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Are serum estrogen concentrations associated with menopausal symptom bother among postmenopausal women? Baseline results from two MsFLASH clinical trials

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Abstract

Objectives: To evaluate whether a single measure of serum estradiol (E_2), estrone (E_1) and sex hormone-binding globulin (SHBG) concentration distinguishes between women with and without menopausal symptom bother.

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Ethical statement: MsFLASH study participants provided written informed consent. The MsFLASH study was approved by institutional review boards at participating institutions.

Study Design: We analyzed baseline data from two clinical trials conducted in 2012-2017: MsFLASH 03 (178 peri-/post-menopausal women aged 40-62 years with bothersome vasomotor symptoms, mean age 54) and MsFLASH 05 (181 post-menopausal women aged 45-70 years with moderate-to-severe vulvovaginal symptoms, mean age 61).

Main outcome measures: Symptom bother (hot flushes or flashes, night sweats, sweating, aching in muscles and joints, change in sexual desire, vaginal dryness during intercourse, and avoiding intimacy) in the past month was assessed using the Menopause-Specific Quality of Life questionnaire. Using logistic regression, we calculated the area under the receiver operating characteristic curve (AUC) values for E_1, E_2, and SHBG concentration in relation to being at least somewhat bothered (symptom bother score ≥3) by each symptom within each trial study population.

Results.—AUC values (95% confidence interval) ranged between 0.51 (0.41-0.60) and 0.62 (0.53, 0.72) for MsFLASH 03 and between 0.51 (0.42, 0.59) and 0.64 (0.53, 0.75) for MsFLASH 05. There was little evidence of associations between serum hormone levels and bother by a given menopausal symptom.

Conclusion.—These findings do not support the clinical utility of a single measure of serum of E_1, E_2, or SHBG concentrations in differentiating between women who are bothered by a given menopausal symptom and those who are not.

Introduction

The cessation of ovarian function (i.e., estrogen production), particularly in the late perimenopause[1], coincides with an acute increase in the prevalence of vasomotor symptoms for many women (VMS; hot flashes[2] and/or nights sweats[2]), raising the question of whether endogenous estrogen concentrations are associated with VMS. In addition to VMS, several other symptoms have been attributed to the menopause transition: myalgia and/or arthralgia[2], decreased sexual desire[3], vaginal dryness during intercourse [2–4], and avoidance of intimacy.[5] A clinically important question is whether single serum measurements of estrone (E_1), estradiol (E_2), and/or sex hormone-binding globulin (SHBG), which binds to E_2, testosterone and dihydrotestosterone to control the amount of sex hormones delivered to tissues[6], can assist with clinical decision-making regarding initiation of hormone therapy.

Although some studies have reported longitudinal associations between repeated serum hormone concentrations and menopausal symptoms [7–12], those studies generally focused on VMS and did not comprehensively examine other menopausal symptoms.

To address these knowledge gaps, we used baseline data from two randomized clinical trials to examine associations between serum E_1, E_2, and SHBG concentrations and VMS, aching in muscles and/or joints, change in sexual desire, vaginal dryness during intercourse, and avoiding intimacy. In this cross-sectional study, we examined associations to answer the question: are single measures of serum reproductive hormone concentrations clinically useful for this purpose?

Methods

The Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) network conducted three randomized clinical trials (RCTs) testing the efficacy of interventions for the treatment of menopausal symptoms, including VMS[13] and postmenopausal vulvovaginal symptoms.[14, 15]

For this study, we used baseline data from two of the MsFLASH RCTs: MsFLASH 03 and MsFLASH 05. For the MsFLASH 03 trial, participants were peri- or post-menopausal, aged 40-62 years, with ≥14 hot flashes or nights sweats/week based on a hot flash diary (n = 339, recruited in Boston, Philadelphia, and Seattle in 2012).[13, 14, 16] Participants were assigned to oral E_2, venlafaxine, or placebo. For the MsFLASH 05 trial, participants were at least 2 years postmenopausal, aged 45-70 years with moderate-to-severe vulvovaginal symptoms based on a vaginal symptom diary (n = 302, recruited in Minneapolis and Seattle in 2016-2017).[14, 15] Participants were assigned to vaginal E_2 (Vagifem), placebo, vaginal lubricant (Replens), or placebo. These two trials were specifically chosen for this analysis in order to provide a greater range of symptoms and ages to address our question of interest.

Serum E_2, E_1, and SHBG concentrations were measured at baseline, prior to initiation of study medications, for participants with available specimens in the oral E_2 and placebo groups of MsFLASH 03 (200 of 212 participants) and the Vagifem and placebo groups of MsFLASH 05 (194 of 199 participants). Participants were asked to be fasting at the time of phlebotomy for MsFLASH 03, but there was no requirement to fast prior to phlebotomy for MsFLASH 05 participants.

Of the 394 women with available baseline serum E_2, E_1, and SHBG concentrations, we excluded data from participants for whom data were missing regarding outcome measures (n =12 for MsFLASH 03, n = 7 for MsFLASH 05) or covariates (n =10 for MsFLASH 03, n = 6 for MsFLASH 05) (Figure 1). The final analytic sample included 359 women (178 women in MsFLASH 03, 181 women in MsFLASH 05).

Outcome ascertainment

We selected *a priori* specific symptoms included in the Menopause-Specific Quality of Life (MENQOL) Questionnaire that was administered in both the 03 and 05 trials at baseline.[17] The following symptoms, all selected *a priori*, were each assessed using individual questionnaire items: hot flushes or flashes, night sweats, sweating, aching in muscles and joints, change in your sexual desire, vaginal dryness during intercourse, and avoiding intimacy. The questionnaire asked “For each of the following items, indicate whether you have experienced the problem in the *past month*. If you have, rate how much you have been bothered by the problem”. Based on published MENQOL algorithms, each individual MENQOL symptom indicator and bother was combined into an eight-point scale, ranging from 1 (no symptom) to 8 (symptom, extremely bothered). For each symptom, we considered a score of 5 or greater (at least somewhat bothered by symptoms) to indicate bothersome symptoms.

Serum E_1, E_2, and SHBG assays

Blood samples were obtained by trained research staff in study clinics. For MsFLASH 03, participants were requested to fast for 12 hours prior to morning phlebotomy; for MsFLASH 05, participants were not asked to fast prior to phlebotomy. Serum E_2 and E_1 concentrations were measured by the Brigham Research Assay Core Laboratory (Boston, MA) using a liquid chromatography-tandem mass spectrometry (LC/MS/MS) method certified by the Centers for Disease Control and Prevention (CDC) Hormone Standardization Program. The assay details have been published.[18] For the E_2 and E_1 assays, the lower limit of quantitation was 1 pg/mL, linear range 1 to 500 pg/mL, the intra-assay coefficient of variation was <5%, and the inter-assay coefficient of variation was <12%. For LC-MS/MS E_2 assay, the mean bias for quality control samples provided by the CDC's Hormone Standardization Program was 0.81 pg/mL for E_2 concentrations less than or equal to 20mg/mL, and 1.9% for samples with E_2 concentrations >20 pg/mL. SHBG was measured using a two-site directed chemiluminescent immunoassay (Access Chemiluminescent Immunoassay, Beckman Coulter, Fullerton, CA). For the SHBG assay, the lower limit of quantitation was 0.33 nmol/L, linear range 0.33-200 nmol/L, the intra-assay coefficient of variation was 4.5-4.8%, and the inter-assay coefficient of variation was 5.2-5.5%.

Questionnaire data

Participants were asked to provide information regarding age, race/ethnicity, education, marital status, smoking, alcohol use, menopausal transition stage, time since menopause, and bilateral oophorectomy on self-assessment questionnaires. Perimenopause was defined as amenorrhea ≥60 days in the past year (for MsFLASH 03).[16] Postmenopause was defined as ≥12 months since last menstrual period, bilateral oophorectomy, or follicle-stimulating hormone level above 20 mIU/mL in the absence of a reliable menstrual marker[16]. Body mass index was calculated from clinic measurements of height and weight and expressed as body weight in kg divided by the square of height in meters.

Statistical analysis

Due to differences in eligibility criteria for the two trials, we performed two sets of analyses: one for MsFLASH 03 (peri- and post-menopausal women with VMS) and one for MsFLASH 05 (postmenopausal women with vulvovaginal symptoms). Natural logarithm transformations were applied to serum E_1, E_2, and SHBG concentrations to accommodate modeling assumptions. We used logistic regression to examine associations between log-transformed serum E_2, E_1, and SHBG concentrations (quantified per 20% higher value) and the odds of being at least somewhat bothered (score ≥5) by symptoms. We adjusted for for covariates: clinical center, age, peri- vs. post-menopausal status (MsFLASH 03 analyses), SHBG (in E_1 and E_2 models), BMI, alcohol intake, and smoking. Each symptom was the outcome of a separate logistic regression model: hot flushes or flashes, night sweats, sweating, aching in muscles and joints, change in sexual desire, vaginal dryness during intercourse, and avoiding intimacy.

To examine the ability of each hormonal measure to discriminate between women who did and women who did not have bother (score ≥3) from each symptom of interest, we

estimated the area under the receiver operating characteristic curve (AUC) values. AUC values were calculated using logistic regression models with the symptom of interest as a function of log-transformed continuous hormone values. An AUC value of 0.5 would indicate no discrimination, i.e., that the hormonal concentration is no better than chance in discriminating between who did and did not have symptom bother score ≥3.[19, 20] AUC values between 0.7 and 0.8 are considered acceptable; AUC values of 1.0 indicate perfect discrimination

No adjustments were made for multiple comparisons; statistical significance was defined as $p<0.05$.

Results

Participant Characteristics

Mean (SD) age of the participants was 54.2 (5.1) years in MsFLASH 03 and 60.7 (4.1) years in MsFLASH 05; 100% of MsFLASH 05 participants were postmenopausal, 17% of MsFLASH 03 and 0% of MsFLASH 05 participants were perimenopausal, and 10% of MsFLASH 03 participants had indeterminate menopausal status (i.e., experienced menstrual period in the past year and underwent endometrial ablation, hysterectomy, placement of progestogen intrauterine device, or bilateral oophorectomy) (Table 1). Based on the MENQOL scale (0 points for not having symptom to 8 points for being extremely bothered by the symptom), the mean (SD) bother score due to hot flashes/night sweats/day in MsFLASH 03 was 7.7 (4.8); the mean (SD) bother score due to vaginal dryness during intercourse for MsFLASH 05 was 6.2 (2.2) for MsFLASH 05.

Differences in the prevalence of being at least somewhat bothered by symptoms were largely determined by differences in the enrollment criteria between MsFLASH 03 and MsFLASH 05 trials: 87.6% vs. 29.9% for hot flushes or flashes, 77.5% vs. 24.4% for night sweats, 62.5% vs. 25.0% for sweating, 39.4% vs. 40.3% for aching in muscles and joints, 33.8% vs. 44.2% for change in sexual desire, 29.2% vs. 82.9% for vaginal dryness during intercourse, and 24.1% vs. 61.4% for avoiding intimacy (Table 2).

Associations of serum E_2 concentration with symptoms

Figure 2a (MsFLASH 03 trial) and Figure 2b (MsFLASH 05 trial) show unadjusted geometric means and 95% CI for E_2 by symptom. Compared with asymptomatic women, symptomatic women in MsFLASH 05 had higher (geometric) mean serum E_2 concentrations for each evaluated symptom, but these differences did not reach statistical significance (Figure 2b).

After adjustment for covariates, bother from night sweats, sweating, hot flushes or flashes, aching in muscles and joints, change in sexual desire, vaginal dryness during intercourse, and avoiding intimacy were not statistically significantly associated with serum E_2 concentration in either trial (Table 3).

Associations of serum E_1 concentration with symptoms

Figure 2c (MsFLASH 03 trial) and Figure 2d (MsFLASH 05 trial) show the mean (unadjusted) geometric means and 95% CI for E_1 by symptom. In MsFLASH 05, compared with asymptomatic women, symptomatic women had higher (geometric) mean serum E_1 concentrations for each evaluated symptom, but these differences did not reach statistical significance (Figure 2d).

Higher serum E_1 concentration was significantly associated with lower odds of bother from aching in the muscles and joints in both trials (Table 3). For each 20% greater E_1 concentration, the odds of aching in muscles and joints was 12% lower (OR 0.88, 95% CI 0.78-0.99) in MsFLASH 03 and 17% lower (OR 0.83, 95% CI 0.73-0.94) in MsFLASH05, after adjustment for covariates. Higher serum E_1 concentration was significantly associated with lower odds of bother from sweating in the MsFLASH 03 trial (OR per 20% higher E_1 concentration 0.84, 95% CI 0.74-0.95).

Serum E_1 concentration was not significantly associated with odds of bother from hot flushes or flashes, night sweats, change in sexual desire, vaginal dryness during intercourse, or avoiding intimacy in either trial.

Associations of serum SHBG concentration with symptoms

Figure 2e (MsFLASH 03 trial) and Figure 2f (MsFLASH 05 trial) show unadjusted geometric means and 95% CI for SHBG by symptom. In MsFLASH 05, compared with asymptomatic women, symptomatic women had higher serum SHBG concentrations for each evaluated symptom, but these differences did not reach statistical significance (Figure 2f).

Serum SHBG concentration was associated with lower odds of bother from night sweats in MsFLASH 03 (OR 0.84, 95% CI 0.73-0.98), but not in MsFLASH 05. Serum SHBG concentration was not statistically significantly associated with the odds of bother from hot flushes or flashes, sweating, aching in muscles and joints, change in sexual desire, vaginal dryness during intercourse, or avoiding intimacy in either trial.

Distinguishing between Women with, versus without, Symptoms: AUC results

Table 4 displays AUC values, indicating the ability of a single measure of E_1, E_2, and SHBG concentration to discriminate between women with and without symptoms. Within each of the two trials, AUC values were low, ranging from 0.51 (95% CI 0.41-0.60) to 0.64 (0.53-0.75).

Discussion

In this cross-sectional study of peri- and post-menopausal women in two randomized clinical trials, we found very little evidence of significant associations of serum E_1, E_2, and SHBG concentration with bother due to common symptoms (hot flushes or flashes, night sweats, sweating, aching in muscles and joints, change in sexual desire, vaginal dryness during intercourse, avoiding intimacy). Moreover, for each symptom, a single measurement of E_1, E_2, or SHBG concentration was no better than chance for differentiating between women

who did, and women who did not, have symptom bother (AUC values 0.5-0.6). These findings indicate that a single measurement of these hormones is unlikely to have clinical utility in diagnosis or clinical decision-making for management of these symptoms.

Some of our results were unexpected. The association between greater SHBG concentration and lower odds of night sweats in MsFLASH 03 participants is unexpected because higher SHBG levels might be expected to be associated with lower free E_2 and higher, not lower, odds of night sweats. Also, one would have expected results for sweating and for night sweats to parallel each other, but they did not.

Previous cross-sectional studies evaluated associations between E_1, E_2, and SHBG and symptoms associated with menopause, with mixed findings. In the US Midlife Women's Health Study of pre- and peri-menopausal women, higher E_2 concentrations were associated with decreased frequency and severity of hot flushes. [8–10] In a study of women with a broad age range (35-69 years) who were randomly chosen from 10 employment sites (academic faculty, registered nurses, telephone personnel, nursing assistance), mean E_2 concentration was lower among women with any hot flushes in the past 2 weeks compared to women without hot flushes, even after adjustment for BMI.[21] Estrone (E1) has also been associated with hot flashes, although few studies have evaluated the association. A study of women aged 41-54 years at a single clinical center in Italy, found lower odds of any hot flashes with higher E_1 concentration.[22] Also, the U.S. Midlife Women's Health Study found a significant inverse association between E_1 concentration and VMS presence vs. absence, severity, frequency, and years of duration.[10]

However, several studies have found no association between E_2 concentration and VMS in peri- and post-menopausal women. In a study of perimenopausal women aged 40-59 years living in the UK or Bangladesh, E_2 concentration was not associated with experiencing hot flushes in the past 2 weeks.[23] In the Melbourne Women's Midlife Health Project (women aged 48-59) lower serum E_2 concentration was associated with higher odds of having any VMS in the past two weeks before adjustment for covariates, but no significant association among either peri- or post-menopausal women after adjustment for covariates.[24]

Variations among the studies regarding which covariates were included in statistical models, ages, and menopausal transition stage of participants (peri- vs. post-menopausal), wording of questions regarding symptoms, VMS characterization in statistical models, and E_2 and E_1 assays may explain why some studies found associations between serum E_2 concentration and VMS, and others did not. We also note that, by design, all MsFLASH 03 participants had VMS.

Regarding sexual desire, in older (mean age 65) postmenopausal participants of the Multiple Outcomes of Raloxifene Evaluation (MORE) Trial, higher frequency of sexual desire during the previous 6 months was reported by women with E_2 <20 pmol/l than by those with E_2 >20 pmol/l.[25] In the MORE trial, the score representing "not feeling pain/discomfort during intercourse" in the previous 4 weeks was more favorable with E_2 >20 pmol/l vs. E_2 <20 pmol/l. These findings from MORE (older women) are not consistent with the results

of the current study, although MORE study participants were, on average, much older than those in the current study.

Our results regarding joint pain can be compared with those of two prior studies. We found associations between 20% higher E_1 concentration and lower odds of having muscle/joint aches. The robustness of these associations is supported by its reproducibility in both the 03 and 05 trials. In women aged 41-54 years at a single clinical center in Italy, the odds of having joint pain did not significantly vary by E_1 concentration.[22] In another study (women aged 35-69 years randomly chosen from 10 employment sites), serum E_2 concentration was not significantly associated with aches/stiffness of joints.[21] The previous study did not stratify or adjust results by age or reproductive stage. Further studies regarding associations between serum estrogen concentrations and joint pain are warranted.

The current study was designed to examine the associations between serum hormone concentration measured at a single point in time and menopause-related symptoms. Such results are critical to inform the clinical question of whether a single serum measurement of hormone concentration can assist with hormone therapy dosing. Therefore, the results of this study should not be compared with studies that examined hormonal concentrations longitudinally over time (e.g., [12]). This is important because early in the menopausal transition, serum E_2 concentrations fluctuate and can be intermittently elevated.[26] Moreover, VMS are experienced well before the increasing variability in cycle length of the late menopausal transition (cessation of menses for at least 60 days), highlighting the complexity of associations between serum estrogen concentrations and menopausal symptoms.

This study has limitations. We performed 63 statistical tests in our primary models, so we expect three to four p-values to be <0.05 by chance. Most of the participants were White, and there are known differences in menopause-related symptoms across race/ethnicity among women in the U.S.[1] Participants of MsFLASH 03 were selected on the basis of having VMS so we could not focus on women with fewer than 2 VMS per day, and only 25% of MsFLASH 05 participants had bothersome VMS. Although we adjusted for potential confounders, residual confounding is possible. The mean age of MsFLASH 03 participants was 60.7 years, an age at which one might expect little variability in E_1 and E_2 concentrations. Indeed, in Figure 2a, the Y axis spans only 5.0 pg/mL.

Strengths of our study include the use of standardized, well-validated questionnaires, the carefully-characterized reproductive stage of participants, and the high-quality, sensitive LC-MS/MS assays certified by the CDC's Hormone Standardization Program with high level of precision and accuracy in the lower range prevalent in postmenopausal women. The availability of information regarding degree of bother from symptoms is also an advantage compared with previous studies based on frequency or binary (present/absent) characterizations of symptoms.

In conclusion, we found little evidence to support significant, biologically plausible, clinically important associations between serum E_2 and E_1 concentrations and several symptoms common among midlife women. Moreover, our results indicate that single

measurements of serum E_1 and E_2 concentrations are not clinically useful to differentiate between women who have these symptoms from those who do not. Change in estrogen or SHBG concentrations or their variability may be more important than a single measurement.

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Abbreviations:

AUC	area under the receiver operating characteristic curve
CDC	Centers for Disease Control and Prevention
E_1	estrone
E_2	estradiol
LC/MS/MS	liquid chromatography-tandem mass spectrometry
MENQOL	Menopause-Specific Quality of Life Questionnaire
MORE	Multiple outcomes of Raloxifene Evaluation Trial
MsFLASH	Menopause Strategies: Finding Lasting Answers for Symptoms and Health trial network
RCT	randomized clinical trial
SHBG	sex hormone-binding globulin
VMS	vasomotor symptoms

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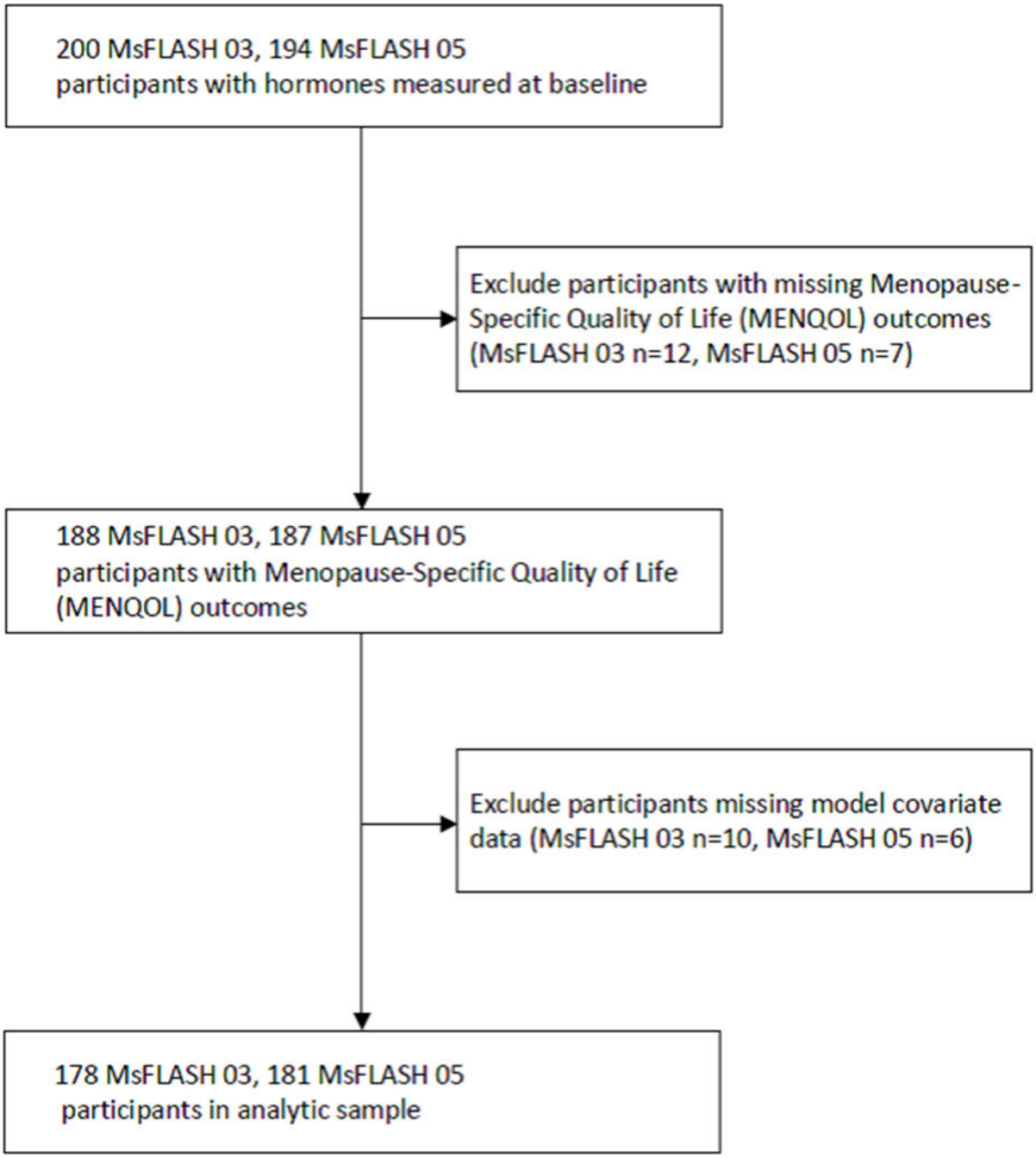

Figure 1.
STROBE Analytic Sample Flow Diagram

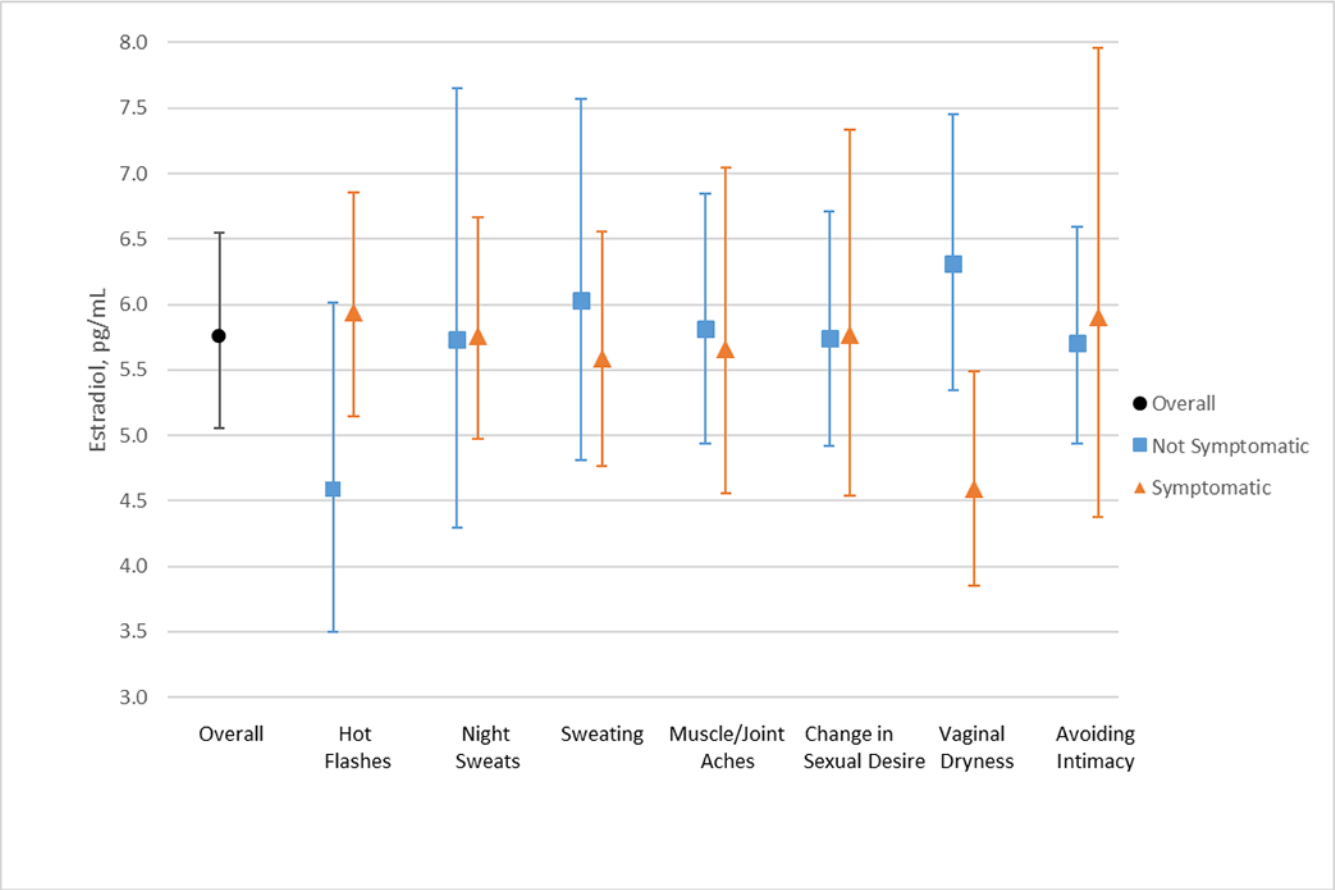

Figure 2a.

Estradiol geometric means (unadjusted) and their corresponding 95% confidence intervals by symptoms in the Menopause Strategies: Finding Lasting Answers for Symptoms and Health network Trial 03 (MsFLASH 03)

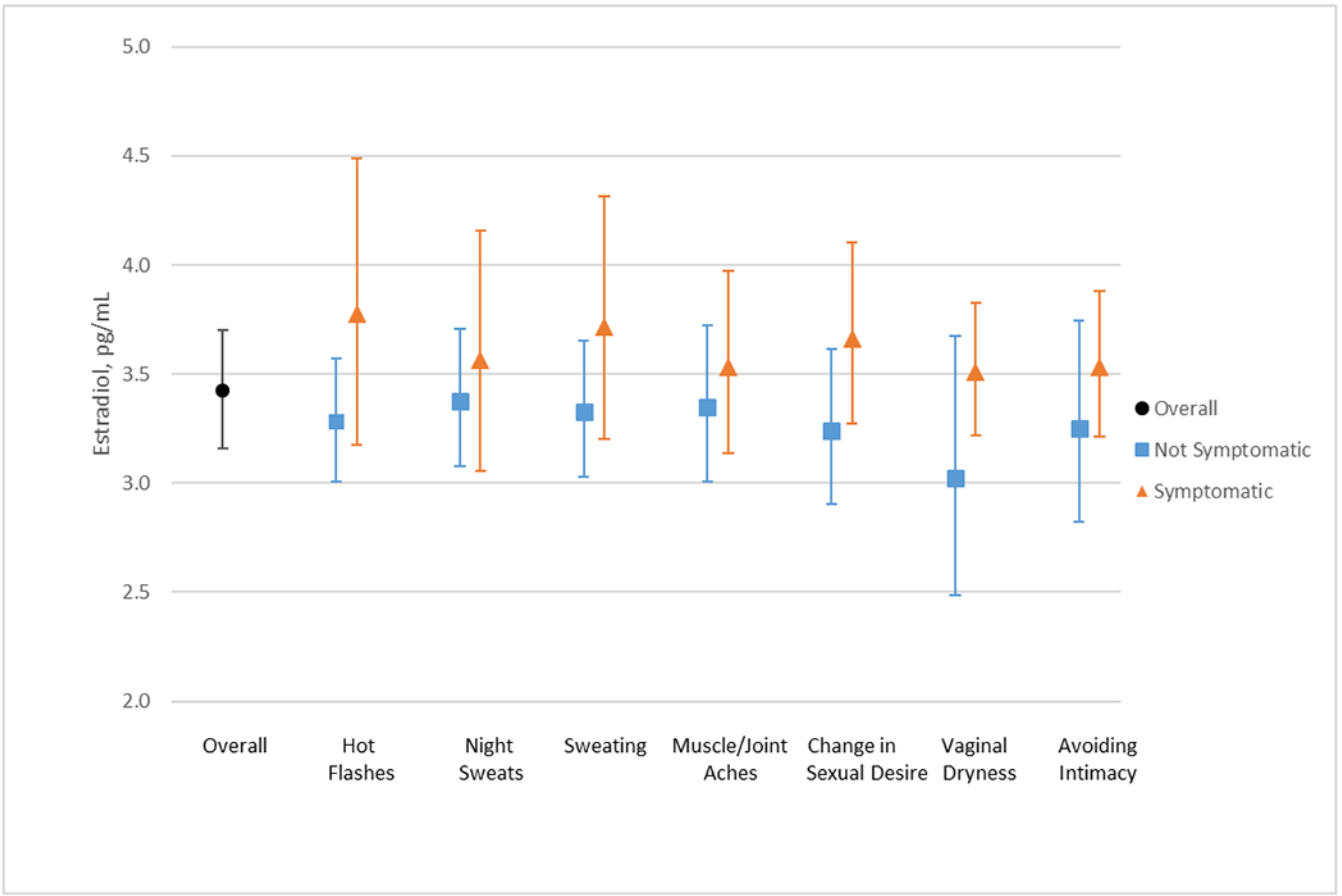

Figure 2b.

Estradiol geometric means (unadjusted) and their corresponding 95% confidence intervals by symptoms in the Menopause Strategies: Finding Lasting Answers for Symptoms and Health network Trial 05 (MsFLASH 05)

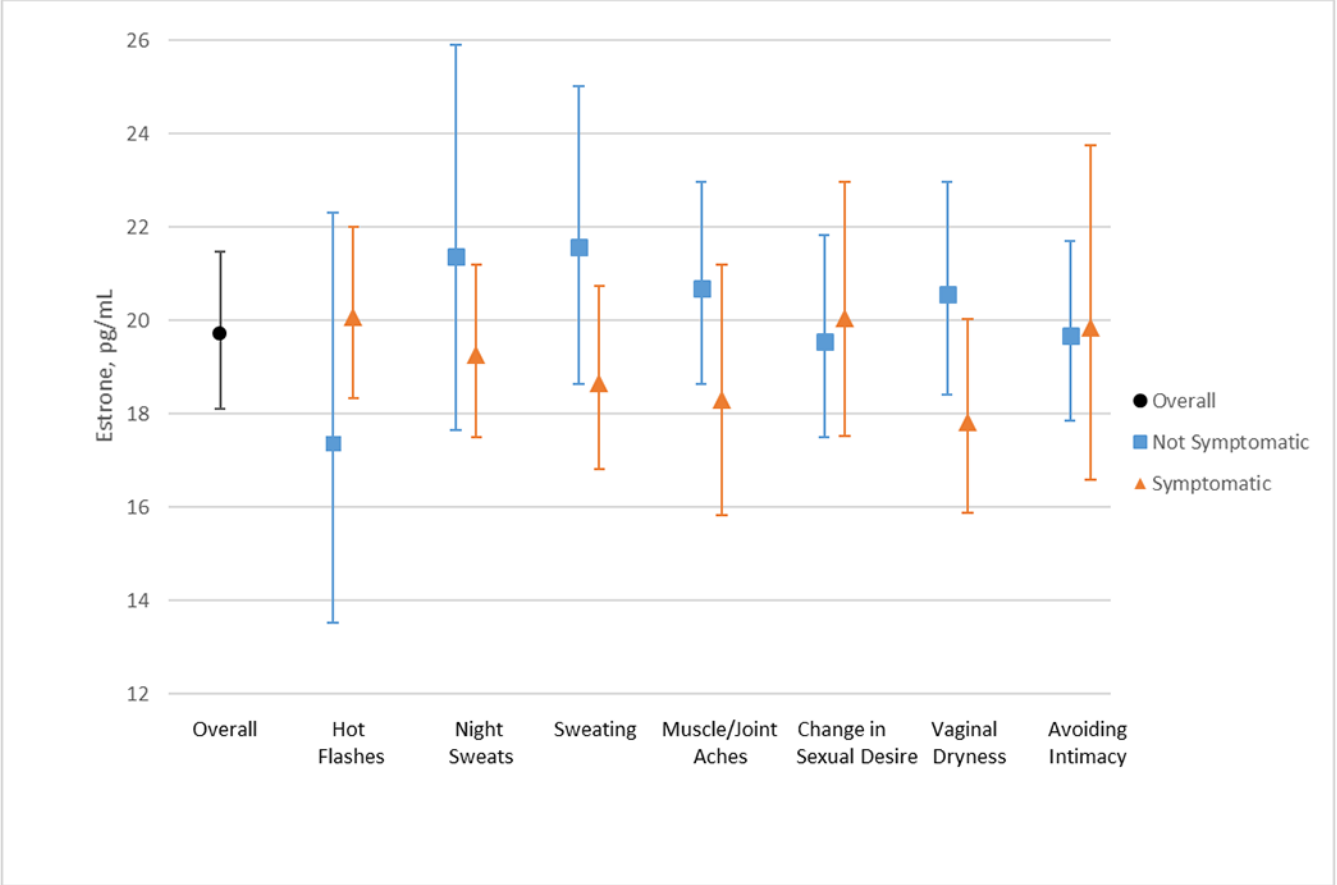

Figure 2c.

Estrone geometric means (unadjusted) and their corresponding 95% confidence intervals by symptoms in the Menopause Strategies: Finding Lasting Answers for Symptoms and Health network Trial 03 (MsFLASH 03)

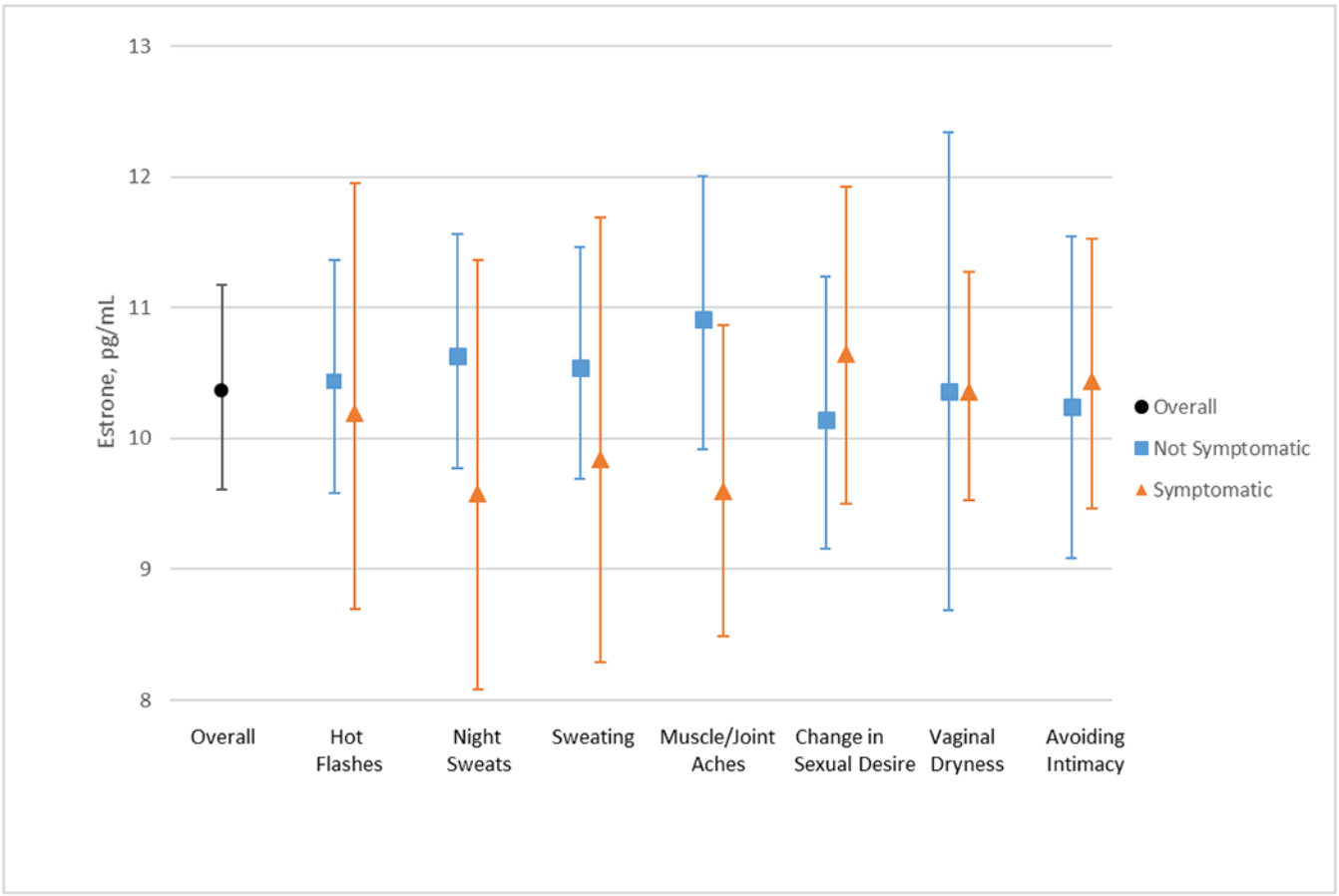

Figure 2d.

Estrone geometric means (unadjusted) and their corresponding 95% confidence intervals by symptoms in the Menopause Strategies: Finding Lasting Answers for Symptoms and Health network Trial 05 (MsFLASH 05)

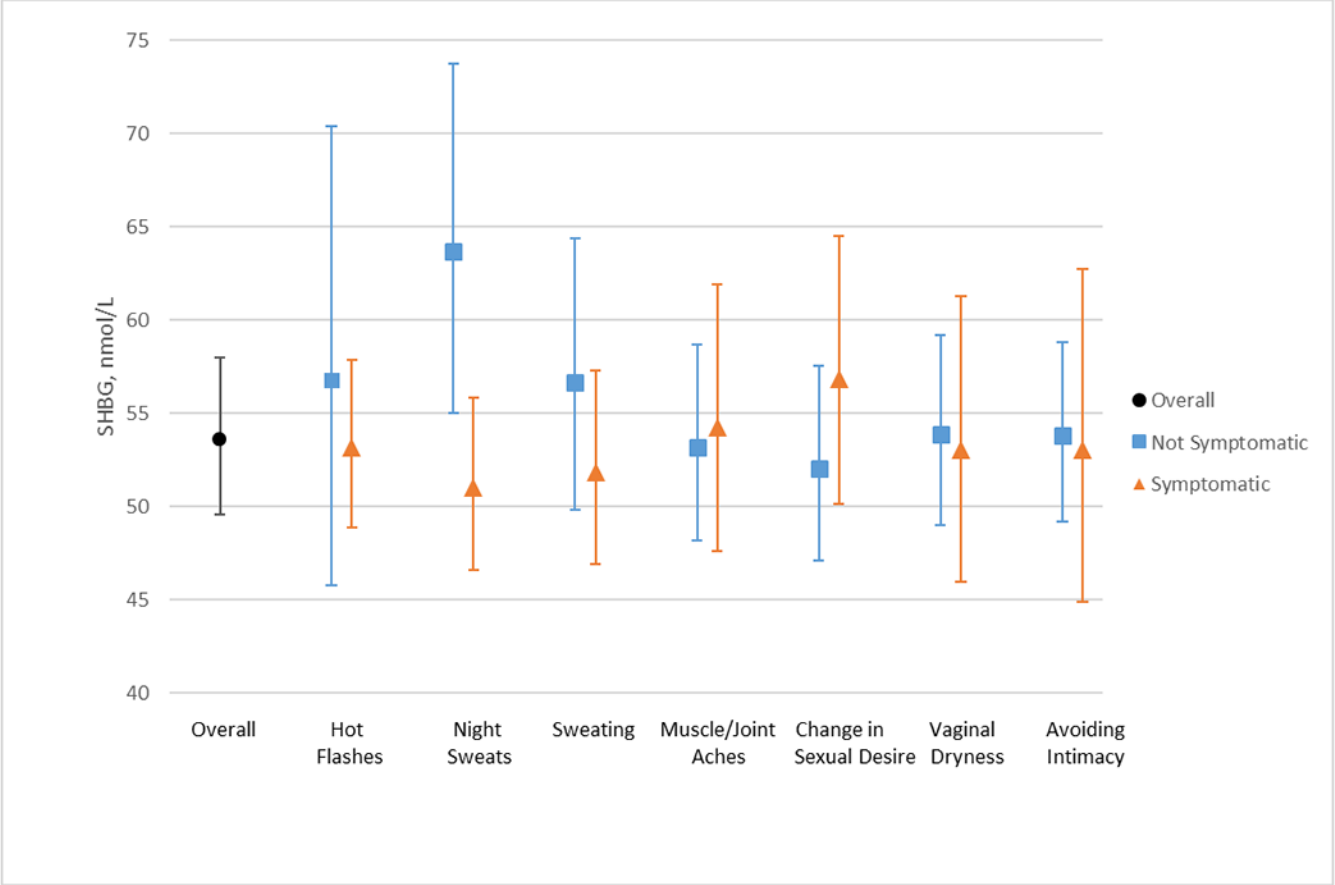

Figure 2e.

Sex hormone-binding globulin geometric means (unadjusted) and their corresponding 95% confidence intervals by symptoms in the Menopause Strategies: Finding Lasting Answers for Symptoms and Health network Trial 03 (MsFLASH 03)

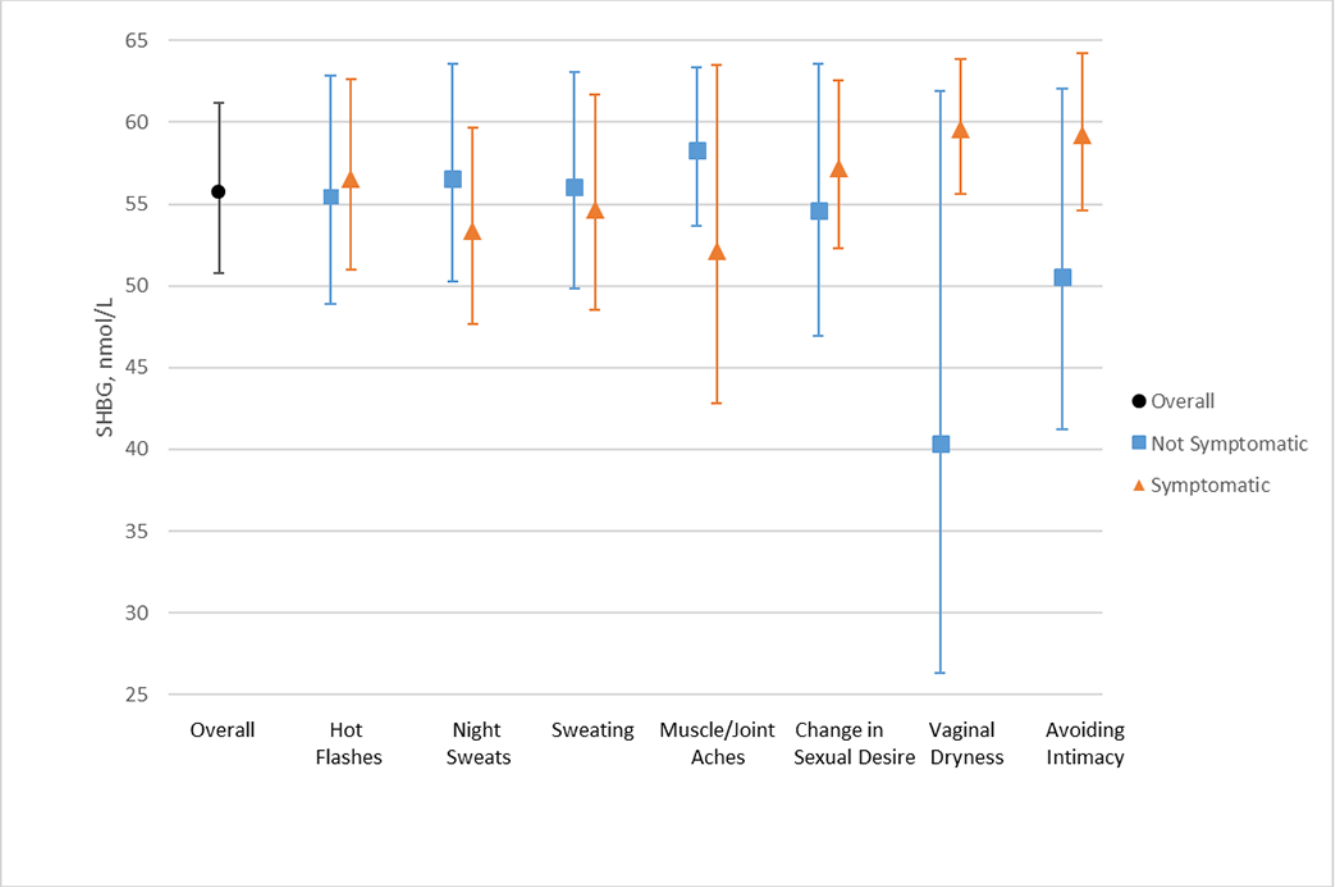

Figure 2f.

Sex hormone-binding globulin geometric means (unadjusted) and their corresponding 95% confidence intervals by symptoms in the Menopause Strategies: Finding Lasting Answers for Symptoms and Health network Trial 05 (MsFLASH 05)

Table 1.

Sociodemographic and Clinical Characteristics of the Study Population

	All Participants (n=359)		Trial			
			MsFLASH* 03 (n=178)		MsFLASH 05 (n=181)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Clinical site						
Boston	63	17.5	63	35.4	0	0.0
Minnesota	90	25.1	0	0.0	90	49.7
Philadelphia	53	14.8	53	29.8	0	0.0
Seattle	153	42.6	62	34.8	91	50.3
Age at Screening, mean (SD) years	57.5	(5.1)	54.2	(3.9)	60.7	(4.1)
Race						
White	276	76.9	117	65.7	159	87.8
Black	58	16.2	50	28.1	8	4.4
Other/Unknown	25	7.0	11	6.2	14	7.7
Education						
≤High school / general equivalency diploma	30	8.4	22	12.4	8	4.4
School after high school	112	31.2	53	29.8	59	32.6
College graduate	216	60.2	103	57.9	113	62.4
Marital status						
Never married	35	9.7	24	13.5	11	6.1
Divorced / separated	49	13.6	30	16.9	19	10.5
Widowed	7	1.9	6	3.4	1	0.6
Married / partnered	268	74.7	118	66.3	150	82.9
Smoking						
Never	210	58.5	92	51.7	118	65.2
Past	116	32.3	59	33.1	57	31.5
Current	33	9.2	27	15.2	6	3.3
Alcohol use, drinks/wk						
0	110	30.6	57	32.0	53	29.3
>0 - <7	174	48.5	82	46.1	92	50.8
≥7	75	20.9	39	21.9	36	19.9
Body mass index (kg/m^2), mean (SD)	27.0	(6.2)	27.9	(6.9)	26.1	(5.2)
<25	155	43.2	68	38.2	87	48.1
25 - <30	116	32.3	59	33.1	57	31.5
≥30	88	24.5	51	28.7	37	20.4
Menopausal status						

	Trial					
	All Participants (n=359)		MsFLASH* 03 (n=178)		MsFLASH 05 (n=181)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Postmenopausal†	311	86.6	130	73.0	181	100.0
Perimenopausal‡	30	8.4	30	16.9	0	0.0
Indeterminate§	18	5.0	18	10.1	0	0.0
≥ 5 years since menopause	229	64.0	75	42.4	154	85.1
Bilateral oophorectomy	45	12.6	18	10.2	27	14.9

*MsFLASH: Menopause Strategies: Finding Lasting Answers for Symptoms and Health Network

†Met one of the following criteria: 1. Bilateral oophorectomy; 2. No menstrual period in the past year *and* no prior endometrial ablation, hysterecomty, placement of progestogen IUD, or bilateral oophorectomy

‡Menstrual period in the past year *and* underwent endometrial ablation, hysterectomy, placement of progestogen intrauterine device, or bilateral oophorectomy

§No menstrual period in the last year and age <55 years

Table 2.

Frequencies of symptoms examined:

			Symptom													
			Hot flushes or flashes		Night Sweats		Sweating		Aching in muscles and joints		Change in Sexual Desire		Vaginal dryness during Intercourse		Avoiding Intimacy	
Trial	Value	Description (Bother)	n	%	n	%	n	%	n	%	n	%	n	%	n	%
MsFLASH 03	1	None	1	0.6	13	7.3	29	16.3	54	30.3	98	55.1	105	59.0	111	62.4
	2	Not at all	0	0.0	0	0.0	0	0.0	1	0.6	1	0.6	3	1.7	3	1.7
	3		6	3.4	9	5.1	14	7.9	24	13.5	11	6.2	9	5.1	16	9.0
	4		15	8.4	18	10.1	24	13.5	29	16.3	8	4.5	9	5.1	5	2.8
	5	Somewhat	34	19.1	28	15.7	38	21.4	32	18.0	19	10.7	12	6.7	7	3.9
	6		60	33.7	39	21.9	30	16.9	17	9.6	9	5.1	11	6.2	12	6.7
	7		31	17.4	39	21.9	19	10.7	13	7.3	11	6.2	7	3.9	10	5.6
	8	Extremely	31	17.4	32	18.0	24	13.5	8	4.5	21	11.8	22	12.4	14	7.9
MsFLASH 05	1	None	82	45.3	110	60.8	98	54.1	55	30.4	81	44.8	19	10.5	44	24.3
	2	Not at all	5	2.8	4	2.2	4	2.2	2	1.1	0	0.0	1	0.6	1	0.6
	3		24	13.3	11	6.1	18	9.9	21	11.6	8	4.4	1	0.6	10	5.5
	4		16	8.8	12	6.6	16	8.8	30	16.6	12	6.6	10	5.5	15	8.3
	5	Somewhat	20	11.1	20	11.1	20	11.1	27	14.9	14	7.7	16	8.8	25	13.8
	6		14	7.7	9	5.0	11	6.1	24	13.3	16	8.8	26	14.4	24	13.3
	7		13	7.2	10	5.5	7	3.9	16	8.8	30	16.6	40	22.1	23	12.7
	8	Extremely	7	3.9	5	2.8	7	3.9	6	3.3	20	11.1	68	37.6	39	21.6

Table 3.

Associations of serum estradiol, estrone, and sex hormone-binding globulin (SHBG) concentration with being at least somewhat bothered by symptom *

		MsFLASH 03			MsFLASH 05		
		Adjusted			Adjusted		
Marker	**Symptom**	**Adjusted**	**OR (95% CI)**	**p-value**	**Adjusted**	**OR (95% CI)**	**p-value**
Estradiol (E_2)	Hot flushes or flashes	1.08	(0.92, 1.27)	0.33	1.11	(0.98, 1.25)	0.11
	Night sweats	0.97	(0.90, 1.06)	0.59	1.02	(0.90, 1.15)	0.80
	Sweating	0.92	(0.86, 1.00)	0.06	1.02	(0.90, 1.16)	0.70
	Aching in muscles and joints	0.96	(0.89, 1.04)	0.38	0.98	(0.87, 1.10)	0.72
	Change in sexual desire	1.00	(0.92, 1.07)	0.89	1.05	(0.94, 1.17)	0.39
	Vaginal dryness during intercourse	0.90	(0.81, 1.00)	0.05	1.16	(0.99, 1.35)	0.06
	Avoiding intimacy	0.99	(0.91, 1.08)	0.80	1.04	(0.93, 1.16)	0.50
Estrone (E_1)	Hot flushes or flashes	1.08	(0.91, 1.28)	0.39	0.97	(0.85, 1.10)	0.59
	Night sweats	0.90	(0.80, 1.03)	0.12	0.91	(0.80, 1.04)	0.17
	Sweating	0.84	(0.74, 0.95)	0.005	0.90	(0.78, 1.03)	0.11
	Aching in muscles and joints	0.88	(0.78, 0.99)	0.03	0.83	(0.73, 0.94)	0.004
	Change in sexual desire	1.01	(0.90, 1.13)	0.87	0.97	(0.86, 1.09)	0.60
	Vaginal dryness during intercourse	0.93	(0.83, 1.05)	0.27	1.02	(0.88, 1.18)	0.79
	Avoiding intimacy	0.97	(0.86, 1.10)	0.66	0.98	(0.87, 1.10)	0.75
Sex hormone-binding globulin (SHBG)	Hot flushes or flashes	0.88	(0.74, 1.05)	0.16	1.01	(0.90, 1.14)	0.83
	Night sweats	0.84	(0.73, 0.98)	0.03	1.01	(0.90, 1.14)	0.82
	Sweating	0.96	(0.85, 1.09)	0.52	1.05	(0.93, 1.18)	0.46
	Aching in muscles and joints	1.04	(0.92, 1.18)	0.52	1.01	(0.90, 1.13)	0.85
	Change in sexual desire	1.05	(0.93, 1.19)	0.40	1.06	(0.96, 1.18)	0.27
	Vaginal dryness during intercourse	0.96	(0.85, 1.09)	0.57	1.21	(1.00, 1.47)	0.05
	Avoiding intimacy	0.98	(0.86, 1.13)	0.82	1.11	(0.99, 1.26)	0.08

* "At least somewhat bothered by symptom", the outcome of the logistic regression models, was defined as a symptom severity score ≥5".

MsFLASH: The Menopause Strategies: Finding Lasting Answers for Symptoms and Health clinical trials network; OR: odds ratio; 95% CI: 95% confidence interval.

ORs are adjusted for clinical center, age, race, menopause status (post- vs. peri-menopausal or indeterminate), SHBG (estradiol and estrone models only), body mass index, alcohol intake, and smoking.
ORs are expressed per each 20% higher concentration of E1, E2, and SHBG.

Table 4.

Area under the Receiver Operating Characteristic Curve (AUC) of Serum E_1, E_2, and Sex Hormone-Binding Globulin (SHBG) concentrations for Discriminating between Women with and Without Bothersome Symptoms:*

		MsFLASH 03		MsFLASH 05	
Marker	**Symptom**	**AUC (95% CI)**		**AUC (95% CI)**	
Estradiol (pg/mL)	Hot flushes or flashes	0.561	(0.430, 0.692)	0.558	(0.461, 0.655)
	Night sweats	0.506	(0.403, 0.608)	0.532	(0.431, 0.633)
	Sweating	0.523	(0.434, 0.612)	0.574	(0.476, 0.672)
	Aching in muscles and joints	0.513	(0.423, 0.603)	0.542	(0.456, 0.628)
	Change in sexual desire	0.516	(0.424, 0.608)	0.576	(0.492, 0.660)
	Vaginal dryness during intercourse	0.610	(0.519, 0.701)	0.569	(0.457, 0.680)
	Avoiding intimacy	0.506	(0.401, 0.611)	0.563	(0.478, 0.649)
Estrone (pg/mL)	Hot flushes or flashes	0.533	(0.400, 0.665)	0.522	(0.425, 0.618)
	Night sweats	0.553	(0.453, 0.653)	0.587	(0.488, 0.686)
	Sweating	0.574	(0.487, 0.661)	0.553	(0.453, 0.653)
	Aching in muscle and joints	0.541	(0.453, 0.629)	0.576	(0.490, 0.661)
	Change in sexual desire	0.508	(0.417, 0.599)	0.522	(0.437, 0.607)
	Vaginal dryness during intercourse	0.600	(0.510, 0.690)	0.515	(0.403, 0.626)
	Avoiding intimacy	0.533	(0.428, 0.638)	0.515	(0.428, 0.602)
Sex hormone-binding globulin (nmol/L)	Hot flushes or flashes	0.540	(0.416, 0.664)	0.514	(0.425, 0.604)
	Night sweats	0.621	(0.525, 0.716)	0.566	(0.473, 0.659)
	Sweating	0.548	(0.460, 0.636)	0.546	(0.449, 0.643)
	Aching in muscles and joints	0.519	(0.431, 0.606)	0.531	(0.445, 0.618)
	Change in sexual desire	0.555	(0.465, 0.644)	0.509	(0.424, 0.594)
	Vaginal dryness during intercourse	0.505	(0.410, 0.599)	0.642	(0.532, 0.752)
	Avoiding intimacy	0.512	(0.408, 0.616)	0.545	(0.459, 0.631)

*"At least somewhat bothered by symptom", the outcome of the logistic regression models, was defined as a symptom severity score ≥5".

MsFLASH: The Menopause Strategies: Finding Lasting Answers for Symptoms and Health clinical trials network; 95% CI: 95% confidence interval.

AUC calculated using logistic regression models with the symptom of interest as a function of log-transformed continuous hormone value.