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Increasing serum 25-hydroxyvitamin D (25(OH)D) is associated with reduced odds of long menstrual cycles in a cross-sectional study of African-American women

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Abstract

Objective—To examine the association between serum 25-hydroxyvitamin D (25(OH)D) and menstrual cycle length and regularity.

Design—Community-based, cross-sectional study of serum 25(OH)D (adjusted for seasonal differences in timing of blood draw) and menstrual cycle length. Women ages 23-34 reported their gynecologic history. Menstrual cycles were described with four independent categories (normal, short, long, irregular). We used polytomous logistic regression to estimate the association between a doubling of seasonally-adjusted 25(OH)D and the odds of each cycle category.

Setting—Women from the Detroit, Michigan area attended a study clinic visit.

Participants—1102 African-American women ages 23-34.

Intervention—None

Main Outcome Measure—Self-reported menstrual cycle length over the previous 12 months excluding women who were using cycle-regulating medications over the entire year. Women who reported that their cycles were “too irregular to estimate” were classified as having irregular cycles. A typical cycle length of <27 days was considered “short,” >34 days was “long,” and 27-34 days was “normal”.

Results—The median 25(OH)D level was 14.7 ng/ml (interquartile range: 10.9, 19.6). A doubling of 25(OH)D was associated with half the odds of having long menstrual cycles (adjusted odds ratio (aOR) (95% Confidence interval (CI): 0.54 (0.32, 0.89)). 25(OH)D was not associated

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Dr. Jukic began this work at NIEHS and completed it while at Yale University, thus the study took place at both locations.

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with the occurrence of short (aOR(CI): 1.03 (0.82, 1.29)) or irregular (aOR(CI): 1.46 (0.88, 2.41) menstrual cycles. Results were robust to several sensitivity analyses.

Conclusions—These findings suggest that vitamin D status may influence the menstrual cycle and play a role in ovarian function. Further investigation of 25(OH)D and ovarian hormones, and prospective studies of 25(OH)D and cycle length, are needed.

Keywords

vitamin D; ovarian function; ovulation; PCOS

Background

Vitamin D is important for bone health (1), and its importance for reproduction is a burgeoning area of research (2-4). Vitamin D receptor is expressed in several reproductive tissues including the ovary, placenta, and the uterus (2-4). Recent data suggest that lower vitamin D may be associated with several reproductive endpoints including uterine fibroids (5) and early menarche (4), but data are limited.

Diet-induced vitamin D deficiency reduces fertility in both rats and mice. The probability of becoming pregnant is reduced 45-70% with a concomitant 67-100% reduction in the number of viable pups (2). Knock-out mice lacking the enzyme for converting the circulating form of vitamin D to its active form show estrus cycle disturbances including arrested follicular development, prolonged estrous cycles, and anovulation (6, 7).

Vitamin D deficiency has been associated with polycystic ovarian syndrome (PCOS) in multiple studies (reviewed in (8)). Moreover, among women with PCOS, supplementation with vitamin D has been reported to normalize menstrual cycles and improve ovarian folliculogenesis and ovulation (9, 10). Despite the growing PCOS literature, data regarding vitamin D and menstrual cycle function in healthy women are sparse. Only one previous study has examined the association between concentrations of 25-hydroxyvitamin D (25(OH)D), the accepted biomarker of vitamin D status, and menstrual cycle length and regularity (11). This previous study, in 35-44 year olds (N=636), reported that decreasing 25(OH)D was associated with an increase in the odds of irregular menstrual cycles.

Our primary objective was to examine the association of vitamin D with menstrual cycle length and regularity in a population of African-American women from the Detroit area.

Methods

Study sample

The Study of Environment, Lifestyle, & Fibroids (SELF) was designed to prospectively measure the incidence and growth of uterine fibroids (14). Vitamin D was one of the primary environmental exposures of interest. A complete description of the eligibility requirements, recruitment and other study methods has been published (14). Briefly, in 2010-2012 African-American women ages 23-34 were recruited from the Detroit, Michigan area through letters from the collaborating health system, local radio, television, newspaper and

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magazine advertisements, fliers and brochures at health clinics throughout the community, and information booths at community events. Women were not eligible for the study if they reported a prior clinical diagnosis of fibroids. Enrollment involved completion of several steps including a computer-assisted telephone interview (CATI), a computer-assisted web-based interview (CAWI), a self-administered hard copy questionnaire, and a clinic visit.

Information was collected on demographics, alcohol, smoking, physical activity, hormone use, gynecologic and reproductive history, and history of medical diagnoses including vitamin D deficiency. At enrollment, the participants attended a clinic visit where height and weight were measured and a blood sample was collected.

All of the enrolled women (N=1696) provided informed consent, and the study protocol was approved by the institutional review boards at NIEHS and Henry Ford Health System in Detroit.

Menstrual cycle characteristics

Women were excluded from the menstrual cycle analysis if they reported that their last menses was more than one year prior to the interview (N=90) or they had only had one period in the last year (N=37) (the majority of both groups lacked periods due to pregnancy/breastfeeding). Women were also excluded if they reported currently using hormonal contraception (N=403) or any other medication that regulated their menstrual cycles for “all” of the year prior to interview (N=33). (Women who reported using a medication that regulated their menstrual cycles for “some” of the year prior to interview were included, and investigated in a sensitivity analysis that is described in the “statistical analysis” section.) After these exclusions, 1133 women were eligible for our menstrual cycle analyses.

Women were asked to report their typical menstrual cycle length in the past year during the CATI. The CATI was completed close in time to the clinic visit, and most women completed the CATI the month before, or during, the clinic visit. Menstrual cycle length and regularity was described with four mutually exclusive categories. Women who reported that their cycles were “too irregular to estimate” were classified as having irregular cycles (N=53). Women who reported a typical cycle length of ≤26 days were classified as having “short” cycles (N=380) and ≥35 days were classified as having “long” cycles (N=55). “Normal” cycle length was 27-34 days (N=632). Eight women said they did not know their typical cycle length and one woman refused to answer, these women were excluded from the analysis. Four women reported a typical cycle length of less than 12 days and were also excluded. After these exclusions, 1120 women remained eligible for our analyses.

Use of contraceptive methods to treat menstrual pain or irregularity

The analysis of menstrual cycle characteristics was limited to women not using hormonal contraception. This exclusion could potentially bias the analysis: if lower vitamin D causes menstrual problems, and women tend to use hormonal contraception to treat menstrual problems, we would be excluding the very women who are showing the physiologic effects of low vitamin D. We do not have data on current use of a hormonal contraception for treatment of menstrual problems, but we do have ever/never data. Therefore, as a secondary analysis, we examined whether women with a previous diagnosis of vitamin D deficiency

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were also more likely to have ever used a hormonal contraceptive for irregular cycles or for menstrual pain.

Women were asked about their use of several different hormonal contraceptive methods. They were also asked, for each method, if they had used that method to treat menstrual pain or to treat irregular menstrual cycles. We created two composite variables: one to summarize whether she had ever used any contraceptive method to treat menstrual pain (yes/no), and another to describe whether she had ever used a contraceptive method to treat irregular menstrual cycles (yes/no). All of the 1696 participants provided enough information to be classified as yes or no for both of these variables (i.e. none of the women were "missing").

Vitamin D status

Vitamin D status was quantified in stored serum samples through the measurement of 25-hydroxyvitamin D (25(OH)D), the accepted biomarker of vitamin D status (15). Eighteen women had an unsuccessful blood draw and thus did not have a measure of 25(OH)D, leaving 1102 women in our analyses of 25(OH)D and menstrual cycles.

25(OH)D was quantified with an FDA approved direct, competitive chemiluminescence immunoassay (CLIA) using the DiaSorin LIAISON 25-OH Vitamin D Total assay (16, 17). This assay is co-specific for 25-hydroxyvitamin D_3 and 25-hydroxyvitamin D_2. The sensitivity of the assay is 2.5 ng/ml and the recovery of endogenous 25(OH)D is 100% (18). The intra- and inter-assay CVs based on blind replicates were 2.9% and 8.6%, respectively. Despite the acceptable inter-assay CV, we found that the second, smaller batch sent for assay showed somewhat lower values for the blind controls than the first batch. To account for any potential batch-effects, all primary analyses were rerun using only women whose samples were assayed in the first shipment. Our results did not change, and only the full-sample results are shown.

Because 25(OH)D varies with season or temporal changes in supplement use, and because our menstrual cycle questions asked about cycles in the last 12 months, we estimated an annual mean 25(OH)D using a cosinor model (19) (Supplemental Text). Data collected on supplement use was incorporated into this model because there was less seasonal variation for supplement users. For simplicity, this estimated annual mean 25(OH)D will be referred to as "25(OH)D".

History of vitamin D deficiency

Participants were asked, "Has a doctor or other health professional ever told you that you had any of the following conditions…Vitamin D deficiency?" If she said yes, she was further asked at what age (in years) she received the diagnosis. Eighteen women were missing data for this question, which left 1678 women in our analysis of vitamin D deficiency and the use of contraceptive methods for menstrual pain or irregularity.

Potential covariates

Potential covariates were selected from the literature due to their associations with menstrual cycle length and/or vitamin D status and included: age (20, 21), education (22, 23), income,

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body mass index (19, 23-26), alcohol intake (21), cigarette smoking (20, 21, 23, 27), and physical activity (19, 21, 23, 26). Most data on covariates were collected through the CATI, CAWI, and clinic interviews. A 5-level physical activity variable was created based on data from several questions about walking, sports, exercise routines/classes, recreational activities like dancing, household chores, and time spent doing heavy manual labor at work (see supplemental text for details). BMI was calculated from weight and height measured during the clinic visit.

Statistical analysis

Analyses of 25(OH)D and menstrual cycle characteristics—To achieve normality, and for ease of interpretation (see below) 25(OH)D was modeled on the $\log_2$ scale. We examined the univariable associations between 25(OH)D and the covariates of interest using medians and the corresponding interquartile ranges.

We used polytomous logistic regression (also known as multinomial regression) to simultaneously estimate the associations between 25(OH)D and short, long and irregular cycles. Women who reported a typical cycle length of 27-34 days were considered the referent group. We estimated two separate models, one with a dichotomous 25(OH)D measure and one with a continuous measure (on the $\log_2$ scale). The dichotomous 25(OH)D variable was defined as “sufficient” versus “deficient” based on the Institute of Medicine cutpoint of 20 ng/mL (28). The regression coefficient from the continuous model was exponentiated to obtain the association between a doubling of 25(OH)D and the odds of each cycle category. The levels of 25(OH)D in this population are low (median: 14.8 ng/ml), so a doubling of 25(OH)D can be thought of as changing a woman from the range of deficiency to sufficiency. This model has more power than the dichotomous exposure measure because it is continuous, and because the majority of participants are deficient (76%). The multivariable model was adjusted for age (continuous), education (three categories), income (three categories), BMI (four categories), smoking (never, former, <10 cig/day, ≥10 cig/day), alcohol (three categories), and physical activity (five categories). Nine women were missing information for income, one woman was missing education, and three women were missing physical activity information. These women were excluded from the multivariable model, leaving 1089 women in the analysis.

We performed several sensitivity analyses. First, we excluded women with a recent diagnosis of vitamin D deficiency. We did this because once diagnosed, women are likely to begin supplements. Thus, a current 25(OH)D measurement would reflect the recent supplement use, but her reporting of menstrual cycles over the past 12 months would likely reflect, at least in part, her pre-supplement cycle characteristics. Because we wanted to identify diagnoses of vitamin D deficiency that occurred within the past 12 months, and we only asked about age at diagnosis, we conservatively excluded women with a vitamin D deficiency at an age that was within 2 years of her age at enrollment (N=81).

We performed three additional, independent, sensitivity analyses in which we removed women whose cycles might be influenced by other medical conditions or experiences: 1) Women who reported a history of PCOS (N=36), 2) women who reported that, over the past year, they used a medication that regulated their menstrual cycles “some of the time”

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(N=155), and 3) women who had been pregnant during the past year but were cycling at the interview (N=100).

As a final sensitivity analysis, we adjusted for the presence of fibroids detected at the enrollment ultrasound because prior studies have reported an association between vitamin D deficiency and fibroids (reviewed in (29)).

Analyses of vitamin D deficiency and use of contraceptive methods to treat menstrual pain or irregularity—The associations of a history of vitamin D deficiency with ever/never use of a contraceptive method to treat either 1) menstrual pain, or 2) menstrual irregularity, were examined initially with frequency tables. Two multivariable logistic regression models were used to estimate the associations between a history of vitamin D deficiency and ever/never contraceptive use to treat 1) menstrual pain or 2) menstrual irregularity. Due to the retrospective nature of the data for this analysis, we did not adjust for current behaviors or characteristics as these do not reflect the relevant time period for this analysis, with the exception of BMI. Because current BMI tends to be highly correlated with a past BMI measure (30), we adjusted for current BMI as a surrogate for BMI during the relevant time period. We also adjusted for smoking history (ever/never) as smoking is a suspected risk factor for menstrual pain (31-33). We adjusted for education as a potential marker of a woman's access to healthcare and treatment-seeking behavior. We also adjusted for age at enrollment because older women had more years during which they could have been diagnosed with a vitamin D deficiency or have used hormonal contraception to manage menstrual cycle problems.

Results

25(OH)D and menstrual cycle characteristics

The median cycle length was 28 days (interquartile range: 25, 30). The median 25(OH)D level was 14.7 ng/ml (interquartile range: 10.9, 19.6). The majority of women were vitamin D deficient, with 76% of the women (N=838) having a 25(OH)D of 20 ng/ml or less. 25(OH)D was lower in women who reported long menstrual cycles (Table 1). Average 25(OH)D was also lower among women who reported lower education, lower income, higher BMI, current smoking, high alcohol use, and low physical activity.

The overall adjusted association between continuous 25(OH)D and cycle category (normal cycle length of 27-34 days, short, long, irregular) was statistically significant by a 3 degree-of-freedom likelihood ratio test (p=0.04). A doubling of 25(OH)D was associated with about half the odds of having long menstrual cycles (Adjusted odds ratio (aOR) (95% Confidence interval (CI): 0.54 (0.32, 0.89)) (Table 2). 25(OH)D was not statistically significantly associated with the occurrence of short or irregular menstrual cycles. Women who were sufficient in their 25(OH)D (>20 ng/ml) had about half the odds of long cycles compared with women who were deficient (aOR(CI): 0.42 (0.17, 1.0)) (Table 2). Sufficiency was not associated with short or irregular menstrual cycles (Table 2).

The association between continuous 25(OH)D and long menstrual cycles persisted with sensitivity analyses (Supplemental Table 1). The aOR did not change, but the confidence

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interval was even smaller when the sample was limited to women who were not recently diagnosed with vitamin D deficiency (long aOR(CI): 0.48 (0.28, 0.83)). Removing women who reported a history of PCOS had only minor effects (long aOR(CI): 0.57 (0.33, 0.97)). Nor was there substantial change in the results with removal of women who reported using a medication that regulated their menstrual cycles “some of the time” or women who had been pregnant during the past year or after adjustment for fibroid status at enrollment (Supplemental Table 1).

History of vitamin D deficiency and ever use of contraception for menstrual pain or irregularity

Of 1678 women, 223 (13%) reported that a doctor or other health care professional had told them they were vitamin D deficient. The timing of diagnosis of the deficiency ranged from their current age to 28 years earlier, but most were diagnosed within 4 years of enrollment (91%). Fifty (23%) were the same age at baseline as they were at their diagnosis and 77 (35%) had been diagnosed one year earlier. Of the 1678, 251 women reported ever use of hormonal contraceptives for menstrual pain and 579 reported ever use for irregular menstrual cycles. Of the 223 women with a history of vitamin D deficiency, 17 (7.6%) also reported being told by a health care professional that they had PCOS. This was a higher proportion than among women who did not report a history of vitamin D deficiency (2.5%), thus history of vitamin D deficiency was also associated with PCOS.

Women with a history of vitamin D deficiency were more likely to report ever using a contraceptive method for either menstrual pain or for irregular cycles (Table 3). The results were unchanged when we excluded women who were first diagnosed with vitamin D deficiency at less than 15 years of age (N=4) (data not shown). Given the observed associations between history of vitamin D deficiency and PCOS, we performed a sensitivity analysis excluding women with PCOS. The estimate for menstrual pain was slightly stronger (aOR(CI): 1.63 (1.12, 2.37)), while the estimate for ever use of a method to treat irregular cycles was slightly weaker (aOR(CI): 1.33 (0.98, 1.81)).

Discussion

Our study is the first to examine the association between 25(OH)D and menstrual cycle length and regularity in reproductive aged African-American women. We observed that an increase in 25(OH)D was associated with a reduced odds of long menstrual cycles (but not short or irregular cycles). This association remained robust after several sensitivity analyses. Only 24% of our participants were sufficient in vitamin D, which reduced our power to detect an effect of sufficiency. However, the analysis comparing women with sufficient and deficient 25(OH)D showed the same direction of effect and borderline significance, i.e., women with sufficient 25(OH)D had a reduced likelihood of long cycles.

One previous study has reported a shortening of long (30-38 days) menstrual cycles among women exposed to phototherapy in a crossover design (it is unclear if the participants received any ultraviolet light exposure) (34). In the only previous study of 25(OH)D and menstrual cycles, increasing 25(OH)D was associated with a reduced odds of irregular cycles (but not with long menstrual cycles)(11). The differences between these two studies

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could be the result of the disparate study populations, as the women in the previous analysis were older (35-44 years). Long and irregular cycles may be different in younger versus older women. For example, the irregular cycles of PCOS may resolve with age (35), while the irregular cycles associated with perimenopause will be rare in young women.

Our menstrual cycle analysis required the exclusion of women using hormonal contraceptives because they were not having natural cycles. Because some women use these to manage menstrual problems, this analysis could be biased by selective removal of women with menstrual problems. Therefore, we used an indirect approach to investigate the association between vitamin D and menstrual cycle problems for which our whole sample could be analyzed. We looked at the association between having a history of vitamin D deficiency and having ever used a contraceptive for menstrual pain or for irregular menstrual cycles, and found positive associations. These findings further support our primary analysis, again suggesting that vitamin D influences menstrual cycle characteristics. These results are also consistent with one recent randomized trial that found that treatment with vitamin D reduced the symptoms of dysmenorrhea (13). Vitamin D may influence menstrual pain through its hypothesized roles as an immune modulator or a prostaglandin inhibitor (12).

25(OH)D is converted to its active form $1,25(OH)_2D$ by the enzyme 1α-hydroxylase, coded by the *CYP27B1* gene. Mice that lack either *Cyp27b1* or the vitamin D receptor have shown hypogonadism, arrested follicular development, prolonged estrous cycles, and hypoplastic uteri (6, 7, 36, 37). The reproductive phenotypes in these studies may be the result of either suboptimal gonadotropin secretion from the pituitary or hypothalamus, or defects in the ovarian response to gonadotropins (6). In one study, the prolonged estrous cycles were reversed with vitamin D_3 supplementation and occurred independently of calcium (6). Although in another study the effects appeared to be calcium dependent (38).

In humans, long menstrual cycles are typically the result of a long follicular phase (22, 39, 40). Long menstrual cycles can arise from several mechanisms including decreased ovarian responsiveness to gonadotrophin stimulation(39) and hypoestrogenic intervals during the follicular phase (also known as “inactive phases”) (41). These inactive phases have mostly been described for perimenopausal women, however, they do occur in premenopausal women (41), but the reasons for their occurrence in younger women are unknown. The hormonal milieu of long cycles is variable (42). Some long cycles show a delay in the follicular rise of estrogen (42, 43), while others show typical early follicular increases in estrogen followed by either episodic rises and falls or by prolonged high estrogen {Harlow, 2000 #259}. A SNP in the follicle stimulating hormone receptor that induces a higher ovarian threshold to FSH has been related to longer menstrual cycle length (44). Anovulation appears to occur in both short and long menstrual cycles and therefore does not explain consistently long cycles (43).

The associations between vitamin D and cycle length may involve Anti-Müllerian hormone (AMH), which helps regulate follicle recruitment in the ovary (4) (also reviewed in (8)). AMH is produced in the granulosa cells of early-developing follicles, and its hypothesized actions include inhibition of primordial follicle recruitment, slowing of follicular growth and thus delaying or preventing atresia, and inhibiting granulosa cell differentiation (8, 45).

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AMH, antral follicle count and ovarian volume have been positively associated with menstrual cycle length in 200 healthy women and several lines of evidence support a role for AMH in menstrual cycle function (46). The promoter region for the human gene encoding AMH contains a domain for the vitamin D response element, suggesting that vitamin D may regulate AMH expression (47). Vitamin D has also been shown to modulate AMH signaling in human luteinized granulosa cells (48).

This study has several limitations. First, this analysis is limited by the use of self-reported cycle length and by the relatively small number of women with extreme cycle lengths, particularly long or irregular cycles. Second, this study is based on a cross-sectional design: women gave a blood sample around the time that they retrospectively reported their typical cycle length for the past year. Thus, this study is susceptible to reverse causation, i.e. it is possible that the occurrence of long cycles affects diet, supplement use, or another behavior (such as seeking medical advice) that leads to changes in 25(OH)D status. Third, it is possible that some of the women in our analysis had undiagnosed PCOS. Our finding that vitamin D sufficiency might protect against long cycles, may derive from a subset of women with subclinical PCOS that is characterized by both low vitamin D and long menstrual cycles. We did not have hormonal or ultrasound markers with which to identify women with PCOS. However, our results were robust to the exclusion of women with known PCOS. Fourth, we did not have information regarding current use of oral contraceptives to treat menstrual pain or irregularity, and thus our secondary analysis was confined to data on history of vitamin D deficiency and ever/never use of hormonal contraception for menstrual pain or irregularity. Fifth, 76% of our sample was deficient in vitamin D, while only 13% reported a history of clinically-diagnosed vitamin D deficiency. This indicates that the majority of those with deficient vitamin D concentrations were not previously clinically diagnosed and suggests misclassification of history of vitamin D deficiency, which could bias our observed associations toward the null.

This study has several strengths. The sample size was large and focused on a clinically-relevant population, African-American women, who tend to have lower 25(OH)D levels (49). Several community-based recruitment methods were used to generate a representative sample. Generalizability might be limited somewhat as only motivated women were likely to complete all enrollment steps. Collection of menstrual cycle data was standardized. Vitamin D status was assessed with the accepted biomarker, 25(OH)D (15), which was carefully adjusted for seasonal variation. The study data collection was extensive, allowing for adjustment of potential confounders. In addition, we performed several sensitivity analyses to evaluate the potential for bias and our results were robust to each of them.

Conclusions

These findings suggest that vitamin D status may influence the menstrual cycle and may play a role in ovarian function. The role of vitamin D in reproduction is an emerging field of research (8), and these findings need replication. Further investigation of 25(OH)D and cycle characteristics, including ovarian hormones and symptoms of PCOS, is warranted. Detailed studies of the possible role(s) of vitamin D in follicular recruitment and selection, as well as

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follicular growth, would be of interest. Prospective trials of vitamin D and cycle length are feasible.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Participant characteristics SELF cohort (N=1102)

	N (%)	Median 25(OH)D (ng/ml) (interquartile range)
Menstrual cycle length		
Short (< 27 days)	373 (34)	14.8 (11.1, 19.2)
Long (≥ 35 days)	55 (5)	11.8 (9.8, 14.5)
Irregular	51 (5)	16.6 (10.7, 21.5)
Normal (27 – 34 days)	623 (57)	14.8 (11.0, 20.3)
Season[a]		
Winter	225 (20)	13.3 (9.8, 17.7)
Spring	253 (23)	13.4 (9.9, 19.4)
Summer	326 (30)	17.8 (12.9, 22.6)
Fall	298 (27)	14.1 (10.9, 19.2)
Age		
23 – 25	227 (21)	14.3 (11.0, 19.4)
26 – 30	460 (42)	14.6 (10.7, 18.8)
31 – 35	415 (38)	15.1 (11.0, 20.7)
Education		
High school graduate or less	269 (24)	13.3 (9.9, 17.8)
Some college/technical	548 (50)	14.7 (11.1, 19.4)
College graduate or more	284 (26)	16.4 (11.4, 22.7)
Missing	1	
Annual income		
< 20K	534 (49)	13.8 (10.5, 18.5)
20 – 50K	392 (36)	15.1 (10.9, 19.9)
> 50K	167 (15)	16.6 (12.4, 21.9)
Missing	9	
Body mass index		
< 25 kg/m^2	208 (19)	17.2 (12.3, 21.8)
25 - < 30	208 (19)	15.2 (11.2, 20.2)
30 - <35	208 (19)	16.2 (11.2, 22.3)
≥ 35	478 (43)	13.5 (10.3, 17.6)
Smoker		
Non-smoker	776 (70)	14.9 (11.1, 20.7)
Former	86 (8)	16.1 (12.5, 19.2)
Current		
< 10 cig/day	174 (16)	13.3 (9.8, 17.0)
≥ 10 cig/day	66 (6)	12.9 (9.3, 17.4)
Alcohol[b]		
Low	343 (31)	14.8 (11.3, 20.2)
Medium	530 (48)	15.0 (11.0, 19.8)
High	229 (21)	13.5 (9.9, 18.3)

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	N (%)	Median 25(OH)D (ng/ml) (interquartile range)
Physical activity		
Low	181 (16)	13.3 (10.2, 18.1)
Low/Moderate	257 (23)	14.3 (10.7, 18.7)
Moderate	280 (25)	14.9 (10.9, 19.5)
High	212 (19)	15.8 (11.3, 21.9)
Very high	169 (15)	15.9 (11.1, 20.7)
Missing	3	

[a]25(OH)D levels in this row are the unadjusted, measured values. The other rows of the table show the average annual mean 25(OH)D (see Methods).

[b]Medium: 1 – 5 drinks/day or ≥ 4 drinks on a single occasion once per month or less, High: ≥ 6 drinks/day or ≥ 4 drinks on a single occasion more than once per month.

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Table 2

The association between 25(OH)D and menstrual cycle length and regularity among African-American women in the SELF study (N=1089).

	N	Adjusted* OR (95% CI) for a doubling† of 25(OH)D
Short cycles (≤26 days)	367	1.03 (0.82, 1.29)
Long cycles (≥35 days)	54	0.54 (0.32, 0.89)
Irregular cycles	51	1.46 (0.88, 2.41)
		Sufficient 25(OH)D (compared with deficient)
Short cycles (≤26 days)	367	0.82 (0.60, 1.13)
Long cycles (≥35 days)	54	0.42 (0.17, 1.02)
Irregular cycles	51	1.39 (0.72, 2.69)

*Adjusted for: age, BMI, education, income current smoking, alcohol use, and physical activity. Referent category: 27 -34 days (N=617)

†Given the low levels of 25(OH)D in this population, a “doubling” of 25(OH)D can be thought of as changing most of the women from the range of deficiency to sufficiency.

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Table 3

Associations between a history of clinically-recognized vitamin D deficiency and the use of contraceptive methods to treat menstrual pain or irregularity among African-American women in the SELF study (N=1678).

	History of clinically-recognized vitamin D deficiency		
	Yes (N=223) N (%)	**No (N=1455) N (%)**	**Adjusted* OR (95% CI) for history of vitamin D deficiency**
Ever used a contraceptive method to treat menstrual pain	46 (21)	205 (14)	1.53 (1.06, 2.21)
Ever used a contraceptive method to treat irregular menstrual cycles	94 (42)	485 (33)	1.37 (1.04, 1.84)

*Adjusted for age, BMI, education, and ever smoking, all measured at enrollment.