

# Abnormal uterine bleeding is associated with fatigue during the menopause transition

Siobán D. Harlow, PhD,<sup>1</sup> Ellen B. Gold, PhD,<sup>2</sup> Michelle M. Hood, MSc,<sup>1</sup> Alain A. Mukwege, MD, MSc,<sup>1</sup> John F. Randolph, MD,<sup>3</sup> and Gail A. Greendale, MD<sup>4</sup>

## Abstract

**Objective:** During the menopause transition (MT), abnormal uterine bleeding, characterized by prolonged (PMB) or heavy (HMB) menstrual bleeding, occurs often. We assessed whether PMB or HMB was associated with fatigue.

**Methods:** We used longitudinal daily menstrual calendar data from 2,329 participants in the Study of Women's Health Across the Nation to identify episodes of HMB and PMB. At seven annual follow-up visits, four symptoms of fatigue were queried (worn out, feeling tired, full of pep, having energy). General linear mixed models with random intercepts for each woman assessed the association between each fatigue variable and PMB or HMB recorded during the 6 months prior to each annual follow-up visit. Models were adjusted for race and ethnicity, age, body mass index, hormone therapy use, depressive and anxiety symptoms, perceived stress, sleep problems, cigarette use, and discrimination.

**Results:** After adjustment, reporting three or more episodes of HMB in the prior 6 months was positively associated with feeling tired (odds ratio [OR] = 1.62, 95% CI = 1.11 to 2.38) and being worn out (OR = 1.44, 95% CI = 0.98 to 2.13), whereas three or more episodes of PMB in the prior 6-month window was negatively associated with being full of pep (OR = 0.68, 95% CI = 0.49 to 0.95).

**Conclusions:** HMB and PMB during the MT were associated with increased odds of experiencing three symptoms of fatigue. Greater clinical attention to bleeding changes and associated symptoms, including fatigue and lack of energy, is warranted, as is education of women about potential health consequences of excessive menstrual bleeding during the MT.

**Key Words:** Abnormal uterine bleeding, Fatigue, Menopause, Menorrhagia.

(*Menopause* 2025;32:00–00)

Received October 26, 2024; revised and accepted December 9, 2024.

From the <sup>1</sup>Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI; <sup>2</sup>Department of Public Health Sciences, School of Medicine, University of California Davis, Davis, CA; <sup>3</sup>Division of Reproductive Endocrinology and Infertility, Michigan Medicine, University of Michigan, Ann Arbor, MI; and <sup>4</sup>Division of Geriatrics, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA.

Funding/support: The Study of Women's Health Across the Nation (SWAN) has grant support from the National Institutes of Health (NIH), Department of Health and Human Services, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the NIH Office of Research on Women's Health (ORWH) (grants U01NR004061; U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, U01AG012495, and U19AG063720). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH, or the NIH.

Financial disclosure/conflicts of interest: A.A.M. has a past financial relationship with CVS. The other authors have nothing to disclose.

Address correspondence to: Siobán D. Harlow, PhD, Department of Epidemiology, School of Public Health, University of Michigan, 1415 Washington Heights, Ann Arbor, MI 48109. E-mail: harlow@umich.edu

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eISSN: 1530-0374

DOI: 10.1097/GME.0000000000002525

Most women transitioning through menopause experience changes in the amount and duration of menstrual flow, with many reporting episodes of prolonged (PMB) or heavy (HMB) bleeding that meet the criteria for abnormal uterine bleeding (AUB). AUB is defined as menstrual bleeding within a 6-month period that is excessive in amount, frequency, or duration.<sup>1</sup> In the Study of Women's Health Across the Nation (SWAN), analyses of prospectively recorded daily menstrual calendars revealed that one in three women transitioning through the menopause had episodes of AUB, including both PMB or HMB.<sup>2</sup> Similarly, in a cross-sectional survey of Swedish women aged 40 to 45 years, 32% reported experiencing HMB.<sup>3</sup>

Although studies are few, available evidence points to adverse effects of AUB on women's quality of life.<sup>4,5</sup> A systematic review found that women with AUB scored below the 25th percentile on health-related quality of life measured by the 36-item Short Form Health Survey (SF-36),<sup>5</sup> whereas a large cross-national European study of women aged 18 to 57 years reported that women associated their experiences of unusual fatigue, tiredness, or exhaustion with HMB.<sup>6,7</sup> However, despite the documented increase in the frequency of AUB during the menopause transition (MT),<sup>2</sup> no studies, to our knowledge, have focused on AUB and whether it is associated with negative symptoms during this life stage.

We hypothesized that AUB during the MT, especially when characterized by HMB, would be related to fatigue symptoms, because HMB is linked to iron deficiency anemia, a well-recognized etiology of fatigue.<sup>8–11</sup> In the United States, midlife women were two to four times as likely to experience debilitating forms of syndromic fatigue when compared with their male counterparts, with the MT and gynecological morbidities suspected as risk factors.<sup>12–14</sup> The present analysis used prospectively collected, longitudinal, daily menstrual calendar data from midlife women to assess whether HMB or PMB recorded during the 6 months prior to a follow-up visit was associated with reporting four specific symptoms of fatigue (feeling worn out, feeling tired, not feeling full of pep, or not having energy) reported at that follow-up visit.

## METHODS

In 1996 to 1997, the longitudinal cohort of SWAN enrolled 3,202 women aged 42 to 52 years who were premenopausal or early perimenopausal. Participants were followed approximately annually.<sup>15</sup> To be eligible for the cohort at baseline, women could not be pregnant, lactating, or using exogenous sex hormones, and they had to have a uterus and at least one ovary intact and to have had a menstrual cycle in the previous 3 months. Each of the seven participating clinical sites enrolled White women and either Black (Boston, Chicago, Pittsburgh, and southeast Michigan), Chinese (northern California), Japanese

(Los Angeles), or Hispanic (New Jersey) women. At baseline and each follow-up visit, women completed questionnaires about their menstrual, gynecological, and medical history, including information on surgeries and exogenous hormone use as well as about their symptoms, lifestyle, and life context. Height and weight were measured. From enrollment through the follow-up visit 10, women also maintained a monthly menstrual calendar in which they recorded their menstrual bleeding until 2 years after their final menstrual period or for up to 10 years. The institutional review board at each study site approved the study protocol, and participants provided written, informed consent at each visit.

To be eligible for the present analyses, SWAN participants had to have provided menstrual calendars for at least 6 months ( $n = 2,755$ , 86.0% of the cohort) and to have had at least one bleeding episode within a 6-month window prior to follow-up visits 1 through 6 and 8, which included the fatigue variables. Mean follow-up time was 3.7 years, with a range of 0.5 to 8.1 years. Among the 2,329 women included in the analyses, 733 (31.5%) contributed one to two observations, 688 (29.5%) contributed three to four observations, and 908 (39.0%) contributed five to seven observations.

### Abnormal uterine bleeding

In the monthly menstrual calendars, participants prospectively recorded each day they bled and the amount of flow using prespecified categories: spotting (bleeding not requiring the use of a sanitary product or not filling a regular-sized sanitary product), light to moderate bleeding (sanitary protection was required but needed to be changed only a few times per day or every 3 to 4 hours), or very heavy bleeding (needing to change sanitary product every 1-2 hours for more than 4 hours during the day). PMB was defined as episodes that lasted more than 8 days and HMB as a report of very heavy bleeding for 3 or more days.<sup>16,17</sup> For each 6-month window preceding an eligible follow-up visit, we created four variables indicating whether a woman had had at least one episode of PMB, at least one episode of HMB, three or more episodes of PMB, and three or more episodes of HMB.

Vitality and fatigue were assessed using four items from the SF-36.<sup>18</sup> To gauge vitality, women were asked: "During the past 4 weeks, how much time they felt full of pep" ("Did you feel 'full of pep'?" or full of energy ("Did you have a lot of energy?"). To estimate fatigue, they were queried about feeling worn out ("Did you feel worn out?") or tired ("Did you feel tired?"). Response options included "all of the time," "most of the time," "a good bit of the time," "some of the time," "a little of the time," and "none of the time." Answers to each question were dichotomized: all of the time, most of the time, or a good bit of the time versus some of the time, a little of the time, or none of the time. Rather than combining the four items into a total score (ie, the SF-36 Vitality Scale), we examined each as a separate outcome, because fatigue is considered a distinct construct from a lack of energy; each construct is therefore best measured independently.<sup>19</sup>

### Covariates

Self-reported race/ethnicity (Black, Chinese, Hispanic, Japanese, and White) was ascertained at baseline. Time-varying

covariates included age, measured body mass index (BMI,  $\text{weight}/[\text{height}]^2$ ), smoking status, depressive symptoms, anxiety symptoms, discrimination, perceived stress, sleep quality, and use of menopausal hormone therapy (HT). Smoking status was categorized as current smoker versus former/never smoker. Depressive symptoms were assessed by the Center for Epidemiological Studies Depression Scale and categorized (yes/no) based on scoring in the upper quartile (score  $\geq 13$ ).<sup>20</sup> Anxiety symptoms were assessed as reporting irritability or grouchiness, feeling tense or nervous, heart pounding or racing, and feeling fearful for no reason in the past 4 weeks; response options included not at all (0), 1 to 5 days (1), 6 to 8 days (2), 9 to 13 days (3), and every day (4), which were summed across the four questions. Women were classified as having anxiety symptoms (yes/no) based on scoring in the top quintile (score  $\geq 4$ ).<sup>21</sup> Discrimination was assessed via the Detroit Area Study Everyday Discrimination Scale,<sup>22</sup> which includes nine questions about experiences of everyday discrimination in the past year; in SWAN, an additional item was included regarding "people ignore you or act as if you aren't there."<sup>23</sup> We averaged across responses to each item of never experiencing (0) to often experiencing (3) to create a continuous summary score of discrimination. Perceived stress in the past 2 weeks was measured using the four-item Cohen's Perceived Stress Scale,<sup>24</sup> with item responses scored on a 1- (never) to 5-point (very often) scale. A total score (range, 4-20) was calculated by summing across responses to the four items after reverse scoring the two positive items. Sleep problems (yes/no) were based on whether in the past 2 weeks a woman reported trouble falling asleep, waking up several times, or waking earlier than planned. HT use within the past 6 months (yes/no) was ascertained from the monthly menstrual calendars.

### Analyses

We calculated means and SD of continuous variables and frequencies of categorical variables. We ran generalized linear mixed models with a binomial distribution and logit link with random intercepts for each woman, modeling each vitality and fatigue variable separately, first with PMB and then with HMB as predictors. Bleeding variables, assessed in the 6 months preceding ascertainment of fatigue, were modeled in two ways: (1) experiencing any PMB or HMB in the past 6 months and (2) experiencing three or more episodes of PMB or HMB in the past 6 months. Covariates were identified based on a priori knowledge of factors associated with AUB and with fatigue. We first ran models unadjusted for covariates. Next, models were adjusted for race and ethnicity and time-varying age, BMI, and HT use. Finally, we additionally adjusted for time-varying depressive symptoms, anxiety symptoms, perceived stress, sleep problems, smoking, and discrimination. We retained all covariates as the fully adjusted models had the best fit based on the Bayesian information criterion. All time-varying covariates were measured concurrently with the fatigue outcomes or, if not assessed at the concurrent visit, were carried forward from the closest prior visit. As a sensitivity analysis, we ran adjusted models with the SF-36 Vitality Scale (sum of scores for all four items) as the outcome. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). Statistical significance was set at  $\alpha < 0.05$ .

## RESULTS

The study sample included 552 (23.7%) Black, 1,177 (50.5%) White, 222 (9.5%) Chinese, 125 (5.4%) Hispanic, and 253 (10.9%) Japanese women. At the first follow-up visit, study participants had a mean age of 47.3 (SD, 2.6) years and a mean BMI of 27.8 (SD, 7.1) kg/m<sup>2</sup>. A total of 138 participants (5.9%) reported using HT in their menstrual calendars; 303 (13.1%) were current smokers. Depressive symptoms, anxiety symptoms, and sleep problems were reported at the first follow-up visit by 24.9%, 17.6%, and 29.6% of women, respectively. The mean perceived stress score was 8.06 (SD, 2.88), and the mean discrimination score was 1.71 (SD, 0.48).

During the 6 months prior to the first follow-up visit, 20.7% of women recorded at least one episode of HMB, whereas 5.0% recorded HMB at least three times (Table 1). Similarly, 24.4% recorded PMB, with 4.6% recording PMB at least three times (Table 1). At the first follow-up visit, about one quarter of study participants reported fatigue: 26.6% reported feeling tired in the past 2 weeks, and 24.2% reported feeling worn out in the past 2 weeks. In contrast, half of the women reported having energy (50.2%) and being full of pep (50.0%).

In unadjusted longitudinal analyses, women who reported any HMB had about a 30% greater odds of feeling tired (odds ratio [OR] = 1.33, 95% CI = 1.10-1.62) or worn out (OR = 1.34, 95% CI = 1.10-1.63), and a lower odds of having energy (OR = 0.78, 95% CI = 0.64-0.95) or being full of pep (OR = 0.81, 95% CI = 0.67-0.99) compared with women who did not report HMB (Table 2). Odds were about 70% higher among women who reported three or more episodes of HMB for feeling tired (OR = 1.75, 95% CI = 1.21-2.53) or worn out (OR = 1.67, 95% CI = 1.15-2.41), whereas odds for having energy and feeling full of pep changed little and were no longer statistically significantly different from the odds in women who did not. Except

for lower odds of reporting being full of pep (OR = 0.72, 95% CI = 0.52-0.99) among women reporting PMB at least three times in the past 6 months, PMB was not significantly associated with any of the other vitality/fatigue symptoms.

The odds of feeling tired or feeling worn out in association with reporting any HMB and at least three episodes of HMB within 6 months were slightly attenuated after adjustment for age, race and ethnicity, BMI, and HT use. After further adjustment for depressive and anxiety symptoms, smoking, perceived stress, and discrimination, report of any HMB was no longer associated with these two fatigue symptoms, but reporting  $\geq 3$  episodes of HMB in the prior 6 months remained statistically significantly related to feeling tired (OR = 1.62, 95% CI = 1.11-2.38) and marginally statistically significantly associated with being worn out (OR = 1.44, 95% CI = 0.98-2.13). In the fully adjusted model, reporting PMB three or more times in the prior 6-month window remained associated with lower odds of being full of pep (OR = 0.68, 95% CI = 0.49-0.95).

As a sensitivity analysis, we ran adjusted models with the SF-36 Vitality Scale (sum of all four items) as the outcome. Women with 3+ episodes of HMB or PMB within a 6-month window had lower SF-36 Vitality Scale scores, but 95% CI included the null value (data not shown).

## DISCUSSION

This study is the first, of which we are aware, to longitudinally evaluate the association between HMB and PMB during the MT and women's reports of vitality or fatigue. We found that HMB, specifically HMB occurring at least three times within the prior 6 months, was associated with 40% to 60% increased odds of reporting fatigue (feeling tired or worn out), whereas PMB occurring at least three times within the prior 6-month window was associated with a 32% lower odds of endorsing vitality (being full of pep). These findings persisted after adjusting for several factors that may be related to attributes of bleeding and may contribute to vitality or fatigue, including demographic characteristics, trouble sleeping, symptoms of anxiety and depression, smoking, stress, and discrimination.

Although prior studies have reported an association between the MT and either absence of energy or presence of fatigue, most used a cross-sectional design, and none examined possible etiologies of these symptoms.<sup>25-27</sup> In an Australian cross-sectional comparison, 46% of perimenopausal women, compared with 38% of premenopausal and postmenopausal women, reported having a lack of energy.<sup>25</sup> Similarly, a cross-sectional study from Brazil found that fatigue, the most frequently reported symptom, was more frequent in perimenopausal (81%) than premenopausal (61%) women.<sup>26</sup> In a Nigerian study, physical and mental exhaustion was the second most frequently reported menopause symptom (43%).<sup>27</sup> Prospective examination of longitudinal symptom clusters among SWAN participants revealed that low energy and fatigue symptoms were characteristic of all six identified clusters and were the principal symptoms present in the least symptomatic cluster.<sup>28</sup> None of these studies considered specific risk factors for reporting either absence of energy or presence of fatigue. However, given the higher prevalence of low energy or feeling fatigued among perimenopausal women, and results of the current study documenting higher odds of these symptoms associated with HMB and PMB, it is

**TABLE 1.** Proportion of women reporting heavy or prolonged menstrual bleeding<sup>a</sup> during the 6 months prior to the first follow-up visit and symptoms of fatigue based on the SF-36 scale at the first follow-up visit: The Study of Women's Health Across the Nation (N = 2,329)

Characteristics	n (%)
Heavy bleeding $\geq 3$ d at least once	481 (20.65)
Heavy bleeding $\geq 3$ d at least three times	117 (5.02)
Prolonged bleeding at least once	568 (24.39)
Prolonged bleeding at least three times	107 (4.59)
Feeling tired <sup>b</sup>	620 (26.63)
Feeling worn out <sup>b</sup>	562 (24.16)
Having energy <sup>b</sup>	1,168 (50.24)
Full of pep <sup>b</sup>	1,163 (50.02)

SF-36, 36-item Short Form Health Survey.

<sup>a</sup>Menstrual bleeding was prospectively recorded each day in a monthly menstrual calendar. Heavy menstrual bleeding was defined as bleeding that required changing one's sanitary product every 1 to 2 hours for more than 4 hours during the day for at least 3 days. Prolonged bleeding was defined as bleeding for more than 8 days.

<sup>b</sup>Missing n = 1 for feeling tired, n = 3 for feeling worn out, n = 4 for having energy and full of pep.

**TABLE 2.** Unadjusted and adjusted odds ratios and 95% CI from generalized linear mixed models for associations between four fatigue symptoms and heavy or prolonged menstrual bleeding<sup>a</sup> during the 6 months prior to an annual visit in the Study of Women's Health Across the Nation

	Unadjusted		Adjusted for Demographic Factors, HT and BMI <sup>b</sup>		Fully Adjusted <sup>c</sup>	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Feeling tired	n = 2,328		n = 2,309		n = 2,281	
Any heavy bleeding	<b>1.33 (1.10-1.62)</b>	<b>0.004</b>	<b>1.24 (1.02-1.52)</b>	<b>0.035</b>	1.16 (0.94-1.42)	0.162
Heavy bleeding 3+ times	<b>1.75 (1.21-2.53)</b>	<b>0.003</b>	<b>1.69 (1.16-2.47)</b>	<b>0.007</b>	<b>1.62 (1.11-2.38)</b>	<b>0.014</b>
Any prolonged bleeding	1.01 (0.86-1.20)	0.902	1.00 (0.84-1.19)	0.984	1.04 (0.87-1.24)	0.660
Prolonged bleeding 3+ times	1.19 (0.85-1.66)	0.316	1.22 (0.87-1.72)	0.254	1.31 (0.93-1.84)	0.122
Feeling worn out	N = 2,328		N = 2,309		N = 2,281	
Any heavy bleeding	<b>1.34 (1.10-1.63)</b>	<b>0.004</b>	<b>1.25 (1.02-1.53)</b>	<b>0.031</b>	1.13 (0.92-1.39)	0.247
Heavy bleeding 3+ times	<b>1.67 (1.15-2.41)</b>	<b>0.007</b>	<b>1.50 (1.02-2.20)</b>	<b>0.039</b>	<b>1.44 (0.98-2.13)</b>	<b>0.065</b>
Any prolonged bleeding	0.96 (0.81-1.14)	0.658	0.99 (0.83-1.18)	0.885	1.00 (0.84-1.20)	0.983
Prolonged bleeding 3+ times	1.03 (0.73-1.44)	0.872	1.08 (0.76-1.53)	0.666	1.22 (0.86-1.73)	0.273
Having energy	N = 2,328		N = 2,309		N = 2,281	
Any heavy bleeding	<b>0.78 (0.64-0.95)</b>	<b>0.013</b>	0.84 (0.69-1.04)	0.102	0.89 (0.73-1.10)	0.285
Heavy bleeding 3+ times	0.71 (0.48-1.04)	0.081	0.76 (0.51-1.15)	0.191	0.75 (0.49-1.13)	0.166
Any prolonged bleeding	0.98 (0.84-1.16)	0.846	0.99 (0.84-1.18)	0.939	0.95 (0.80-1.13)	0.578
Prolonged bleeding 3+ times	0.94 (0.68-1.30)	0.694	0.98 (0.70-1.38)	0.904	0.90 (0.64-1.26)	0.530
Full of pep	N = 2,329		N = 2,310		N = 2,281	
Any heavy bleeding	<b>0.81 (0.67-0.99)</b>	<b>0.036</b>	0.87 (0.71-1.07)	0.182	0.94 (0.77-1.16)	0.569
Heavy bleeding 3+ times	0.75 (0.52-1.09)	0.127	0.83 (0.56-1.22)	0.338	0.79 (0.53-1.19)	0.261
Any prolonged bleeding	0.97 (0.82-1.14)	0.683	0.97 (0.82-1.15)	0.743	0.92 (0.78-1.09)	0.348
Prolonged bleeding 3+ times	<b>0.72 (0.52-0.99)</b>	<b>0.040</b>	0.77 (0.55-1.07)	0.114	<b>0.68 (0.49-0.95)</b>	<b>0.026</b>

Bold indicates statistically significant associations.

BMI, body mass index; HT, menopausal hormone therapy; OR, odds ratio.

<sup>a</sup>Menstrual bleeding was prospectively recorded each day in a monthly menstrual calendar. Heavy menstrual bleeding was defined as bleeding that required changing one's sanitary product every 1 to 2 hours for more than 4 hours during the day for at least 3 days. Prolonged bleeding was defined as bleeding for more than 8 days.

<sup>b</sup>Adjusted for age, race/ethnicity, BMI, and hormone therapy use.

<sup>c</sup>Adjusted for age, race/ethnicity, BMI, hormone therapy use, depressive symptoms, anxiety, perceived stress, sleep problems, smoking, and discrimination.

reasonable to hypothesize that excessive bleeding may contribute to these symptoms during the MT. One plausible mechanism of the relationship between AUB and either vitality or fatigue is iron deficiency and iron deficiency anemia, which are well-recognized etiologies of fatigue and are complications of AUB.<sup>7,8,29</sup> Bernardi and colleagues found that African American women who reported having heavy or very heavy menstrual bleeding had significantly lower hemoglobin, hematocrit, and ferritin levels than women who did not report HMB.<sup>11</sup>

This study has some limitations. We did not have sufficient information to permit clinical diagnoses of AUB, nor did we have measures of iron status to link low energy or fatigue directly to anemia. Therefore, we cannot discern whether the observed associations between these symptoms and heavy or prolonged bleeding are mediated, at least in part, by anemia. However, based on our results, we suggest that the evaluation of complaints of low energy or fatigue in midlife women should include inquiry about HMB and PMB and consideration of tests for anemia and iron stores. Nonetheless, this analysis, conducted within a multiracial and ethnic cohort, had several strengths. First, it is one of the first community-based studies of which we are aware to evaluate the association between the experience of PMB and/or HMB during the MT and reports of low energy or fatigue based on prospectively collected, daily

menstrual bleeding records collected during the 6 months prior to each energy/fatigue assessment after accounting for several known risk factors. Second, the broad representation of women of diverse races and ethnicities enhances the generalizability of our findings. Third, the study collected information about a variety of relevant covariates that may contribute to feelings of energy or fatigue in midlife women; we adjusted for these variables to reduce the likelihood of confounding. Finally, SWAN's large sample size provides sufficient statistical power to detect modest but meaningful associations.

### CONCLUSIONS

HMB and PMB during MT were associated with increased likelihood of reporting symptoms of low energy or fatigue. Although these symptoms may be associated with other symptoms of menopause, including sleep problems, pain, and depression, we observed a persistent relationship between AUB and energy/fatigue in these analyses after adjustment for potential confounders. Fatigue as a presenting symptom occurs remarkably frequently in adult women with a long list of possible etiologies and a complicated diagnostic algorithm.<sup>30</sup> Given the increased frequency of AUB as women transition through menopause, greater clinical awareness of bleeding changes during

this life stage, particularly heavy or prolonged bleeding, and associated low energy or fatigue symptoms, is warranted. Quantified measures of AUB are not included in clinical guidelines on diagnosis or management of fatigue, but our findings suggest that a menstrual bleeding history is warranted in midlife women presenting with fatigue symptoms.<sup>31-33</sup> Because iron deficiency and related anemia can be readily treated, their early assessment and remediation in women experiencing AUB during the MT are warranted, consistent with the American College of Obstetricians and Gynecologists treatment guidelines<sup>34</sup> for AUB, and may help alleviate associated symptoms of fatigue during this life stage.

Also, despite their high prevalence and impact on women's quality of life, limited attention has been afforded to bleeding problems during the MT in research, the lay press, and social media.<sup>35-38</sup> Notably, one of the most frequently used scales to assess menopause symptoms in research studies globally, the Menopause Rating Scale,<sup>39</sup> does not include questions about menstrual bleeding. Future studies of menopause should include assessment of AUB and evaluate its potential impact on women's experience of menopause and quality of life. Education of women about the likelihood of excessive menstrual bleeding during MT and its potential health consequences is also warranted.

### Acknowledgments

**Clinical Centers:** University of Michigan, Ann Arbor—Carrie Karvonen-Gutierrez, PI 2021 to present, Siobán Harlow, PI 2011-2021, MaryFran Sowers, PI 1994-2011; Massachusetts General Hospital, Boston, MA—Sherri-Ann Burnett-Bowie, PI 2020 to present; Joel Finkelstein, PI 1999-2020; Robert Neer, PI 1994-1999; Rush University, Rush University Medical Center, Chicago, IL—Imke Janssen, PI 2020 to present; Howard Kravitz, PI 2009-2020; Lynda Powell, PI 1994-2009; University of California, Davis/Kaiser—Elaine Waetjen and Monique Hedderson, PIs 2020 to present; Ellen Gold, PI 1994-2020; University of California, Los Angeles—Arun Karlamangla, PI 2020 to present; Gail Greendale, PI 1994-2020; Albert Einstein College of Medicine, Bronx, NY—Carol Derby, PI 2011 to present, Rachel Wildman, PI 2010-2011; Nanette Santoro, PI 2004-2010; University of Medicine and Dentistry—New Jersey Medical School, Newark—Gerson Weiss, PI 1994-2004; and the University of Pittsburgh, Pittsburgh, PA—Rebecca Thurston, PI 2020 to present; Karen Matthews, PI 1994-2020. **NIH Program Office:** National Institute on Aging, Bethesda, MD—Rosaly Correa-de-Araujo 2020 to present; Chhanda Dutta 2016 to present; Winifred Rossi 2012-2016; Sherry Sherman 1994-2012; Marcia Ory 1994-2001; National Institute of Nursing Research, Bethesda, MD—Program Officers. **Central Laboratory:** University of Michigan, Ann Arbor—Daniel McConnell (Central Ligand Assay Satellite Services). **Coordinating Center:** University of Pittsburgh, Pittsburgh, PA—Maria Mori Brooks, PI 2012 to present; Kim Sutton-Tyrrell, PI 2001-2012; New England Research Institutes, Watertown, MA—Sonja McKinlay, PI 1995-2001.

**Steering Committee:** Susan Johnson, Current Chair; Chris Gallagher, Former Chair

The authors thank the study staff at each site and all the women who participated in SWAN.

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