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Serum and Dietary Vitamin D and Cardiovascular Disease Risk in Elderly Men: A Prospective Cohort Study

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INTRODUCTION

Cardiovascular disease (CVD) is the most common cause of death worldwide. Low 25(OH) vitamin D has been associated with several risk factors for cardiovascular disease (CVD), including elevated hypertension (1, 2), hyperlipidemia (1, 3), and metabolic syndrome (4, 5). Whether vitamin D is a risk factor for CVD remains unclear.

A protective effect of vitamin D on CVD is plausible. Vitamin D may inhibit the renin-angiotensin system, lowering blood pressure (6); deactivate inflammatory response elements (7, 8), which cause atherosclerosis; reduce parathyroid hormone levels (9); and decrease coagulation through the upregulation of thrombomodulin and downregulation of tissue factor (10).

Recent prospective epidemiological studies have suggested that low serum 25(OH) vitamin D and 1,25 (OH) vitamin D may be associated with myocardial infarctions (11, 12), strokes (12, 13), CVD mortality (14–16), and all-CVD events (17). Of the eight epidemiologic studies, only one study resulted in a non-statistically significant association between low 25(OH) vitamin D and CVD (18). In the Framingham Offspring Study, this statistically significant association was only among participants with hypertension at baseline (17). Most of the evidence comes from mortality studies and does not address the association of vitamin D intake with CVD.

Evidence from clinical trials has been limited and has not reported a cardio-protective effect. In the Women's Health Initiative, 32,282 post-menopausal women were randomized to vitamin D (400 IU/day) and calcium (1000 mg/day) or placebo. After 7 years of follow-up,

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vitamin D plus calcium were not associated an increased risk for either coronary heart disease or heart attacks (19), although a low dose of vitamin D and inclusion of calcium may have explained the null result (20). In a British trial, 2,686 older participants were randomized to 100,000 IU of cholecalciferol or placebo given every four months. Despite achieving 8.4 ng/mL more circulating 25(OH) vitamin D, participants receiving cholecalciferol supplements did not have a significantly reduced risk for CVD after 5 years of follow-up (21).

Using data from the Osteoporotic Fractures in Men (MrOS) Study, we studied the association of 25(OH) vitamin D with both CVD and cardiovascular mortality. This is the first longitudinal cohort study to analyze the association of vitamin D intake with CVD.

METHODS

POPULATION

Details of the Osteoporotic Fractures in Men (MrOS) Study have been described (22). Briefly, MrOS is a prospective cohort study designed to elucidate predictors of fractures in men aged 65 and older at 6 recruitment sites (Birmingham, Alabama; Palo Alto, California; San Diego, California; Minneapolis, Minnesota; Portland, Oregon; Pittsburgh, Pennsylvania). Exclusion criteria included: (1) inability to walk without assistance from another person, (2) bilateral hip replacements, (3) inability to provide self reported data(23). 5,995 men were enrolled between 2000 and 2004.

The MrOS Sleep Study is an ancillary study of MrOS in which a subset of men were enrolled beginning in 2003 at all six study sites. Unlike the MrOS parent study, all sleep study participants were actively followed for both fatal and non-fatal CVD endpoints. All incident cases were adjudicated. Participants were excluded from the study if they reported any of the following: (1) sleeping with a CPAP or BiPAP mask in the last 3 months, (2) sleeping with a mouthpiece in the last 3 months, (3) having an open tracheotomy, or (4) using oxygen therapy during sleep in the last 3 months. There were 3,135 participants meeting these criteria who enrolled in the sleep study. Of these, 16 were excluded due to unreliable (<400 kcal/day) food frequency responses, and 25 were excluded due to incomplete CVD event data. In all, there were 3,094 participants included in the final vitamin D intake analyses.

Upon enrollment in the MrOS Sleep Study, participants completed a self-administered questionnaire, including medical history; lifestyle summary; a clinical interview questionnaire, which included information about medication use; and clinical measurements, including anthropometric measures and blood pressure. At baseline of the parent cohort, roughly two years earlier, a food frequency questionnaire was administered, medications were recorded, blood serum samples were taken in the morning while fasting, and physical activity was assessed using the Physical Activity Scale for the Elderly (PASE) (24). Data collected from the study was compiled and analyzed using SAS software.

Serum 25(OH) vitamin D data was analyzed in 1,608 men who were randomly chosen from the baseline parent MrOS cohort. Of the 1,608, 821 men participated in the MrOS Sleep Study; of whom, 8 were excluded due to incomplete CVD ordietary data, leaving 813 men for these 25(OH) vitamin D analyses.

This study was approved by Institutional Review Boards at each participating institution. All subjects gave written informed consent.

ASSESSMENT OF VITAMIN D

Our food frequency questionnaire is an abbreviated version of the Block 98 food-frequency questionnaire, which has been developed from an in-depth analysis of the NHANES III survey (25). Developed to specifically study osteoporosis, our self-administered questionnaire used nine categorical responses for frequency for 69 different food and drink categories to ensure accurate determination of dietary vitamin D and calcium. Dietary intake was measured at baseline and combined with self-reported vitamin D supplementation in order to estimate the average daily intake of vitamin D.

Serum for vitamin D was collected at baseline, protected from UV exposure, and frozen at -80°C . Concentrations of 25(OH)D₂ and 25(OH)D₃ were determined at the Mayo Clinic Reference Laboratories by mass spectrometry, an accurate and precise method free of the artifacts that have affected other radioimmunoassay based methods (26). Samples were prepared by incubation for 15 minutes with stable isotope 25(OH)D₃-d₆ followed by precipitation with acetonitrile. 50 μL of the supernatant was injected onto Cohesive Turbo Flow Cyclone extraction columns followed by chromatography on a Supelco LC-18 column and analysis by tandem mass spectrometry. Functional sensitivity is 4 ng/mL for 25(OH)D₂ and 2 ng/mL for 25(OH)D₃. The assay is linear to 200 ng/mL for both analyses. Inter assay coefficient of variation is 4.4%.

ASSESSMENT OF CORONARY HEART DISEASE AND CARDIOVASCULAR DISEASE

Self-reported cardiovascular events were adjudicated for 472 participants in the MrOS Sleep study, including 140 participants in the serum vitamin D sub-cohort. Coronary heart disease (CHD) included fatal and non-fatal myocardial infarction, sudden death attributed to CHD, coronary artery revascularization, hospitalization for unstable angina, and ischemic congestive heart failure. A stroke or cerebrovascular attack (CVA) was defined as a sudden loss of central nervous system function which caused death or left permanent impairment. CHD and CVA combined were defined as CVD.

All non-fatal and fatal events during follow-up were adjudicated centrally by staff physicians. For non-fatal events, adjudicators used ICD9 code from medical records. For fatal events, physicians used medical records and death certificates to adjudicate cause of death. To be adjudicated as a CVD death, CVD had to be the underlying cause of death.

STATISTICAL ANALYSIS

CVD event survival was calculated from the date of enrollment to the date of first CVD event or last follow-up. Differences in baseline characteristics of men with and without a follow-up CVD event and across quartiles of 25(OH) vitamin D were evaluated using a Chi-square test for categorical variables and an analysis of variance (ANOVA) or a Kruskal-Wallis test for continuous variables. The correlation between vitamin D intake and 25(OH) vitamin D levels was assessed by the Pearson correlation coefficient.

The impact of low 25(OH) vitamin D or low vitamin D intake on risk of CVD event was examined using the Kaplan-Meier method and Cox proportional hazards model. We estimated hazard ratios (HR) and 95% confidence for three models: an age-adjusted and two multivariable-adjusted models. In the first multivariable model, we adjusted for standard disease risk factors and variables known to affect vitamin D metabolism. These were age, race, BMI, study site and season (serum model only). For the other multivariable model, we kept the covariates from the first multivariable-adjusted model and added conventional risk factors for CVD. These were physical activity score (PASE); low- and high-density lipoprotein cholesterol; history of CV event, hypertension, and diabetes; systolic and

diastolic blood pressure; blood glucose; insulin; smoking status (ever or never); alcohol consumption (drinks/week); and anti-coagulant or anti-hypertensive medication use.

In order to eliminate potential bias due to prevalent CVD, we performed a secondary analysis by removing men who reported a prior CVD event at baseline and refitting the models with incident events only. Lastly, we analyzed the serum sub-cohort based on commonly used cut-points for 25(OH) vitamin D; “sufficiency” as ≥ 30 ng/mL, “insufficiency” as 15–29.9 ng/mL, and “deficiency” as <15 ng/mL (27). Using these cut-points, we estimated hazard ratios and 95% confidence intervals in an age-adjusted model and the same multivariable-adjusted models, with the highest vitamin D quartile category as referent. P values are 2-sided, and $p < 0.05$ was considered statistically significant.

RESULTS

During a median 4.4 years of follow up, there were 472 new CVD events – 371 (79%) CHD events and 101 (21%) CVA events. Of these, 52 (11%) were fatal and 420 (89%) were non-fatal. From the 25(OH) vitamin D sub-cohort of 813 men, there were 140 CVD events – 115 from coronary heart disease and 25 from CVA. Of the 140 events, 18 (13%) were fatal and 122 were (87%) non-fatal. Vitamin D intake was not strongly correlated with 25(OH) vitamin D ($r=0.25$).

Table 1 shows baseline characteristics in those with and without CVD events for selected demographic, lifestyle, and biological characteristics in the serum 25(OH) vitamin D sub-cohort. Cases were significantly more likely to have a history of stroke, heart attack, and diabetes; to use statin medications; consume alcohol and be older than non-cases. Mean vitamin D intake and serum 25(OH) vitamin D were not statistically significantly different.

Characteristics of the serum vitamin D sub-cohort are summarized by quartile of 25(OH) vitamin D (Table 2). Men in higher 25(OH) vitamin D quartiles had higher vitamin D intake; were younger; had a lower body mass index, serum insulin levels, blood glucose, and triglyceride levels; and had higher PASE scores and HDL cholesterol. No significant differences were observed for blood pressure, LDL, total cholesterol, or education.

Table 3 presents the hazard ratios and 95% confidence intervals for CVD outcomes by quartiles of both serum 25(OH) vitamin D and vitamin D intake. The results of 3 different models are shown: an age-adjusted model and two multivariable models, which included standard risk factors for CVD and known confounders for 25(OH) vitamin D levels. Results did not vary substantially between the three models for either serum or intake analyses. In the age-adjusted model, low vitamin D intake was non-significantly associated with a decrease in CVD incidence when compared to the highest quartile of vitamin D intake (HR 0.65, 95% CI 0.40–1.07). After adjusting for age in the serum sub-cohort, low 25(OH) vitamin D was not associated with CVD incidence (HR 1.19, 95% CI 0.72–1.94). In the first multivariable model, the association of both low vitamin D intake (HR 0.78, 95% CI 0.58–1.05) and low 25(OH) vitamin D (HR 1.22, 95% CI 0.72–2.05) with CVD incidence did not change substantially from the age-adjusted model. In the final multivariable model, the lowest quartile of vitamin D intake and 25(OH) vitamin D remained not significantly associated with CVD incidence when compared to the highest quartile (HR 0.76, 95% CI 0.56–1.04; HR 1.18, 95% CI, 0.69–2.03, respectively). Trends across quartiles were also not statistically significant ($p = 0.22$).

Of the 472 incident CVD events in the vitamin D intake population, 299 occurred among men reporting no history of CVD. When we analyzed this group, low vitamin D intake remained non-significantly associated with reduced CVD risk (HR 0.74; 95% CI, 0.48–1.13). In the 25(OH) vitamin D sub-cohort, of the 140 total cases, 79 were first-event cases.

When we analyzed just these cases in the final multivariable-adjusted model, there remained no significant association between low serum 25(OH) vitamin D and CVD risk (HR 1.34, 95% CI 0.65–2.77).

We further analyzed CVD risk by three standard 25(OH) vitamin D cut-points (Figure 1). Of those who were deficient (<15 ng/ml), 15 (22%) were cases; of those who were insufficient (15–29.9 ng/ml), 92 (17%) were cases; and of those who were sufficient (≥30 ng/ml), 33 (16%) were cases. In the age-adjusted model, vitamin D deficiency was not associated with CVD when compared to men who were sufficient (HR, 1.40; 95% CI, 0.76–2.59). The results were non-significant in both multivariable adjusted models (HR 1.53, CI 95% 0.80–2.95; HR 1.34, 95% CI 0.65–2.77, respectively). HRs for vitamin D insufficiency were also not significant.

DISCUSSION

In these older men, there was no significant association between 25(OH) vitamin D or vitamin D intake and CVD outcomes. Standard risk factors for CVD, such as age, history of CVD and medication use, were strong predictors of CVD and included as covariates, but 25(OH) vitamin D and vitamin D intake were not independently associated with CVD incidence.

These non-significant results are inconsistent with previous studies. To our knowledge, there have been seven large, prospective epidemiological studies (11–17) supporting a significant inverse association of vitamin D with CVD and one study reporting a non-significant inverse association (18). The discrepancy between our results and the findings of other studies may be the result of a number of different factors.

First, epidemiological studies on vitamin D and CVD risk support a threshold for 25(OH) vitamin D between 15 ng/ml and 20 ng/mL. Evidence from longitudinal studies suggests that the only statistically significant difference in CVD risk exists below 20 ng/mL when compared to populations with at least 30 ng/mL vitamin D (12, 14, 15, 17, 18). With a median of 25.3 ng/mL, our population had the second highest 25(OH) vitamin D levels compared to other studies and may not reflect the effects of vitamin D deficiency (<15 ng/mL) on CVD risk. When evaluated by cut-points, vitamin D deficiency (<15 ng/mL) remained not associated with increased CVD risk when compared to vitamin D sufficiency (≥30 ng/mL). With 8% having 25(OH) vitamin D levels less than 15 ng/mL, this analysis may have been limited by statistical power. Overall, our study's null findings and higher 25(OH) vitamin D distribution may indicate that increasing dietary vitamin D to prevent CVD may only be advantageous for populations that are severely vitamin D deficient.

Second, the association between vitamin D and CVD may be strong only with life-long deficiency. Of the seven studies with a significant protective association, only three were populations from southern latitudes (14, 16, 18). Since our population was geographically diverse, almost half living in the southern United States, our cohort may not reflect the effects of sustained life-long vitamin D deficiency that are more likely at northern latitudes.

Third, it is understood that a diagnosis of CVD may lead to dietary or lifestyle changes which may bias the results. While we adjusted for history of CVD, it was not an exclusion criterion in our primary analyses. For comparability with other studies, we used a multivariable-adjusted Cox proportional hazards model to evaluate only incident cases in the 25(OH) vitamin D sub-cohort. In this analysis, men in the lowest 25(OH) vitamin D quartile were not at significantly reduced risk for CVD when compared to the highest quartile. With only 79 incident cases, our analysis was limited, but suggested that including men with a history of a CVD did not bias our results toward the null.

Due to concerns of skin cancer with increased UV exposure, fewer individuals may be able to attain sufficient vitamin D levels without supplementation. Thus, understanding the role of vitamin D supplementation in the prevention of CVD may have important clinical relevance. Although vitamin D intake has been associated with fracture prevention (28), increased muscle strength (29), and decreased cancer risk (30), there is limited causal evidence to support an association of vitamin D intake with CVD risk (19, 21). In our population, vitamin D intake was associated with higher overall 25(OH) vitamin D, but was not strongly correlated with 25(OH) vitamin D and was not significantly associated with CVD incidence. The weak correlation between 25(OH) vitamin D in serum and vitamin D intake suggests that even in these older adults, endogenous vitamin D synthesis from sun exposure may be the primary source of circulating 25(OH) vitamin D and may demonstrate that in order to achieve sufficient 25(OH) vitamin D levels, vitamin D supplementation may need to be increased. Moreover, the null findings in our study and others (19, 21) may suggest that short-term, low-dose vitamin D supplementation may be ineffective in preventing CVD; or alternatively, these null findings may support the presence of uncontrolled confounders in longitudinal studies, leading to their significant results.

The current analyses are limited by a short median follow-up period of 4.4 years, compared to 27.1 years in another cohort (12). Second, with only 140 CVD cases with 25(OH) vitamin D data, we were unable to perform many secondary analyses, such as evaluating fatal and non-fatal events or analyzing CHD and CVA risk separately. Third, since we included cases with history of CVD, our primary analysis is not an analysis of first incident cases. Nevertheless, including participants with a history of CVD provided the opportunity to evaluate both the preventative and therapeutic effects of vitamin D. Moreover, if there is a biological basis for the role of vitamin D in the prevention of CVD, it is likely to be expressed in patients with and without a history of CVD.

This analysis is strengthened by its geographically diverse population. With six enrollment sites across the United States at varying latitudes, our participants' sunlight exposure levels may be one of the most accurate reflections of exposure in the actual U.S. population and may have contributed to our higher average 25(OH) vitamin D levels compared to other studies, which were predominately from northern latitudes. Moreover, our study was also strengthened by its longitudinal design, standard adjudication of all CVD events, and availability of multiple covariates.

In conclusion, 25(OH) vitamin D and vitamin D intake were not significantly associated with CVD outcomes in a population of elderly men. Given the limited data from clinical trials and the prevalence of vitamin D deficiency, additional investigations are necessary to evaluate the efficacy of vitamin D supplementation on CVD risk.

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Figure 1. CVD event-free survival by serum 25(OH) vitamin D deficiency (<15 ng/mL), insufficiency (15–29 ng/mL), and sufficiency (≥30 ng/mL).

Table 1

Baseline Characteristics by Event Outcome in Serum 25(OH) Vitamin D Sub-Cohort, Osteoporotic Fractures in Men (MrOS) Study

Characteristics	CVD Event (n=140)	No CVD Event (n=673)	P-value
25(OH)D, median (IQR), ng/mL	25.1 (19.6–29.7)	25.4 (20.4–30.1)	0.29 ^a
Vitamin D intake, median (IQR), IU	432.4 (162.0–601.3)	428.0 (145.9–560.4)	0.29 ^a
Age, mean ± SD	77.4 ± 5.5	76.1 ± 5.6	0.02
Race, No. (%)			
White	129 (92)	614 (91)	0.72
Region, No. (%)			
Birmingham	108 (16)	21 (15)	
Minneapolis	106 (16)	16 (11)	
Palo Alto	114 (17)	24 (17)	
Pittsburgh	113 (17)	39 (28)	
Portland	117 (17)	14 (10)	
San Diego	115 (17)	26 (19)	0.02
Education, No. (%)			
High school or less	38 (27)	147 (22)	
Some after high school	26 (19)	149 (22)	
College or more	76 (54)	377 (56)	0.34
Body mass index, mean ± SD, kg/m ²	27.5 ± 3.9	27.3 ± 3.8	0.51
Blood pressure, mean ± SD, mmHg			
Systolic	128.6 ± 19.7	126.7 ± 15.4	0.19
Diastolic	67.5 ± 8.9	67.9 ± 9.8	0.62
PASE score, mean ± SD	143.8 ± 80.7	143.2 ± 67.7	0.93
Cholesterol level, mean ± SD, mg/dL			
Total	189.8 ± 35.1	195.2 ± 33.1	0.09
LDL	113.2 ± 30.8	116.3 ± 30.5	0.29
HDL	47.3 ± 13.1	49.4 ± 14.1	0.12
Triglyceride level, median (IQR), mg/dL	127.5 (97.0–175.0)	120.5 (88.0–179.0)	0.24 ^a
Blood glucose, median (IQR), mg/dL	98.0 (93.0–113.0)	99.0 (92.0–109.0)	0.45 ^a
Insulin level, median (IQR), mg/dL	7.7 (5.5–10.2)	7.6 (5.2–11.6)	0.88 ^a
History of smoking, No. (%)	86 (61)	402 (60)	0.71
History of diabetes mellitus, %	22 (16)	60 (9)	0.02
History of hypertension, No. (%)	81(58)	332(49)	0.07
History of heart attack, No. (%)	55 (39)	103 (15)	<.0001
History of stroke, No. (%)	10 (7)	20 (3)	0.02
Alcohol consumption, No. (%)			
0 drinks/week	209 (31)	58 (41)	
1–3 drinks/week	282 (42)	45 (32)	
4 drinks/week	179 (27)	36 (26)	0.04
Medication Use, %			

Characteristics	CVD Event (n=140)	No CVD Event (n=673)	P-value
β-blocker	66 (47)	159 (24)	<.0001
Angiotensin Inhibitor	17 (12)	68 (10)	0.47
Statin	71 (51)	274 (41)	0.03
NSAIDS	29 (21)	138 (21)	0.96
Aspirin	91 (65)	392 (58)	0.14

Abbreviations: IQR, interquartile range; SD, standard deviation.

^aWilcoxon ranked test

Table 2
Selected Baseline Characteristics by Quartile of Serum 25(OH) Vitamin D, Osteoporotic Fractures in Men (MrOS) Study

Characteristics	Serum 25(OH) Vitamin D Quartile				p value
	1 (n=204)	2 (n=203)	3 (n=202)	4 (n=204)	
25(OH)D, (range), ng/mL	4.9–20.1	20.2–25.2	25.3–30.1	30.2–55.4	
Dietary vitamin D, median (IQR), IU	207.3 (87.3–482)	367.9 (147.0–550.3)	484.1 (184.3–601.5)	476.0 (274.9–608.0)	
Age, mean ± SD	77.3 ± 6.2	76.1 ± 5.1	76.6 ± 5.6	75.3 ± 5.1	0.004
Race					
White	175 (86)	188 (92)	187 (93)	193 (96)	0.004
Region, No. (%)					
Birmingham	39 (19)	34 (17)	26 (13)	30 (15)	
Minneapolis	38 (16)	33 (16)	32 (16)	24 (12)	
Palo Alto	35 (17)	32 (16)	38 (19)	33 (16)	
Pittsburgh	43 (21)	41 (20)	42 (21)	26 (13)	
Portland	33 (16)	33 (16)	31 (15)	34 (17)	
San Diego	21 (11)	30 (15)	33 (16)	57 (28)	0.01
Education, No (%)					
High school or less	46 (23)	42 (21)	52 (26)	45 (22)	
Some after high school	45 (22)	44 (22)	43 (21)	43 (21)	
College or more	113 (55)	117 (58)	107 (53)	116 (57)	0.94
Body mass index, mean, mean± SD, kg/m ²	27.9 ± 4.3	27.6 ± 3.8	27.3 ± 3.9	26.6 ± 3.1	0.003
Blood pressure, mean± SD, mean					
Systolic	127.1 ± 17.1	127.4 ± 15.8	126.8 ± 15.6	126.7 ± 16.5	0.97
Diastolic	66.6 ± 9.3	68.3 ± 10.1	67.8 ± 9.3	68.7 ± 9.8	0.14
Physical activity, PASE score, mean ± SD	131.6 ± 72.8	145.5 ± 70.1	142.8 ± 66.8	153.4 ± 69.1	0.02
Cholesterol level, mean ± SD, mg/dL					
Total	191.8 ± 33.4	196.6 ± 32.8	194.4 ± 31.4	194.3 ± 36.2	0.59
LDL	113.9 ± 30.8	118.7 ± 31.4	114.8 ± 29.4	115.6 ± 30.6	0.46
HDL	47.6 ± 13.8	47.2 ± 12.5	50.4 ± 14.5	50.9 ± 14.4	0.01
Triglyceride level, median (IQR), mg/dL	126.5 (90.0–185.0)	127.0 (97.0–176.0)	113.5 (88.0–172.0)	118.0 (88.0–168.0)	0.24 ^a
Blood glucose, median (IQR), mg/dL	99.0 (93.0–111.0)	100.0 (92.0–109.0)	99.0 (93.0–112.0)	96.0 (91.0–106.0)	0.01 ^a

Characteristics	Serum 25(OH) Vitamin D Quartile				p value
	1 (n=204)	2 (n=203)	3 (n=202)	4 (n=204)	
Insulin level, median (IQR), mg/dL	8.3 (5.5–11.9)	7.8 (5.6–12.2)	7.9 (5.2–11.9)	7.0 (4.8–9.4)	0.006 ^a
Current smoker, No. (%)	7 (37)	5 (26)	3 (16)	4 (21)	0.61
Medication Use, No. (%)					
β-blocker	55 (27)	52 (26)	62 (31)	56 (27)	0.92
Angiotensin Inhibitor	20 (10)	23 (11)	23 (11)	19 (9)	0.87
Statin	78 (38)	88 (43)	80 (40)	99 (48)	0.15
NSAIDs	44 (22)	41 (20)	38 (19)	44 (22)	0.88
Aspirin	119 (58)	121 (59)	118 (58)	125 (61)	0.92
Disease history, No. (%)					
Diabetes mellitus	26 (32)	17 (21)	24 (29)	15 (18)	0.20
Hypertension	97 (23)	96 (23)	122 (30)	98 (24)	0.02
Heart Attack	41 (26)	32 (20)	48 (30)	37 (23)	0.21
Stroke	5 (17)	6 (20)	10 (33)	9 (30)	0.49

Abbreviations: IQR, interquartile range; SD, standard deviation.

^aKruskal-Wallis test used

Table 3
Cardiovascular Outcomes by 25(OH) Vitamin D Quartile, Osteoporotic Fractures in Men (MrOS) Study

	Quartile				
	1	2	3	4	p-value (trend)
25(OH) Vitamin D (n=813)					
Range, ng/mL	4.8–20.1	20.2–25.2	25.3–30.0	30.1–55.4	
Events, No. (%)	39 (19.1)	33 (16.3)	35 (17.3)	33 (16.2)	
Events per 1000 men-year (95% CI)	50 (37–69)	40 (28–56)	43 (31–60)	40 (29–57)	
Hazard Ratio (95% CI)					
Model 1 ^a	1.19 (0.72–1.94)	0.99 (0.60–1.60)	1.03 (0.64–1.67)	1.00 (ref)	0.67
Model 2 ^b	1.22 (0.72–2.05)	1.00 (0.60–1.65)	1.03 (0.63–1.67)	1.00 (ref)	0.53
Model 3 ^c	1.18 (0.69–2.03)	1.11 (0.65–1.91)	0.97 (0.57–1.64)	1.00 (ref)	0.85
Vitamin D Intake (n=3094)					
Range, IU	<168.6	168.6–437.8	437.9–572.3	>572.3	
Events, No. (%)	107 (13.8)	125 (16.2)	108 (14.0)	132 (17.1)	
Events per 1000 men-year (95% CI)	35 (29–42)	41 (35–49)	35 (29–42)	43 (37–52)	
Hazard Ratio (95% CI)					
Model 1 ^a	0.65 (0.40–1.07)	0.94 (0.61–1.45)	0.64 (0.40–1.03)	1.00 (ref)	0.22
Model 2 ^b	0.78 (0.58–1.05)	0.98 (0.74–1.29)	0.88 (0.66–1.18)	1.00 (ref)	0.34
Model 3 ^c	0.76 (0.56–1.04)	0.97 (0.72–1.30)	0.85 (0.63–1.15)	1.00 (ref)	0.29

^a Adjusted for age

^b Adjusted for age, race, BMI, site and season (serum model only)

^c Adjusted for age, race (white/non-white), BMI, site and season (serum model only), HDL, LDL, triglycerides, glucose, insulin, PASE score, systolic blood pressure, diastolic blood pressure, history of smoking, alcohol use (drinks/week), statin use, history of hypertension, history of diabetes, and history of CV event