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# Physical activity, sedentary behavior, and vitamin D metabolites

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## Abstract

Physical activity is associated with circulating 25-hydroxyvitamin D (25(OH)D). However, the influence of activity and/or sedentary behavior on the biologically active, seco-steroid hormone 1α,25-dihydroxyvitamin D ($1,25(OH)_2D$) is unknown. We conducted a cross-sectional analysis among ursodeoxycholic acid (UDCA) randomized trial participants (n=876) to evaluate associations between physical activity, sedentary behavior, and circulating vitamin D metabolite concentrations. Continuous vitamin D metabolite measurements and clinical thresholds were evaluated using multiple linear and logistic regression models, mutually adjusted for either $1,25(OH)_2D$ or 25(OH)D and additional confounding factors. A statistically significant linear association between $1,25(OH)_2D$ and moderate-vigorous physical activity per week was strongest among women (β (95% CI): 3.10 (1.51–6.35)) versus men (β (95% CI): 1.35 (0.79–2.29)) in the highest tertile of activity compared to the lowest (p-interaction=0.003). Furthermore, 25(OH)D was 1.54 ng/ml (95% CI 1.09–1.98) higher per hour increase in moderate-vigorous activity (p=0.001) and odds of sufficient 25(OH)D status was higher among physically active participants (p=0.001). Sedentary behavior was not significantly associated with either metabolite in linear regression models, nor was a statistically significant interaction by sex identified. The current study identified novel associations between physical activity and serum $1,25(OH)_2D$ levels, adjusted for 25(OH)D concentrations. These results identify the biologically active form of

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vitamin D as a potential physiologic mechanism related to observed population-level associations between moderate-vigorous physical activity with bone health and chronic disease risk. However, future longitudinal studies are needed to further evaluate the role of physical activity and vitamin D metabolites in chronic disease prevention.

**Keywords**

Physical activity; sedentary behavior; vitamin D; 25-hydroxyvitamin D; 1α, 25-dihydoxyvitamin D

## Introduction

Low physical activity levels, and more recently high levels of sedentary behavior, are associated with increased risk of common diseases including cardiovascular disease, diabetes, and cancer [1–6]. Furthermore, the evidence for a role of sedentary behavior, independent of physical activity, in chronic disease etiology is growing, but equivocal [7–10]. Hypotheses suggested for the underlying biological mechanism of action for higher physical activity and lower sedentary behavior in disease etiology include reduced inflammation, increased insulin sensitivity, and epigenetic modifications of genes [11–14]. However, the relationship with vitamin D metabolites is not well understood. Previous studies demonstrate that physical activity is associated with higher 25-hydroxyvitamin D (25(OH)D) levels [15–17], though to date, only a single small study has evaluated the biologically active form of vitamin D, the seco-steroid hormone 1α,25-hydroxyvitamin D ($1,25(OH)_2D$), and none the role of overall sedentary behavior. Thus, it is not known if physical activity or sedentary behaviors act to influence vitamin D metabolite concentrations independently or in combination.

Research has established that vitamin D is essential to human health [18–21]. Low vitamin D status, which is commonly evaluated through 25(OH)D levels, is associated with increased risk of several diseases [21–26]. A variety of factors are related to 25(OH)D concentration [15,16,27] and previous studies evaluating predictive models for circulating 25(OH)D have consistently identified physical activity as an important factor [15–17], though total sedentary behavior has not been evaluated. In contrast, previous studies also propose that activity level is not associated with $1,25(OH)_2D$, since it is hypothesized that concentrations are maintained within a narrow range due to its central role in calcium homeostasis [18,28]. Yet, other studies demonstrate that circulating $1,25(OH)_2D$ levels may be associated with disease risk [26,29], and also related to physical activity [30]. However, researchers and practitioners debate the clinical thresholds for optimal 25(OH)D status [31,32] and $1,25(OH)_2D$ is not commonly measured clinically. Furthermore, no identified studies have evaluated the independent associations between physical activity and total sedentary behavior with 25(OH)D or $1,25(OH)_2D$ levels in adults.

In the present study, we hypothesized that high physical activity is associated with increased $1,25(OH)_2D$ and 25(OH)D concentrations, and that sedentary behavior is associated with lower 25(OH)D. Furthermore, we hypothesized that high physical activity is associated with higher odds of clinically optimal vitamin D levels. In order to evaluate the independent role

of activity versus sedentary behavior in vitamin D metabolite levels, we conducted the first study to mutually adjust all physical activity models for sedentary behavior, $1,25(OH)_2D$ models for 25(OH)D, as well as the reverse in each case. The results from this study will improve our understanding of the relationship between physical activity and sedentary behavior in circulating vitamin D metabolite levels, and inform future studies evaluating chronic disease prevention.

## Methods

### Study population

The ursodeoxycholic acid (UDCA) trial was a randomized, double blind, placebo-controlled phase III trial to evaluate the influence of UDCA on colorectal adenoma recurrence conducted at the University of Arizona, which has been described in detail previously [33]. Participants included Arizona residents from 40 to 80 years of age with at least one colorectal adenoma (>3mm in diameter) removed within 6 months of study enrollment. Participants were recruited between 1999–2000 and were followed for approximately 3 years [33,34]. The present study included all participants with complete data for circulating vitamin D metabolite concentrations and activity levels (n= 876) at the baseline visit. This University of Arizona Human Subjects committee approved this trial.

### Assessment of Physical Activity, Sedentary Behavior, and Vitamin D Metabolites

Non-occupational physical activity and sedentary behavior were measured at baseline using the Arizona Activity Frequency Questionnaire (AAFQ), a validated instrument that measures 59 activities with indicators of frequency and duration during the prior month [35]. “Sedentary behavior” was classified as behaviors ≤1.5 METs, “light” between 1.5 METs and 3 METs, and “moderate-vigorous” ≥ 3 METs per physical activity” [36,37]. In order to reduce bias introduced by measurement error, the reported time in each activity was proportionally adjusted to allow for the duration of all reported activities plus sleep to total 24 hours [38]. Examples of the activities evaluated by the AAFQ have been described previously [9]. Briefly, sedentary behaviors included activities such as reading, general sitting, watching television, or driving. In contrast, light activity included activities such as light cleaning, grocery shopping, yoga, and billiards. Moderate-vigorous activity included activities such as jogging, swimming, and bicycling [9]. Dietary intake was measured using the Arizona Food Frequency Questionnaire (AFFQ). The AFFQ is a validated, semi-quantitative, scannable instrument that evaluates 113-dietary items and asks participants to report usual dietary intake during the prior year [39].

Circulating $1,25(OH)_2D$ and 25(OH)D concentrations were measured at baseline, prior to the start of the intervention. Serum concentrations of vitamin D metabolites were evaluated by Heartland Assays (Ames, IA). Metabolites were measured using established methods, a $^{1,25}I$-based radioimmunoassay for $1,25(OH)_2D$ and competitive chemiluminescence immunoassay for 25(OH)D, described previously [40–42]. Blinding and standard quality assurance measures were utilized by the laboratory, and the coefficient of variation is less than 7.0% and 11.5% for 25(OH)D and $1,25(OH)_2D$, respectively [40,42,43].

### Statistical Analysis

In a cross-sectional analysis at baseline, vitamin D metabolites were evaluated as continuous variables and by clinical thresholds. Dichotomous variables were created using a clinical threshold for $1,25(OH)_2D$ concentrations (26 pg/ml) [29], whereas proposed thresholds of vitamin D status (20 versus 30 ng/ml) were evaluated for 25(OH)D levels [31,32]. Continuous measures and sex-specific tertiles of light and moderate-vigorous physical activity were compared using adjusted hours per day and METs-hours per day. Sedentary behavior was only evaluated using adjusted hours per day.

Multivariate linear and logistic regression models were employed, and because we found that $1,25(OH)_2D$ and 25(OH)D levels are moderately correlated in this population [44,45], individual models were mutually adjusted for the respective metabolite. Concentrations of $1,25(OH)_2D$ and 25(OH)D were normally distributed in this population [26,44,45] and sensitivity analysis determined that use of the commonly applied log transformation did not significantly change the results (data not shown). We evaluated confounding factors for vitamin D metabolites in this population, as previously described [25,26]. Overall, we assessed including age, body mass index (BMI), sex, race, sleep, current smoking, total energy intake, treatment arm, supplement use, aspirin, seasonality of vitamin D metabolite measurements, as well as dietary intake of various nutrients (Table 1). Confounding variables were included in the final model if the point-estimate changed by 10% or greater, or there was a biological basis for adjustment. Interactions by sex, BMI, and between activity types were also evaluated, using likelihood ratio tests ($\alpha$=0.10). The STATA statistical software package (version 13.0, Stata Corporation,College Station, TX) was used for all data analysis.

## Results

Among 876 total participants, the mean age was 66.1 years, and the majority of participants were White (94.3%) and men (66.2%) (Table 1). Individuals with $1,25(OH)_2D$ below the reference value of 26 pg/ml were marginally older with higher BMI, but lower frequency of current cigarette use and higher reported use of aspirin and dietary supplements. In comparison, individuals with insufficient 25(OH)D status (<20 ng/ml) were younger with higher BMI, less frequently White, and more likely to be women and current smokers compared to those with sufficient 25(OH)D. In addition, the insufficient 25(OH)D group used aspirin and supplements less frequently, but also reported higher total energy, calcium, and vitamin D intake.

### Physical Activity, Sedentary Behavior, and Vitamin D Metabolite Levels

Table 2 presents the results of linear regression analyses of vitamin D metabolites and activity. Circulating $1,25(OH)_2D$ concentration was 0.80 pg/ml (95% CI 0.23–1.37) higher per hour increase in moderate-vigorous physical activity per week ($p \leq 0.006$), with all models adjusted for 25(OH)D levels. However, among women, circulating $1,25(OH)_2D$ concentration was 2.31 pg/ml (95% CI 1.06–3.57) higher for every hour increase in moderate-vigorous physical activity per day (p=0.001). In contrast, there was no association among men ($\beta$=0.22 95% CI −0.40–0.84; p=0.48; p-interaction=0.003). Similar associations

were observed using MET-hours per day for moderate-vigorous physical activity (p-interaction=0.004).

Furthermore, for every hour increase in moderate-vigorous activity, 25(OH)D concentration was 1.54 ng/ml higher (95% CI 1.09–1.98; p=0.001) (Table 2). This relationship was similar by sex and no statistically significant interaction was identified (p=0.34). No statistically significant associations were identified between sedentary behavior and circulating $1,25(OH)_2D$ or 25(OH)D levels, with no significant differences by sex (p-interaction=0.23 and 0.25, respectively). There were also no statistically significant associations observed for light activity using either hours per day or MET-hours per day measurements.

### Clinical Thresholds for Vitamin D Status

We also evaluated overall population estimates for clinical vitamin D status thresholds (Table 3). Greater odds of $1,25(OH)_2D$ above the 26 pg/ml threshold were observed with higher moderate-vigorous activity (p=0.001) (Table 3). Furthermore, the odds of 25(OH)D above 20 ng/ml and 30 ng/ml were statistically significantly greater in the highest compared to lowest activity tertiles (3.45 95% CI (2.11–5.67); 3.42 95% CI (1.58–3.59; p=0.001, respectively). More than 9 hours per day of sedentary behavior was also associated with higher odds of sufficient 25(OH)D (OR 1.37 95% CI (0.87–2.18); 1.80 95% CI (1.04–2.99)) for those in the two highest tertiles of sedentary time, respectively (p=0.02). The results for 30 ng/ml 25(OH)D were similar, as well as using MET-hour measurements for activity. Light physical activity was not associated with status measures of either vitamin D metabolite.

We also conducted stratified analyses of $1,25(OH)_2D$ and 25(OH)D status by sex (Table 4). The odds of 25(OH)D greater than 20 ng/ml were also similarly increased with higher moderate-vigorous activity for both men and women (p-interaction= 0.96). We observed a borderline significant interaction (p-value=0.10) by sex between tertiles of sedentary behavior and 25(OH)D >20 ng/ml. The odds of meeting the clinical threshold of 20 ng/ml 25(OH)D were 2.72 (95% CI 1.31–5.64) and 3.45 (95% CI 1.55–7.62) among women in the second and third tertiles of sedentary behavior, respectively, compared to the lowest (p-trend=0.001). In contrast, there were no significant interactions by gender for the $1,25(OH)_2D$ threshold, using METs measurements or the 30 ng/ml threshold of 25(OH)D status. Finally, there were no interactions by BMI or sedentary behavior (data not shown).

## Discussion

The results of the current study identified a novel association between physical activity and circulating $1,25(OH)_2D$ concentrations, the biologically active seco-steroid hormone. Significant interactions by sex were identified for the linear relationship between moderate-vigorous activity and $1,25(OH)_2D$, with stronger associations observed among women. Higher physical activity was also associated with greater odds of clinically sufficient $1,25(OH)_2D$ and 25(OH)D, regardless of the definition of vitamin D status evaluated. Finally, this study provides novel estimates of effect for the relationship between physical activity and 25(OH)D levels through adjusted models. Overall, these innovative results have important implications for understanding the lifestyle factors influencing the vitamin D

endocrine system, as no previous studies evaluated the relationship with total sedentary behavior and most evaluated only the 25(OH)D metabolite.

The results of the current study are novel in that, unlike previous studies, we evaluated $1,25(OH)_2D$ levels in models adjusted for circulating 25(OH)D as a potential confounding factor. This approach suggests that physical activity may influence $1,25(OH)_2D$ levels outside of the usual pathways known to influence the vitamin D endocrine system, including sun exposure and dietary intake. This is critical in evaluating the role of $1,25(OH)_2D$, as 25(OH)D is the precursor metabolite to $1,25(OH)_2D$ and highly influenced by external factors [27,46]. However, $1,25(OH)_2D$ levels are rarely evaluated in epidemiologic studies, which is likely related to two limitations. First, circulating $1,25(OH)_2D$ concentrations are maintained within a relatively tight homeostatic range due to its importance in calcium homeostasis [18,47,48], thus it has been difficult for epidemiologic studies to obtain the resource requirements for a sample size with sufficient power to identify statistically significant associations on such a small range of effects. Secondarily, there were historically technical challenges associated with the $1,25(OH)_2D$ assay [42]. However, these issues were not a concern in the present study in addition to a growing number of additional studies evaluating the role $1,25(OH)_2D$ in health.

Overall, only a single identified study evaluated the relationship between physical activity and $1,25(OH)_2D$, while none were identified that explored the influence of sedentary behavior. Tartibian et al. evaluated the effect of an exercise intervention on osteoporosis biomarkers among women, and demonstrated significantly increased $1,25(OH)_2D$ concentrations (n=21), following a 24-week program of moderate-vigorous activity three times per week compared to the control group (n=18) [30]. The mean $1,25(OH)_2D$ level in the exercise group was $54.9 \pm 23.1$ compared to $38.0 \pm 9.9$ among controls following the intervention ($p=0.02$), while baseline measures did not differ between groups [30]. However, circulating 25(OH)D levels were not measured in this trial, which is critical in establishing an independent relationship with $1,25(OH)_2D$ [30]. The results of the current study support these findings. However, understanding the relationship between activity and vitamin D metabolites, including the ability to mutually adjust for both vitamin D metabolites, are strengths of the present work.

The biological mechanism driving the observed relationship between physical activity and $1,25(OH)_2D$ is untested. We suggest that, moving beyond the role of sun exposure, this relationship may be linked to the role of both physical activity and $1,25(OH)_2D$ in bone health [48]. Parathyroid hormone (PTH) and $1,25(OH)_2D$ are known to act within a negative feedback loop to regulate each other and serum calcium concentrations [18,49,50], which is moderated in part by PTH-induced expression of 1α-hydroxylase or CYP27B1 [51–53]. Scott et al. recently demonstrated that PTH was significantly higher among men engaging in vigorous activity, as part of a counterbalanced trial testing the effect of exercise intensity on bone metabolism biomarkers [54]. Furthermore, Lester et al. reported a statistically significant increase in PTH following a randomized trial of aerobic and resistance training, or combination, in 69 healthy, college-aged women [55]. While these trials were comparatively small and provided limited direct evidence that physical activity changes circulating $1,25(OH)_2D$ levels, the hypothesis that physical activity influences $1,25(OH)_2D$

through PTH-directed bone homeostasis pathway hypothesis warrants testing in future longitudinal and interventions trials.

Furthermore, studies support the results from the current study that sex may influence the relationship between physical activity and vitamin D metabolites. Studies found variation in circulating 25(OH)D levels by sex with women often demonstrating lower concentrations, though trends varied [27,56–58]. A recent study by Wanner et al. observed a statistically significant interaction on the association between self-reported moderate-vigorous physical activity and circulating 25(OH)D levels in men versus women (p-interaction=0.003) [59]. Ding et al. suggest that estrogen may interact vitamin D metabolites in colorectal cancer risk [60], while Protiva et al. demonstrated that estrogen replacement therapy in postmenopausal women increased expression of vitamin D endocrine system genes [61]. However, estrogen levels and data on use of hormone replacement therapy were not available for the UDCA population. Overall, while there is growing evidence to support the influence of sex on the relationship between physical activity and vitamin D metabolites, future studies with reproductive hormones levels and estrogen replacement therapy history data are necessary to clarify this relationship.

There are also a growing number of epidemiologic studies identifying associations between circulating $1,25(OH)_2D$ concentrations and a variety of diseases, providing additional evidence that the role of $1,25(OH)_2D$ may warrant continued investigation. Lee et al. reported that risk of overall mortality was significantly associated with lower circulating $1,25(OH)_2D$ concentrations among European men (n=2816), after adjusting for 25(OH)D levels (HR 1.24, 95% CI 1.02–1.51) [62]. Hirani et al. reported that lower $1,25(OH)_2D$ was also associated with increased risk of frailty, again independent of 25(OH)D, in a population of 1,659 elderly men [63]. Furthermore, Platz et al. reported that women in the lowest circulating $1,25(OH)_2D$ quartile had increased odds of distal colorectal adenoma (OR 1.58, 95% CI 1.03–2.40), among Nurses' Health Study participants, though the model was not adjusted for 25(OH)D [29]. We also recently reported 29% reduced odds of proximal metachronous adenoma (OR 0.71, 95% CI0.52–0.98) for those within the highest $1,25(OH)_2D$ tertile compared to the lowest (p-trend = 0.04) [26]. However, 25(OH)D was not associated with colorectal adenoma recurrence in the UDCA population [25]. In contrast, other studies reported no significant association between $1,25(OH)_2D$ concentration and fracture risk [64] or breast [65], prostate [66,67], and colorectal cancer [68,69]. However, many of the above studies were conducted in sex-specific populations and support the results of the current study for continued evaluation of differences in the relationship between physical activity and $1,25(OH)_2D$ by sex. Overall, these equivocal results also support our hypothesis that in large populations it may be possible to identify factors influencing $1,25(OH)_2D$ concentrations and associations with mortality as well as chronic disease risk.

In contrast to $1,25(OH)_2D$, there is substantial evidence for associations between 25(OH)D and disease risk [70–72]. The current study also confirms the results of several previous studies that moderate-vigorous physical activity is associated with circulating 25(OH)D, and adds evidence-based support to the hypothesis that intensity is an important factor [15–17,73]. A previous analysis in the UDCA population did not identify total physical activity

(expended kcal/day) as a significant factor in prediction of 25(OH)D levels [74]. However, the current study implemented the Sedentary Behavior Research Network guidelines to define activity categories within a larger sample size [37]. No previous studies to date evaluated the relationship between total sedentary behavior and vitamin D metabolite levels among adults.

It is known that circulating 25(OH)D concentrations are more sensitive to lifestyle and environmental factors compared to $1,25(OH)_2D$ [14,27,75]. In the current study, sedentary behavior was not statistically significantly associated with circulating $1,25(OH)_2D$ or 25(OH)D levels overall. However, an association was observed with higher odds of 25(OH)D above the 20 ng/ml threshold for vitamin D sufficiency. Overall, this was the first study to evaluate associations between total sedentary time and 25(OH)D among elderly adults. Hypönnen et al. reported lower 25(OH)D with increasing hours of television viewing ($p<0.01$) among adults in the Great Britain (n=6538) [58]. However, this association was only adjusted for sex and season [58]. In addition, Kumar et al. reported lower 25(OH)D levels among children who watched greater than 4 hours of television per day in the National Health and Nutrition Examination Survey 2001–2004 (n=6275), though these results were not adjusted for other factors [76]. However, we suggest that the unexpected results of the current study should be interpreted with caution, as we cannot rule out the role of chance in these findings. We also emphasize that this Southern Arizona population is unique and there is limited potential for generalizability of these results to additional populations. We hypothesize that there may be residual confounding influencing this relationship by factors that were unmeasured or inadequately measured in the UDCA population such as genetic variation, reproductive hormone levels, or sun exposure. The unique UDCA population includes primarily older, likely retired, individuals who may spend a large portion of their leisure-time sedentary time outdoors, year-round in Southern Arizona. Although we utilized season of randomization and models mutually adjusted for respective vitamin D metabolites to account for sun exposure, we do not have data available on the setting of individual activities (indoor versus outdoor), sun safety behavior, or tanning practices. It is possible that the influence of ultraviolet B radiation (UVB) on 25(OH)D concentrations in this population was not completely captured by the variables available for the present study. Future studies, testing interventions to decrease sedentary time, either at home or in the workplace, with sensitive measures of UVB exposure are necessary to evaluate the influence of sun exposure on the relationship between sedentary time and 25(OH)D.

The strengths of the current study include a large overall sample size, in addition to use of models mutually adjusted for vitamin D metabolites and activity. We also evaluated both hours per day and MET-hours per day of activity. Furthermore, this is the first study to evaluate associations between physical activity and sedentary behavior with $1,25(OH)_2D$ levels. The limitations include the cross-sectional design and approximate measures of sun exposure. While we adjusted for the influence of season of blood draw and mutually adjusted models for vitamin D metabolites in an attempt to control for the influence of sun exposure, carefully collected data on sun exposure and sun protective behaviors during physical activity and/or sedentary time are necessary in future studies to more directly control for the influence of sun exposure in this relationship. This is especially true for this

unique population of older, likely retired individuals in Southern Arizona. Furthermore, this study utilized measures of self-reported physical activity, which may be prone to bias, and future studies should utilize additional measures, such as pedometers or other devices, in order to obtain more accurate measures of activity. In addition, no other circulating measures of hormones such as PTH or estrogen were available for this population and should be measured in future studies. Overall, physical activity interventions and/or longitudinal studies, with carefully measured confounding factors, are necessary to further clarify the relationship between activity and vitamin D metabolites.

## Conclusions

Higher levels of moderate-vigorous physical activity were associated with increased $1,25(OH)_2D$ in the UDCA study population, though the relationship was most striking for women. In addition, physically active individuals had higher odds of clinically sufficient vitamin D status, at both the 20 ng/ml and 30 ng/ml thresholds. These results demonstrate that physical activity may influence circulating vitamin D metabolite concentration in a sex-specific fashion. Furthermore, these relationships may be independent of respective vitamin D metabolites or activity type. Future research is necessary to improve understanding of the relationship between activity and vitamin D metabolites, at both the population and cellular levels, to provide clarity on the influence of these factors in the role of the vitamin D endocrine system in bone health and chronic disease prevention.

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## Highlights

- Moderate-vigorous physical activity is linked to higher $1,25(OH)_2D$ among women.
- Moderate-vigorous physical activity is associated with higher 25(OH)D levels.
- Sedentary behavior was not associated with circulating vitamin D metabolite levels.

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**Table 1**

Baseline demographics by Vitamin D Status

| | | $1,25(OH)_2D$ Threshold | | 25(OH)D Threshold | |
|---|---|---|---|---|---|
| **Characteristic** | **Overall (n=876)** | **<26.0 pg/ml (n=232)** | **26.0 pg/ml (n=644)** | **<20 ng/ml (n=210)** | **20 ng/ml (n=666)** |
| Mean age, y ± SD | 66.1 ± 8.4 | 67.5 ± 7.5 | 65.6 ± 8.5 | 65.4 ± 8.7 | 66.3 ± 8.3 |
| Male, n(%) | 580 (66.2) | 144 (62.1) | 436 (67.7) | 93 (44.3) | 487 (73.1) |
| White, n (%) | 828 (94.3) | 215 (94.3) | 598 (94.5) | 186 (89.4) | 627 (96.0) |
| BMI, $k/m^2$ ± SD | 28.3 ± 4.9 | 29.1 ± 5.4 | 28.0 ± 4.7 | 29.9 ± 6.2 | 27.8 ± 4.4 |
| Current Smoker, n (%) | 105 (12.0) | 23 (9.9) | 82 (12.7) | 28 (13.3) | 77 (11.6) |
| Aspirin use, n (%) | 247 (28.1) | 70 (30.2) | 173 (26.9) | 46 (21.9) | 197 (29.6) |
| Regular Supplement Use, n (%) | 649 (74.1) | 175 (75.4) | 474 (73.6) | 144 (68.6) | 505 (75.8) |
| Sleep | 7.7 ± 1.7 | 8.0 ± 1.9 | 7.7 ±1.7 | 7.8 ± 1.7 | 7.7 ± 1.7 |
| Season of Randomization, n(%) | | | | | |
| December–February | 224 (25.6) | 64 (27.6) | 160 (24.8) | 74 (35.2) | 150 (22.5) |
| March–May | 224 (25.6) | 59 (25.4) | 165 (25.6) | 64 (30.5) | 160 (24.0) |
| June–August | 185 (21.1) | 50 (21.6) | 135 (21.0) | 30 (14.3) | 155 (23.3) |
| September–November | 243 (27.7) | 59 (25.4) | 184 (28.6) | 42 (20.0) | 201 (30.2) |
| Energy, kcal/d ± SD | 1973.0 ± 819.7 | 1950.0 ± 842.6 | 1971.5 ± 814.9 | 1840.7 ± 875.8 | 2005.2 ± 800.8 |
| Calcium, mg/d ± SD | 1008.4 ± 491.9 | 979.2 ± 484.5 | 1015.2 ± 495.3 | 885.9 ± 464.1 | 1043.5 ± 495.5 |
| Total fiber, g/d ± SD | 22.1 ± 10.8 | 21.9 ± 10.3 | 21.8 ± 10.7 | 21.1 ± 11.1 | 22.1 ± 10.4 |
| Total fat, g/d ± SD | 60.8 ± 31.1 | 61.5 ± 31.5 | 60.5 ± 30.8 | 57.9 ± 33.1 | 61.6 ± 30.2 |
| Saturated fat, g/d ± SD | 19.6 ± 11.2 | 19.6 ± 10.7 | 19.6 ± 11.2 | 18.3 ± 11.3 | 20.0 ± 11.0 |
| Magnesium, mg/d ± SD | 335.5 ± 136.1 | 330.1 ± 135.0 | 334.3 ± 134.3 | 312.1 ± 136.3 | 339.8 ± 133.2 |
| Dietary Vitamin D, IU/day ± SD | 136.8 ± 100.9 | 132.9 ± 104.9 | 138.6 ± 99.4 | 111.7 ± 94.1 | 145.1 ± 101.7 |

## Table 2

Linear associations between physical activity, sedentary behavior, and circulating vitamin D metabolite levels

| | $1,25(OH)_2D^a$ (pg/ml) | | $25(OH)D^b$ (ng/ml) | |
|---|---|---|---|---|
| | β (95% CI) | | β (95% CI) | |
| Overall Population | | | | |
| Activity (hours/day)[c] | | | | |
| Sedentary Behavior | 0.22 (−0.07–0.52) | | 0.18 (−0.05–0.42) | |
| Light | −0.07 (−0.56–0.42) | | 0.15 (−0.25–0.29) | |
| Moderate-Vigorous | 0.80 (0.23–1.37) | | 1.54 (1.09–1.98) | |
| Physical Activity (MET-hr/day)[3] | | | | |
| Light | −0.02 (−0.25–0.21) | | 0.10 (−0.09–0.29) | |
| Moderate-Vigorous | 0.15 (0.02–0.29) | | 0.36 (0.25–0.46) | |
| Activity (hours/day)[c] | | p-interaction | | p-interaction |
| Sedentary Behavior | | | | |
| Men | 0.27 (−0.07–0.61) | | 0.03 (−0.25–0.31) | |
| Women | 0.13 (−0.44–0.71) | 0.23 | 0.48 (0.02–0.94) | 0.25 |
| Light | | | | |
| Men | −0.10 (−0.66–0.46) | | 0.04 (−0.43–0.52) | |
| Women | −0.07 (−1.03–0.90) | 0.36 | 0.44 (−0.34–1.21) | 0.66 |
| Moderate-Vigorous | | | | |
| Men | 0.22 (−0.40–0.84) | | 1.35 (0.86–1.85) | |
| Women | 2.31 (1.06–3.57) | 0.003 | 2.15 (1.16–3.15) | 0.34 |
| Physical Activity (MET-hrs/day)[c] | | p-interaction | | p-interaction |
| Light | | | | |
| Men | −0.05 (−0.32–0.21) | | 0.05 (−0.17–0.28) | |
| Women | 0.00 (−0.44–0.44) | 0.30 | 0.21 (−0.15–0.56) | 0.22 |
| Moderate-Vigorous | | | | |
| Men | 0.01 (−0.14–0.16) | | 0.31 (0.19–0.42) | |
| Women | 0.52 (0.22–0.81) | 0.004 | 0.53 (0.30–0.76) | 0.60 |

[a] $1,25(OH)_2D$ models adjusted for: age, sex, BMI, race, sleep and 25(OH)D.

[b] 25(OH)D models were adjusted for: age, sex, BMI, race, sleep, $1,25(OH)_2D$, and season of randomization.

[c] Moderate-vigorous and light activity models were adjusted for sedentary behavior models, whereas the sedentary behavior estimates were adjusted by moderate-vigorous behavior.

**Table 3**

Categorical measures of activity and clinical thresholds for $1,25(OH)_2D$ and 25(OH)D

| Activity[a] (hours/day) | 1,25(OH)$^2$D[b] >26.0 pg/ml OR (95% CI) | 25(OH)D >20 ng/ml OR (95% CI) | 25(OH)D >30 ng/ml OR (95% CI) |
|---|---|---|---|
| Sedentary Behavior | | | |
| T1 (5.7 ± 1.4) | REF | REF | REF |
| T2 (9.0 ± 0.8) | 1.35 (0.89–2.07) | 1.37 (0.87–2.18) | 1.24 (0.82–1.87) |
| T3 (12.2 ± 1.6) | 1.55 (0.99–2.45) | 1.80 (1.09–2.99) | 1.48 (0.94–2.33) |
| p-trend | 0.06 | 0.02 | 0.09 |
| Light Activity | | | |
| T1 (1.8 ± 0.8) | REF | REF | REF |
| T2 (3.2 ± 1.0) | 1.17 (0.78–1.74) | 0.79 (0.51–1.24) | 1.21 (0.82–1.77) |
| T3 (5.5 ± 1.6) | 1.24 (0.79–1.94) | 1.29 (0.77–2.15) | 1.16 (0.75–1.80) |
| p-trend | 0.34 | 0.34 | 0.49 |
| Moderate-Vigorous | | | |
| T1 (0.5 ± 0.3) | REF | REF | REF |
| T2 (1.4 ± 0.5) | 1.85 (1.25–2.73) | 1.62 (1.07–2.47) | 1.61 (1.08–2.40) |
| T3 (3.3 ± 1.1) | 1.93 (1.27–2.93) | 3.45 (2.11–5.67) | 3.42 (1.58–3.59) |
| p-trend | 0.001 | 0.001 | 0.001 |
| Physical Activity[a] (METs/day) | | | |
| Light | | | |
| T1 (3.8 ± 1.8) | REF | REF | REF |
| T2 (6.8 ± 2.2) | 1.06 (0.71–1.57) | 0.69 (0.44–1.08) | 1.23 (0.84–1.81) |
| T3 (11.6 ± 3.4) | 1.09 (0.70–1.69) | 1.34 (0.80–2.43) | 1.16 (0.75–1.79) |
| p-trend | 0.70 | 0.28 | 0.47 |
| Moderate-Vigorous | | | |
| T1 (1.9 ± 1.3) | REF | REF | REF |
| T2 (5.9 ± 2.0) | 1.98 (1.34–2.94) | 1.55 (1.02–2.37) | 1.70 (1.13–2.55) |
| T3 (14.2 ± 4.7) | 2.13 (1.40–3.23) | 3.41 (2.09–5.56) | 2.56 (1.69–3.86) |
| p-trend | 0.001 | 0.001 | 0.001 |

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[a] Logistic regression model adjusted for: age, sex, BMI, race, and sleep. Moderate-vigorous and light activity models were adjusted for sedentary behavior, while sedentary models were adjusted for moderate-vigorous activity.

[b] All 1,25(OH)2D models were adjusted for 25(OH)D and 25(OH)D models were adjusted for 1,25(OH)2D as well as season of randomization.

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**Table 4**

Association between tertiles of activity and odds of vitamin D above clinical thresholds

| Men (n=580) | | | Women (n=296) | | | |
|---|---|---|---|---|---|---|
| $1,25(OH)_2D$ (Threshold = 26.0 pg/ml) | | | $1,25(OH)_2D$ (Threshold = 26.0 pg/ml) | | | |
| **Activity[a] (hours/day)** | **n (%)** | **OR (95% CI)** | **Activity[a] (hours/day)** | **n (%)** | **OR (95% CI)** | **p-interaction** |
| Sedentary Behavior | | | Sedentary Behavior | | | |
| T1 (5.8 ± 1.4) | 140 (72.2) | REF | T1 (5.5 ± 1.2) | 72 (72.7) | REF | |
| T2 (9.2 ± 0.8) | 149 (77.2) | 1.90 (1.10–3.26) | T2 (8.6 ± 0.7) | 68 (68.7) | 0.87 (0.43–1.76) | |
| T3 (12.4 ± 1.6) | 147 (76.2) | 1.83 (1.03–3.28) | T3 (11.7 ± 1.2) | 68 (69.4) | 1.25 (0.58–2.70) | |
| p-trend | | 0.04 | p-trend | | 0.57 | 0.39 |
| Light Activity | | | Light Activity | | | |
| T1 (1.3 ± 0.4) | 143 (73.7) | REF | T1 (2.7 ± 0.7) | 68 (68.7) | REF | |
| T2 (2.6 ± 0.4) | 146 (75.7) | 1.33 (0.80–2.21) | T2 (4.5 ± 0.5) | 71 (71.7) | 0.99 (0.51–1.94) | |
| T3 (4.9 ± 1.4) | 147 (76.2) | 1.47 (0.84–2.56) | T3 (6.7 ± 1.1) | 69 (70.4) | 0.94 (0.42–2.09) | |
| p-trend | | 0.18 | p-trend | | 0.88 | 0.96 |
| Moderate-Vigorous | | | Moderate-Vigorous | | | |
| T1 (0.6 ± 0.3) | 134 (69.1) | REF | T1 (0.3 ± 0.2) | 54 (54.6) | REF | |
| T2 (1.7 ± 0.4) | 149 (77.2) | 1.48 (0.90–2.44) | T2 (0.9 ± 0.2) | 75 (75.8) | 2.62 (1.37–5.03) | |
| T3 (3.7 ± 1.0) | 153 (79.3) | 1.35 (0.79–2.29) | T3 (2.7 ± 1.0) | 79 (80.6) | 3.10 (1.51–6.35) | |
| p-trend | | 0.24 | p-trend | | 0.001 | 0.11 |
| 25(OH)D (Threshold = 20 ng/ml) | | | 25(OH)D (Threshold = 20 ng/ml) | | | |
| Activity[a] (hours/day) | n (%) | OR (95% CI) | Activity[a] (hours/day) | n (%) | OR (95% CI) | p-interaction |
| Sedentary Behavior | | | Sedentary Behavior | | | |
| T1 (5.8 ± 1.4) | 159 (82.0) | REF | T1 (5.5 ± 1.2) | 49 (49.5) | REF | |
| T2 (9.2 ± 0.8) | 162 (83.9) | 0.75 (0.39–1.44) | T2 (8.6 ± 0.7) | 66 (66.7) | 2.72 (1.31–5.64) | |
| T3 (12.4 ± 1.6) | 166 (86.0) | 1.04 (0.52–2.10) | T3 (11.7 ± 1.2) | 64 (65.3) | 3.45 (1.55–7.62) | |
| p-trend | | 0.89 | p-trend | | 0.002 | 0.10 |
| Light Activity | | | Light Activity | | | |
| T1 (1.3 ± 0.4) | 169 (87.1) | REF | T1 (2.7 ± 0.7) | 62 (62.6) | REF | |

| Men (n=580) | | | Women (n=296) | | | |
|---|---|---|---|---|---|---|
| 1,25(OH)$_2$D (Threshold = 26.0 pg/ml) | | | 1,25(OH)$_2$D (Threshold = 26.0 pg/ml) | | | |
| **Activity[a] (hours/day)** | **n (%)** | **OR (95% CI)** | **Activity[a] (hours/day)** | **n (%)** | **OR (95% CI)** | **p-interaction** |
| T2 (2.6 ± 0.4) | 153 (79.3) | 0.64 (0.35–1.16) | T2 (4.5 ± 0.5) | 61 (61.6) | 1.04 (0.52–2.08) | |
| T3 (4.9 ± 1.4) | 165 (85.5) | 1.14 (0.57–2.27) | T3 (6.7 ± 1.1) | 56 (57.1) | 1.70 (0.75–3.86) | |
| p-trend | | 0.69 | p-trend | | 0.22 | 0.47 |
| Moderate-Vigorous | | | Moderate-Vigorous | | | |
| T1 (0.6 ± 0.3) | 146 (30.0) | REF | T1 (0.3 ± 0.2) | 47(47.5) | REF | |
| T2 (1.7 ± 0.4) | 162 (33.3) | 1.58 (0.91–2.75) | T2 (0.9 ± 0.2) | 60 (60.6) | 1.75 (0.90–3.43) | |
| T3 (3.7 ± 1.0) | 179 (36.8) | 3.27 (1.65–6.47) | T3 (2.7 ± 1.0) | 72 (73.5) | 4.63 (2.14–10.03) | |
| p-trend | | 0.001 | p-trend | | 0.001 | 0.96 |

[a]Logistic regression model adjusted for: age, BMI, race, sleep, and 25(OH)D levels. Moderate-vigorous and light activity models were adjusted for sedentary behavior, while sedentary models were adjusted for moderate-vigorous activity