1 (0,3)	0.03*b, d
MRS item 2: Heart Discomfort	0 (0,1)	0 (0,0)	0.58
MRS item 3: Sleep Problems	2 (1,3)	2 (0,2)	0.04*
MRS item 4: Depressive Mood	2 (1,3)	1 (0,1)	0.001**
MRS item 5: Irritability	2 (0,2)	1 (0,1)	0.05*
MRS item 6: Anxiety	1 (0,2)	0 (0,1)	0.02*
MRS item 7: Physical and Mental Exhaustion	1 (0,2)	1 (0,2)	0.31
MRS item 8: Sexual Problems	1 (0,3)	1 (0,2)	0.25
MRS item 9: Bladder Problems	1 (0,2)	0 (0,2)	0.33
MRS item 10: Dryness of vagina	0 (0,2)	0 (0,1)	0.41
MRS item 11: Joint and muscular discomfort	1 (0,2)	1 (0,2)	0.97

†MRS assesses presence and severity of menopause symptoms. Data are reported as mean/SD and median (IQR=interquartile range) for data that are not normally distributed;

*=P≤0.05,

**=P≤0.01 After adjustment for current smoking and history of substance abuse,

*a*P=0.08 and

*b*P=0.06. After adjustment for hot flash frequency,

*c*P=0.03 and

*d*P=0.12.

Table 3

Differences in Hot Flash Related Interference in Perimenopausal HIV-Infected and Non-HIV-Infected Women

Hot Flash Interference	HIV + (N= 33)	HIV − (N= 33)	P-Value
Total Hot Flash Related Daily Interference Scale Score [†](HFRDIS; range 0–100)	37 (10,60)	6 (0, 20)	0.001**a,b
Individual HFRDIS Item Responses (range 0–10; do not interfere-completely interfere)			
HFRDIS item 1: Work (outside the home and housework)	2 (0,5)	0 (0,1)	0.01**
HFRDIS item 2: Social Activities	2 (0,5)	0 (0,1)	0.009**
HFRDIS item 3: Leisure Activities	3 (0,5)	0 (0,1)	0.001**
HFRDIS item 4: Sleep	5 (2,8)	2 (0,5)	0.01**
HFRDIS item 5: Mood	5 (1,8)	0 (0,4)	0.0003**
HFRDIS item 6: Concentration	4 (0,7)	0 (0,3)	0.004**
HFRDIS item 7: Relations with others	2 (0,7)	0 (0,2)	0.003**
HFRDIS item 8: Sexuality	1 (0,8)	0 (0,3)	0.02*
HFRDIS item 9: Enjoyment of life	2 (0,7)	0 (0,2)	0.003**
HFRDIS item 10: Overall quality of life	3 (0,7)	0 (0,2)	0.002**

Data are reported as mean/SD and median (IQR=interquartile range) as data are not normally distributed.

*=P≤0.05,

**=P≤0.01. After adjustment for current smoking and history of substance abuse,

*a*P=0.02. After adjustment for hot flash frequency,

*b*P=0.002.