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Presence of vasomotor symptoms is associated with lower bone mineral density:

a longitudinal analysis

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Abstract

Objective—To determine whether women with vasomotor symptoms (VMS) have lower bone mineral density (BMD) than women without VMS.

Design—We analyzed data from baseline to annual follow-up visit 5 for 2213 participants in the bone substudy of the Study of Women's Health Across the Nation. At baseline, women were aged 42 to 52 years, had intact uterus and ≥1 ovary, were not using exogenous hormones, were not pregnant or lactating, and were pre- or early perimenopausal. Menopausal stage and VMS were assessed by annual questionnaire. Menopausal stages were premenopausal, early perimenopausal, late perimenopausal, and postmenopausal. Using repeated measures mixed models, we determined the association between VMS (any vs. none) and BMD (by dual x-ray absorptiometry) within each menopause status category.

Results—After controlling for age, time within each menopausal stage, race/ethnicity, study site, and baseline menopause stage, postmenopausal women with any VMS had lower lumbar (0.008g/cm^2 lower, P=0.001) and lower total hip (0.005 g/cm^2 lower, P=0.04) BMD than postmenopausal women without VMS. Compared to early perimenopausal women without VMS, early perimenopausal women with any VMS had lower femoral neck BMD (0.003g/cm^2 lower, P=0.0001). Premenopausal women with any VMS had lower femoral neck BMD (0.003g/cm^2 lower, P=0.03), compared to premenopausal women without VMS.

Conclusions—Even in the earliest menopause transition stages, women with VMS had lower BMD than women without VMS. Effects varied by anatomical site, being most evident in postmenopausal women at the lumbar spine and total hip, and among premenopausal and early perimenopausal women at the femoral neck.

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Conflict of Interest
All authors have no conflicts of interest.

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Keywords

Menopause; hot flashes; vasomotor symptoms; bone mineral density

Introduction

Hot flashes occur among most women undergoing the menopause transition and increase in prevalence over the menopause transition [1]. They are experienced by approximately 20% of premenopausal women and peak in prevalence at approximately 60% in the late perimenopause [1]. Whether menopausal hot flashes and night sweats, jointly termed vasomotor symptoms (VMS), may be indicative of adverse bone health is largely unknown [2].

During the late perimenopause, when VMS prevalence peaks, lumbar spine and total hip bone mineral density (BMD) are decreasing [3]. We therefore hypothesized that VMS may be associated with lower BMD in women undergoing the menopause transition. Although not all studies have found an association between a decline in estradiol levels and VMS [4] VMS have been associated with a decline in estradiol levels in some studies [5, 6]. Because low serum estradiol levels may also be associated with low BMD [7, 8], we theorized that VMS might provide information regarding BMD level beyond that conveyed by menopause status alone. Of particular interest was whether a subset of midlife women who had not yet become postmenopausal but were nonetheless at risk of having low BMD could be identified by assessment of the presence of VMS, which are easily assessable in clinical practice.

Studies of the VMS-BMD association have not prospectively followed women as they undergo the menopause transition; rather, they have mostly focused on women many years after their menopause transitions [9-12]. The two studies in younger women were of short duration [13, 14], did not assess BMD at the lumbar spine or hip [13], or analyzed sweating but not hot flash symptoms *per se* [13]. To determine whether VMS are associated with BMD in younger women, and to determine if the association might differ according to stage of the menopause transition (pre-, early peri-, late peri-, and post-menopause), we analyzed the association between VMS and BMD from the Study of Women's Health Across the Nation, a large prospective study of women undergoing the menopause transition.

Materials and Methods

Study Sample

We used data from the Study of Women's Health Across the Nation (SWAN) study, a prospective study characterizing health status across the menopause transition in a multi-racial/ethnic community-based cohort of 3302 women. Recruitment strategy and eligibility criteria have been described in detail elsewhere [15]. Participants were aged 42-52 years at baseline, had an intact uterus, had at least one intact ovary, were not currently using exogenous reproductive hormones, were not pregnant or lactating, and had experienced at least one menstrual period in the 3 months preceding the baseline visit. In addition to recruiting Caucasian women, each of the 7 study sites recruited women of another ethnic group: African American women (Boston, Massachusetts; Chicago, Illinois; Pittsburgh, Pennsylvania; Detroit, Michigan), Hispanic women (Hudson County, New Jersey), Chinese women (Oakland, California), and Japanese women (Los Angeles, California). The SWAN bone substudy, which measured BMD annually, consisted of Caucasian, African American, Chinese, and Japanese women recruited at 4 of the SWAN sites: Boston, Pittsburgh, Detroit, Oakland, and Los Angeles Study. The study was approved by each study site's institutional review board, and written informed consent was obtained from each participant.

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For this study, we analyzed data spanning baseline through annual visit 5 from participants of the SWAN bone substudy who underwent at least one BMD measurement and at least one contemporaneous assessment of hot flashes and night sweat symptoms during the observation period. To clearly characterize the VMS-BMD association prospectively across the stages of menopause, during follow-up we censored women at the time they reported having hysterectomy, bilateral oophorectomy, or pregnancy/breastfeeding. We also excluded women taking medications that might influence bone density (corticosteroids, alendronate, etidronate, raloxifene, calcitonin, or calcitriol) and women taking exogenous hormones by censoring them starting at the time they first reported taking the exclusionary medications, resulting in an analytic sample of 2213 participants.

Bone Mineral Density Measurements

Lumbar spine, total hip, and femoral neck BMD was measured at baseline and annually using Hologic (Hologic, Inc., Bedford, MA) 2000 (Pittsburgh and Oakland sites) or 4500A (Boston, Detroit, and Los Angeles sites) densitometers. Reproducibility of hip measurements was optimized using Osteodyne (Research Triangle Park, NC) positioning devices [16]. At all study sites, quality control measures consisted of daily anthropomorphic spine phantoms, cross-site and cross-time calibration with a Hologic spine phantom, and an on-site review of all scans according to pre-designated criteria. Five percent of scans, as well as scans with potential problems, were reviewed by Synarc, Inc. (Waltham, MA), resulting in a designation of each scan as acceptable, requiring reanalysis, or rejected [3].

Serum Estradiol and Follicle-Stimulating Hormone (FSH) Measurements

In women who were not postmenopausal, a fasting blood samples was obtained annually in the 2- to 5-day window of the early follicular phase of the menstrual cycle [3]. If irregular menstrual cycles precluded an early follicular phase blood draw, blood sampling was performed without respect to the timing of menstrual bleeding. Estradiol was assayed using a semi-automated, competitive ACS:180 (e2-6) Immunoassay [17]. At an estradiol level of 50 pg/mL, the inter-assay coefficient of variation was 10.6% and the intra-assay coefficient of variation was 6.4% [3]. Serum FSH concentrations were measured with a 2-site chemiluminometric immunoassay [3]. The assay used two monoclonal antibodies, each directed to different regions on the FSH beta-subunit. For the FSH assay, the inter-assay coefficient of variation was 6.0%, and the intra-assay coefficient of variation was 12.0% at an FSH level of 15 IU/L [3]. Blood samples were taking in the early follicular phase in 84% of premenopausal, 75% of early perimenopausal, and 6% of late perimenopausal participants.

Questionnaire-based and Anthropometric Measurements

At baseline and at each annual follow-up visit, women completed a questionnaire that included a symptom checklist. The symptom checklist was worded as follows: “Below is a list of common problems which affect us from time to time in our daily lives. Thinking back over the past two weeks, please circle the number corresponding to how often you experienced any of the following”. Response choices were not at all, 1-5 days, 6-8 days, 9-13 days, or every day. For each visit, we classified women who had hot flashes or night sweats as having *vasomotor symptoms (*VMS). We classified women with VMS for 6 or more days in the past 2 weeks as having *frequent VMS*.

Baseline and annual follow-up questionnaires served as the source of information regarding age, ethnicity, current medication use, and current menopause status. We defined *exogenous hormone therapy* as estrogen pills, progestin pills, progesterone pills, estrogen patches, birth control pills, estrogen injections, tamoxifen pills, diethyl-stilbesterol pills, progestin injection, fertility medications, hormone creams or hormone suppositories. *Menopausal status* was defined as follows based on self-reported menstrual cycle characteristics recalled over the past

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year: premenopausal (menstruation in the past 3 months with no change in menstrual regularity in past year), early perimenopausal (menstruation in past 3 months with decreased regularity in past year), late perimenopausal (no menses for 3-11 months), and postmenopausal (no menses for past 12 months.

At baseline and at each annual follow-up visit, height and weight were measured using calibrated electronic or balance beam scales and stadiometers.

Statistical Analysis

For baseline and each annual follow-up visit, we assessed the mean lumbar spine, total hip, and femoral neck BMD, prevalence of VMS, and menopausal stage. We estimated the duration of time each women spent in each menopause stage category using an algorithm that took into account self-reported menopause stage at each annual interview (Finkelstein et al, submitted for publication).

We performed repeated measures mixed models with BMD of each anatomical site (lumbar spine, total hip, and femoral neck) as the outcome. For the main exposure, for each visit, we created an index that accounted for whether the participant reported having VMS (any vs. none in the past 2 weeks) as well as her menopausal status (premenopausal, early peri-, late peri-, or post-menopausal). The resulting 8 categories for the main exposure variable were: premenopausal without VMS, premenopausal with VMS, early perimenopausal without VMS, early perimenopausal with VMS, late perimenopausal without VMS, late perimenopausal with VMS, postmenopausal without VMS, and duration of being postmenopausal with VMS. Using the 8-category main exposure variable, we performed two sets of repeated measures mixed models. In the first set of models, we controlled for baseline age, cumulative time spent in each menopausal stage, baseline VMS, baseline menopausal status, race/ethnicity, and study site. In the second set of models, we additionally controlled for baseline weight, baseline height, and change in weight since baseline. Finally, we repeated the models to account for frequency of VMS as the main exposure by using a similar 8-category indicator for frequent VMS (≥6 days vs. ≤5 days in past 2 weeks) within each menopausal stage. While we controlled for the main effect of race/ethnicity, we did not explore effect modification by race/ethnicity, as we had no reason to believe that the association between VMS and BMD would vary by race/ethnicity, and adding the effect modification term to the models would reduce our power to detect the association of interest.

In secondary analyses, we explored the role of circulating estradiol and FSH in the association between VMS and BMD, we sequentially added log-transformed baseline and follow-up serum estradiol and FSH levels and an indicator of whether each serum sample was taken outside of the 2-5-day follicular phase window to the repeated measures mixed models described above. All analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

Characteristics of the Participants

After censoring participants at the time they reported hysterectomy, bilateral oophorectomy, pregnancy, breastfeeding, or use of medications influencing BMD, the analytic sample consisted of 2213 women who had complete information regarding at least 1 BMD measurement at any anatomical site of interest and at least 1 concurrent VMS assessment (Table 1). Compared to the participants of the SWAN Bone Substudy sites who were excluded from our analytic sample, the participants comprising the analytic sample were significantly less likely to have prior fracture since age 20 (18% vs. 27%, p=0.0007) or to have anorexia or bulimia (1% vs. 3%, p=0.02); they also had lower BMI (28 vs. 32 kg/m^2, p<0.0001)(data not

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shown). However, the prevalence of smoking and alcohol consumption, ethnicity, menopause status, and family history of osteoporosis was not different in included vs. excluded participants. Because SWAN is a prospective study of women undergoing the menopause transition, no women were late perimenopausal or postmenopausal at baseline (Table 2). Participants were on average 46 years-old at study entry. The ethnic composition of the analytic sample was as follows: 28% African American, 49% Caucasian, 11% Chinese, 12% Japanese (Table 2). The proportions of women with frequent VMS over the 5 years of follow-up ranged 4.6%-9.3% among premenopausal women, 13%-15% among early perimenopausal women, 30%-39% among late perimenopausal women, and 31%-36% among postmenopausal women (Table 3).

Association between Presence of any VMS and BMD

In models adjusted for baseline age, cumulative time in each menopausal stage, race/ethnicity, study site, and baseline menopause stage, BMD was consistently lower among women with any VMS than among women without VMS, regardless of menopausal stage. The pattern of lower BMD among women with any VMS compared to women without VMS persisted after further adjustment (for baseline height, baseline weight, and change in weight since baseline), was present at all menopausal stages, and was apparent at all three anatomical BMD sites. However, the anatomical BMD site at which the relation between BMD and VMS was statistically significant varied according to menopausal stage. Among postmenopausal women, BMD was statistically significantly lower among women with VMS than among women without any VMS at the lumbar spine (0.008 g/cm^2 lower, p=0.001) and at the total hip (0.005 g/cm^2 lower, p=0.008)(data not shown). In contrast, among early perimenopausal women and among premenopausal women, the difference in BMD between women with VMS and women without VMS was statistically significant at the femoral neck (premenopausal women 0.003 g/cm^2 lower with VMS vs. without VMS, p=0.03; early perimenopausal women 0.003 g/cm^2 lower with VMS vs. without VMS, p=0.0001)(data not shown).

The patterns of lower BMD among women with VMS compared to without VMS, and the patterns by anatomical site and menopause stage, persisted after additional adjustment for baseline height, baseline weight, and change in weight since baseline (the final model.)

We compared BMD among women with and without VMS after adjustment for baseline age, cumulative time in each menopausal stage, ethnicity, and study site. Differences in mean BMD among women with, compared to women without, VMS, were apparent at the lumbar spine, total hip, and femoral neck, and depended on menopausal stage (Figure 1). For example, compared to postmenopausal women without VMS, postmenopausal women with VMS had significantly lower BMD at the lumbar spine (1.043 g/cm^2 vs. 1.051 g/cm^2, p<0.05) and total hip (0.941 g/cm^2 vs. 0.946 g/cm^2, p<0.05)(Figures 1a, 1b). Compared to premenopausal women without VMS, premenopausal women with VMS had significantly lower femoral neck BMD (0.833 g/cm^2 vs. 0.836 g/cm^2, p <0.05) (Figure 1c). Compared to early perimenopausal women without VMS, early perimenopausal women with VMS had significantly lower femoral neck BMD (0.833 g/cm^2 vs. 0.837 cm^2, p<0.05)(Figure 1c).

Association between Frequent vs. Infrequent VMS and BMD

We also compared BMD among women with frequent VMS compared to women without frequent VMS. In models adjusted for baseline age, cumulative time in each menopausal stage, ethnicity, study site, baseline menopause status, baseline height, baseline weight, and weight change since baseline, BMD was consistently lower among women with frequent VMS than among women without frequent VMS. Lumbar spine BMD was statistically significantly lower among women with frequent VMS compared to women without frequent VMS among early perimenopausal women (0.004 g/cm^2 lower, p=0.003) and among postmenopausal women

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(0.006 g/cm^2 lower, p=0.01). Among early perimenopausal women, femoral neck BMD was significantly lower in women with frequent VMS compared to women without frequent VMS (0.003 g/cm^2 lower, p=0.02). Among early perimenopausal women, the difference in total hip BMD among women with frequent VMS compared to women without frequent VMS was not statistically significant.

Secondary analyses

To explore a possible role of circulating estradiol and/or FSH in the association between VMS and BMD, we added baseline and follow-up serum estradiol levels, as well as an indicator of whether each serum sample was taken outside of the 2-5-day follicular phase window, to our final repeated measures mixed models. The association between VMS and BMD was somewhat weakened by addition of the estradiol parameters, although the difference in mean femoral neck BMD between women with VMS compared to women without VMS remained the same before and after adjustment for current serum estradiol levels in premenopausal women and early perimenopausal women (data not shown). Further adjustment for FSH level did not appreciably influence the results.

Discussion

In this large prospective study of women undergoing the menopause transition, BMD was lower among women with VMS compared to without VMS, and effects varied by menopause stage. Among premenopausal and early perimenopausal women, women with VMS had lower femoral neck BMD than women without VMS, whereas among postmenopausal women, women with VMS had lower lumbar spine and total hip BMD than postmenopausal women without VMS. We also found that BMD was lower among women with frequent VMS than among women without frequent VMS; this effect was apparent at the lumbar spine among postmenopausal and early perimenopausal women, and at the femoral neck among early perimenopausal women.

Only two prior studies of middle-aged women have focused on the VMS-BMD association; the results of the prior studies are generally consistent with our study results. In the first study, focused on women 45 years old and older (average age 51 years), the rate of forearm BMD loss over 2 years was greater among women with current “frequent sweating” (≥5 times daily) than women reporting no current sweating [13]. Sweating remained an independent predictor of the rate of BMD loss, even after adjustment for serum estradiol level [13]. The study did not assess lumbar spine or hip BMD, complicating comparison with our study. In the second study, focused on premenopausal women 44 to 50- years-old, baseline total hip and lumbar spine BMD were significantly lower among women with current hot flashes compared to women without current hot flashes [14]. In addition, presence of any current menopausal symptom (hot flashes, irregular duration between menstrual cycles, irregular duration of menstrual bleeding) was associated with higher rate of lumbar spine bone loss over 30 months compared to asymptomatic women, although the presence of hot flashes alone did not predict rates of lumbar or hip bone loss [14]. The longer duration of follow-up and the larger sample size in our study compared to the prior study may have enhanced our statistical power to detect the VMS-BMD association at multiple sites. Neither previous study compared the VMS-BMD association among women in different menopausal stages. Additional support for a VMS-BMD association in middle-aged women comes from a study of young infertile women showing that women with VMS had lower BMD and higher bone turnover than women without VMS [18].

A few prior studies focused on older women much beyond the menopause transition and generally did not find a significant association between VMS and BMD or between VMS and fracture [10-12]. One case-control study of older women found that significantly more women with vertebral osteoporosis (low BMD and/or vertebral fracture) remembered ever having

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VMS at the time of menopause compared to women without vertebral osteoporosis [9]. However, the VMS-BMD and VMS-fracture associations may be different in older women than in younger women. Moreover, with one exception [12], the studies of older women retrospectively assess VMS many years (often decades) after the VMS actually occurred, introducing potential for inaccurate recall [9-11].

Several possible mechanisms might be involved in the association of VMS with BMD. First, the presence of VMS may indicate more advanced menopausal transition stage, and in this way be linked to low BMD. However, the experience of hot flashes adds no information beyond hormonal and bleeding criteria in classifying menopause transition stage [19, 20]. Second, the relation between VMS and BMD may be mediated by low estradiol levels. Although low serum estradiol levels are suspected to be a risk factor for low BMD [7], a few studies have found no link between presence of VMS and low serum estradiol levels e.g.[21-24]. Furthermore, estradiol levels do not substantially decline until late in the perimenopause [25, 26], and may actually increase in some women in the early perimenopause [27-29]. Thus, our finding of a VMS-BMD association in early perimenopausal women suggests that the mechanisms underlying the VMS-BMD association are likely to be more complex than an isolated measure of low serum estradiol level. Indeed, although adjustment for concurrent estradiol levels somewhat weakened the association we found between VMS and BMD, the association between VMS and BMD remained unaltered and statistically significant at the femoral neck in pre- and early peri-menopausal women after adjustment for estradiol levels. A third possible pathway linking VMS and BMD is the sympathetic nervous system. Increases in epinephrine levels may precede hot flashes [30], and brain norepinephrine metabolites increase during hot flashes [31]. In animal studies, sympathetic nervous system activation has deleterious effects on BMD. For example, in mice, chronic stress-associated bone loss is associated with increases in norepinephrine levels [32]. The bone loss is prevented by medication (propranolol) that blocks sympathetic nervous system activation [32]. Finally, cortisol may be a candidate as a VMS-BMD mediating factor. Serum cortisol levels may increase after hot flashes [33, 34]. Women with VMS might therefore have greater overall cortisol exposure, which has well-established adverse effects on BMD [35].

Our study had several strengths, including a large sample size, ability to observe VMS and BMD longitudinally, comparison across menstrually-defined menopause stages, and measurement of BMD at several key anatomical sites under stringent quality control. We also accounted for possible confounding due to exogenous hormonal medication by censoring women at the time they first reported using exogenous hormone therapy. This is important because women with VMS are more likely to use exogenous estrogen therapy (which is also associated with higher BMD) [11].

Our study has limitations. First, SWAN did not collect daily VMS diaries which could have taken into account VMS severity, duration, and bothersomeness. However, we expect that our method of VMS assessment (via annual questionnaire, which is frequently used in longitudinal studies of VMS) would have conservatively biased VMS reporting. Second, whereas we found several statistically significant results in comparing women with any VMS vs. women without any VMS, we observed fewer statistically significant results when we compared women with frequent VMS vs. women without frequent VMS. The smaller numbers of women with frequent VMS may have led to reduced statistical power to detect statistically significant differences. Third, because the correlates of VMS are not yet well-elucidated, confounding by unknown variables remains a possibility, despite our having adjusted for age, race/ethnicity, weight, and weight change. Fourth, our results cannot be generalized to pregnant women or women using exogenous hormone therapy, women who were excluded from our analysis. Finally, it is possible that participant dropout may have biased our results. Although women with VMS were statistically significantly more likely to drop out than women without VMS, spine BMD

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was (not statistically significantly) positively related to dropout. In addition, we controlled for concurrent VMS, a predictor of subsequent VMS, likely reducing bias related to dropouts.

In conclusion, women with VMS have lower BMD than women without VMS, and the anatomical BMD site at which differences in BMD are manifest varies according to menopause stage. The presence of VMS may predict lower BMD not only in postmenopausal women, but also in premenopausal and perimenopausal women. Future longitudinal studies should focus on neurobiological pathways linking VMS and BMD.

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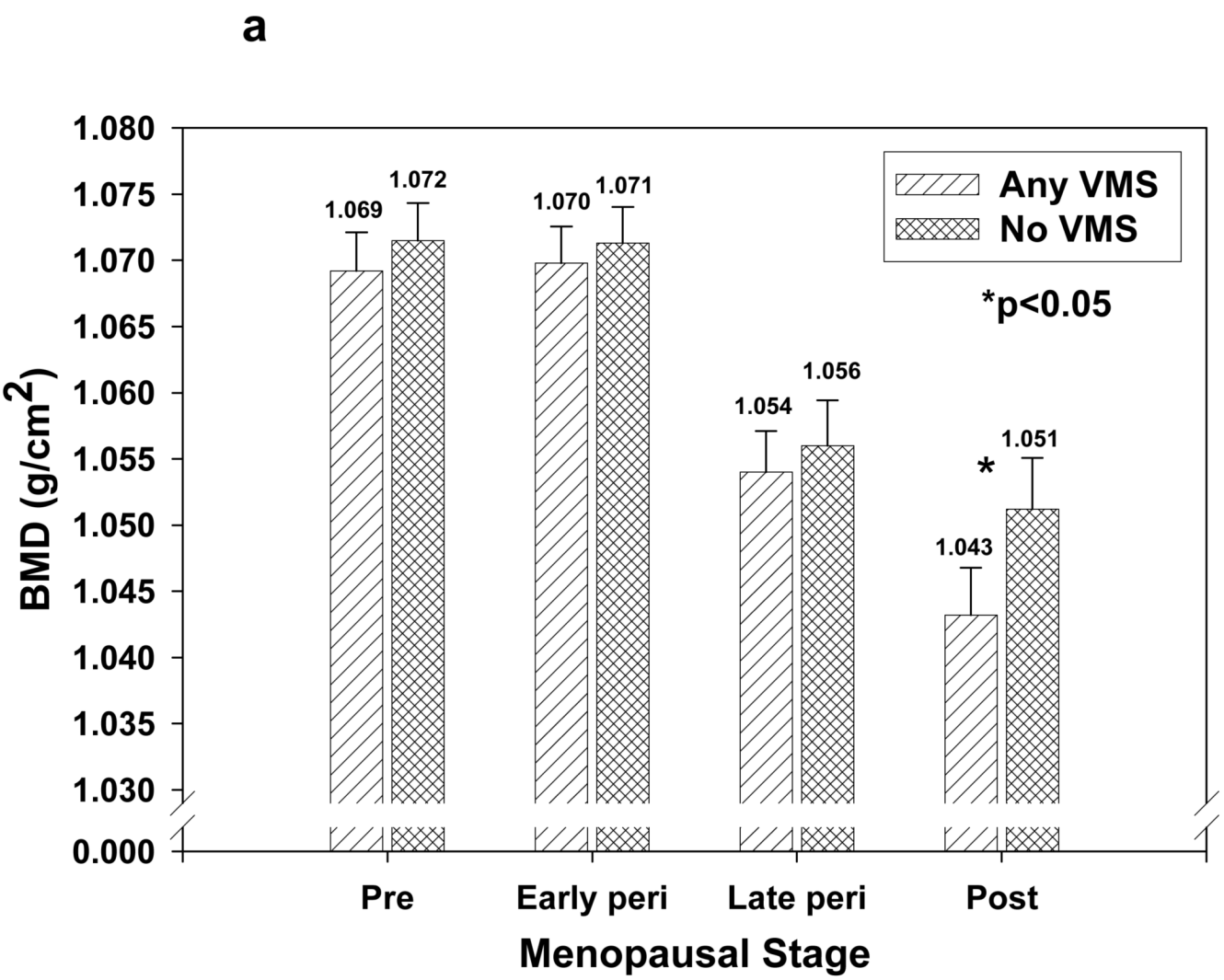

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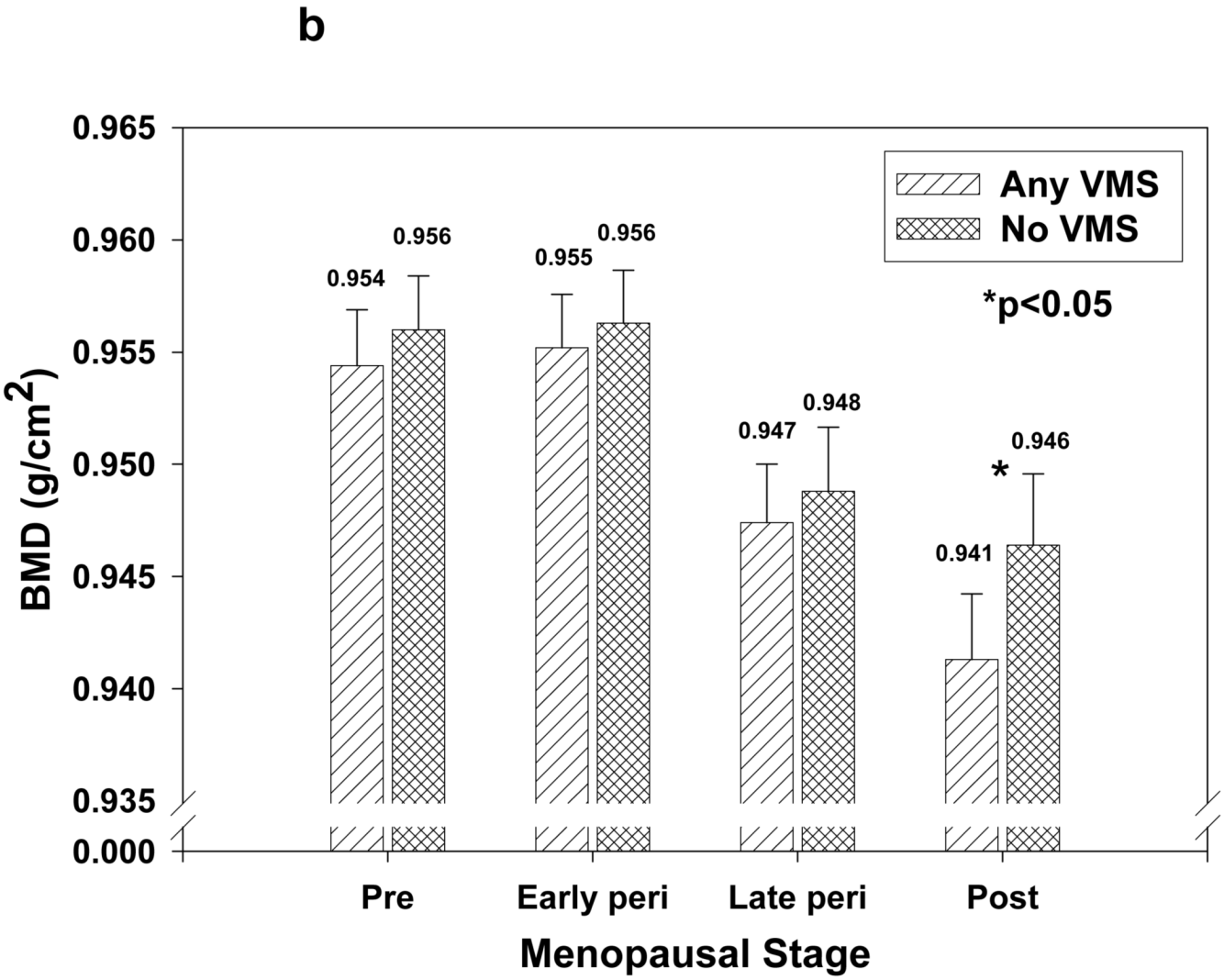

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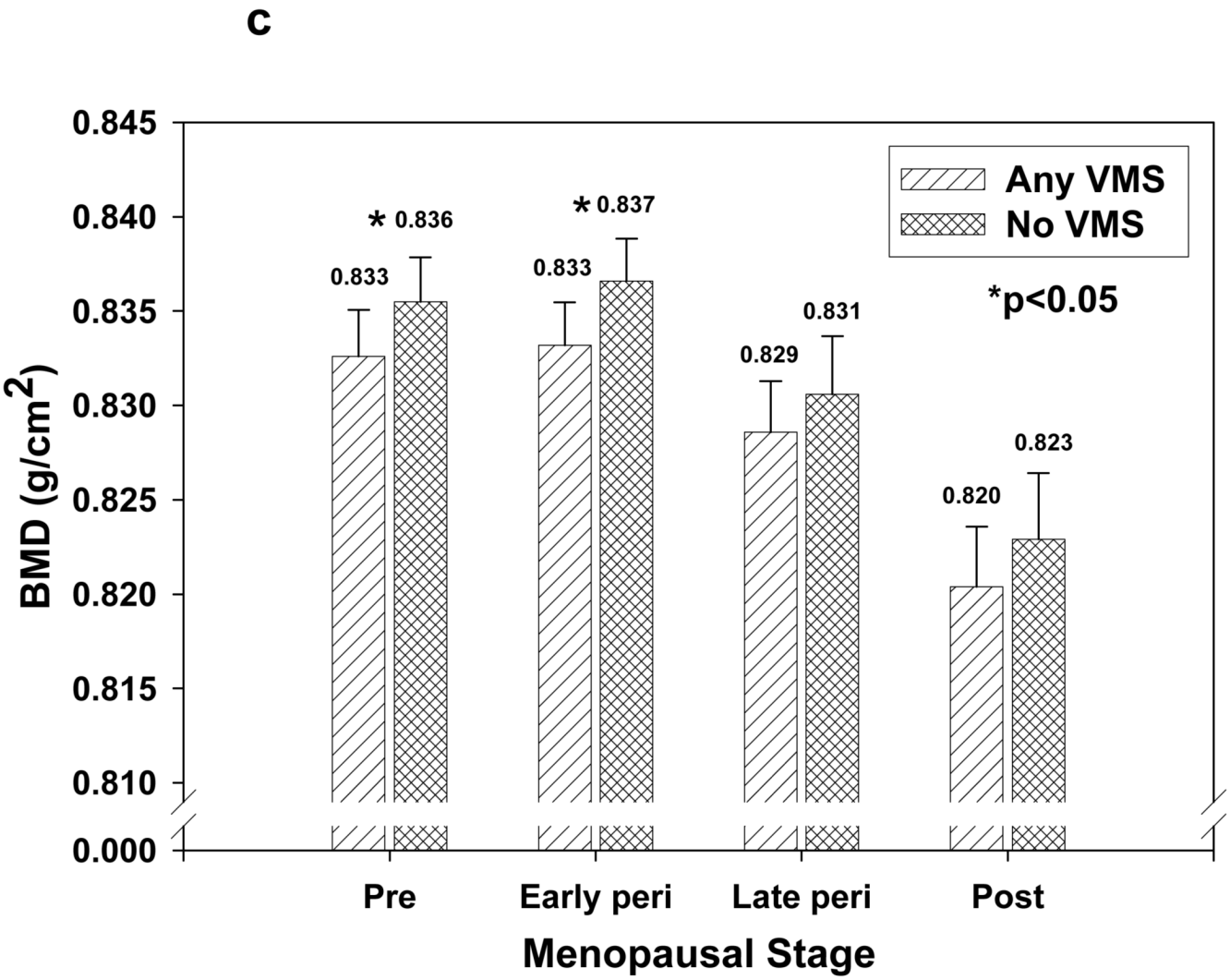

Figure 1. For each menopausal stage, mean BMD in g/cm^2 is compared among women with, compared to women without, VMS, and is adjusted for baseline age, cumulative time in each menopausal stage, ethnicity, study site.

a: Adjusted Lumbar Spine BMD According to Vasomotor Symptoms Within Menopausal Stage

b: Adjusted Total Hip BMD According to Vasomotor Symptoms Within Menopausal Stage

c: Adjusted Femoral Neck BMD According to Vasomotor Symptoms Within Menopausal Stage

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Table 1

Numbers of participants with available bone mineral density measurements according to year of follow-up and anatomical site

	Hip					
Visit number	**00**	**01**	**02**	**03**	**04**	**05**
# of participants having data regarding BMD, VMS, and menopausal stage	2328	2008	1922	1843	1761	1735
# of participants after censoring of women with hysterectomy, bilateral oophorectomy, pregnancy, breastfeeding, hormone therapy use, and use of medication influencing BMD.	2149	1672	1473	1328	1230	1196
	Spine					
Visit number	**00**	**01**	**02**	**03**	**04**	**05**
# of participants having data regarding BMD, VMS, and menopausal stage	2307	1999	1921	1832	1744	1731
# of participants after censoring of women with hysterectomy, bilateral oophorectomy, pregnancy, breastfeeding, hormone therapy use, and use of medication influencing BMD.	2133	1663	1473	1320	1218	1194
	Femoral neck					
Visit number	**00**	**01**	**02**	**03**	**04**	**05**
# of participants having data regarding BMD, VMS, and menopausal stage	2329	2009	1923	1843	1761	1731
# of participants after censoring of women with hysterectomy, bilateral oophorectomy, pregnancy, breastfeeding, hormone therapy use, and use of medication influencing BMD.	2150	1672	1472	1328	1230	1194

Medications influencing bone density included: corticosteroid pills, use of medications to prevent or treat osteoporosis, including alendronate, etidronate, raloxifene, calcitonin, and calcitriol. Women were censored at the time they began taking any of those medications.

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Table 2

Key baseline characteristics of participants (N=2156)[a]

Characteristic		Mean (SD)	Number (%)
Weight (kg)		73.1 (19.5)	
Height (cm)		162.4 (6.6)	
Body mass index (kg/cm^2)		27.6 (6.9)	
	Underweight (<19 kg/cm^2)		77 (3.6%)
	Normal (19 - 24.9 kg/cm^2)		894 (41.9%)
	Overweight (25 - 29.9 kg/cm^2)		512 (24.0%)
	Obese (≥30 kg/cm^2)		651 (30.5%)
Smoking:			
	Never		1242 (58.1%)
	Past		553 (25.9%)
	Current		344 (16.1%)
Previous fracture since age 20 [b]			388 (18.1%)
Any alcohol consumption [c]			997 (48.7%)
Eating disorder (anorexia, bulimia)			26 (1.2%)
Family history of broken hip/osteoporosis (from 2nd annual followup visit)			388 (18.1%)
Age (years)		45.9 (2.7)	
Ethnicity	African American		608 (28.2%)
	Caucasian		1062 (49.3%)
	Chinese		235 (10.9%)
	Japanese		251(11.6%)
Meno pause Status[d]	Premenopausal		1174 (54.5%)
	Early perimenopausal		982 (45.5%)
Lumbar bone mineral density (g/cm^2)	Premenopausal	1.079 (0.138)	
	Early perimenopausal	1.076 (0.139)	
Total hip bone mineral density (g/cm^2)	Premenopausal	0.960 (0.147)	
	Early perimenopausal	0.965 (0.146)	
Femoral neck bone mineral density (g/cm^2)	Premenopausal	0.846 (0.136	
	Early perimenopausal	0.845 (0.134)	

[a] 2156 participants of the SWAN Bone Substudy remained after censoring of women at the time they reported hysterectomy, bilateral oophorectomy, pregnancy, breastfeeding, or medications influencing bone mineral density. Fifty-seven of the 2156 participants did not have baseline BMD measurements.

[b] assessed at 2nd annual follow-up visit

[c] typical daily consumption

[d] SWAN study eligibility required that women be pre- or early peri-menopausal at study entry

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Table 3

Menopause status and symptom reporting in each year of follow-up

Menopause Status	Annual follow-up visit											
	0		**1**		**2**		**3**		**4**		**5**	
Pre	N=1174		N=479		N=304		N=203		N=116		N=75	
	No VMS	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**
	818 (69.7%)	356 (30.3%)	329 (68.7%)	150 (31.3%)	226 (74.5%)	78 (25.5%)	148 (72.9%)	55 (27.1%)	85 (73.3%)	31 (26.7%)	44 (58.7%)	31 (41.3%)
	Infreq. VMS	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**
	1075 (93.9%)	85 (7.3%)	445 (92.9%)	34 (7.1%)	290 (95.4%)	14 (4.6%)	190 (93.6%)	13 (6.4%)	108 (93.1%)	8 (6.9%)	68 (90.7%)	7 (9.3%)
Early peri	N=973		N=1097		N=968		N=791		N=660		N=520	
	No VMS	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**
	525 (53.9%)	448 (46.1%)	614 (56.1%)	483 (43.9%)	536 (55.4%)	432 (44.6%)	429 (54.2%)	362 (45.8%)	352 (53.3%)	308 (46.7%)	270 (51.9%)	250 (48.1%)
	Infreq. VMS	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**
	839 (85.4%)	143 (14.6%)	939 (85.6%)	158 (14.4%)	840 (86.8%)	128 (13.2%)	687 (86.9%)	104 (13.1%)	573 (86.8%)	87 (13.2%)	446 (85.8%)	74 (14.2%)
Late peri	N=0		N=79		N=125		N=148		N=158		N=165	
	No VMS	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**
	0	0	25 (31.7%)	54 (68.3%)	32 (25.6%)	93 (74.4%)	39 (26.4%)	109 (73.6%)	60 (38.0%)	98 (62.0%)	55 (33.3%)	110 (66.7%)
	Infreq. VMS	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**
	0	0	53 (67.1%)	26 (32.9%)	79 (63.2%)	46 (36.8%)	90 (60.8%)	58 (39.2%)	111 (70.3%)	47 (29.7%)	108 (65.5%)	57 (34.5%)
Post	N=0		N=23		N=86		N=189		N=302		N=446	
	No VMS	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**	**No VMS**	**VMS**
	0	0	5 (21.7%)	18 (78.3%)	37 (43.0%)	49 (57.0%)	65 (34.4%)	124 (65.6%)	102 (33.8%)	200 (66.2%)	185 (41.5%)	261 (58.5%)
	Infreq. VMS	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**	**Infreq. VMS**	**Freq. VMS**
	0	0	15 (65.2%)	8 (34.8%)	57 (66.3%)	29 (33.7%)	121 (64.0%)	68 (36.0%)	198 (65.6%)	104 (34.4%)	310 (69.5%)	136 (30.5%)

VMS is defined as hot flashes or night sweats in the past two weeks in the annual self-administered questionnaire. Freq. VMS is defined as having hot flashes or night sweats on more than 5 days in the past two weeks in the annual self- administered questionnaire.