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Abdominal adiposity and hot flashes among midlife women

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Abstract

Objective—Two competing hypotheses suggest how adiposity may affect menopausal hot flashes. The “thin hypothesis” asserts that aromatization of androgens to estrogens in body fat should be associated with decreased hot flashes. Conversely, thermoregulatory models argue that body fat should be associated with increased hot flashes. The study objective was to examine associations between abdominal adiposity and hot flashes, including the role of reproductive hormones in these associations.

Design—The Study of Women's Health Across the Nation Heart Study (2001-2003) is an ancillary study to the Study of Women's Health Across the Nation, a community-based cohort study. Participants were 461 women (35% African American, 65% white) ages 45 to 58 years with an intact uterus and at least one ovary. Measures included a computed tomography scan to assess abdominal adiposity; reported hot flashes over the previous 2 weeks; and a blood sample for measurement of follicle-stimulating hormone, estradiol, and sex hormone-binding globulin-adjusted estradiol (free estradiol index). Associations were evaluated within multivariable logistic and linear regression models.

Results—Every 1-SD increase in total (odds ratio [OR] = 1.28; 95% CI: 1.06-1.55) and subcutaneous (OR = 1.30; 95% CI: 1.07-1.58) abdominal adiposity was associated with increased odds of hot flashes in age- and site-adjusted models. Visceral adiposity was not associated with hot flashes. Associations were not reduced when models included reproductive hormone concentrations.

Conclusion—Increased abdominal adiposity, particularly subcutaneous adiposity, is associated with increased odds of hot flashes, favoring thermoregulatory models of hot flashes. Body fat may not protect women from hot flashes as once thought.

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Keywords

Hot flashes; Abdominal adiposity; Vasomotor symptoms; Body fat; Central adiposity; Menopause

Approximately 70% of women in the United States experience hot flashes during the menopausal transition[1,2] or episodes of intense heat often accompanied by flushing and sweating.[2] Hot flashes are associated with reported sleep disturbance,[3] negative mood,[4] and impaired quality of life[5] and are a leading determinant of seeking menopause-related medical care during midlife.[6] However, the safety of a leading treatment for hot flashes, hormone therapy (HT), has come into question following the release of the Women's Health Initiative findings,[7] leading to calls for other safe and effective methods for the management of hot flashes.[8] An obstacle to developing other treatments has been the incomplete understanding of the risk factors for and etiology of hot flashes.

It has been proposed that body size and composition can influence the risk of hot flashes. The "thin hypothesis"[9,10] asserts that women with more adipose tissue would have higher circulating estrogen and thus would have a lower risk of hot flashes. Hot flashes are believed to be due in part to declining estrogen levels. With diminished cyclic estradiol (E_2) secretion from the ovary during the menopausal transition,[2] adipose tissue may provide a supplemental source of estrogen due to aromatization of androstenedione to estrone (E_1) and limited conversion of E_1 to E_2 via 17β-hydroxysteroid dehydrogenase. Thus, according to the thin hypothesis, women with more adipose tissue would have a lower risk of hot flashes.

Recent findings showing increased hot flashes among women with higher body mass index (BMI) have called the thin hypothesis into question.[1,11,12] These findings are consistent with thermoregulatory models of hot flashes, emphasizing the altered thermoregulatory functioning observed among symptomatic menopausal women.[13] According to these models, the thermoneutral zone of symptomatic menopausal women is narrowed, small increases in core body temperature are perceived as too hot, and hot flashes are attempts to dissipate heat and reduce core body temperature. Thus, factors that inhibit heat dissipation, such as adiposity, would increase hot flashes. This effect would be particularly apparent for subcutaneous fat, which has potent insulating properties.[14,15]

Despite the critical role of adipose tissue in both the thin hypothesis and thermoregulatory models of hot flashes,[9,10,13] little research has examined the association between body composition and hot flashes. Previous research has been limited to weight or BMI, which does not discriminate between lean and adipose tissue. Thus, the nature of the association between adiposity and hot flashes is unclear.

Our primary aim was to examine associations between abdominal adiposity and hot flashes among African American and white women transitioning through menopause. Consistent with thermoregulatory models, we hypothesized that women with greater abdominal adiposity would be more likely to report hot flashes. We considered total abdominal adiposity and its components: subcutaneous adiposity (adipose tissue between skin and abdominal muscle wall) and visceral adiposity (adipose tissue behind the abdominal muscle wall and in the peritoneal space around internal organs). We hypothesized that the association between adiposity and hot flashes would be strongest for subcutaneous adiposity. Finally, we evaluated evidence of the thin hypothesis, examining associations between reproductive hormones and hot flashes, adiposity and reproductive hormones, and the role of reproductive hormones in the association between adiposity and hot flashes. We considered the hormones most consistently linked to hot flashes: folliclestimulating

hormone (FSH), E_2, and free estradiol index (FEI), the estimate of biologically active E_2.[16,17]

Methods

Study population

The Study of Women's Health Across the Nation (SWAN) is a multiethnic cohort study designed to characterize the biological and psychosocial changes over the menopausal transition. This study was conducted across seven sites in the United States. SWAN participants (N = 3,302) were aged 42 to 52 years at time of enrollment, had an intact uterus and at least one ovary, were not pregnant or breast-feeding, had menstruated within the past 3 months, and were not using oral contraceptives or HT. Details of the study design and recruitment procedures have been previously reported.[18] The baseline SWAN examination occurred in 1996 to 1997. The study was approved by the institutional review board at each site, and each participant provided written informed consent.

A subcohort of women at Pittsburgh and Chicago SWAN sites participated in the SWAN Heart Study, an ancillary study that included computed tomography (CT) for assessment of abdominal adiposity (n = 558). The present analysis is a cross-sectional analysis of SWAN Heart Study data. The SWAN Heart CT assessment occurred once during SWAN study years 4 to 7 (2001-2003) within 3 months following the corresponding annual core SWAN interview and blood draw. By design,[18] Pittsburgh and Chicago sites recruited only non-Hispanic white and African American women; therefore, all enrolled SWAN Heart participants described themselves as either white or African American. All eligible SWAN participants were invited to participate in the SWAN Heart Study, and of these eligible women, 76% enrolled. Exclusions for SWAN Heart included pregnancy; hysterectomy or bilateral oophorectomy; self-reported cardiovascular disease or diabetes; and medications for hypertension, cardiovascular disease, arrhythmias, or HT at the time of enrollment. The majority of enrollment for SWAN Heart occurred in SWAN years 4 to 7. However, because screening and enrollment began at the Pittsburgh site in year 1, by the time of the CT scan in SWAN years 4 to 7, a minority of participants (n = 51) were using HT at the time of the scan.

Of these 558 SWAN Heart participants, 13 women were excluded from this analysis due to having undergone hysterectomy or bilateral oophorectomy, and 77 women were excluded due to missing values on one or more covariates (hot flashes, n = 53; menopausal status, n = 3; anxiety symptoms, n = 8; HT use, n = 3; education; n = 19; nine women had more than one missing value). An additional seven women were excluded for physiologically implausible abdominal adiposity values. Missing smoking data were carried forward from the last completed assessment for one woman. Women with versus women without missing data were more likely to be younger ($P = 0.007$), African American ($P = 0.0009$), and from the Chicago site ($P < 0.0001$). The final sample for evaluation of the primary hypotheses included 461 women (160 African American, 301 white). Analyses including hormonal measures excluded an additional 19 women missing hormonal data.

Design and procedures

Hot flashes—All participants completed an interview, physical examination, blood draw, and questionnaires at the core SWAN baseline and annually thereafter. Hot flashes assessed at the annual core SWAN interview corresponding to the SWAN Heart assessment were used in the present analyses. Participants self-reported the number of days on which hot flashes were experienced (not at all, 1-5 d, 6-8 d, 9-13 d, every day) in the 2 weeks before

the interview. Women were categorized as experiencing any or no hot flashes based upon indication of a threshold effect at any versus no hot flashes.

Abdominal adiposity—Adiposity was measured using an electron beam CT scan taken during the SWAN Heart baseline assessment, occurring within 3 months after the annual core SWAN interview and blood draw. A 6-mm thick transverse image between L4 and L5 was obtained during suspended respiration with a C-150 Ultrafast CT Scanner (GE Imatron, San Francisco, CA). Scans were read by a single reader at the University of Pittsburgh. A pixel range of −30 to −190 Hounsfield units was used to define fat in the scan circumference. The area of adipose tissue was defined using image analysis (AcuImage software, South San Francisco, CA). A region of interest line was drawn at the interior of abdominal musculature along the fascial plane. Fat within this area was considered visceral fat area. The fat area for the entire image was determined, and subcutaneous fat was calculated as the difference between the whole image and visceral fat area. Interobserver reliability was determined by repeat reads performed on 10 scans, revealing intraclass coefficient values of 0.97 and 0.94 for total and visceral fat area, respectively. Abdominal adiposity was correlated with BMI at $r = 0.86$ ($P < 0.0001$) for total adiposity, $r = 0.81$ ($P < 0.0001$) for subcutaneous adiposity, and $r = 0.71$ ($P < 0.0001$) for visceral adiposity.

Reproductive hormones—Concentrations of FSH, E_2, and sex hormone-binding globulin (SHBG) were obtained from a single morning fasting blood sample during the annual core SWAN visit corresponding to the baseline SWAN Heart visit. Participants were scheduled for venipuncture on days 2 to 5 of a spontaneous menstrual cycle. Two attempts were made to obtain a day 2 to 5 sample. If a timed sample could not be obtained, a random fasting sample was taken. A timed sample was obtained for 35% of the sample. Blood was refrigerated before centrifugation 1 to 2 hours after phlebotomy, and the serum was aliquotted, frozen, and batched for shipment to the central laboratory. Samples were catalogued and assayed in a batch monthly on arrival. Assays were performed on the ACS-180 automated analyzer (Bayer Diagnostics Corporation, Tarrytown, NY) using a double-antibody chemiluminescent immunoassay with a solid phase anti-IgG immunoglobulin conjugated to paramagnetic particles, anti/ligand antibody, and competitive ligand labeled with dimethylacridinium ester. The FSH assay is a modification of a manual assay kit (Bayer Diagnostics) using two monoclonal antibodies directed to different regions on the beta subunit, with a lower limit of detection of 1.05 mIU/mL. The E_2 assay modifies the rabbit anti/E2-6 ACS-180 immunoassay to increase sensitivity, with a lower limit of detection of 1.0 pg/mL. The SHBG assay was developed on site using rabbit anti/DHEA-S and anti-SHBG antibodies, with a lower limit of detection of 1.52 μg/dL and 1.95 nM, respectively. Duplicate E_2 assays were conducted with results reported as the arithmetic mean for each participant, with a coefficient of variation of 3% to 12%. All other assays were single determinations. FEI, an estimate of bioavailable E_2, was calculated as $100 \times E_2$ (pg/ mL)/$272.11 \times$ SHBG (nM).[19] The laboratory performing the assays was blinded to adiposity status.

Covariates—Race/ethnicity and educational attainment (years of completed education, categorized into high school, some college/vocational school, college degree or higher) were derived from the baseline SWAN interview. Race/ethnicity was determined in response to the open-ended question: “How would you describe your primary racial or ethnic group?” Age, smoking status (current versus past/never), menopausal status, and anxiety symptoms assessed annually were derived from the annual core SWAN interview corresponding to the SWAN Heart visit. Menopausal status was obtained annually from self-reported bleeding patterns reflecting the year preceding the visit and were categorized as follows: bleeding in the previous 3 months with no change in cycle predictability in the past year was considered

premenopausal, bleeding the previous 3 months with a decrease in cycle predictability in the past year was considered early perimenopausal, less than 12 and more than 3 months of amenorrhea was considered late perimenopausal, and 12 months or more of amenorrhea was considered postmenopausal. Women previously classified as pre- or perimenopausal who reported hormone use (HT or oral contraceptives) since the last study were classified as indeterminate status due to the potential impact of hormone use on bleeding patterns. Women reporting taking hormones within the past 3 months were classified as hormone users. Given the impact of certain antidepressants on hot flashes,[20] antidepressant use (reported use of medications for a nervous condition, eg, sedatives, antidepressants since the last study visit) was also considered as a covariate. Anxiety symptoms, strongly associated with hot flashes,[1,16] were a sum score of the number of days in the past 2 weeks (0 = no days to 4 = every day) reporting irritability or grouchiness, feeling tense or nervous, heart pounding or racing, and feeling fearful for no reason.

Data analysis

Demographic, psychosocial, and medical characteristics associated with hot flashes or adiposity were estimated by *t* tests and χ^2 analyses. Associations between adiposity (total, visceral, subcutaneous) and hot flashes were estimated in three separate logistic regression models. Results are presented with standardized adiposity values to increase interpretability of findings, and thus odds ratios reflect those associated with a 1-SD increase in adiposity. Covariates included age, site, race/ethnicity, educational attainment, menopausal status, smoking status, hormone use, antidepressant use, and anxious symptoms.

Associations between reproductive hormones FSH, E_2, and FEI and hot flashes were estimated with logistic regression. Associations between adiposity and log-transformed FSH, E_2, and FEI measures, considered separately, were estimated with linear regression. Covariates for hormonal models included age, site, race/ethnicity, cycle day of blood draw, education, hormone use, and smoking. Reproductive hormones significantly associated with both hot flashes and adiposity were included in logistic regression models examining associations between adiposity and hot flashes. Effect modification by race/ethnicity and menopausal status were evaluated in all models. Because no significant interactions were observed, interactions were not included in final models. Analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC) and were two sided at $\alpha = 0.05$.

Results

Sample characteristics are presented in Table 1. Consistent with the full SWAN cohort,[1,17] factors significantly associated with reporting hot flashes were age, race/ethnicity, education, menopausal status, anxiety symptoms, FSH, E_2, and FEI. Mean (SD) adiposity levels were 455.3 (195.3) cm^2 for total abdominal adiposity and 121.5 (64.3) cm^2 and 333.7 (150.7) cm^2 for components visceral and subcutaneous adiposity, respectively. African American women had higher total adiposity (mean [SD], African American women: 486.7 [187.8] cm^2 versus white women: 438.6 [197.5] cm^2, $P = 0.01$) and subcutaneous adiposity (African American women: 368.4 [151.3] cm^2 versus white women: 315.4 [147.4] cm^2, $P = 0.0003$), but not visceral adiposity (African American women: 118.3 [53.0] cm^2, white women: 123.2 [69.6] cm^2, *P* = not significant), relative to white women.

Greater total abdominal adiposity was significantly associated with higher odds of reporting hot flashes (Table 2). Examination of components visceral and subcutaneous adiposity indicated that this association was driven by significant associations observed for subcutaneous adiposity. For example, a 1-SD (151 cm^2) increase in subcutaneous adiposity conferred 30% increased odds of hot flashes in an age- and site-adjusted model. These associations remained statistically significant in fully adjusted models. Visceral adiposity

was not significantly related to hot flashes. Examination of mean (SD) adiposity levels by hot flashes confirmed this pattern of results for total (with hot flashes: 479.3 [193.2] cm^2, without hot flashes: 431.9 [194.9] cm^2, $P = 0.008$), subcutaneous (with hot flashes: 351.8 [148.9] cm^2, without hot flashes: 315.4 [150.9] cm^2, $P = 0.008$), and visceral adiposity (with hot flashes: 127.5 [65.9] cm^2, without hot flashes: 116.5 [62.5] cm^2, $P = 0.06$). No significant interactions in the relationship between adiposity and hot flashes by race/ethnicity or by menopausal stage (P values > 0.25) were observed.

Considering evidence of the thin hypothesis, FSH (OR = 1.64; 95% CI: 1.28-2.11) was significantly and positively associated with hot flashes, and E_2 (OR = 0.65; 95% CI: 0.53-0.81) and FEI (OR = 0.73; 95% CI: 0.61-0.89) were significantly and negatively associated with hot flashes in fully adjusted models. Moreover, linear regression models indicated that increased total, subcutaneous, and visceral adiposity was associated with lower levels of FSH and higher levels of FEI (Table 3). Inclusion of FSH and FEI, the hormones significantly related to adiposity and hot flashes, failed to diminish the positive association between adiposity and hot flashes (Table 4). For example, when FSH and FEI were added to fully adjusted models, every 1-SD (151 cm^2) increase in subcutaneous adiposity was associated with a 37% and 33% increased odds of hot flashes, respectively.

Discussion

These findings challenge standard thinking that thinner women, or those with less body fat, are at increased risk of hot flashes. The present findings demonstrated that women with increased abdominal adiposity, and particularly subcutaneous abdominal adiposity, were more likely to report hot flashes. Because previous research has solely considered BMI, which does not measure adipose tissue, these findings provide stronger evidence against the thin hypothesis. Together with findings with BMI,[1,11,12] they suggest the potential importance of considering obesity, and subcutaneous adiposity in particular, as a risk factor for hot flashes.

The overall association between abdominal adiposity and hot flashes was positive, consistent with thermoregulatory models of hot flashes. We also evaluated the contribution of reproductive hormones, recognizing that these concentrations reflect the contribution of estrogen from the ovary rather than aromatization of androstenedione from adipose tissue, limiting conclusions about peripheral production. However, we are operating under the assumption that these measures are a fair approximation of the total estrogen contribution because 70% of women are not postmenopausal and E_2 is a more potent estrogen than E_1. Although FSH and FEI were associated with both adiposity and hot flashes, adjusting for these hormones failed to attenuate the association between abdominal adiposity and hot flashes. Further investigation with more complete hormonal assessment is warranted. However, these findings suggest that although abdominal adipose tissue may have both thermoregulatory and endocrine properties, the insulating properties of adipose tissue may be more strongly related to hot flashes.

Thermoregulatory models of hot flashes conceptualize hot flashes as attempts to dissipate heat in the context of a narrowed thermoneutral zone.[13] The observation that positive associations between abdominal adiposity and hot flashes were most pronounced for subcutaneous fat is consistent with these models. The potent insulating properties of subcutaneous fat are well known, with evidence indicating that it insulates three times as well as muscle.[14] Moreover, in these investigations, the amount of heat dissipated is inversely related to subcutaneous adipose tissue thickness.[15] Thus, increased subcutaneous adiposity would prevent the heat-dissipating action of hot flashes and require more hot flashes to achieve requisite heat loss.[13]

The adiposity values obtained here are consistent with what would be expected of a multiethnic community sample of women in this age range.[21-26] However, it is notable that large community-based studies that include CT-assessed abdominal adiposity in a sample of African American and white midlife women are few. In the present investigation, a differential distribution of adiposity was observed between racial/ethnic groups, with proportionately lower contribution of visceral to total adiposity levels among African American relative to white women. This finding is consistent with previous investigations.[26-28]

There is considerable interest in behavioral interventions for hot flashes. For example, aerobic exercise has been suggested as one initial approach to managing hot flashes.[29] However, associations between exercise and hot flashes have been highly inconsistent,[30-32] and randomized trials are few. In light of the present findings, interventions focused on fat reduction for the management of hot flashes may deserve further investigation. These interventions may be particularly important during a period of life characterized by progressive increases in adiposity,[33] including abdominal adiposity.[34]

The present findings should be interpreted in the context of several limitations. First, SWAN Heart participants underwent a single annual blood draw, which, given the hormonal fluctuations during perimenopause, is a less optimal measure than daily hormone assessments. This method may have increased error and biased findings to the null. However, significant associations were observed for hormonal measures in relation to both adiposity and hot flashes. Second, this study included assessment of abdominal adiposity rather than total adiposity. The relationship between total adiposity and hot flashes cannot be determined from this study. Third, this study was a cross-sectional analysis, limiting conclusions about the causal nature of associations and how the observed associations may change over time, including later in postmenopause. Fourth, not unlike most epidemiologic investigations, hot flashes were measured via a brief self-report instrument that yields limited information about hot flashes. Compared with physiologic measures, reported hot flashes may be influenced by factors such as mood and affect.[35] However, controlling for anxious symptoms, strongly related to hot flashes,[1,16] did not reduce these associations. Finally, this study included African American and white women. Whether these findings extend to other groups is unknown.

Conclusions

This study has several notable strengths. It is the first to examine associations between abdominal adiposity and hot flashes, providing the strongest evidence to date that the association between abdominal adiposity and hot flashes is positive. This study evaluated how subtypes of adiposity, such as visceral versus subcutaneous abdominal adiposity, may show differential associations with hot flashes. Moreover, these results can help to provide further evidence in support of key etiologic models, such as thermoregulatory models of hot flashes. Should these results be replicated, they may point to promising interventions, such as fat loss, for the prevention and management of hot flashes. Finally, clinicians treating menopausal symptoms should not presume that obese women escape debilitating hot flashes.

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TABLE 1

Participant characteristics by reported hot flashes

	Reporting hot flashes (n = 217)	Not reporting hot flashes (n = 244)	*P*
Age, mean (SD), y	50.8 (2.9)	50.0 (2.8)	0.001
Site, n (%)			
Chicago	125 (57.6)	126 (51.6)	0.20
Pittsburgh	92 (42.4)	118 (48.4)	
Race, n (%)			
White	129 (59.5)	172 (70.5)	0.01
African American	88 (40.5)	72 (29.5)	
Menopausal status, n (%)			
Premenopausal	9 (4.2)	35 (14.4)	<0.0001
Early perimenopausal	78 (35.9)	132 (54.1)	
Late perimenopausal	29 (13.4)	21 (8.6)	
Postmenopausal	91 (41.9)	44 (18.0)	
Indeterminate[a]	10 (4.6)	12 (4.9)	
Education, n (%)			
High school	37 (17.1)	37 (15.2)	0.01
Some college/vocational	80 (36.9)	62 (25.4)	
College/grad school	100 (46.1)	145 (59.4)	
Anxious symptoms, mean (SD)	2.3 (2.0)	1.9 (1.9)	0.02
Smoker, n (%)			
Yes	38 (17.5)	36 (14.8)	0.42
No	179 (82.5)	208 (85.2)	
Antidepressant use, n (%)			
Yes	22 (10.1)	39 (16.0)	0.06
No	195 (89.9)	205 (84.0)	
HT use, n (%)			
Yes	24 (11.1)	27 (11.1)	0.99
No	193 (88.9)	217 (88.9)	
BMI	29.8 (6.1)	28.4 (6.1)	0.02
FSH, mean (SD), mIU/mL[b]	67.3 (50.3)	38.7 (34.7)	<0.0001
E_2, mean (SD), pg/mL[b]	47.4 (70.5)	82.4 (104.2)	<0.0001
SHBG, mean (SD), nM[b]	47.8 (29.1)	49.4 (28.9)	0.50
FEI, mean (SD)[b]	0.5 (1.3)	1.0 (2.6)	<0.0001

HT, hormone therapy; BMI, body mass index; FSH, follicle-stimulating hormone; E_2, estradiol; SHBG, sex hormone/binding globulin; FEI, free estradiol index.

[a] Women previously classified as pre- or perimenopausal who reported HT use since the last study visit.

[b] Statistical comparisons conducted with transformed FSH (log), E_2 (log), FEI (log), and SHBG (square root) values.

TABLE 2

Odds ratios of hot flashes associated with three measures of abdominal adiposity

	Odds ratio (95% CI)[a]	
	Model 1	**Model 2**
Total abdominal adiposity	1.28 (1.06-1.55)[b]	1.24 (1.01-1.52)[b]
Visceral	1.15 (0.95-1.39)	1.15 (0.93-1.41)
Subcutaneous	1.30 (1.07-1.58)[c]	1.26 (1.02-1.55)[b]

Model 1: Adjusted for age and site.

Model 2: Adjusted for age, site, race/ethnicity, education, smoking, menopausal status, hormone use, antidepressant use, anxious symptoms.

[a] Odds ratios correspond to every 1-SD increase in adiposity.

[b] $P < 0.05$.

[c] $P < 0.01$.

TABLE 3

Associations between reproductive hormones and three measures of abdominal adiposity

	FSH (log)		E_2 (log)		FEI (log)	
	b	***P***	***b***	***P***	***b***	***P***
Total abdominal adiposity	−0.12	0.003	−0.07	0.19	0.14	0.01
Visceral	−0.11	0.008	−0.08	0.11	0.14	0.009
Subcutaneous	−0.12	0.005	−0.05	0.30	0.12	0.03

FSH, follicle-stimulating hormone; E_2, estradiol; FEI, free estradiol index. Adjusted for age, site, race/ethnicity, education, smoking, hormone use, and cycle day of blood draw.

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TABLE 4

Odds ratios of hot flashes associated with abdominal adiposity adjusted for reproductive hormones

	Odds ratio (95% CI)[a]	
	Model 1 (+ FSH)	**Model 2 (+ FEI)**
Total abdominal adiposity	1.35 (1.09-1.69)[b]	1.32 (1.06-1.64)[c]
Visceral	1.21 (0.98-1.51)	1.20 (0.97-1.49)
Subcutaneous	1.37 (1.09-1.71)[b]	1.33 (1.07-1.66)[c]

FSH, follicle-stimulating hormone; FEI, free estradiol index.

Model 1: Adjusted for age, site, race/ethnicity, education, smoking, hormone use, antidepressant use, anxious symptoms, cycle day of blood draw, FSH.

Model 2: Adjusted for age, site, race/ethnicity, education, smoking, hormone use, antidepressant use, anxious symptoms, cycle day of blood draw, FEI.

[a] Odds ratios correspond to every 1-SD increase in adiposity.

[b] $P < 0.01$.

[c] $P < 0.05$.