# Vitamin D Concentrations and Obstructive Sleep Apnea in a Multicenter Cohort of Older Males

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Vitamin D and obstructive sleep apnea


## Abstract:

**Rationale:** Seasonal nadirs in 25-hydroxyvitamin D (25[OH]D) concentrations overlap with increased incidence and severity of obstructive sleep apnea (OSA) in winter. We hypothesized that because lower 25(OH)D concentrations might lead to upper airway muscle dysfunction, low 25(OH)D would be associated with higher apnea-hypopnea index (AHI), a measure of OSA severity.

**Objectives:** To determine if lower 25(OH)D concentration is associated with greater prevalence and increased severity of OSA, independent of established OSA risk factors.

**Methods:** Using unconditional logistic regression, we performed a cross-sectional analysis in the Outcomes of Sleep Disorders in Older Men study which included in-home overnight polysomnography, serum 25(OH)D measurement, and collection of demographic and co-morbidity data. The primary outcome was severe sleep apnea as defined by AHI $\geq$ 30/hr.

**Measurements and Main Results:** Among 2,827 community-dwelling, largely Caucasian (92.2%), elderly ([mean±SD] age 76.4±5.5 years) males, mean 25(OH)D concentration was 28.8±8.8 ng/mL. Subjects within the lowest quartile of 25(OH) D (6-23 ng/mL) had greater odds of severe sleep apnea in unadjusted analyses (OR 1.45; 95% CI: 1.02-2.07) when compared to the highest 25(OH)D quartile (35-84 ng/mL). However, further adjustment for established OSA risk factors strongly attenuated this association (multivariable adjusted OR 1.05; 95% CI: 0.72-1.52), with body mass index and neck circumference as the main confounders. There was also no evidence of an independent association between lower 25(OH)D levels and increased odds of mild (AHI 5.0-14.9/hr) or moderate (AHI 15.0-29.9/hr) sleep apnea.

**Conclusions:** Among community-dwelling older men, the association between lower 25(OH)D and sleep apnea was largely explained by confounding by larger BMI and neck circumference.

## Introduction:

Obstructive sleep apnea (OSA) is a disease of recurrent, partial or complete upper airway closure during sleep. The pathogenesis of OSA is complex[1] and a recent study reported increased OSA incidence and severity during winter months[2]. Although the magnitude of the effect was modest (median difference in apnea-hypopnea index [AHI] of 3.3 events/hr), the authors hypothesized that winter-related fat redistribution, medication use, fluid displacement to the neck, and/or air pollution were the reasons for their observation. However, an alternative explanation of the seasonal variation in OSA may be the coinciding winter nadir of vitamin D[3].

Low circulating 25-hydroxyvitamin D [25(OH)D] concentrations are associated with poor musculoskeletal function[4, 5]. Control of upper airway muscle tone is felt to be a major contributor to OSA[1] and therefore, patients with low 25(OH)D concentrations might have an increased risk of OSA due to worse function of the skeletal muscle supporting upper airway patency during sleep. Low 25(OH)D concentrations are also associated with airway inflammation, chronic rhinitis and repeated upper airway infections leading to tonsillar enlargement[6-10] , which may additionally contribute to OSA incidence and severity. Low 25(OH)D concentrations are also associated with type 2 diabetes mellitus, metabolic syndrome and obesity, all of which are frequently found in patients with OSA[11, 12]. Only a few studies have studied the association between lower 25(OH)D levels and OSA and these have reported inconsistent results[13-15].

To better address this knowledge gap, we analyzed data from a large, multi-center,

community-based cohort study and tested the hypothesis that lower blood concentrations of 25(OH)D are associated with greater prevalence and increased severity of OSA, independent of classic OSA risk factors.

## Methods:

### Study participants

The Osteoporotic Fractures in Men (MrOS) Study enrolled 5,995 community-dwelling men aged 65 and older during the baseline examination between 2000 and 2002[16, 17]. To be eligible for the study, men had to be able to walk without assistance and not have had a bilateral hip replacement. Participants were recruited at six clinical centers (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA). The Outcomes of Sleep Disorders in Older Men Study (MrOS Sleep) visit occurred on average 3.4 ± 0.5 years (range 1.9–4.9) after the baseline examination, between December 2003 and March 2005. Ethics approval was obtained from the institutional review board at each site and the Coordinating Center and Reading Center. Written informed consent for participation in the MrOS Sleep Study was obtained for all individuals. The MrOS Sleep Study was an ancillary study with a target recruitment number of 3,000 men from the parent MrOS Study. Exclusions for the MrOS Sleep Study included use of nocturnal positive airway pressure or oral appliance devices, use of supplemental oxygen use, and presence of an open tracheostomy. Of the 5,995 MrOS participants, 3,135 participated in the MrOS Sleep Study, while 2,860 participants in the main cohort did not participate in the MrOS Sleep Study. Of the non-participants in the MrOS Sleep Study, 1,997 refused participation, and compared to those who participated in MrOS Sleep, those who refused participation were older by 1 year

(74.01 years ± 5.88 vs. 73.05 years ± 5.55, p<0.001) and not significantly different with respect to body mass index (BMI; 27.20 ± 3.72 kg/m$^2$ vs. 27.38 ± 3.72 kg/m$^2$, p=0.10)[18].

Of 3,135 MrOS Sleep Study participants, 2,911 (92.8 %) had at least 4 hours of technically adequate sleep study data for analysis, and of these, 2,827 (90.2 %) had 25(OH)D concentrations measured. These 2,827 men constituted the analytical cohort for the current study.

**Polysomnography and other sleep-related measures**

In-home sleep studies using unattended polysomnography (Safiro, Compumedics, Inc., Melbourne, Australia) were performed. The recording montage consisted of C3/A2 and C4/A1 electroencephalograms, bilateral electrooculograms, a bipolar submental electromyogram, thoracic and abdominal respiratory inductance plethysmography, airflow (using nasal-oral thermocouple and nasal pressure cannula), finger pulse oximetry, electrocardiogram, body position (mercury switch sensor), and bilateral leg movements (piezoelectric sensors). Trained certified staff members performed home visits for setup of the sleep study units. After sensors were placed and calibrated, signal quality and impedance were checked, and sensors were repositioned as needed to improve signal quality, replacing electrodes if impedances were greater than 5 kΩ, using approaches similar to those in the Sleep Heart Health Study[19]. After studies were downloaded, they were transferred to the Case Reading Center (Cleveland, OH) for centralized scoring by a trained technician. Polysomnography data quality was excellent, with a failure rate of less than 4% and more than 70% of studies graded as being of excellent or outstanding quality. Quality codes for signals and studies were graded

using previously described approaches, which included coding the duration of artifact-free data per channel and overall study quality (reflecting the combination of grades for each channel). We note that central apnea events were included in the overall apnea-hypopnea index (AHI), but such events were rare (only 7% of study participants had a central apnea index ≥5/hr).

**Vitamin D analysis:**

Serum for vitamin D analysis was collected at baseline of the MrOS Sleep Study and immediately frozen at -70˚C. Concentrations of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (ThermoFisher Scientific, Franklin, Massachusetts 02038 and Applied Biosystems-MDS Sciex, Foster City, CA 94404) at the Mayo Clinic Reference Laboratories (Singh RJ, PhD, Mayo Clinic Laboratory, Rochester, MN), using fasting samples collected at the Sleep Visit. Deuterated stable isotope (d3-25-hydroxyvitamin D) was added to a 0.2 ml serum sample as internal standard. 25-hydroxyvitamin D2, 25-hydroxyvitamin D3, and the internal standard were extracted using acetonitrile precipitation. The extracts were then further purified online and analyzed by LC-MS/MS using multiple reaction monitoring. Using three different target markers as quality controls for each assay, inter-assay CVs for 25-hydroxyvitamin D3 were 9.7% at 9.0 IUs, 7.5% at 29 IUs, and 5.8% at 76 IUs. For 25-hydroxyvitamin D2, CVs were 11.2% at 11 IUs, 8.5% at 28 IUs, and 7.7% at 74 IUs. The minimum detectable limit for 25-hydroxyvitamin D2 was 4 ng/ml and for 25-hydroxyvitamin D3 was 2 ng/ml. Total 25-hydroxyvitamin D [25(OH)D] was calculated by adding 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3.

**Clinical data:**

All covariate data were collected at the time of the sleep study visit. All participants completed questionnaire data, which included questions about medical history, smoking, and alcohol intake. Hypertension was defined as a positive response to the question, "Has a doctor or other healthcare provider told you that you have hypertension or high blood pressure?". Race was based on self-report and categorized as Caucasian, African American, Asian, or Hispanic/other. BMI was calculated as weight (kg)/height ($m^2$), and obesity was defined as a BMI greater than 30 $kg/m^2$. During the home or clinic visits, body weight was measured using a standard balance beam scale and height using a wall-mounted Harpenden stadiometer (Holtain, UK). Neck and waist circumference were also measured using standard methods. Snoring was assessed according to self-report. The MacArthur Subjective Status Scale (range 1–10) was used to assess perceived social status, with higher scores representing higher perceived social status. Participants were asked to bring in all current medications used within the preceding 30 days. All prescription and non-prescription medications were entered into an electronic database and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA). A variable for season (January-March=Winter; April-June=Spring; July-September=Summer; October-December=Fall) was calculated using the date of the participant's clinic exam.

**Statistical analysis:**

In primary analyses, we expressed 25(OH)D concentrations in quartiles and compared baseline characteristics across quartiles using analysis of variance or

chi-square testing for continuous or categorical variables, respectively. We also used the following fixed 25(OH)D categories in our analyses: <20 ng/mL, 20-29.9 ng/mL, and ≥30 ng/mL; but because results were similar, we present quartiles as our primary 25(OH)D variable.

We used unconditional logistic regression models to calculate odds ratios and 95% confidence intervals for 25(OH)D quartiles (referent group quartile 4) for the primary dichotomous outcome of severe sleep apnea as defined by AHI ≥30/hr and a secondary dichotomous outcome of at least moderate sleep apnea defined by AHI ≥15/hr. We created four logistic regression models including an unadjusted model, a model adjusted for established OSA risk factors[18, 20-22](age, BMI, neck circumference and hypertension), a model further adjusted for season of blood draw[23] and a fully adjusted model that included the above variables along with medications that may affect upper airway patency (opiates, benzodiazepines and alcohol)[20, 24, 25], race, smoking and clinic site. We conducted a sensitivity analysis to evaluate the effect of selected variables (BMI, neck circumference, hypertension) on the outcome by adding one variable at a time to the crude model. We also conducted two secondary analyses expressing 25(OH)D using clinical cutpoints (<20 ng/mL, 20-29.9 ng/mL, and ≥30 ng/mL)[26] and a polytomous regression model comparing outcomes of AHI 0-4.9/hr (no OSA) to standard OSA severity categories of mild (AHI 5-14.9/hr), moderate (AHI 15-29.9/hr) and severe (AHI ≥30/hr) OSA.

In exploratory analyses, to examine effect modification by BMI, we evaluated the association between 25(OH)D and OSA excluding men with BMI ≥30 kg/m$^2$ hypothesizing that the relationship between 25(OH)D and OSA would be stronger

in non-obese men. We also tested for an interaction between 25(OH)D and BMI for the prediction of severe OSA, using the log-likelihood ratio test.

## Results:

Among 3,135 participants who attended the MrOS Sleep visit, 2,911 (92.9 %) participants had at least 4 hours of technically adequate sleep study data for analysis. 2,827 (90.2 %) of these men had 25(OH)D concentrations measured and constituted the analytical cohort.

The study cohort consisted of largely Caucasian (92.2%) older men ([mean±SD] age 76.4±5.5 years), with a mean BMI of 27.2±3.8 kg/m$^2$. The demographic and co-morbid disease characteristics of the study participants are provided in Table 1.

The mean 25(OH)D concentration was 28.8±8.8 ng/mL, with concentrations ≥30 ng/mL (widely considered to represent replete vitamin D status) in 1,247 (44.1%), between 20-29.9 ng/mL (widely considered vitamin D insufficient) in 1,205 (42.6%), and <20 ng/mL (widely considered vitamin D deficient) in 375 (13.3%). The distribution of AHI categories 0-4.9, 5-14.9, 15-29.9 and ≥ 30 events/hour was 1,105 (39%), 977 (34.6%), 470 (16.6%) and 276 (9.8%) respectively. Among the 276 participants with AHI ≥30/hr, 50 (18.1%) were 25(OH)D deficient (<20 ng/mL), compared to 134 (12.1%) who were 25(OH)D deficient among those with AHI <5/hr (p=0.06).

Participants in the lowest quartile of 25(OH) D (6-23 ng/mL) had greater odds of AHI ≥30/hr (crude OR 1.45; 95% CI 1.02-2.07), compared to participants in the highest 25(OH)D quartile (35-84 ng/mL) (Table 2). After adjustment for

traditional OSA risk factors, this association was no longer evident (adjusted OR 1.05; 95%CI 0.72-1.52). Further adjustment for season and other covariates did not alter these results. Findings were similar when AHI ≥15/hour was substituted for AHI ≥30/hr, when 25(OH)D was expressed using clinical cutpoints of <20 ng/mL, 20-29.9 ng/mL, and ≥30 ng/mL, and in polytomous regression evaluating the association between 25(OH)D quartiles and odds of no OSA vs. mild/moderate/severe OSA (Table 3).

Sensitivity analysis suggested that the association between lower 25(OH)D concentrations and higher odds of OSA was largely explained by greater BMI and larger neck circumference among those men with lower 25(OH)D concentrations (Table 4).

In exploratory analysis restricted to those with BMI <30 kg/m$^2$ (n=2,255; 79.8% of overall cohort), the modest association between low 25(OH)D and higher odds of severe sleep apnea did not reach significance (fully-adjusted OR [quartile 1 vs. quartile 4] of AHI ≥30/hr = 1.27; 95%CI 0.82-1.97; fully-adjusted OR [25(OH)D <20 ng/mL vs. ≥30 ng/mL] of AHI ≥30/hr = 1.44 ; 95% CI 0.90-2.28). There was no evidence of an interaction between obesity (BMI <30 vs. ≥30 kg/m$^2$) and 25(OH)D for the prediction of AHI ≥30/hr, when 25(OH)D was categorized by quartiles (p=0.197) or by clinical cutpoints (p=0.562).

## Discussion:

Despite plausible mechanisms potentially connecting vitamin D deficiency to OSA pathogenesis and severity, we found no evidence of an independent

association between 25(OH)D concentration and OSA in our analyses of this cohort of older community-dwelling men.

Our findings suggest that the association between lower 25(OH)D levels and a higher odds of OSA was due in large part to greater BMI and larger neck circumference among participants with lower 25(OH)D levels. These results indicate that low 25(OH)D may simply be a marker of larger BMI and neck circumference, rather than directly contributing to OSA pathogenesis.

Several lines of evidence link obesity with lower 25(OH)D concentrations. Obese subjects are more likely to be restricted in physical activity, thus limiting their exposure to sunlight and resulting in lower 25(OH)D concentrations[27]. Additionally, inflammatory cytokines upregulated in adiposity are known to inversely affect 25(OH)D bioavailability and increase its metabolic clearance[28]. Finally, poor dietary habits leading to obesity often provide a poor source of oral vitamin D intake.

We explored the possibility that 25(OH)D effects on OSA pathogenesis might be most pronounced in non-obese participants, since mechanisms other than soft tissue accumulation and external airway pressure might account for loss of upper airway patency during sleep in non-obese individuals. In these analyses, we observed similar non-significant findings, although the adjusted OR point estimates for low 25(OH)D and AHI≥30/hr were higher than in analyses that included both obese and non-obese individuals. There was no evidence of an interaction between obesity and 25(OH)D on OSA, but further studies with larger sample sizes are needed to more definitively evaluate the potential role of vitamin D deficiency in the pathogenesis of OSA in non-obese individuals.

Vitamin D and obstructive sleep apnea

Despite reasons to believe that vitamin D deficiency may play a role in the pathogenesis of OSA, few studies to date have explored this potential association and these have reported mixed results. In a selected population of 150 adult OSA patients (50 patients each with mild, moderate and severe OSA) and controls matched on BMI, gender and age (n=32), Mete and colleagues[13] noted no significant difference in 25(OH)D concentrations between OSA patients and controls (17.9 ± 9.3 μg/dL vs. 19.2 ± 7.2 μg/dL; p=0.468). However, the authors reported that among those with AHI >30/hr, 78% were 25(OH)D deficient (<20 μg/dL), compared to 50% among controls with AHI <5/hr (p=0.02). We found similar results in our population of older men, although our observed difference in prevalence of 25(OH)D deficiency was smaller in magnitude (18.1% among those with AHI ≥30/hr, and 12.1% among those with AHI <5/hr). However, the study by Mete and colleagues notably preselected obese patients in their study (mean BMI of 32 kg/m$^2$), and they were therefore not able to adjust for the effect of BMI on the relationship between 25(OH)D and AHI. We have addressed this in our study by enrolling an unselected population of community-dwelling older men with a wide range of BMI (and AHI) and adjusting our analysis for BMI and several other potential confounders.

In contrast to the results of Mete and colleagues and our study, Kheirandish-Gozal and colleagues[14] found a statistically significant correlation between 25(OH)D concentrations and AHI ($r = -0.285$, $p < 0.001$) in pediatric OSA patients (mean age 6.5 to 7.2 years). The relevance of these results to adult OSA is not clear, because pediatric OSA has a very different pathogenesis than adult OSA. In children, upper airway inflammation, in the form of adenotonsillar hypertrophy, is felt to be the major contributor to OSA[29] as opposed to adults, in whom fat

redistribution, upper airway muscle dysfunction and age-related changes in upper airway anatomy are felt to be the major contributors[1].

More recently, Bertisch and colleagues[15] studied the association between 25(OH)D concentrations and various sleep measures including AHI in a multi-center, multi-ethnic cohort of 1,721 adults with a mean age of 68.2 years. The authors reported that those with 25(OH)D <20 ng/mL had a statistically higher median AHI (2.1 events/hr higher) than those with 25(OH)D >29 ng/mL. Similar to our findings, those with lower 25(OH)D concentrations were also more obese. Also similar to our findings, the AHI difference was no longer significant after adjusting for covariates such as age, gender, and waist circumference. In exploratory analyses, the authors found that AHI was higher by 7.1 events/hour in Chinese-American participants, (n=205) with low 25(OH)D compared to higher 25(OH)D, but this was not found in the Caucasian, African-American or Hispanic-American participants. The authors importantly noted that 25(OH)D concentrations were measured an average of 10.3 years prior to the collection of polysomnography data, so whether or not 10-year old 25(OH)D measures reflect 25(OH)D status at the time of polysomonography is a major limitation. Our 25(OH)D and polysomnography data were concurrent and therefore truly cross-sectional. Nevertheless, the data from their cohort and our cohort would appear to be consistent with an overall lack of association between 25(OH)D concentrations and sleep apnea.

The main strengths of our study are the large sample size and the community-based sample of older men. Our participants were not preselected for presence of any condition, particularly OSA, vitamin D deficiency, or obesity, thus minimizing selection biases. Despite the community-based sampling design, we

had a wide distribution of AHI, 25(OH)D concentrations, and BMI, thus allowing us to analyze such relationships across a wide range of these variables seen in clinical practice. Additional strengths of our study include performance of 25(OH)D assays at an experienced, high-quality reference laboratory, careful review and cleaning of sleep study data, and accurate measurement of potential confounders of 25(OH)D and OSA.

Our study has some inherent limitations as well. Our study participants were generally healthy, largely Caucasian, elderly males, so we cannot generalize these findings to non-Caucasians, females and younger patients. This was also a cross-sectional analysis with a single night's measurement of sleep and a single 25(OH)D measurement. Although our data suggest that low 25(OH)D is not likely to predict future development of OSA, a longitudinal study design would be required to specifically test such a hypothesis. We also note that although measures of OSA typically display high night-to-night reliability[30], 25(OH)D levels vary by season, latitude, skin tone, sunscreen use, and time spent outdoors. We adjusted for season in our regression analysis, but we had no measures of within-participant seasonal variation in 25(OH)D concentrations or other factors that may have varied over time. Therefore, our single 25(OH)D measure may not fully reflect seasonal variations throughout the year. The aim of our study was also to assess vitamin D status irrespective of vitamin D source (outdoor sunlight exposure, diet, or oral supplement use). Our analyses were adjusted for season of blood draw and geographic region, but we acknowledge that different sources of vitamin D may have differential impacts on factors such as seasonal variations in 25(OH)D concentrations and prevalence of individuals with vitamin D deficiency. Lastly, we note that some data suggest that myopathy related to vitamin D deficiency may be most pronounced at very low 25(OH)D concentrations such as

<12 ng/mL[31]. Because our community-dwelling cohort had very few persons with such low levels (only 2.1% had concentrations <12 ng/mL), our study is not able to adequately address whether profound vitamin D deficiency could be independently associated with OSA.

## Conclusions:

Among community-dwelling older men, the association between lower serum 25(OH)D concentrations and higher odds of sleep apnea was explained by greater BMI and larger neck circumference among those with lower 25(OH)D levels.

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**Table 1.** Characteristics of 2827 participants by 25(OH)D quartiles

| Variable | Overall Cohort (n=2827) | Serum 25(OH) D Quartiles | | | | *P* Value |
|---|---|---|---|---|---|---|
| | | Q1 6-23 ng/mL (n=767) | Q2 24-28 ng/mL (n=686) | Q3 29-34 ng/mL (n=678) | Q4 35-84 ng/mL (n=696) | |
| Age, years | 76.4 ± 5.5 | 76.8 ± 5.6 | 76.4 ± 5.5 | 76.1 ± 5.4 | 76.3 ± 5.6 | 0.10 |
| Caucasian, % | 92.2 | 88.7 | 92.4 | 93.7 | 94.4 | 0.0002 |
| BMI, kg/m$^2$ | 27.2 ± 3.8 | 28.1 ± 4.2 | 27.5 ± 4.0 | 26.7 ± 3.4 | 26.3 ± 3.1 | <.0001 |
| Neck circumference, cm | 39.4 ± 2.8 | 40.0 ± 2.9 | 39.6 ± 2.9 | 39.2 ± 2.6 | 38.9 ± 2.6 | <.0001 |
| Systolic blood pressure, mmHg | 126.8±16.2 | 126.8±16.9 | 126.7±16.1 | 126.8±16.3 | 126.9±15.7 | 0.99 |
| Current Smoker, % | 2.0 | 2.4 | 2.2 | 1.2 | 2.2 | 0.68 |
| Alcohol intake, > 14 drinks/wk, % | 5.4 | 3.9 | 6.0 | 3.6 | 8.2 | <.0001 |
| Benzodiazepine use, % | 4.63 | 4.82 | 4.52 | 4.28 | 4.89 | 0.95 |
| Opiate use, % | 3.30 | 5.22 | 3.64 | 3.10 | 3.30 | 0.137 |
| Winter (Jan-March), % | 33.4 | 42.6 | 32.1 | 31.0 | 26.7 | <.0001 |
| Spring (April-June), % | 25.3 | 26.6 | 27.1 | 26.3 | 21.0 | <.0001 |
| Summer (July-Sept), % | 22.6 | 15.8 | 24.1 | 23.0 | 28.2 | <.0001 |
| Fall (October-Dec), % | 18.8 | 15.0 | 16.8 | 19.8 | 24.1 | <.0001 |
| AHI 0-4.9/hr, % | 39.1 | 37.2 | 39.7 | 39.1 | 40.5 | 0.26 |
| AHI 5-14.9/hr, % | 34.6 | 34.9 | 31.3 | 36.3 | 35.6 | 0.26 |
| AHI 15-29.9/hr, % | 16.6 | 16.8 | 17.8 | 15.9 | 16.0 | 0.26 |
| AHI ≥30/hr, % | 9.8 | 11.1 | 11.2 | 8.7 | 7.9 | 0.26 |
| AHI, events/hr | 11.8 ± 12.9 | 12.4 ± 13.3 | 12.4 ± 13.2 | 11.4 ± 12.7 | 10.9 ± 12.5 | 0.08 |
| 25(OH)D, ng/mL | 28.8 ± 8.8 | 18.5 ± 4.0 | 26.0 ± 1.4 | 31.4 ± 1.7 | 40.37 ±5.5 | <.0001 |

**Table 2:** Logistic regression for odds of obstructive sleep apnea

| 25(OH)D Quartiles | OR (95% CI) of AHI ≥15/hr | OR (95% CI) of AHI ≥30/hr |
|---|---|---|
| Crude | | |
| Q1 vs. Q4 | 1.24 (0.98-1.56) | 1.45 (1.02-2.07) |
| Q2 vs. Q4 | 1.31 (1.03-1.66) | 1.47 (1.02-2.12) |
| Q3 vs. Q4 | 1.04 (0.82-1.34) | 1.11 (0.76-1.63) |
| p-for-trend | 0.027 | 0.016 |
| Adjusted for typical OSA risk factors* | | |
| Q1 vs. Q4 | 0.96 (0.75-1.23) | 1.05 (0.72-1.52) |
| Q2 vs. Q4 | 1.11 (0.87-1.43) | 1.18 (0.81-1.72) |
| Q3 vs. Q4 | 0.98 (0.76-1.27) | 1.06 (0.72-1.57) |
| p-for-trend | 0.940 | 0.737 |
| Adjusted for typical OSA risk factors* and 25(OH)D modifiers# | | |
| Q1 vs. Q4 | 0.94 (0.72-1.22) | 0.97 (0.65-1.44) |
| Q2 vs. Q4 | 1.13 (0.87-1.46) | 1.15 (0.78-1.70) |
| Q3 vs. Q4 | 1.00 (0.77-1.29) | 1.05 (0.71-1.56) |
| p-for-trend | 0.827 | 0.931 |
| Fully adjusted^ | | |
| Q1 vs. Q4 | 0.94 (0.72-1.23) | 0.96 (0.65-1.43) |
| Q2 vs. Q4 | 1.13 (0.87-1.47) | 1.15 (0.78-1.70) |
| Q3 vs. Q4 | 0.98 (0.75-1.27) | 0.99 (0.66-1.48) |
| p-for-trend | 0.884 | 0.993 |

*: "typical OSA risk factors" covariates: age, body mass index, neck circumference, hypertension
#: winter season: January – March
^: fully adjusted covariates: age, body mass index, neck circumference, hypertension, winter season, clinic site, race, alcohol consumption, smoking, benzodiazepine use, opioid use
25(OH)D = 25-hydroxyvitamin D
AHI = apnea-hypopnea index
CI = confidence interval
OR = odds ratio
OSA = obstructive sleep apnea

**Table 3:** Polytomous logistic regression for odds of obstructive sleep apnea

| | OR (95% CI) | | |
|---|---|---|---|
| **25(OH)D Quartiles** | **AHI 5-14.9/hr vs. AHI 0-4.9/hr** | **AHI 15-29.9/hr vs. AHI 0-4.9/hr** | **AHI ≥30/hr vs. AHI 0-4.9/hr** |
| Crude | | | |
| Q1 vs. Q4 | 1.07 (0.84-1.36) | 1.15 (0.85-1.56) | 1.53 (1.05-2.23) |
| Q2 vs. Q4 | 0.90 (0.70-1.15) | 1.14 (0.84-155) | 1.45 (0.99-2.13) |
| Q3 vs. Q4 | 1.06 (0.83-1.35) | 1.04 (0.76-1.42) | 1.14 (0.76-1.71) |
| p-for-trend | | 0.073 | |
| Adjusted for typical OSA risk factors* | | | |
| Q1 vs. Q4 | 0.89 (0.69-1.14) | 0.87 (0.64-1.19) | 0.97 (0.65-1.45) |
| Q2 vs. Q4 | 0.80 (0.62-1.03) | 0.96 (0.70-1.32) | 1.07 (0.72-1.60) |
| Q3 vs. Q4 | 1.00 (0.78-1.28) | 0.95 (0.69-1.31) | 1.05 (0.69-1.59) |
| p-for-trend | | 0.534 | |
| Adjusted for typical OSA risk factors* and 25(OH)D modifiers# | | | |
| Q1 vs. Q4 | 0.91 (0.70-1.18) | 0.88 (0.63-1.24) | 0.91 (0.59-1.39) |
| Q2 vs. Q4 | 0.82 (0.63-1.06) | 0.99 (0.72-1.38) | 1.06 (0.70-1.61) |
| Q3 vs. Q4 | 1.01 (0.79-1.30) | 0.98 (0.70-1.36) | 1.05 (0.69-1.60) |
| p-for-trend | | 0.720 | |
| Fully adjusted^ | | | |
| Q1 vs. Q4 | 0.91 (0.70-1.19) | 0.89 (0.63-1.25) | 0.90 (0.59-1.38) |
| Q2 vs. Q4 | 0.81 (0.62-1.06) | 0.99 (0.71-1.38) | 1.06 (0.70-1.61) |
| Q3 vs. Q4 | 0.99 (0.7-1.28) | 0.98 (0.70-1.36) | 0.98 (0.64-1.50) |
| p-for-trend | | 0.739 | |

*: "typical OSA risk factors" covariates: age, body mass index, neck circumference, hypertension
#: winter season: January – March
^: fully adjusted covariates: age, body mass index, neck circumference, hypertension, winter season, clinic site, race, alcohol consumption, smoking, benzodiazepine use, opioid use
25(OH)D = 25-hydroxyvitamin D
AHI = apnea-hypopnea index
CI = confidence interval
OR = odds ratio
OSA = obstructive sleep apnea

**Table 4.** Sensitivity Analysis. Logistic regression with adjustment for only one typical OSA risk factor (age, BMI, neck circumference, hypertension).

| 25(OH)D Quartiles | OR (95% confidence Intervals) | |
|---|---|---|
| | AHI ≥15 vs. <15 | AHI ≥30 vs. <30 |
| Adjusted for continuous age | | |
| Q1 vs. Q4 | 1.22 (0.97-1.55) | 1.43 (1.00-2.04) |
| Q2 vs. Q4 | 1.30 (1.02-1.65) | 1.47 (1.02-2.11) |
| Q3 vs. Q4 | 1.05 (0.82-1.34) | 1.12 (0.77-1.65) |
| p-trend | 0.035 | 0.024 |
| Adjusted for continuous BMI | | |
| Q1 vs. Q4 | 0.99 (0.78-1.27) | 1.12 (0.77-1.61) |
| Q2 vs. Q4 | 1.14 (0.89-1.45) | 1.23 (0.85-1.78) |
| Q3 vs. Q4 | 0.99 (0.77-1.27) | 1.04 (0.70-1.53) |
| p-trend | 0.806 | 0.429 |
| Adjusted for neck circumference | | |
| Q1 vs. Q4 | 1.07 (0.84-1.36) | 1.22 (0.85-1.75) |
| Q2 vs. Q4 | 1.18 (0.92-1.50) | 1.29 (0.89-1.87) |
| Q3 vs. Q4 | 0.99 (0.77-1.28) | 1.07 (0.73-1.57) |
| p-trend | 0.354 | 0.201 |
| Adjusted for hypertension | | |
| Q1 vs. Q4 | 1.23 (0.97-1.56) | 1.45 (1.01-2.06) |
| Q2 vs. Q4 | 1.32 (1.04-1.68) | 1.49 (1.03-2.14) |
| Q3 vs. Q4 | 1.04 (0.81-1.33) | 1.11 (0.75-1.63) |
| p-trend | 0.028 | 0.016 |

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