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Vitamin D and uterine leiomyoma among a sample of US women: Findings from NHANES, 2001–2006

Susanna D. Mitro[a] and **Ami R. Zota**[a]

[a]Department of Environmental and Occupational Health, Milken Institute School of Public Health at the George Washington University, Washington, DC

Abstract

Scientific understanding of the etiology of uterine leiomyomata (UL) remains incomplete, but recent investigations have suggested an association between low Vitamin D and UL risk. In this study, we conducted a cross-sectional analysis of Vitamin D exposure, measured using serum levels of 25(OH)D (a Vitamin D metabolite), and self-reported UL diagnosis among 3,590 women aged 20–54 in the National Health and Nutrition Examination Survey (NHANES 2001–2006). Multivariate logistic regression models comparing each quartile of 25(OH)D to the lowest quartile indicated no relationship between 25(OH)D and odds of UL in the whole population (P_{trend} = 0.37), or in sensitivity analyses. However, a probabilistic analysis correcting outcome misclassification indicated that insufficient 25(OH)D was associated with UL in white (Odds ratio (OR) median estimate: 2.17; 2.5, 97.5 percentiles: (1.26, 23.47)), but not black women (OR median estimate: 1.70; 2.5, 97.5 percentiles: (0.89, 3.51)), suggesting misclassification may have driven some of the null findings.

Keywords

Uterine Leiomyoma; Fibroid; Vitamin D; Misclassification; Race; NHANES; Reproductive Health

1. Introduction

Uterine leiomyomata (UL), hormonally dependent benign tumors of the uterus, are a major source of morbidity for U.S. women [1]. However, despite the high prevalence and morbidity associated with UL, scientific understanding of risk factors remains incomplete [2, 3].

Corresponding Author: Ami R. Zota, Milken Institute School of Public Health, Environmental and Occupational Health, 950 New Hampshire Avenue NW 414—Floor 4, Washington, DC 20052, **Phone:** 202-994-9289, azota@email.gwu.edu.

Conflict of Interest

The authors declare that they have no conflict of interest.

One of the strongest established risk factors for UL is race. Black women are more likely to develop UL, develop tumors at a younger age, develop a greater number of tumors, have more severe symptoms, and are more likely to undergo hysterectomy as a treatment when compared to white women [4–8]. UL prevalence is also associated with age [9], body mass index (BMI) [10, 11], and parity [12, 13]. However, the known risk factors do not fully explain the elevated risk in black women [14].

Vitamin D may be an unrecognized risk factor for UL and contribute to racial/ethnic disparities in UL. Serum levels of 25-hydroxyvitamin D (25(OH)D), a Vitamin D metabolite, have been inversely associated with various female reproductive health conditions, including infertility, polycystic ovarian syndrome, and preterm birth [15]. As a result, the possibility of an association between serum 25(OH)D and UL has been suggested. At the cellular level, treatment with biologically active $1,25(OH)_2D_3$ inhibits leiomyoma cell growth *in vitro* [16–18], and leiomyoma cells have reduced expression of the Vitamin D receptor [19]. Women with darker skin are also more likely to be Vitamin D deficient [20, 21]. In one recent population-based study, around 80% of non-Hispanic black women had deficient or inadequate levels of Vitamin D, while only about 20% of white women had deficient or inadequate levels [22].

Several recent epidemiological studies suggest an inverse association between serum levels of 25(OH)D and UL prevalence. A cross-sectional study found that serum 25(OH)D was inversely associated with UL prevalence in both black and white women aged 35–49 [23]. Similarly, a second cross-sectional study reported that infertile Vitamin D-deficient women had greater than twice the odds of UL than did infertile women without deficiency [24], and a third study found that women seeking treatment for symptomatic fibroids had lower serum 25(OH)D than healthy women [25]. Finally, a genetic study reported that SNPs associated with Vitamin D metabolism and skin color are associated with UL in black women [26]. While these studies reduced the likelihood of misclassifying UL case status by ascertaining cases using ultrasound or prospectively ascertaining cases [4], they were subject to other methodological limitations. For example, several studies recruited cases and controls from clinical populations, and most were limited by small sample sizes or incomplete adjustment for confounders.

Although preliminary research suggests that Vitamin D may play a role in UL risk, no population-based study of Vitamin D exposure and UL has been conducted. In this cross-sectional analysis, we used data from the National Health and Nutrition Examination Survey (NHANES) to investigate the relationship between serum 25(OH)D and self-reported UL.

2. Methods

We used data from three cycles of NHANES (2001–2002, 2003–2004, 2005–2006) to examine the association between serum 25(OH)D and self-reported UL. NHANES is an ongoing series of cross-sectional national surveys conducted by the US Centers for Disease Control and Prevention (CDC), including both physical exams and questionnaires. Due to the probability-based sampling methods used, NHANES data are representative of the non-institutionalized population of the U.S. [27]. All participants provided written informed

consent, and the National Center for Health Statistics (NCHS) obtained institutional review board approval to conduct the surveys [27].

2.1 Study Population

NHANES 2001–2006 included the examination of 30,070 individuals [27]. Serum 25(OH)D was measured in 27,266 participants. Only women aged 20–54 years were eligible to contribute data on UL diagnosis (n=4,953). We first removed individuals who were missing information about BMI (n=306) and individuals who self-identified as a race or ethnicity other than non-Hispanic white, non-Hispanic Black, or Mexican American (n = 464). We then removed those who did not provide any reproductive health data (n = 405) or were missing parity data (n = 445), reducing the eligible population to 3,785 individuals. Finally, we removed individuals who reported not knowing whether they had been diagnosed with UL (n = 11) or were missing serum 25(OH)D (n = 184). The final study population was 3,590 individuals. Women excluded from the study population due to missing data were significantly younger, less likely to be white, and less likely to have sufficient Vitamin D (not shown).

2.2 Vitamin D analysis

Serum 25(OH)D was measured in NHANES participants aged 1 year and older [28]. Vials were stored at −20°C between collection and analysis. Analytical methods for serum 25(OH)D measurements are described extensively in Yetley et al. 2010 [29]. Briefly, hydroxylated metabolites including 25(OH)D were extracted from serum samples using acetonitrile, and the treated sample was assayed using the DiaSorin radioimmunoassay kit, an equilibrium radioimmunoassay procedure with an antibody that has specificity to 25(OH)D [30]. Measured 25(OH)D values below 5 ng/mL or greater than 70 ng/mL were verified by reassay. Values less than 5 ng/mL (the lowest standard) were recorded as 3 ng/mL (n = 17, 0.47% of the study population). Blinded split replicate samples were sent to the National Center for Environmental Health laboratory at the CDC [29], and samples with a coefficient of variation greater than 10% were also reassayed. The sensitivity of the assay is at or below 1.5 ng/mL [30]. Information on the number of samples below sensitivity was not available from NHANES.

2.3 UL Ascertainment

UL diagnosis was assessed using the following question in the reproductive health questionnaire, “Has a doctor or other health care professional ever told you that you had uterine fibroids?” Women who answered yes were recorded as having a UL diagnosis.

2.4 Statistical Analysis

Serum 25(OH)D (ng/mL) levels were categorized as deficient, insufficient, or sufficient, and then compared between women with and without reported UL diagnosis using chi-squared tests. To assess the odds of UL by serum OH(25)D level, multiple logistic regression was used. Serum 25(OH)D was log transformed for continuous analyses, and was additionally assessed by quartiles. Data on season, parity, BMI, age, race/ethnicity, history of hysterectomy or oophorectomy, current pregnancy status, age at menarche, last menstrual

period, and menopausal status were obtained from NHANES. Models were adjusted for risk factors determined *a priori*: age (years), race/ethnicity (White, Black, Mexican American), parity (continuous), BMI (continuous), season (November-April or May-October), and average daily physical activity (Mainly sit, Walk a lot, Carry light loads or climb stairs, Heavy work). Models additionally adjusting for current pregnancy (yes or no) and age at menarche (years) did not result in substantially altered results, and those covariates were excluded in final analyses. We did not adjust for oral contraceptives because they may be a consequence of the outcome [31].

2.4 Sensitivity Analysis

Several sensitivity analyses were also done. Models were run without including physical activity because of concerns that adjusting for physical activity constitutes an over-adjustment for confounding [23]. Analyses were conducted in a population including only premenopausal women (excluding women who had undergone hysterectomy or oophorectomy, or had not had periods for 12 months due to menopause), and separately in each racial/ethnic group. To increase the sensitivity of the outcome measure, the population was limited to women younger than 35. To increase the precision of the exposure measure, we conducted an analysis excluding women missing supplement data or who reported using Vitamin D supplements. Finally, we repeated all analyses using a binary version of serum 25(OH)D (sufficient (> 20 ng/mL) versus insufficient (0–20 ng/mL)), based on published nutritional guidelines [32]. All analyses were conducted using SAS 9.3 (Cary, NC) adjusting for the clustered sampling design and the NHANES sample population weights. A (two-sided) P-value <0.05 was considered statistically significant.

To quantify the potential magnitude of effect of the misclassification of undiagnosed women in our analysis, we stratified by race and used a probabilistic sensitivity analysis to model the odds of UL that would have been observed among women with Vitamin D insufficiency in the absence of misclassification, based on race-specific sensitivity and specificity values [33]. We modeled sensitivity as 23%–32% for whites and 34%–58% for blacks, and modeled specificity as 86%–96% in both races, based on Myers et al. 2012 [34]. We ran the model 1000 times for each race, incorporating both systematic and random error in the simulation, to produce probabilistic estimates of the odds ratio (OR) [33].

3. Results

Four hundred sixty-nine women reported a UL diagnosis. About 60% of the overall population had sufficient serum levels of 25(OH)D (Table 1).

Serum 25(OH)D levels also varied by ethnic group. About 93% of non-Hispanic black women and 76% of Mexican American women had serum 25(OH)D levels below the population median, while only 45% of white women did (Table 2).

In multiple logistic regression models, adjusted odds of UL in the whole population were not associated with serum log(25(OH)D) in continuous models, and did not vary by quartile of serum 25(OH)D (Table 3, all p > 0.05). Similarly, adjusted odds of UL were not associated

with serum log(25(OH)D) in continuous models, and did not vary by quartile of serum 25(OH)D among premenopausal women (Table 3, all $p > 0.05$).

Adjusted odds of UL were not associated with serum log(25(OH)D) in continuous models, and also did not vary by serum 25(OH)D quartile in any racial/ethnic group in stratified analysis (Table 4, all $p > 0.05$).

Most sensitivity analyses did not produce a meaningfully different pattern of results. Excluding physical activity as a covariate did not substantially alter results (not shown). Among women who reported not taking Vitamin D supplements (not shown), and among women aged 35 and younger, adjusted odds of UL were not associated with serum log(25(OH)D) in continuous models, and did not vary by serum 25(OH)D quartile (Table 5). Finally, analysis using the binary 25(OH)D variable (sufficient versus insufficient) also did not produce significant differences in adjusted odds of UL in the whole population, in any racial/ethnic group after stratification, or in premenopausal women only (not shown).

In contrast with the other analyses, the probabilistic sensitivity analysis suggested that insufficient serum 25(OH)D was associated with significantly elevated odds of UL in white, but not black, women (white OR median estimate: 2.17 (2.5 and 97.5 percentiles: 1.26, 23.47); black OR median estimate: 1.70 (2.5 and 97.5 percentiles: 0.89, 3.51), not shown).

4. Discussion

Several previous studies have suggested an association between low serum 25(OH)D and increased prevalence of UL [23–26]. However, in this analysis of 3,590 women from NHANES 2001–2006, we did not observe a relationship between UL and serum 25(OH)D. Adjusted analyses in the whole population, in premenopausal women, and in all racial/ethnic groups did not indicate a consistent association between quartile of serum 25(OH)D and UL. In contrast to those results, the probabilistic sensitivity analysis correcting for potential misclassification suggested that insufficient serum 25(OH)D was significantly associated with the odds of UL in white, but not black, women.

The most substantial difference between this study and previous research examining this association is the method of case ascertainment. Most previous studies investigating the association between UL and Vitamin D used ultrasound screening to assess cases, while this study relied on self-reported UL diagnosis. The relatively recent use of ultrasound screening to ascertain case status in observational UL research has cast doubt on the accuracy of self-reported UL data. Based on ultrasound measurements, it has been suggested that a large portion of asymptomatic women may in fact have UL [4], and the proportion of undiagnosed cases may vary by race [34], leading to differential misclassification of outcome in self-reported data. In this study, the different pattern of results produced by the probabilistic sensitivity analysis suggests that misclassification of the outcome likely affected some of our results, though it may not explain all of the null associations reported here.

Despite the potential for misclassification, much of the epidemiological literature on UL depends on self-reported outcomes, including studies based on the Black Women's Health Study (e.g., [11, 26, 35]), and the Nurses' Health Study (e.g. [10, 36, 37]), though those

cohorts both prospectively assess cases, while our study was limited by its cross-sectional design. However, other NHANES studies (e.g., [31, 38, 39]), have relied on cross-sectional self-reported UL data, suggesting that even cross-sectional self-reported UL data can be used to suggest possible risk factors. Additionally, self-reported data may better represent the population of women with serious or symptomatic cases, because it excludes the large number of undiagnosed women, who have smaller tumors on average [4], and may not realize they have UL because they experience fewer symptoms. Therefore, self-reported data may reflect a more clinically relevant measurement of UL outcomes because it may better reflect more severe cases of UL.

Other than the probabilistic sensitivity analysis, sensitivity analyses largely confirmed the overall null association found in the main analysis. Analysis removing women who took Vitamin D supplementation did not alter the null association between serum 25(OH)D and UL (not shown). Neither removing physical activity from the models, nor reclassifying 25(OH)D exposure as insufficient versus sufficient, produced a significant association between 25(OH)D and UL. The sensitivity analysis done in women under age 35 suggested an inverse association between serum 25(OH)D and UL, but the trend was not significant (Table 5, $P_{trend} = 0.25$).

There are several reasons other than misclassification that our results may differ from the results of previous studies examining this association. Our analysis used a population-based, geographically diverse population with varying levels of access to screening and insurance, and was not selected based on any other clinical or reproductive considerations such as infertility, and so may reflect a different base population than previous analyses. This study is also unique because it includes women over a wider age range (20–54 years) and includes those who had undergone hysterectomies. Because hysterectomy is used to treat UL [7] excluding women with hysterectomy leaves open the question of whether Vitamin D and UL are associated in women who underwent hysterectomy, who perhaps had more serious symptoms or more advanced cases. Excluding women with hysterectomy may also alter the population under study so that it no longer matches the base population of women with UL, as about 250,000 women with UL choose to undergo hysterectomy every year [40]. Furthermore, our use of NHANES data allowed for precise measurement of serum 25(OH)D with a state-of-the-art biological marker of exposure and important possible confounders, such as season and physical activity, in a large population, strengthening this analysis. Finally, our analysis was the first to test this association in Mexican American women, as every previous analysis has examined the association in blacks and whites only.

Similar to previous studies, our analysis was limited by the cross-sectional nature of the data and thus we cannot infer causal inference. Serum 25(OH)D was measured after UL diagnosis because of the design of NHANES; in some cases, many years had elapsed between diagnosis and Vitamin D measurement. However, Vitamin D level has been shown to be moderately stable over time in both blacks and whites, though subject to seasonal variation [41, 42]. NHANES data are typically collected in northern latitudes during the summer months and in southern latitudes during the winter months [43], though information on the precise geographic location and month of data collection were not available.

Therefore, although we were able to adjust for season, we could not separately adjust for geographic location.

5. Conclusions

Several recent studies have reported an inverse association between serum Vitamin D levels and odds of UL. In this population-based study of women aged 20–54, we found no association between serum Vitamin D levels and adjusted odds of UL in the whole population, in premenopausal women only, in any stratified racial/ethnic group, in women under age 35, or in women not taking Vitamin D supplements. Because we used self-reported UL diagnosis as the outcome measure, our null findings may be attributable to under-reporting of true cases. However, because much of the literature on UL is based on self-reported case status, a null finding using population-based NHANES data adds an important perspective to the literature investigating this association. Additional prospective epidemiology research and animal studies are needed to clarify the relationship between Vitamin D and UL risk.

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Abbreviations

UL	Uterine leiomyomata
BMI	body mass index
25(OH)D	25-hydroxyvitamin D
NHANES	National Health and Nutrition Examination Survey
CDC	US Centers for Disease Control and Prevention
NCHS	National Center for Health Statistics
OR	odds ratio
AOR	Adjusted Odds Ratio

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Research Highlights

- We tested the relationship between Vitamin D exposure and uterine leiomyoma
- No relationship was found in population-based analyses
- We used self-reported outcomes, so misclassification may explain the null results
- An analysis correcting for misclassification suggests an association in white women

Table 1

Demographic characteristics and serum OH(25)D levels in the whole population. Percentages are weighted to reflect the national population.

Characteristic	Whole Population (n=3590) n (weighted %)
UL diagnosis (yes)	469 (14.3%)
Age	
20–35	1847 (42.9%)
36–45	947 (29.8%)
46–54	796 (27.3%)
Race	
Non-Hispanic Black	808 (13.3%)
Non-Hispanic White	1896 (77.3%)
Mexican American	886 (9.4%)
BMI	
< 25	1228 (40.7%)
25 – 30	1009 (24.9%)
> 30	1353 (34.4%)
Parity	
0	860 (26.5%)
1–2	1723 (48.0%)
> 2	1007 (25.5%)
Hysterectomy	352 (30.9%)
Serum 25(OH)D	
At risk of deficiency (<10 ng/mL)	354 (6.8%)
At risk of inadequacy (10–20 ng/mL)	1280 (30.9%)
Sufficient (>20 ng/mL)	1956 (62.3%)

Table 2

Distribution of participants within each racial/ethnic group, by quartiles of 25(OH)D.

Quartiles of 25(OH)D	Non-Hispanic Black	Non-Hispanic White	Mexican American	p
Lowest (3.0–17.0 ng/mL)	74.5%	15.3%	44.7%	< 0.01*
Second (18.0–24.0 ng/mL)	18.9%	29.7%	31.5%	
Third (25.0–30.0 ng/mL)	5.0%	26.0%	15.4%	
Highest (31.0–80.0 ng/mL)	1.6%	29.0%	8.3%	

* $p < 0.05$

Table 3

Unadjusted and adjusted[a] odds of UL by quartile of serum OH(25)D.

Vitamin D	Cases/n		OR (95%CI)	Adjusted OR (95% CI)
Whole Population				
Continuous[b]	469/3590		0.76 (0.65, 0.90)*	1.17 (0.89, 1.55)
Q1 (3.0–17.0 ng/mL)	192/1227		Reference	Reference
Q2 (18.0–24.0 ng/mL)	127/943		1.08 (0.79, 1.46)	1.33 (0.94, 1.89)
Q3 (25.0–30.0 ng/mL)	87/691		1.07 (0.84, 1.35)	1.42 (0.97, 2.07)
Q4 (31.0–80.0 ng/mL)	63/729		0.66 (0.50, 0.88)*	1.18 (0.81, 1.72)
			$P_{trend} < 0.01$*	$P_{trend} = 0.37$
	Highest Q	**Lowest 3 Q**	**OR (95%CI)**	**AOR[c] (95%CI)**
Highest v Lowest 3 Q	63/729	406/2861	0.63 (0.49, 0.82)*	0.91 (0.67, 1.23)
Premenopausal Women				
Continuous[b]	218/2873		0.69 (0.52, 0.92)*	1.09 (0.67, 1.78)
Q1 (3.0–17.0 ng/mL)	93/945		Reference	Reference
Q2 (18.0–24.0 ng/mL)	60/737		0.94 (0.63, 1.41)	1.07 (0.66, 1.74)
Q3 (25.0–30.0 ng/mL)	35/567		0.88 (0.62, 1.26)	1.13 (0.68, 1.87)
Q4 (31.0–80.0 ng/mL)	30/624		0.59 (0.36, 0.94)*	1.05 (0.58, 1.91)
			$P_{trend} = 0.01$*	$P_{trend} = 0.82$
	Highest Q	**Lowest 3 Q**	**OR (95%CI)**	**AOR[c] (95%CI)**
Highest v Lowest 3 Q	30/624	188/2249	0.62 (0.40, 0.97)*	0.97 (0.62, 1.53)

[a] Adjusted models control for race, age, parity, BMI, season, and physical activity

[b] Continuous odds ratios calculated using log-transformed serum OH(25)D, and represent the change in odds of UL for each natural log-unit increase in OH(25)D.

[c] AOR: Adjusted Odds Ratio

* $p < 0.05$

Table 4

Unadjusted and adjusted[a] odds of UL by quartile of serum OH(25)D, stratified by race.

Vitamin D	Cases/n		OR (95%CI)	Adjusted OR (95%CI)
Whites				
Continuous[b]	221/1896		0.85 (0.63, 1.16)	1.16 (0.78, 1.74)
Q1 (5.0–20.0 ng/mL)	62/458		Reference	Reference
Q2 (21.0–26.0 ng/mL)	63/490		0.97 (0.68, 1.38)	0.98 (0.68, 1.41)
Q3 (27.0–32.0 ng/mL)	50/447		0.92 (0.64, 1.33)	1.00 (0.65, 1.53)
Q4 (33.0–80.0 ng/mL)	46/501		0.72 (0.47, 1.08)	0.97 (0.63, 1.51)
			$P_{trend} = 0.07$	$P_{trend} = 0.93$
	Highest Q	**Lowest 3 Q**	**OR (95%CI)**	**AOR[c] (95%CI)**
Highest v Lowest 3 Q	46/501	175/1395	0.74 (0.53, 1.04)	0.98 (0.69, 1.39)
Blacks				
Continuous[b]	185/808		1.02 (0.74, 1.41)	1.14 (0.78, 1.65)
Q1 (3.0–9.0 ng/mL)	53/241		Reference	Reference
Q2 (10.0–13.0 ng/mL)	44/195		1.05 (0.68, 1.62)	1.17 (0.62, 2.18)
Q3 (14.0–18.0 ng/mL)	50/186		1.34 (1.03, 1.75)*	1.45 (0.95, 2.20)
Q4 (19.0–41.0 ng/mL)	38/186		0.92 (0.55, 1.54)	1.00 (0.58, 1.72)
			$P_{trend} = 0.87$	$P_{trend} = 0.62$
	Highest Q	**Lowest 3 Q**	**OR (95%CI)**	**AOR[c] (95%CI)**
Highest v Lowest 3 Q	38/186	147/622	0.83 (0.54, 1.27)	0.85 (0.57, 1.26)
Mexican Americans				
Continuous[b]	63/886		1.04 (0.52, 2.09)	1.38 (0.64, 2.98)
Q1 (3.0–13.0 ng/mL)	19/219		Reference	Reference
Q2 (14.0–18.0 ng/mL)	11/195		0.66 (0.31, 1.42)	0.84 (0.36, 1.98)
Q3 (19.0–24.0 ng/mL)	15/242		1.03 (0.44, 2.39)	1.19 (0.47, 2.99)
Q4 (25.0–68.0 ng/mL)	18/230		1.07 (0.49, 2.36)	1.71 (0.68, 4.30)
			$P_{trend} = 0.68$	$P_{trend} = 0.25$
	Highest Q	**Lowest 3 Q**	**OR (95%CI)**	**AOR[c] (95%CI)**
Highest v Lowest 3 Q	18/230	45/656	1.19 (0.62, 2.29)	1.66 (0.79, 3.51)

[a] Adjusted models control for age, parity, BMI, season, and physical activity

[b] Continuous odds ratios calculated using log-transformed serum OH(25)D, and represent the change in odds of UL for each natural log-unit increase in OH(25)D.

[c] AOR: Adjusted Odds Ratio

* $p < 0.05$

Table 5

Sensitivity analysis among women under age 35. Unadjusted and adjusted[a] odds of UL by quartile of serum OH(25)D.

Vitamin D	Cases/n		OR (95%CI)	Adjusted OR (95% CI)
Continuous[b]	60/1847		0.61 (0.39, 0.98)*	1.05 (0.50, 2.17)
Q1 (3.0–17.0 ng/mL)	23/561		Reference	Reference
Q2 (18.0–24.0 ng/mL)	16/435		0.90 (0.44, 1.83)	1.00 (0.41, 2.47)
Q3 (25.0–32.0 ng/mL)	9/471		0.33 (0.13, 0.84)*	0.43 (0.14, 1.35)
Q4 (33.0–80.0 ng/mL)	12/380		0.49 (0.21, 1.14)	0.70 (0.26, 1.89)
			$P_{trend} = 0.02$*	$P_{trend} = 0.25$
	Highest Q	**Lowest 3 Q**	**OR (95%CI)**	**AOR[c] (95%CI)**
Highest v Lowest 3 Q	12/380	48/1467	0.67 (0.33, 1.37)	0.95 (0.47, 1.94)

[a] Adjusted models control for race, age, parity, BMI, season, and physical activity

[b] Continuous odds ratios calculated using log-transformed serum OH(25)D, and represent the change in odds of UL for each natural log-unit increase in OH(25)D.

[c] AOR: Adjusted Odds Ratio

* $p < 0.05$