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# Vitamin D status modifies the association between statin use and musculoskeletal pain: A population based study

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ABSTRACT

**Background**: Past studies examining the effect of vitamin D on statin myalgia have been variable; however, these studies were done in limited samples not representative of the general population. We aimed to evaluate whether vitamin D status modifies the association between statin use and musculoskeletal pain in a sample representative of the general population. **Methods**: We conducted a cross-sectional study using the National Health and Nutrition Examination Survey 2001–2004. Musculoskeletal symptoms and statin use were self-reported. Vitamin D status was assessed using serum 25 hydroxyvitamin D (25[OH]D), categorized as <15 ng/mL or ≥15 ng/mL. To evaluate if vitamin D status modifies the association between statin use and prevalent musculoskeletal pain, we performed multivariable-adjusted logistic regression models stratified by 25(OH)D status. **Results**: Among 5907 participants ≥40 years old, mean serum 25(OH)D was 23.6 ng/mL (95% CI, 22.9–24.3). In stratified multivariable-adjusted logistic regression models, individuals with 25(OH)D <15 ng/mL, using a statin had a significantly higher odds of musculoskeletal pain compared to those not using a statin (adjusted odds ratio [aOR], 1.90; 95% CI, 1.18–3.05). Among those with 25(OH)D ≥15 ng/mL, we found no significant association between statin use and musculoskeletal pain (aOR, 0.91; 95% CI, 0.71–1.16). **Conclusion**: Among adults ≥ 40 years old with 25(OH)D <15 ng/mL, statin users had nearly 2 times greater odds of reporting musculoskeletal pain compared to non-statin users. Our findings support the hypothesis that vitamin D deficiency modifies the risk of musculoskeletal symptoms experienced with statin use.


## 1. Introduction

Statin use is associated with a higher risk for musculoskeletal pain [1]. Vitamin D status has been proposed to modify the effect of statin use on musculoskeletal pain, with deficient vitamin D increasing the risk of statin-associated musculoskeletal symptoms [2]. However, prior studies have included statin-users only, and have yielded mixed results [2–6]. Therefore, it remains uncertain whether vitamin D deficiency modifies the effect of statin use by increasing the risk of musculoskeletal pain beyond that associated with statin use or vitamin D deficiency alone, or, alternatively, whether any association exists after adjustment for important confounders. We aimed to examine the effect of vitamin D on the relationship between statin use and musculoskeletal pain in the general population.

## 2. Methods

For this cross-sectional study we analyzed data from the National Health and Nutrition Examination Survey (NHANES), an ongoing, cross-sectional survey that uses a complex, stratified, multistage, probability-cluster design to select a representative sample of the civilian, non-institutionalized US population. All participants gave written informed consent. Public use data files were obtained from the NHANES website, and our analyses of these de-identified data were approved for exemption by the Beth Israel Deaconess Medical Center Committee on Clinical Investigation.

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### 2.1. Study population

NHANES participants underwent in-home interviews to provide information about demographics, medical conditions, prescription medication use, and health and lifestyle risk factors, followed by physical exams and laboratory testing at a mobile examination center. Adults ≥40 years who participated in NHANES between 2001 and 2004 and had serum 25 hydroxyvitamin D (25[OH]D) measured ($n = 6233$) were considered for inclusion in the study. We excluded 326 participants who were missing data on covariates of interest, leaving 5907 participants for our analyses.

### 2.2. Measurements

Serum 25(OH)D was analyzed at the CDC in Atlanta, GA using the DiaSorin RIA kit (Stillwater, MN). Measurements of 25(OH)D were adjusted to take into account assay drifts due to reagent and calibration lot-to-lot variability over time [7]. To ascertain statin use, and other medication use, all participants were asked if they had used any prescription medications in the past 30 days. Those who responded "yes" were asked to provide their medication containers to the interviewer to assure accurate recording of the medication. Containers were unavailable for about 15% of the medications used; in such cases, participants verbally reported the details of medications they used to the interviewer.

Pain was self-reported in response to the initial question: "During the past month, have you had a problem with pain that lasted more than 24 h?" Those who answered "yes" were asked to describe the location(s) of their pain. We defined musculoskeletal pain as report of pain in any of the following areas: lower extremities, upper extremities, buttocks, back, and neck.

### 2.3. Other covariates of interest

Participants reported their age, sex, race/ethnicity, alcohol use, smoking status, physical activity, and health status. Medical conditions were based on a self-report of a physician or health care provider's diagnosis. Coronary heart disease was based on having a diagnosis of coronary heart disease, angina, or a previous heart attack. Chronic lung disease was defined as having current asthma, emphysema or chronic bronchitis. Diabetes status was determined by self-reported prior diagnosis, a blood glucose level of >200 mg/dL, or use of anti-diabetic medication. Body mass index (BMI) was based on measured height and weight. Serum albumin levels were measured using the bichromatic digital endpoint method with Bromocresol purple reagent (Beckman Coulter, Los Angeles, CA). Serum iron concentration was obtained using the timed-endpoint method with Ferrozine iron reagent (Beckman Coulter, Los Angeles, CA).

### 2.4. Statistical analyses

All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and Stata 12 (College Station, TX) using survey weights to represent the US population and to account for non-response and over-sampling of select demographic populations. Crude analyses (unadjusted logistic regression) and adjusted analyses (multivariable logistic regression) were performed. We performed pre-planned analyses stratified by 25(OH)D <15 ng/mL versus ≥15 ng/mL, in order to assess if vitamin D deficiency modifies the effect of statin use on musculoskeletal pain. Exploratory analyses were conducted to assess additional thresholds of serum 25(OH)D, specifically: <15 ng/mL, 15–30 ng/mL, and ≥30 ng/mL. Additionally, we have previously shown the effect of statin use on musculoskeletal pain differs significantly among individuals with and without arthritis [1], but did not include vitamin D status in our prior studies; therefore, we explored the effects of vitamin D status on that association. Finally, because statin users may restrict dietary fat, which could decrease absorption of fat-soluble vitamins, we explored if statin users versus nonusers had differences in serum concentrations of vitamin E or carotenoids in *post-hoc* analyses restricted to participants with 25(OH)D <15 ng/mL.

The following confounders, specified *a priori*, were used in all multivariable models: age, sex, race (non-Hispanic white, non-Hispanic black, or other), smoking (never, past current), average alcohol consumption in the past year (<1, 1 to 3, or >3 servings per day), physical activity during the past 30 days (vigorous, moderate, sedentary), self-reported health status (excellent/very good, good, or fair/poor), coronary heart disease, stroke, congestive heart failure, diabetes, lung disease, arthritis, osteoporosis, body mass index (BMI), serum albumin (continuous), serum iron (continuous, log-transformed due to its skewed distribution), opioid use in the past 30 days, and prescription nonsteroidal anti-inflammatory drug (NSAID) use in the past 30 days.

We considered other factors as potential confounders but did not include them in our final models because they did not substantively alter the association between statin use, vitamin D levels, and musculoskeletal pain. These factors were aspartate aminotransferase, alanine transaminase, cholesterol, glomerular filtration rate, peripheral vascular disease, and cancer.

## 3. Results

Among 5907 participants ≥40 years, 1057 participants, representing 19.6 million individuals, reported statin use. The distribution of serum 25(OH)D for participants is depicted in Fig. 1. The mean serum 25(OH)D for the overall study population (23.6 ng/mL; 95% confidence interval [CI], 22.9–24.3) did not differ from the mean serum 25(OH)D among statin users (23.4 ng/mL; 95% CI, 22.3–24.4). Table 1 shows that participants with 25(OH)D <15 ng/mL, compared to those with higher levels of vitamin D, were less likely to be of non-Hispanic white race/ethnicity and were more likely to be female, current smokers, sedentary; were more likely to report poorer health status and multiple co-morbidities, including coronary heart disease, stroke, congestive heart failure, and diabetes; were more likely to currently use opioids and prescription NSAIDs; and were more likely to have a higher BMI. Characteristics of participants according to statin use or nonuse are shown in Supplementary Table 1. Compared to non-statin users, those who used statins were more likely to be older, male, of non-Hispanic white race/ethnicity, former smokers, and less likely to drink >3 serving of alcohol/day, engage in vigorous physically activity, report very good/excellent health. They were more likely to have a

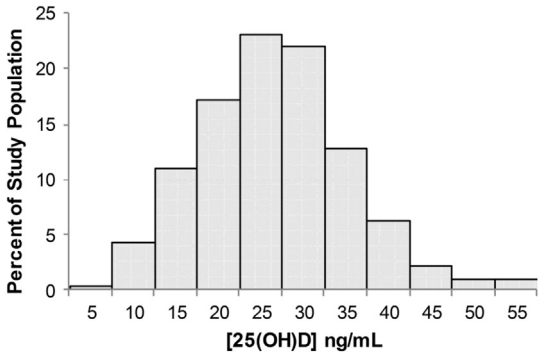


**Fig. 1.** Distribution of serum 25(OH)D (ng/mL) concentration of 2001–2004 NHANES participants ≥40 years ($n = 5907$).