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ORIGINAL STUDY

Toward a better measure of midlife sexual function: pooled analyses in nearly 1,000 women participating in MsFLASH randomized trials

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Abstract

Objective: Evaluate appropriateness of the current Female Sexual Function Index (FSFI)-19 value of <26.6 to designate female sexual dysfunction (FSD) in postmenopausal women, using the Female Sexual Distress-Revised (FSDS-R) scale to measure distress.

Methods: Participant-level data containing standardized measures from five completed Menopause Strategies: Finding Lasting Answers for Symptoms and Health trials was pooled. Baseline characteristics and FSFI-19 scores were compared across trials (F-test, homogeneity). FSFI-19 score associations with the FSDS-R were described. Receiver operating characteristic (ROC) curves were plotted to illustrate the choice of optimal FSFI-19 value to predict sexual distress. ROC curves were also estimated adjusting for trial number, clinical center, age, education, race, smoking, and BMI.

Results: Nine hundred ninety eight women (79.2% postmenopausal), mean age 55.9 (SD 4.8) had complete FSFI-19, FSDS-R, and covariate data. Baseline mean FSFI-19 score among all participants and sexually active participants was 18.7 (SD 9.5) and 22.0 (SD 7.2), respectively. There was a consistent pattern across the trials of inverse association between poorer sexual function (FSFI-19) and greater sexual distress. Based on the ROC curve showing the likelihood of FSDS-R frequent or greater distress according to cut points of FSFI, the optimal cut point for FSD was FSFI-19 <21 for all participants. This cut point corresponded to sensitivity 87.2% (95% CI, 83.4-91.0), specificity 57.9% (95% CI, 54.3-61.6) and adjusted area under the ROC curve 78.8% (95% CI, 75.8-81.8).

Conclusions: A new FSFI-19 cut point of ≥21 should be considered to describe normal sexual function in peri- and postmenopausal women as opposed to the standard cut point of >26.6.

Key Words: Female Sexual Distress Scale-R (FSDS-R) – Female sexual dysfunction (FSD) – Female Sexual Function Index (FSFI-19) cut point – Normal sexual function measure – Postmenopause – Receiver operating characteristic (ROC) curve.

***Video Summary*:** http://links.lww.com/MENO/A915.

Female sexual dysfunction (FSD) is defined by difficulties with desire, arousal, orgasm, or pain resulting in distress and diminished quality of life.[1] Much has been written about defining and measuring FSD and understanding the physiology underlying normal female sexual function, but the preponderance of the epidemiologic, behavioral, and laboratory-based scientific data on FSD comes from premenopausal women.[2,3] Less is known about

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defining and measuring normal sexual function and FSD in peri- and postmenopausal women. Due at least in part to the physiology of aging, peri- and postmenopausal women are more likely than premenopausal women to have diminished libido, diminished genital sensitivity, diminished arousal and lubrication, and increased pain with sexual activity. One would expect that the same scales used to measure FSD in premenopausal women might not be valid or reliable in postmenopausal women or that the measurement cut points for defining FSD may vary. Associated distress and diminished quality of life resulting from a change in sexual function in this population is important to consider. Surveys have shown that a majority (60%-75%) of women reported that ''sexuality'' is important to their well-being and overall quality of life[4,5] and the majority of partnered postmenopausal women are sexually active.[5] Qualitative studies demonstrate that the changes in sexual function at midlife are nuanced and defined by organic and psychosocial factors.[6] These changes may not necessarily reflect ''dysfunction.'' In a national study of more than 31,000 women ages 18 years or older, sexual problems were most prevalent in women 65 or older (80.1%), but sexually related personal distress was lowest in this age group (12.6%), resulting in the lowest prevalence for FSD of all age groups.[7]

The International Consultation on Sexual Medicine committee deemed the Female Sexual Function Index (FSFI)-19 as the gold standard for outcome measurement and diagnostic studies of FSD with evidence grade of A-1.[8] The FSFI-19 is scored from 0 to 36, with lower scores indicating poorer sexual function,[9] but notably the FSFI does not measure distress which must be present for a diagnosis of FSD.[10] According to its scoring system, women who are not sexually active or who are not having penetrative sex will always have an artificially lower FSFI-19 score than those who are, so use in women less commonly having penetrative sex may be problematic. A score less than 26.6 is broadly applied to indicate clinical FSD, however, this cut point is based on research that included mainly premenopausal women (mean age 36.2, range 18-74), a proportion of whom were diagnosed with sexual dysfunction disorders.[11]

Systematic reviews show that the FSFI-19 cut point for FSD validated in predominantly premenopausal women has not been validated in large postmenopausal populations.[2,12] Specifically, the appropriate FSFI-19 cut point for FSD in peri- or postmenopausal women is unknown, although the FSFI-19 has been used in clinical trials of postmenopausal women with FSD to evaluate treatment effects for, among others, ospemifene,[13] and intravaginal prasterone.[14] Neither trial defined FSD by the cut point of 26.6; rather they evaluated differences in change in FSFI-19 total scores from baseline to 12 weeks between the intervention and placebo groups. Average FSFI-19 scores among women in the menopausal transition and postmenopause have been described as lower than premenopausal women.[15,16] As older women often engage in non-penetrative sexual activity due to vaginal changes from aging and estrogen deficiency, modification of the FSFI for women who may or may not be having vaginal penetrative sex may result in a better measurement for sexual function at midlife.[17]

Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) is an NIH-funded network that has completed five clinical trials evaluating interventions for menopausal symptoms with validated standard measures that allow pooling of data across all trials, including the FSFI-19 and Female Sexual Distress-Revised (FSDS-R) questionnaires. MsFLASH has contributed to our understanding of postmenopausal sexual function. Notably, we showed mean composite baseline FSFI-19 scores well below the cut point of 26.6 for FSD in all of our trials with published sexual function data.[18-23] These findings prompted us to evaluate sexual function using pooled data from nearly 1,000 women in our five trials to evaluate the current FSFI-19 cut point for FSD (<26.6) for its appropriateness in a population of peri- and postmenopausal women with distress as measured by the FSDS-R. The large sample size and rich data collected provided an opportunity for this unique analysis. We hypothesized that a new lower cut point for midlife women would be more meaningful in identifying those most likely to have FSD. To our knowledge, there are no published data from cohorts of older women that have attempted to measure FSD using the FSFI-19 and the FSDS-R.

METHODS

Study design

MsFLASH is an NIH funded clinical trials network with methods detailed previously.[24] This exploratory analysis used

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pooled individual-level baseline data from five randomized clinical trials (MsFLASH 01-05) to evaluate sexual function in midlife women. Our primary question was, what FSFI-19 cut point in postmenopausal women best identifies women with diminished function and sexually related personal distress? The analyses presented here were not prespecified in study protocols, but the MsFLASH trials were designed to permit eventual pooled analysis. All MsFLASH studies were approved by the Institutional Review Boards of each clinical site and the Data Coordinating Center. All participants provided written informed consent.

Common measures of sexual function

The MsFLASH trials included two measures of sexual function. First, we used the FSFI-19, a 19-item scale[9] with a standard formula-based scoring system. Total scores range from 2.0 to 36.0 and the six domain scores range from 0.8 to 6.0 for satisfaction, 1.2 to 6.0 for desire, and 0.0 to 6.0 for arousal, lubrication, orgasm, and pain in the past month. In 12 of 19 questions (questions 3-14), scores of 0 indicate ''no sexual activity'' during the past month and in 3 of 19 questions (questions 17-19), scores of 0 indicate ''no sexual intercourse'' during the past month.[21] Higher domain and total scores indicate better sexual functioning.

Second, we used a single item of the FSDS-R across all trials, ''In the past four weeks, how often did you feel distressed or bothered about your sex life?'' 0 = never, 1 = rarely, 2 = occasionally, 3 = frequently, 4 = always. In a prior analysis, we showed this item was a useful screening tool to identify women with sexually-related distress[22] a key aspect of defining FSD.

MsFLASH studies overview

MsFLASH 01 was a randomized, placebo-controlled, double-blind clinical trial designed to determine the efficacy and tolerability of 10 to 20 mg/day of the SSRI escitalopram for reducing vasomotor symptom (VMS) frequency and severity compared to placebo.[25] The study aimed to recruit approximately equal numbers of Black and White women. MsFLASH 02 employed a 3×2 factorial, randomized controlled trial design to compare the effects of yoga and exercise separately to a usual activity control group, and simultaneously to compare omega-3 fatty acid capsules to placebo capsules, on VMS frequency and bother.[26-28] MsFLASH 03 was a randomized, placebo-controlled, double-blind, 8-week trial comparing the efficacy for reducing VMS frequency of low-dose oral 17-beta-estradiol 0.5 mg/day, the SNRI venlafaxine XR (37.5 mg/d for first week, then 75 mg/d), or placebo in a 2:2:3 ratio.[29] MsFLASH 04 was a placebo-controlled trial in which women were randomized to either telephone-delivered CBT-I or menopause education control.[30] This MsFLASH trial focused specifically on the treatment of insomnia symptoms rather than VMS, but VMS outcomes comparable to those collected in the first three MsFLASH trials were measured. MsFLASH 05 was a randomized, double-blind, placebo-controlled 12-week trial that evaluated the effect of estradiol 10 mcg vaginal tablet + placebo vaginal gel; placebo vaginal tablet + Replens vaginal gel; and placebo tablet + placebo gel on vaginal discomfort.[18]

Setting and participants

Participants were recruited from July 2009 to February 2017, primarily by mass mailings to age-eligible women using purchased mailing lists and health-plan enrollment files. In addition, women in MsFLASH 05 were recruited by Facebook ads targeted to women ages 50 to 70 within 20 miles of the clinical sites. There were six MsFLASH network sites (Boston, Indianapolis, Minneapolis, Oakland, Philadelphia, and Seattle).

Eligibility criteria[31] common to the first four trials included: women ages 40 to 62 years; in the late menopausal transition (amenorrhea ≥60 d in the past year), or postmenopausal (≥12 mo since last menstrual period or bilateral oophorectomy), or had a hysterectomy with one or both ovaries remaining and FSH >20 mIU/mL and estradiol ≤50 pg/mL; and, in general, good health as determined by medical history, a brief physical examination, and standard blood tests. In addition to the screening VMS frequency requirement, for MsFLASH 01 to 03 trials, VMS had to be rated as bothersome or severe on at least 4 days or nights per week, and the frequency in screening week 3 could not decrease >50% from the mean weekly levels in screening weeks 1 and 2. For MsFLASH 04, women were eligible if the Insomnia Severity Index score was 12 or higher at screening and at baseline, in addition to reporting ≥ 14 hot flash over the two-week screening period. Women in MsFLASH 05[18] were ages 45 to 70 years, ≥2 years since last menses, report of ≥1 moderate-severe symptom of vulvovaginal itching, pain, irritation, or dryness experienced ≥ weekly within the past 30 days; or pain with penetration ≥ once monthly.

Exclusion criteria common to all trials included[31]: pregnancy or breastfeeding; any current severe or unstable medical conditions; and drug or alcohol abuse (past year). The MsFLASH 01 to 03 trials also excluded participants with history of myocardial infarction, angina, or cerebrovascular events; major depressive episode (past 3 mo); use of prescription or over-the-counter treatments for hot flash (past 30 d); or use of exogenous sex steroid hormones or hormonal contraceptives (past 2 mo), although participants could use FDA approved doses of vaginal estrogen. Women were excluded from MsFLASH 04 if they reported a prior primary sleep disorder diagnosis (eg, sleep apnea), although none of the trials included polysomnography evaluation to rule out undiagnosed sleep disorders. Other exclusion criteria included consuming >3 alcoholic drinks daily, presence of a current major illness interfering with sleep, having a job involving shift work (>3 times a week), or routinely (>3 times a week) using prescription sleeping medications. Additional exclusion criteria for MsFLASH 05 included[18]: current vaginal infection, use of hormonal medication in past 2 months, use of antibiotics or vaginal moisturizer in the past month, and chronic premenopausal vulvovaginal symptoms.

Enrollment and procedures

After telephone screening, women in the VMS trials completed a 2-week symptom diary and a questionnaire, and women in MsFLASH 05 completed a 3-day vaginal symptom diary. Women in MsFLASH 01 to 03 and 05 who remained eligible attended an in-person visit that included a blood draw, physical measures, specimen collections, and another questionnaire. Women in MsFLASH 04 completed the telephone screening, a 2-week sleep and VMS diary, and a questionnaire; an in-person visit was not required. Baseline questionnaires for all studies included the FSFI-19 and FSDS-R, the Patient Health Questionnaire,[32,33] General Anxiety Disorder,[34] and Insomnia Severity Index .[35,36]

Analysis

In the combined MsFLASH trials, there were 1,311 participants randomized. Data from 301 participants (23.0%) were excluded from analysis due to missing FSFI-19 values, since the total score requires responses for all questions (Supplemental Table 1, http://links.lww.com/MENO/A913). Nearly 90% of participants with missing FSFI-19 ($n = 262$) did not respond to two questions in the satisfaction domain. The question, ''How satisfied have you been with your sexual relationship with your partner?'' may be difficult to answer for participants without a sexual partner, and the question, ''How satisfied have you been with your overall sexual life?'' may not be applicable if a participant is not sexually active. A zero score (''No sexual activity'') is not provided for either of these questions. In addition, a satisfaction domain question was inadvertently omitted from the MsFLASH 01 data collection. The missing values were imputed based on the remaining two domain questions, resulting in a total FSFI range of 1.8 to 36.[20] Overall, FSFI-19 missingness varied little between individual FSFI-19 questions other than the satisfaction domain.

Women were queried directly about their sexual activity in the last month in trials 03, 04, and 05, but not in the first two trials. Thus, classification of sexually active or not was derived by identifying a threshold with the highest agreement between the number of FSFI responses of ''No sexual activity" and direct question responses in the last three trials ($\kappa = 0.84$). For all trials, then, a participant was defined as sexually inactive in the past month if she endorsed ''No sexual activity" that met this threshold.

Baseline characteristics and FSFI-19 scores were described and compared across trials via the F-test for homogeneity. The distributions of baseline FSDS-R distress item responses across trials were compared using the chi-square test. To explore the implications of FSFI-19 missingness, baseline characteristics and the FSDS-R distress item were compared across participant groups according to inclusion in the analysis.

The association of FSFI-19 scores with the FSDS-R distress item was described in histograms, according to trial assignment, with FSDS-R in its full five response levels and in dichotomized levels (less than frequently vs frequently or greater, as this is a clinically relevant level of distress). Receiver operating characteristic (ROC) curves were plotted to illustrate the classification of the dichotomized FSDS-R distress item across each integer value of FSFI-19. An adjusted ROC was also estimated to account for demographic variation across trials, including trial number, clinical center, age, education, race, smoking, and BMI. The proposed FSFI-19 cut point was defined by the FSFI-19 value with the highest associated area under the ROC curve (AUC), adjusted model. The utility of the proposed FSFI-19 cut point was explored by recalculating the AUC within various participant subgroups. All analyses were repeated in the subset of sexually active women to explore differences.

Analyses were conducted using SAS for Windows Version 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 1,311 trial participants, 998 women had complete FSFI-19, FSDS-R distress item, and covariate data (Table 1). On average, women were age 55.9 (SD 4.8, range 41-70 years), 72.3% were White, 79.2% were postmenopausal, mean BMI was 27.1 (SD 5.8) kg/m^2, and 60.3% were college graduates. The majority were sexually active (82.0%). Data from our last three trials (MsFLASH 03-05)[18,29,30] showed that, among sexually active participants, 85.5% had sexual activity with male partners, 1.7% with female partners, and 44.1% with self, not mutually exclusive (data not collected in MsFLASH 01-02). Of all women in the five trials, 8.5% had moderate to severe depression, 7.1% had moderate to severe anxiety, and 26.0% had moderate to severe sleep problems. Women excluded from analysis due to missing data were less likely to be married or in a marriage-like relationship than those with complete data, but otherwise, the distribution of characteristics were quite similar across these groups.

The baseline mean FSFI-19 score among all participants and sexually active participants was 18.7 (SD 9.5) and 22.0 (SD 7.2), respectively (Table 2). In general, sexually active participants had a higher mean score across all domains. The proportion of participants with FSFI-19 scores below the standard threshold for FSD of 26.6 was 76.0%. Among sexually active participants, 70.7% were below the threshold. Overall, FSDS-R was rated as never distressed in 19.8%; rarely in 19.5%, occasionally in 30.9%, frequently in 21.6%, and always in 8.1%, with a similar distribution among sexually active participants. As expected, women enrolled in the vaginal symptoms trial (MsFLASH 05) had significantly lower sexual function than those enrolled for VMS and sleep interventions (MsFLASH 01-04): $P < 0.001$ FSFI-19, $P < 0.001$ FSDS-R distress item.

There was a consistent pattern across the trials of the inverse association between sexual function (FSFI-19) and sexual distress (FSDS-R) (Fig. 1A). The dichotomized FSDS-R distress variable captured a substantial portion of this FSFI-19 variability (Fig. 1B). In general, these patterns observed in all women were similar when restricted to sexually active women (Fig. 1C, D).

TABLE 1. *Baseline participant characteristics by trial (n = 998)*

	All Participants (n = 998)		Trial[a] MsFLASH 01 (n = 124)		MsFLASH 02 (n = 287)		MsFLASH 03 (n = 251)		MsFLASH 04 (n = 88)		MsFLASH 05 (n = 248)		
Characteristic	n	%	n	%	n	%	n	%	n	%	n	%	P value[b]
Age (years), mean (SD)	55.9	(4.8)	53.4	(3.9)	54.6	(3.7)	54.5	(3.9)	54.4	(3.9)	60.8	(3.9)	<0.001
<53	249	24.9	53	42.7	91	31.7	79	31.5	26	29.5	0	0.0	
53-55	243	24.3	33	26.6	86	30.0	75	29.9	30	34.1	19	7.7	
56-59	286	28.7	29	23.4	75	26.1	70	27.9	25	28.4	87	35.1	
≥60	220	22.0	9	7.3	35	12.2	27	10.8	7	8.0	142	57.3	
Race													<0.001
White	722	72.3	64	51.6	194	67.6	160	63.7	81	92.0	223	89.9	
Black	212	21.2	54	43.5	67	23.3	82	32.7	1	1.1	8	3.2	
Other[c]/unknown	64	6.4	6	4.8	26	9.1	9	3.6	6	6.8	17	6.9	
Menopause status													<0.001
Postmenopausal	790	79.2	88	71.0	214	74.6	183	72.9	57	64.8	248	100.0	
Perimenopausal	142	14.2	23	18.5	53	18.5	41	16.3	25	28.4	0	0.0	
Indeterminate, at least peri	66	6.6	13	10.5	20	7.0	27	10.8	6	6.8	0	0.0	
Body mass index (kg/m^2), mean (SD)	27.1	(5.8)	29.0	(6.2)	27.0	(4.4)	28.1	(7.1)	25.0	(5.3)	26.1	(5.2)	<0.001
<25	405	40.6	32	25.8	100	34.8	99	39.4	57	64.8	117	47.2	
25-<30	333	33.4	40	32.3	114	39.7	77	30.7	15	17.0	87	35.1	
≥30	260	26.1	52	41.9	73	25.4	75	29.9	16	18.2	44	17.7	
Education													<0.001
≤High school diploma/GED	84	8.4	24	19.4	12	4.2	36	14.3	4	4.5	8	3.2	
School after high school	312	31.3	53	42.7	90	31.4	81	32.3	16	18.2	72	29.0	
College graduate	602	60.3	47	37.9	185	64.5	134	53.4	68	77.3	168	67.7	
Married/marriage-like relationship	791	79.3	85	68.5	223	77.7	188	74.9	76	86.4	219	88.3	<0.001
Sexually active[d]	818	82.0	120	96.8	215	74.9	188	74.9	68	77.3	227	91.5	<0.001
Sexual activity type[e]													
Male partner	413	85.5	N/A		N/A		162	86.7	62	91.2	189	83.3	0.21
Female partner	8	1.7	N/A		N/A		5	2.7	1	1.5	2	0.9	<0.001
Self	213	44.1	N/A		N/A		72	38.3	25	36.8	116	51.1	0.07
Current smoking	97	9.7	26	21.0	25	8.7	41	16.3	1	1.1	4	1.6	<0.001
Alcohol use, ≥7 drinks/wk	135	13.5	14	11.3	34	11.8	39	15.5	11	12.5	37	14.9	0.09
Bilateral oophorectomy	86	8.6	14	11.3	26	9.1	20	8.0	2	2.3	24	9.7	0.23
VMS frequency/d	8.1	(4.5)	9.7	(4.8)	7.6	(3.6)	8.1	(5.3)	7.2	(4.0)	N/A		<0.001
Self-reported health													<0.001
Excellent	200	20.0	16	12.9	47	16.4	58	23.1	16	18.2	63	25.4	
Very good	452	45.3	58	46.8	137	47.7	93	37.1	39	44.3	125	50.4	
Good	297	29.8	42	33.9	93	32.4	77	30.7	28	31.8	57	23.0	
Fair/Poor	49	4.9	8	6.5	10	3.5	23	9.2	5	5.7	3	1.2	
PHQ-8 depression, mean (SD)	3.7	(3.7)	3.0	(3.3)	3.8	(3.6)	3.2	(3.4)	7.8	(4.4)	3.1	(3.0)	<0.001
None (<5)	672	67.3	96	77.4	182	63.4	187	74.5	21	23.9	186	75.0	
Mild (5-9)	237	23.7	18	14.5	81	28.2	46	18.3	40	45.5	52	21.0	
Moderate/severe (≥10)	85	8.5	10	8.1	21	7.3	18	7.2	26	29.5	10	4.0	
GAD-7 anxiety, mean (SD)	3.0	(3.7)	2.2	(3.4)	3.0	(3.5)	2.3	(3.4)	4.9	(4.0)	3.5	(3.8)	<0.001
None (<5)	734	73.5	100	80.6	213	74.2	201	80.1	50	56.8	170	68.5	
Mild (5-9)	193	19.3	19	15.3	54	18.8	34	13.5	27	30.7	59	23.8	
Moderate/severe (≥10)	71	7.1	5	4.0	20	7.0	16	6.4	11	12.5	19	7.7	
ISI insomnia, mean (SD)	10.6	(6.0)	10.9	(6.6)	11.8	(5.4)	10.6	(5.8)	16.1	(3.4)	7.2	(5.2)	<0.001
None (<7)	329	33.0	41	33.1	71	24.7	79	31.5	0	0.0	138	55.6	
Sub-threshold (8-14)	399	40.0	44	35.5	121	42.2	111	44.2	36	40.9	87	35.1	
Moderate/severe (≥15)	259	26.0	38	30.6	91	31.7	56	22.3	52	59.1	22	8.9	

FSFI, Female Sexual Function Index; GAD-7, General Anxiety Disorder (0-21); GED, General Educational Development Test; ISI, Insomnia Severity Index (0-28); MsFLASH, Menopause Strategies: Finding Lasting Answers for Symptoms and Health; PHQ-8, Patient Health Questionnaire (0-24); VMS, vasomotor symptoms.

[a]Recruitment years: MsFLASH 01 (2009-2010); 02 (2011-2012); 03 (2011-2012); 04 (2013-2015); and 05 (2016-2017).

[b]Homogeneity across trials assessed via *F* tests for continuous demographics and chi-square tests for categorical demographics.

[c]Other race/ethnicity includes Hispanic White, American Indian and Asian/Pacific Islander

[d]Derived from the FSFI Questionnaire

[e]Data not collected in trials MsFLASH 01 and 02.

Calculating the sensitivity, specificity, and AUC of FSDS-R distress of frequently or greater by each individual cut point of FSFI, the optimal cut point for FSD was an FSFI-19 score of <21 for all participants (Fig. 2A, Supplemental Table 2, http://links.lww.com/MENO/A914) as well as the subset of those who were sexually active (Fig. 2B). The ROC model performed slightly better in the sexually active women, yielding higher AUC values.

Among all participants, using the newly identified and optimal cut point of FSFI-19 <21, the sensitivity of identifying FSD was 87.2% (95% CI, 83.4-91.0), specificity 57.9% (95% CI, 54.3-61.6) and adjusted AUC of 78.8% (95% CI, 75.8-81.8)

TABLE 2. *Baseline FSFI total and subdomain scores and FSDS-R by trial*

All participants	Combined trials ($n = 998$)	MsFLASH 01 ($n = 124$)	MsFLASH 02 ($n = 287$)	MsFLASH 03 ($n = 251$)	MsFLASH 04 ($n = 88$)	MsFLASH 05 ($n = 248$)	P value[a]
FSFI, mean (SD)							
Total	18.7 (9.5)	24.3 (7.1)	18.5 (10.5)	19.4 (10.4)	19.2 (9.8)	15.4 (6.4)	<0.001
Arousal	3.1 (1.9)	3.8 (1.5)	2.9 (2.1)	3.1 (2.0)	3.2 (1.8)	2.9 (1.6)	<0.001
Desire	2.7 (1.3)	3.2 (1.4)	2.7 (1.4)	2.8 (1.2)	2.6 (1.1)	2.5 (1.0)	<0.001
Lubrication	3.0 (2.0)	4.0 (1.6)	3.0 (2.2)	3.1 (2.2)	3.1 (2.2)	2.2 (1.3)	<0.001
Orgasm	3.4 (2.1)	4.3 (1.4)	3.2 (2.3)	3.3 (2.3)	3.5 (2.2)	3.2 (1.8)	<0.001
Pain	3.2 (2.4)	4.7 (1.6)	3.4 (2.5)	3.6 (2.6)	3.5 (2.5)	1.6 (1.3)	<0.001
Satisfaction	3.5 (1.7)	4.3 (1.6)	3.4 (1.7)	3.5 (1.8)	3.3 (1.7)	3.1 (1.5)	<0.001
FSDS-R, *n* (%)							<0.001
Never	198 (19.8)	39 (31.5)	67 (23.3)	63 (25.1)	19 (21.6)	10 (4.0)	
Rarely	195 (19.5)	21 (16.9)	64 (22.3)	65 (25.9)	14 (15.9)	31 (12.5)	
Occasionally	308 (30.9)	38 (30.6)	90 (31.4)	70 (27.9)	30 (34.1)	80 (32.3)	
Frequently	216 (21.6)	22 (17.7)	42 (14.6)	30 (12.0)	19 (21.6)	103 (41.5)	
Always	81 (8.1)	4 (3.2)	24 (8.4)	23 (9.2)	6 (6.8)	24 (9.7)	
Sexually active participants	**Combined trials ($n = 818$)**	**MsFLASH 01 ($n = 102$)**	**MsFLASH 02 ($n = 215$)**	**MsFLASH 03 ($n = 188$)**	**MsFLASH 04 ($n = 68$)**	**MsFLASH 05 ($n = 227$)**	**P value[a]**
FSFI, Mean (SD)							
Total	22.0 (7.2)	24.8 (6.6)	23.4 (7.2)	24.5 (6.3)	23.6 (6.2)	16.5 (5.5)	<0.001
Arousal	3.7 (1.5)	3.9 (1.4)	3.8 (1.6)	4.0 (1.4)	3.9 (1.3)	3.1 (1.4)	<0.001
Desire	2.9 (1.2)	3.2 (1.4)	2.9 (1.4)	3.1 (1.1)	2.9 (1.1)	2.6 (1.0)	<0.001
Lubrication	3.6 (1.7)	4.1 (1.5)	4.0 (1.6)	4.1 (1.6)	4.0 (1.7)	2.4 (1.2)	<0.001
Orgasm	4.1 (1.6)	4.4 (1.4)	4.2 (1.6)	4.4 (1.4)	4.3 (1.5)	3.5 (1.6)	<0.001
Pain	3.9 (2.1)	4.8 (1.4)	4.5 (1.9)	4.8 (1.8)	4.6 (1.8)	1.8 (1.3)	<0.001
Satisfaction	3.8 (1.5)	4.3 (1.5)	3.9 (1.5)	4.2 (1.5)	3.9 (1.5)	3.2 (1.5)	<0.001
FSDS-R, *n* (%)							<0.001
Never	164 (20.0)	38 (31.7)	50 (23.3)	51 (27.1)	15 (22.1)	10 (4.4)	
Rarely	154 (18.8)	21 (17.5)	45 (20.9)	49 (26.1)	11 (16.2)	28 (12.3)	
Occasionally	264 (32.3)	36 (30.0)	72 (33.5)	57 (30.3)	24 (35.3)	75 (33.0)	
Frequently	184 (22.5)	21 (17.5)	33 (15.3)	21 (11.2)	15 (22.1)	94 (41.4)	
Always	52 (6.4)	4 (3.3)	15 (7.0)	10 (5.3)	3 (4.4)	20 (8.8)	

FSDS-R, Female Sexual Distress Scale-Revised; FSFI, Female Sexual Function Index; MsFLASH, Menopause Strategies: Finding Lasting Answers for Symptoms and Health.
FSFI Ranges: Total 1.8-36.0, Arousal 0-6, Desire 1.2-6.0, Lubrication 0-6, Orgasm 0-6, Pain 0-6, Satisfaction 0.6-6.0. Due to imputation in the satisfaction domain in MsFLASH 01, the lower range for our scores was 1.8 instead of 2.0 as defined.[17]
[a]Homogeneity across trials assessed via F test for FSFI, chi-squared test for FSDS-R.

(Table 3, Fig. 2A). Among the restricted subset of sexually active women, sensitivity was slightly lower at 83.9% (95% CI, 79.2-88.6) and specificity and AUC slightly higher at 69.8% (66.0-73.5) and 81.3% (78.0-84.6). The properties of the cut point varied across subgroups including by trial, menopausal status, and race (Table 3). Sensitivity was lowest in MsFLASH 01, and specificity was lowest in MsFLASH 05, compared to the other trials. Utilizing the newly identified cut point of 21, 55.5% of all participants, and 45.7% of sexually active participants in MsFLASH trials would be considered to have FSD.

DISCUSSION

Combining individual-level data from five randomized clinical trials, three that evaluated interventions for VMS,[25-29] one intervention for sleep (McCurry) and one for bothersome vaginal symptoms,[18] provided the opportunity to evaluate the FSFI-19 in a broader population of nearly 1,000 midlife women. In this population of predominantly postmenopausal women, mean age of 55.9 (SD 4.8), of whom nearly 80% were sexually active, we estimated and propose a new ideal cut point of 21 for FSD, as measured by the FSFI-19 (range 2-36) and anchored in FSDS-R distress (frequently or always). Although the distribution of FSFI-19 score varied between groups of sexually active and sexually inactive participants in our study, the estimated cut point of 21 for FSD was the same in both groups.

Utilizing the newly identified cut point of 21, 55.5% of all participants and 45.7% of sexually active participants in MsFLASH trials would be considered to have FSD. Based on our data, the use of the 26.6 total FSFI-19 score cut point to designate FSD as studied in women of all ages[11] appears inappropriate; 76.0% of women in the MsFLASH studies would have been categorized as having FSD by that standard. As observed in other studies,[37] the proportion of women in the MsFLASH trials who would be classified as having FSD according to the proposed cut point was lower in the subset of sexually active women compared to all participants.

Sensitivity and specificity of the proposed cut point varied by trial, menopausal status, and by Black versus White women. The highest sensitivity and lowest specificity of all subgroups was observed in the MsFLASH 05 trial, the population of which was entirely postmenopausal with older women who enrolled due to GSM. This trial also had the lowest mean FSFI-19 score. The lower specificity observed in MsFLASH 05 was anticipated as the variability of the FSFI-19 score in this population was not as great as that observed in trials recruiting women for VMS and sleep. Our finding comparing cut point performance between Black and White

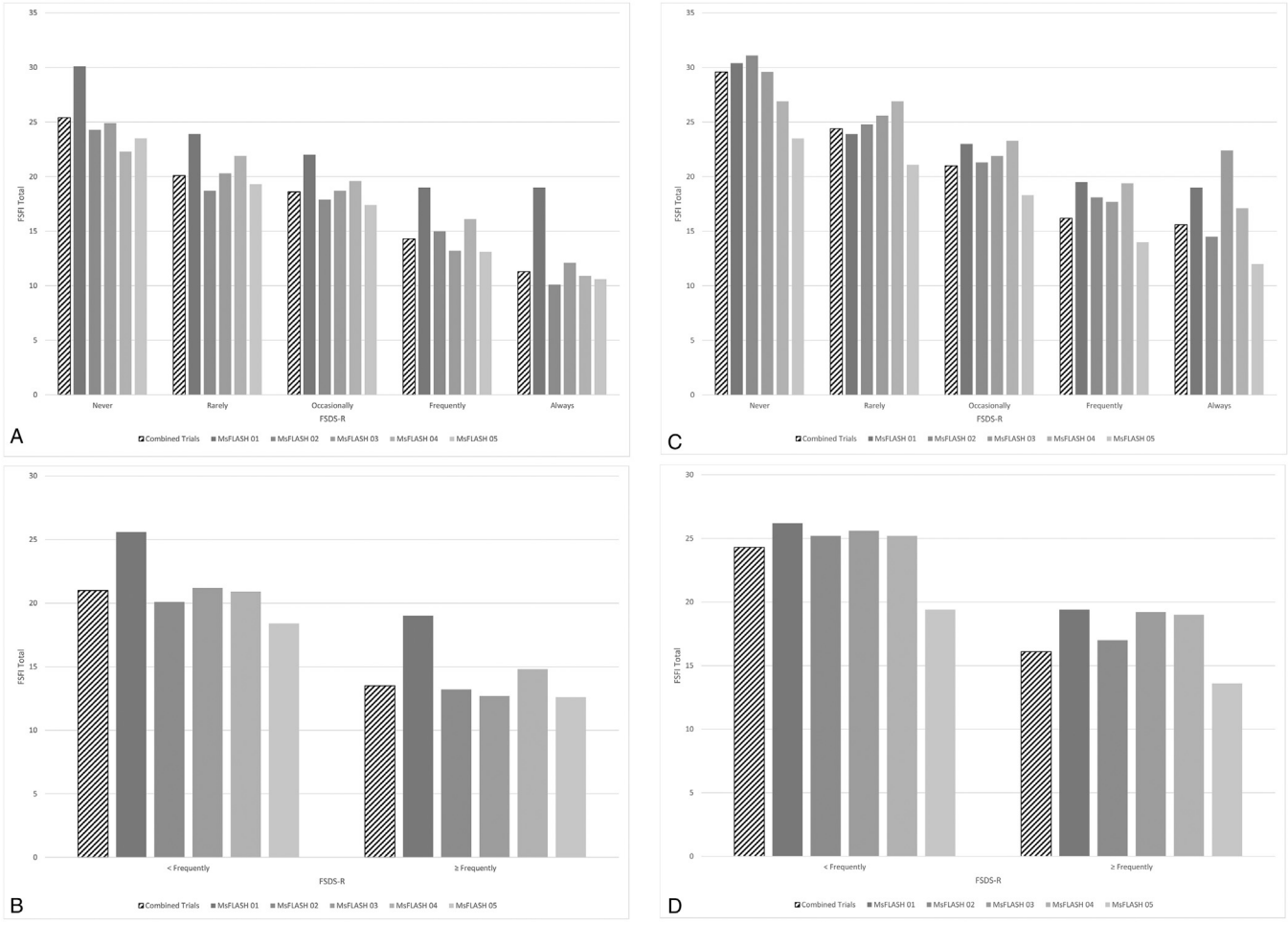

FIG. 1. (A) Mean FSFI total score by FSDS-R ($n = 998$). *X* axis: grouped by FSDS-R from left to right ''never,'' ''rarely,'' ''occasionally,'' ''frequently,'' ''always'' and designated by all participants (hashed bar) and by trial MsFLASH 01 to MsFLASH 05 (darkest to lightest). *Y* axis: mean FSFI total score. **(B)** Mean FSFI total score by dichotomized FSDS-R ($n = 998$). *X* axis: grouped by FSDS-R on left ''<frequently'' and on right ''at least frequently'' designated by all participants (hashed bar) and by trial MsFLASH 01 to MsFLASH 05 (darkest to lightest). *Y* axis: mean FSFI total score. **(C)** Mean FSFI total score by FSDS-R in sexually active participants ($n = 818$). *X* axis: grouped by FSDS-R from left to right ''never,'' ''rarely,'' ''occasionally,'' ''frequently,'' ''always'' and designated by all participants (hashed bar) and by trial MsFLASH 01 to MsFLASH 05 (darkest to lightest). *Y* axis: mean FSFI total score. **(D)** Mean FSFI total score by dichotomized FSDS-R in sexually active participants ($n = 818$). *X* axis: grouped by FSDS-R on left ''<frequently'' and on right ''at least frequently'' designated by all participants (hashed bar) and by trial MsFLASH 01 to MsFLASH 05 (darkest to lightest). *Y* axis: mean FSFI total score. FSDS-R, Female Sexual Distress-Revised; FSFI, Female Sexual Function Index; MsFLASH, Menopause Strategies: Finding Lasting Answers for Symptoms and Health.

women suggests that the relationship between the FSFI-19 and FSDS-R varies across these groups, but we were underpowered to detect a true difference. Any potential differences by race are likely driven by differences in lived experience, including social and physical environment, rather than biological differences between Black and White women. We did not have sufficient numbers in other racial/ethnic groups to add to our findings; sexual function in these groups deserve further exploration.

Descriptions of FSD in older female populations as measured by validated instruments are sparse or inconsistent. It is estimated that 50%-75% of middle-aged women are sexually active and, of those, 42%-88% may have FSD as measured by the FSFI-19 with a cut point of 26.6.[37] It is intuitive that sexual function can change with aging (diminished blood flow, slower nerve conductivity, decreased cellular cross links leading to increased tissue permeability) and that any measure for FSD in a physiologically older population which relies only on physical sensations might artificially inflate the frequency of diagnoses of FSD (up to 88%), without an assessment for distress or a partner's sexual function.

Sex is important to many postmenopausal women, including women who are inactive or without a partner, and diagnosing FSD can lead to appropriate therapies. A majority (60%-75%) of women have reported that ''sexuality'' is important to their well-being and overall quality of life.[4,5] Many factors contribute to FSD, including relationship factors, availability or health of partners, a woman's age, sleep function, and underlying medical and psychological problems.[5,38] Identifying these factors in women diagnosed with

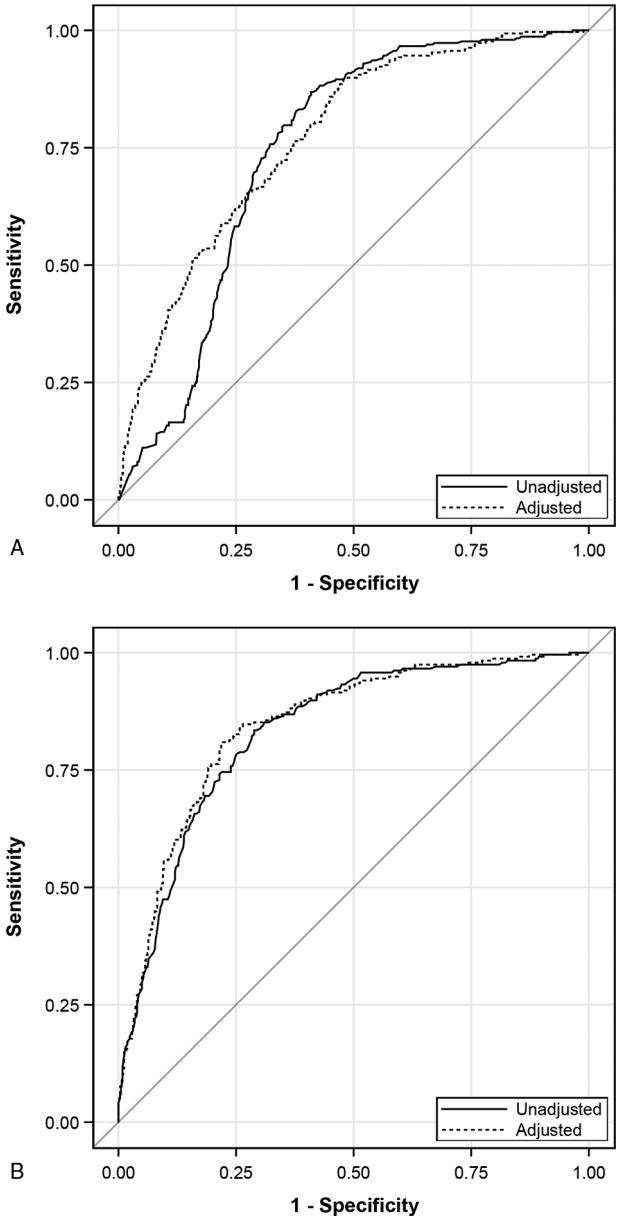

FIG. 2. (A) Unadjusted and adjusted[a] ROC curves for FSDS-R $\geq$ frequently by FSFI ($n = 998$). **(B)** Unadjusted and adjusted[a] ROC curves for FSDS-R $\geq$ frequently by FSFI in sexually active participants ($n = 818$). *X* axis: 1-specificity. *Y* axis: sensitivity. Solid line: unadjusted. Broken line: adjusted. [a]Adjusted for trial, clinical site, age, education, race, smoking, and BMI. FSDS-R, Female Sexual Distress-Revised; FSFI, Female Sexual Function Index; ROC, Receiver operating characteristic.

FSD can guide management. For example, approximately 80% of women in all of our studies were sexually active and nearly 80% of women in MsFLASH 05 reported dyspareunia or vaginal dryness. A targeted intervention in this trial showed improved day-to-day activities, sexual function, emotional well-being, and body image with low dose vaginal estradiol, moisturizer, or topical placebo.[39] Self-reported meaningful benefit from treatment in this trial[18] was reflected by quantifiable changes in the Day-to-Day Impact of Vaginal Aging questionnaire domain scores[39] that may provide meaningful targets for research and clinical efforts once a diagnosis of FSD is established.

Compared with other studies using validated measures of sexual function, our findings are most comparable with those from the Penn Ovarian Aging cohort study,[16] and the Nurses' Health Study (NHS) II.[37] Gracia et al[16] noted a bimodal distribution in the composite FSFI-19 score in their cohort and assigned a cut point of the normal sexual function above 20, rather than the cut point of 26.6.[11] With this definition, 33% of that population had FSD as compared with 55% in MsFLASH with a cut point of 21. This might be explained by differences in the populations – only 19% of the women in Penn Ovarian Aging were postmenopausal, whereas at least 80% were postmenopausal in these MsFLASH analyses.

Other investigators have used the FSFI-6 as a screening tool to identify women at risk for FSD and suggest a score of 19 or greater (scale 2-30) be used to indicate normal function in postmenopausal women.[40] The FSFI-6 has the same domains as the FSFI-19 (desire, arousal, lubrication, orgasm, satisfaction, and pain) but has only one question per domain. The desire domain and the satisfaction domains do not require sexual activity or intercourse in the prior 4 weeks, just as in the FSFI-19. The binary FSD indicator derived from the abbreviated FSFI-6 measure cannot reliably be computed without complete responses to each of the FSFI-6 items,[17,40] a problem held in common with the FSFI-19. Both the FSFI-6 and FSFI-19 are psychometrically strong but cannot be used to evaluate FSD in older sexually inactive women or women who do not engage in ''vaginal penetration'' during sex because zero values are known to artificially inflate the proportion of women screening positive for difficulty with aspects of sexual function. To circumvent this problem, others have proposed adaptations for populations not engaged in penetrative vaginal sex, or have evaluated only the desire and satisfaction domains.[17,37,41] In sum, the FSFI-6 is a validated tool, useful since it is shorter, but it retains the same problems for use in postmenopausal women as the FSFI-19 noted above.

The NHS II had a lower prevalence of screen positive FSD as measured by the FSFI-6 compared with prior studies that used different measures and included sexually inactive women.[37] NHS II, with a 73% prevalence of sexually active women similar to our study at 83%, assessed FSD only among sexually active women and used the FSFI-6 clinical cutoff score of 19 or less for FSD (as recommended for premenopausal women). Among sexually active women in NHS II, 51% of women who were partnered and 42% of women without partners screened positive as being at risk for FSD (FSFI-6 < 19). Sexual distress was not measured. These findings are in contradistinction to the 68%-86.5% FSD observed by others using other measures.[42]

The Women's Health Initiative, Study of Women's Health Across the Nation (SWAN), and the National Health and Nutrition Examination Survey (NHANES) did not use validated measures to assess sexual function. Women in the

TABLE 3. *Sensitivity, specificity, and area under the ROC curve of FSDS-R ≥ frequently by FSFI total score <21*

Group	*n*	Sensitivity (95% CI)			Specificity (95% CI)			AUC (95% CI)			Adjusted[a] AUC (95% CI)		
All participants	998	87.2	(83.4,	91.0)	57.9	(54.3,	61.6)	72.6	(69.9,	75.2)	78.8	(75.8,	81.8)
Trial													
MsFLASH 01	124	61.5	(41.5,	81.6)	78.6	(70.3,	86.8)	70.1	(59.7,	80.4)	79.5	(69.7,	89.2)
MsFLASH 02	287	84.8	(76.0,	93.7)	57.0	(50.4,	63.6)	70.9	(65.5,	76.4)	76.5	(70.2,	82.8)
MsFLASH 03	251	81.1	(70.2,	92.0)	61.1	(54.3,	68.0)	71.1	(64.8,	77.4)	78.9	(72.2,	85.6)
MsFLASH 04[b]	88	80.0	(63.1,	96.9)	61.9	(49.6,	74.2)	71.0	(60.9,	81.0)	78.1	(67.6,	88.6)
MsFLASH 05	248	97.6	(95.0,	100.0)	35.5	(26.9,	44.2)	66.6	(62.1,	71.1)	73.2	(67.0,	79.4)
Menopause status													
Postmenopausal	790	88.4	(84.5,	92.3)	52.9	(48.7,	57.2)	70.7	(67.8,	73.6)	78.1	(74.8,	81.5)
Perimenopausal	142	76.0	(58.0,	94.0)	73.5	(65.4,	81.6)	74.8	(65.3,	84.2)	82.8	(74.3,	91.3)
Race													
White	722	90.6	(86.8,	94.5)	54.0	(49.6,	58.4)	72.3	(69.4,	75.2)	79.9	(76.6,	83.3)
Black[b]	212	73.6	(61.3,	85.9)	74.8	(68.0,	81.7)	74.2	(67.3,	81.1)	77.6	(70.3,	84.9)
Group	*n*	Sensitivity (95% CI)			Specificity (95% CI)			AUC (95% CI)			Adjusted[a] AUC (95% CI)		
Sexually active participants	818	83.9	(79.2,	88.6)	69.8	(66.0,	73.5)	76.8	(73.8,	79.8)	81.3	(78.0,	84.6)
Trial													
MsFLASH 01	120	60.0	(39.4,	80.6)	81.1	(73.0,	89.1)	70.5	(60.0,	81.1)	79.5	(69.4,	89.6)
MsFLASH 02	215	79.2	(67.2,	91.1)	75.4	(68.9,	82.0)	77.3	(70.6,	84.0)	85.2	(78.6,	91.7)
MsFLASH 03	188	67.7	(50.3,	85.2)	77.1	(70.4,	83.7)	72.4	(63.4,	81.4)	79.6	(70.6,	88.5)
MsFLASH 04[b]	68	72.2	(49.3,	95.1)	78.0	(66.1,	89.9)	75.1	(63.0,	87.2)	81.9	(70.3,	93.6)
MsFLASH 05	227	97.4	(94.4,	100.0)	38.1	(29.0,	47.1)	67.7	(63.0,	72.4)	75.2	(69.0,	81.5)
Menopause status													
Postmenopausal	638	85.4	(80.6,	90.3)	65.0	(60.5,	69.6)	75.2	(71.9,	78.5)	80.6	(77.0,	84.2)
Perimenopausal	125	71.4	(50.4,	92.5)	82.7	(75.3,	90.1)	77.1	(66.5,	87.6)	86.9	(79.8,	94.0)
Race													
White	598	88.5	(83.8,	93.1)	64.7	(60.1,	69.3)	76.6	(73.3,	79.8)	82.3	(78.8,	85.8)
Black[b]	174	63.2	(47.1,	79.2)	87.5	(81.9,	93.1)	75.3	(67.1,	83.6)	79.7	(71.3,	88.2)

AUC, area under the ROC curve; CI, confidence interval; MsFLASH, Menopause Strategies: Finding Lasting Answers for Symptoms and Health.
[a]Adjusted for trial, clinical center, age, education, race, smoking, and BMI.
[b]Due to small sample sizes, these adjusted AUC models were reduced to include only trial (01-04 vs 05), age, education, and BMI.

Women's Health Initiative observational cohort ($n = 46,535$) completed the question, ''How satisfied are you with your sexual activity (satisfied versus unsatisfied)?'' Overall, 52% reported sexual activity with a partner in the past year and of those, 77% ($N = 35,719$) reported satisfaction with sexual activity.[43] Data on sexual function from SWAN utilized a 20-item self-administered questionnaire designed to address sexual activity and function over the past 6 months in multi-ethnic women with and without partners.[38] Although not a validated questionnaire, when tracked over time in the cohort, the SWAN sexual function score declined. More important than most aspects of sexual function were relationships, attitudes toward sex and aging, vaginal dryness, sociodemographic factors, and cultural background. NHANES assesses the health and nutritional status of adults and children through a combination of interviews and physical examinations. The survey includes questions on sexual behaviors and provides descriptive data but does not use validated measures that might assess the prevalence of FSD. Of women ages 55 to 64, 62% reported interest in sex and of those who were sexually active, 62% reported good quality of sexual activity.[5] Of NHANES participants, over 60% of women between 57 and 64 years of age reported being sexually active in the past year, and of those 63% reported sexual activity at least 2 to 3 times per month. Up to 43% reported some sexual dysfunction, but not all were bothered by their symptoms.[5,44]

Study findings should be interpreted in the context of study strengths and limitations. With rich data on nearly 1,000 women, this is one of the largest studies to describe female sexual function in midlife peri- and postmenopausal women using validated questionnaires and controlling for confounding factors. The ability to combine data across MsFLASH trials due to standardization of inclusion criteria and outcome assessments provided the opportunity for analyses, which we hope will prompt further studies in larger cohorts of postmenopausal women from the general population. The study was limited by the fact that the women studied were participants in intervention trials for menopausal symptoms (vasomotor, insomnia, or vaginal) from six US study sites that are not necessarily representative of all peri- and postmenopausal women. The range of study sites provided geographic diversity, and although most participating women were Non-Hispanic White, the MsFLASH trial cohorts encompassed greater diversity than most previous trial cohorts. This study did not have information on clinically-derived diagnoses of FSD in its sample. Temporal trends from 2009 to 2017 may have influenced our results. The FSDS-R, although psychometrically strong[22] is not the gold standard for measuring sexual distress.

Our study highlights some of the challenges in using the FSFI-19 in a postmenopausal population that result from missing data and values of zero for sexual inactivity or lack of vaginal penetration resulting in artificial inflation of our

estimates of FSD diagnoses. Women excluded due to missing data were, unsurprisingly, less likely to be married or in a marriage-like relationship than those with complete data. Missing data likely inflated our FSFI-19 cut point estimation. Minor modifications of the FSFI-19 questions for women without partners or who are not sexually active could rectify this problem. For example, questions 14 and 15 ask about partners. Modifying answers such that a woman could respond that she does not have a partner and then adjusting the scoring system accordingly would be one such improvement. And, assessing distress is imperative. To date, we have lacked the tools to assess and redefine normal female sexual function in older women. Research tools that accurately identify FSD in postmenopausal women will provide new data on normal female sexual function and will appropriately guide treatment to improve the quality of clinical care.

CONCLUSIONS

We propose that a new FSFI-19 cut point of <21 and minor modifications to the FSFI questions be considered to describe normal sexual function in midlife women as opposed to the cut point of <26.6 used for the general population.[11] Our study demonstrates the concordance of low FSFI with a measure of distress; future validation work should examine its value in identifying clinically diagnosed FSD. This new proposed cut point is consistent with findings from other studies,[16,40] but larger, nonselected postmenopausal populations are needed to validate its utility. We encourage the use of this FSFI-19 cut point to assist in the interpretation of research in midlife women's sexual function. This approach would reduce the chance that normal sexual function in midlife women will be classified as disordered.

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