FEMORAL VOLUMETRIC BONE DENSITY AND DIMENSIONS IN RELATION TO 25-HYDROXY VITAMIN D IN OLDER MEN

by
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CERTIFICATE OF APPROVAL

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ABSTRACT

Vitamin D deficiency has been previously shown to be associated with increased incidence of hip fracture. Higher serum 25(OH)D levels are also associated with greater femoral neck BMD estimated with DXA. However, there is limited current evidence supporting associations between femoral neck or shaft bone density distributions in cortical and trabecular compartments or bone size and endogenous serum 25(OH)D levels. We evaluated variation in femoral neck and shaft volumetric BMD (vBMD) and size with serum 25(OH)D in men ages ≥ 65 years from the Osteoporotic Fractures in Men Study (MrOS). Baseline fasting serum 25(OH)D levels were measured by LC/MS assays in a randomly selected sample. Femoral neck measures from quantitative computed tomography (QCT) were integral, cortical and trabecular vBMD; cross-sectional area; and integral, cortical, and percent cortical volume. Femoral shaft measures included cross-sectional area, cortical area, medullary area, integral BMD and percent cortical area. The analytic cohort consisted of 888 men with serum 25(OH)D and femoral neck measures. Multivariable linear regression models with adjustments for age, race, BMI, height, latitude of clinic site and season of visit were used to estimate adjusted means of femoral measures and 95% confidence limits within quartiles of vitamin D. Tests of linear trend were performed for each femoral measure across increasing serum 25(OH)D levels. Femoral neck vBMD measures were all found to increase with increasing 25(OH)D level. Overall femoral neck size, represented by cross-sectional area and integral volume, did not vary by serum 25(OH)D level. However, both cortical volume and cortical volume as a percent of integral volume increased with increasing 25(OH)D level. Femoral shaft cortical area and percent cortical area were positively associated with serum 25(OH)D level, but the remaining femoral shaft measures did not demonstrate any association. These observed associations of femoral neck cortical and trabecular vBMD and percent cortical bone volume to serum 25(OH)D among elderly men suggest that higher serum vitamin D levels may inhibit endosteal resorption, independent of the effects of PTH.

INTRODUCTION

Vitamin D deficiency has been identified as a risk factor for increased fracture incidence, and positive associations between increasing vitamin D levels and higher two-dimensional bone mineral density (BMD) have been previously described[1 2]. These findings suggest that vitamin D may have an important role in skeletal structure; however bone density is only one measure of bone strength. It remains unclear whether serum vitamin D levels are associated with specific skeletal dimensions in the proximal femur. The distribution of components within bone including overall skeletal dimensions, compartments of cortical versus trabecular bone, and bone density within each compartment are all important determinants of bone strength. The ability to localize other changes associated with higher vitamin D levels would provide a more complete understanding of the structural changes underlying bone strength, particularly of those variables which can be measured and potentially provide sites of intervention.

Current knowledge of biological pathways suggest that vitamin D acts on the skeleton through promotion of calcium absorption through diet and inhibition of PTH-mediated calcium resorption in bone[3 4 5]. The levels necessary to suppress PTH continue to be under debate, with recent evidence from NHANES III suggesting levels of 40ng/mL to be necessary, and previous evidence supporting levels over 32ng/mL[6 7]. Differences in cortical and trabecular regions of bone associated with vitamin D level have also been described, suggesting another important component to these associations. However, other studies have suggested that the associations observed between vitamin D level and BMD are completely explained by the effects of PTH[8]. Targeted PTH treatment independent of vitamin D supplementation has been shown to decrease fracture risk and increase BMD[9]. As a result, it is important to distinguish not only what changes in skeletal dimensions are associated with declining vitamin D levels, but whether these changes seen with decreasing levels of vitamin D are directly correlated to or are independent of changes in PTH levels.

Bone strength or fracture risk are currently estimated by guidelines based on two-dimensional DXA measures calculating bone mineral density (BMD)[10]. While BMD provides a clinical indicator of fracture risk, quantitative computed tomography (QCT) is a three-dimensional imaging technique that provides information on the distribution of bone into cortical and

medullary compartments, through volumetric density measurements of cortical and trabecular bone and skeletal dimensions[11 12 13 14 15 16 17 18 19]. In this study we use QCT measures of the femoral neck and shaft to identify whether changes in bone structure are associated with serum 25(OH)D and total intact PTH levels. The femoral neck is a common site for hip fractures, with important clinical relevance, while information on the femoral shaft allows us to examine differences across bone types.

Previous Studies

Three studies in the literature have investigated the issue of differences between 25-OH vitamin D categories above and below 30ng/mL and volumetric bone density or skeletal dimensions in men. Two were clinical trials among elderly persons examining supplementation with vitamin D, one in which calcium and vitamin D supplementation through fortified milk was associated with slower expansion of the medullary cavity[20], and a second in which 4 years of supplementation with 600IU vitamin D resulted in less reduction in cortical thickness of the femoral shaft[21]. Results from a third cross-sectional study among Italian elders conflicts somewhat with the above clinical trials in that no association between endogenous vitamin D levels and tibial dimensions was observed in men[22]. In addition, animal models have demonstrated that vitamin D3 supplementation result in higher stress prior to fracture ratios in rats. Qualitative bone measures in these animals identified greater trabecular bone content[23]. No studies have reported on endogenous vitamin D and femoral neck volumetric bone density or dimensions in older men. Further, no studies have determined if associations between vitamin D and bone density and structure differ between the femoral neck and shaft. These are important distinctions when analyzing potential risk factors for hip fractures. The influence of PTH on these outcomes has also not been analyzed, and presents another important question about the mediators of changes in skeletal structure.

METHODS

Using a cross-sectional design we evaluated serum 25(OH) vitamin D levels, total intact PTH levels and QCT measures of the femoral neck and shaft collected by the Osteoporotic Fractures in Men Study (MrOS) Study to determine whether associations exist between these serum hormone levels and specific three-dimensional changes in bone structure.

Study Population

The MrOS Study contains information on a total of 5994 men collected from March 2000 through April 2002[24 25]. Details of the cohort and study design have been previously published[24 25]. In short, these men were recruited at 6 U.S. academic centers in Birmingham AL, Minneapolis MN, Palo Alto CA, Pittsburgh PA, Portland OR, and San Diego CA. Eligibility was based on age (65 and older), ability to walk without assistance from another person, absence of bilateral hip replacement surgery, ability to provide self-reported data, residence near a clinical site for the duration of the study, absence of a medical condition that the investigator judged might result in imminent death, and the ability to understand and sign an informed consent. These participants provided written informed consent when enrolled in the study, and the Institutional Review Board (IRB) at each study center approved the study protocol. At the baseline visit participants completed a self-administered questionnaire, attended a baseline clinic visit and received skeletal, anthropometric (height, weight, etc), and other measures including blood draws for serum 25(OH)D assays at their local site. Participants were of multiple ethnicities including African-American, Asian, Hispanic and Caucasian, as generally representative of the US population of older men.

Baseline Characteristics

Information about age, race/ethnicity, smoking and alcohol history, medication history, and medical history were provided by self-reported questionnaire at baseline. The questionnaire data was then reviewed with the participant and verified by a study team member at the baseline clinic visit.

Height, weight, and BMI were measured at the baseline visit, and the season of the baseline visit and latitude of the study site were also recorded. Physical activity was assessed by the PASE

score, which has been previously described[26]. Seasons of baseline visits were recorded by each study site, and latitudes were assigned based on the location of each study site.

For analysis race/ethnicity categories were grouped as Caucasian/non-Caucasian. Cigarette smoking was classified as current smoker, past smoker, and never smoked. Alcohol consumption was divided into categories of none, 1-7 drinks, or 7 or more drinks. Medication history was limited to the yes/no question of "Have you ever used an osteoporosis medication". Questions describing medical history also included reported health status for age (good/excellent versus fair/poor/very poor), fracture history (previous fracture since age 50, yes/no), osteoporosis diagnosis (yes/no), and arthritis diagnosis (yes/no). Season of baseline visit was divided into Winter (January to March), Spring (April to June), Summer (July to September), and Fall (October to December). Latitude of study site was divided as previously described in Orwoll et al[27]. High latitude was defined as over 44 degrees, based on the findings of Holick et al, and included sites in Minneapolis, Pittsburgh, and Portland[28]. Low latitude included all sites 44 degrees and under, including Birmingham, Palo Alto, and San Diego.

Assay Measurements

Liquid chromatography/mass spectrometry assays to determine serum 25(OH)D level were performed in a random sample of 1608 men from the MrOS Study. Serum 25(OH)D has been shown to provide an accurate measure of available vitamin D stores[28]. These assays were performed on fasting blood stored in foil-wrapped vials to prevent UV exposure, as previously described[27]. All assays were highly precise, with an inter-assay coefficient of variation of 4.4% and intra-assay coefficient of variation of 4.9%[29].

Among this random sample of 1608 men, 1593 also had parathyroid hormone (PTH) immunoradiometric assays completed. The details of this assay have also been previously reported, and the technique is the gold standard for total intact PTH assay. The inter-assay coefficient of variation was 8.4%, with an intra-assay coefficient of variation of 5.6%. Participants needed at least 5 baseline vials in order to be included in the baseline total intact PTH measure.

QCT-Derived Measures

The first 650 men enrolled and all non-Caucasian men enrolled at each site were referred for QCT scans of the hip, lumbar spine, and abdomen as part of their baseline visit. A total of 3,786 participants received QCT scans. Scans were obtained using a standardized protocol according to previously reported methods[30]. This included comparison to hydroxyapatite models of known density to allow conversion from Hounsfield units to g/cm³. All scans were reviewed and processed at UCSF for quality control[30].

Outcome measures in this analysis included baseline QCT measures of the femoral neck and shaft. Processing femoral neck measures provided measurement of cross-sectional area, integral, cortical and medullary volume, integral, cortical and trabecular BMD, and the calculated percent cortical volume. Femoral shaft measures provided included cross-sectional area, cortical area, medullary area, integral BMD and percent cortical area. Scanners at the sites were GE Prospeed (Birmingham), GE Hispeed Advantage (Minneapolis), Phillips MX-8000 (Palo Alto), Seimans Somatom +4 (Pittsburgh), Phillips CT-Twin (April-July 2000, 190 participants, Portland) and Toshiba Acquilion (December 2000- March 2002, 467 participants, Portland), and Picker PQ-5000 (San Diego).

Statistical Analysis

Our analytic cohort consisted of the 888 of these men within the MrOS Study who had both complete QCT measures of the femoral neck, and complete 25(OH)D and PTH assay data. Within this cohort, serum 25(OH)D levels were divided into quartiles, and distributions of the population's baseline characteristics were described across 25(OH)D quartiles by one-way ANOVA for continuous variables, or with chi-square tests for categorical variables. Spearman rank correlation coefficients were calculated between 25(OH)D and PTH levels, and 25(OH)D and each QCT measure. Unadjusted mean femoral neck and femoral shaft measures were calculated across quartiles, and then multivariable generalized linear regression models were used to estimate least square (LS) means of each outcome variable across 25(OH)D and total intact PTH quartiles.

Variables considered for potential confounding of an association between 25(OH)D and femoral measures included age, weight, height, BMI, race, smoking, alcohol consumption, physical activity (PASE score), season of visit and latitude of clinic site. Our final model included adjustments for age, race (white/nonwhite), BMI, height, latitude of clinic site and season of

visit. We evaluated potential confounding factors based on results from Table 1, and confounding variables were included in the model if they altered QCT measures by 10% or more. We evaluated the models including the small number of men with a history of osteoporosis medication use, and refit the models after excluding this group, and found the least square means were nearly identical. Therefore, we did not exclude these men from analyses. No other variables examined confounded the association of 25(OH)D with the femoral measures, and so were not included in the final model. Tests of trend of each femoral neck measure across increasing quartile of 25(OH)D and quartile of PTH were also reported. To demonstrate that adjustment for PTH did not account for the observed associations, results with and without additional adjustment for PTH are shown. Similarly, results with and without additional adjustment for 25(OH)D are shown for data analyzed by PTH quartile. All analyses were conducted using SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA).

RESULTS

While vitamin D and total intact PTH levels within this cohort demonstrated a statistically significant inverse relationship ($r=-0.259$, $p<0.001$), the magnitude was small and PTH did not confound the association with any QCT skeletal measures.

The characteristics of this cohort were similar to those of the larger MrOS vitamin D cohort which has been previously described[27]. Men within higher vitamin D quartiles were found to be younger, to have a smaller BMI, to report better health, to have greater physical activity, and to have a clinic site at under 44 degrees latitude (Table 1). 23% of Caucasian men fell in the lowest quartile of 25(OH)D with a mean serum 25(OH)D level of 15.1, while 26% fell in the highest quartile with a mean level of 34.8. On the other hand, 40% of non-Caucasian men fell in the lowest quartile of 25(OH)D, with only 16% in the highest quartile. Those in lower vitamin D quartiles were more likely to have baseline clinic visits in the fall, winter, or spring.

Femoral neck dimensions estimated by LS means according to 25(OH)D quartile with and without adjustment for PTH level are shown in Table 2. Femoral dimensions of cortical volume and medullary volume were found to be positively associated with 25(OH)D level. The overall bone size was not associated with 25(OH)D level (p-trend 0.42 for cross-sectional area, 0.35 for integral volume).

Femoral neck volumetric bone mineral densities at all sites of cortical, trabecular, and integral were positively associated with 25(OH)D level (p-trend=0.03, 0.006, <0.001 respectively) (Table 3). No associations were found between femoral neck measures and PTH level after adjustment for 25(OH)D level (Tables 4-5).

In the femoral shaft, an association between cortical area and 25(OH)D was seen. Cortical area and percent cortical area were positively associated with increasing 25(OH)D level (p-trend 0.003 and 0.04 respectively). However, unlike in the femoral neck, no other sites of the femoral shaft demonstrated an association with 25(OH)D level (Table 6).

DISCUSSION

Our findings show that within a population of generally healthy, community-dwelling men ages 65 and older, higher 25(OH)D was associated with higher cortical volume of the femoral neck and shaft, smaller medullary volume of the femoral neck, and higher percent cortical volume without a change in overall bone size.

In this population we observed on average a 4% increase in cortical volume of the femoral neck between vitamin D levels averaging 15 ng/ml (Q1) and averaging 34.8 ng/mL (Q4) after adjustment for age, race, latitude, season, weight, BMI and PTH (p-trend 0.01). Medullary volume demonstrated a 5% decrease between Q1 and Q4 25(OH)D levels after adjustment (p-trend 0.01). Percent cortical volume increased 5% between Q1 and Q4 (p-trend 0.0003).

Greater BMD was associated with higher serum 25(OH)D level in all femoral neck compartments. Integral BMD increased 6% between Q1 and Q4 (p-trend <0.001), cortical BMD increased 2% between Q1 and Q4 (p-trend 0.07), and trabecular BMD increased 12% between Q1 and Q4 (p-trend 0.008).

Adjustment for PTH level did not explain the association observed between 25(OH)D and these femoral neck measures. Femoral neck measures were also examined across PTH quartiles, and were not associated with PTH level. As seen in Table 4, cross-sectional area decreased 1.4% with increasing PTH (Q1 to Q4) (p-trend 0.18), and integral and cortical BMD showed very small decreases with increasing PTH that are likely not clinically significant, and no other sites showed consistent changes with increasing PTH level. None demonstrated consistently linear trends.

Within the femoral shaft, cortical area increased 3.6% with increasing 25(OH)D from Q1 to Q4 (p-trend 0.003). Percent cortical area also increased 2% with increasing 25(OH)D from Q1 to Q4 (p-trend 0.04). However, unlike in the femoral neck, no other sites of the femoral shaft were associated with 25(OH)D level.

Therefore, in this cohort of 888 men ages 65 years and older, serum 25(OH)D level was associated with femoral neck measures of cortical volume, medullary volume, integral, cortical and trabecular BMD, and percent cortical volume as a function of integral volume. Total intact

PTH was not associated with femoral neck measures, and did not confound the association seen between 25(OH)D level and these femoral neck measures. In the femoral shaft, unlike the femoral neck, 25(OH)D level was not associated with femoral shaft measures except for cortical area and percent cortical area, and while PTH did not affect this association enough to be considered a confounder, it was seen to have more of an effect than at the femoral neck.

One possible explanation for the results within this population of community dwelling older men is that those with higher vitamin D levels may have decreased endosteal resorption resulting in greater preservation of cortical bone at the femoral neck and shaft, without change in overall bone size. These findings also support previous studies that have found greater cortical area following calcium and vitamin D supplementation. A more detailed understanding of the mechanisms underlying these changes could clarify the role of vitamin D supplementation for osteoporosis in this population. More importantly, adjustment for PTH did not eliminate the observed association, suggesting that suppression of PTH may not be as critical in promoting bone strength as has been previously hypothesized. These results are also important in the context of hip fractures, as Black et al found a hazard ratio of fracture of 1.62 (1.10, 2.38) for each 1 standard deviation decrease in cortical volume, and 3.02 (2.15, 4.23) for each 1 standard deviation decrease in percent cortical volume in the MrOS cohort [31]. Therefore the potential to prevent endosteal resorption and the resulting drop in cortical volume and percent cortical volume could potentially translate into reduced fracture risk.

Study Strengths and Limitations

Some limitations to this study include the fact that due to its cross-sectional design it is unable to determine a direct causal relationship between vitamin D and skeletal measures. Additionally, while it looks at skeletal measures that have been shown to be associated with fracture risk in previous studies, it does not test the likelihood of fracture directly. Due to the small numbers of non-Caucasian men in the vitamin D cohort, we were also unable to analyze this association specifically within African-American, Asian, and Hispanic men, but had to restrict our analysis to Caucasian and non-Caucasian. Inclusion criteria for the MrOS study also limited participants to ambulatory, community-dwelling men who as a result tend to be healthier than the general population. This restricts the generalizability of our study results. However, the MrOS cohort is unique in its size, the precise assay measurements available, and the standardized QCT measures

of the femoral neck and shaft that it provides. This large sample size of QCT measures remains a valuable estimator for the population of ambulatory, community-dwelling men and provides an important tool for assessing vitamin D related outcomes in a significant percentage of the U.S. population. The ability to quantify associations between vitamin D, PTH, and specific 3-dimensional skeletal measures in this population provides important additional insight into reasons higher 25(OH) vitamin D has been associated with decreased fracture risk.

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FIGURES AND TABLES

Figure 1: Correlation between serum 25(OH)D and total intact PTH levels in 888 men aged 65 years and older in the Osteoporosis in Men Study

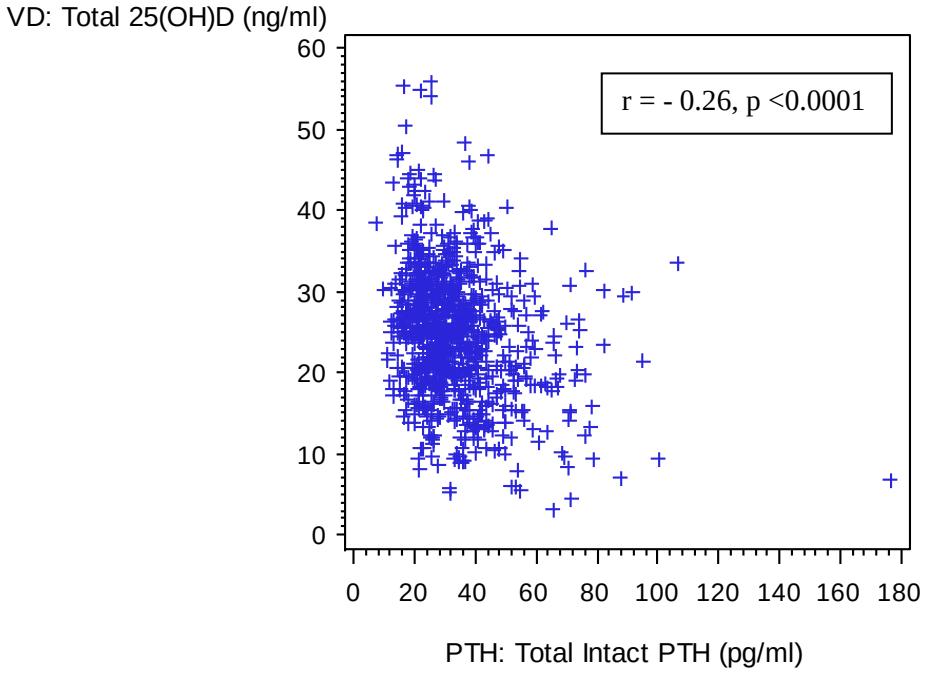

Table 1: Characteristics of the Analytic Cohort of 888 Men Ages 65 Years and Older by 25(OH)D Quartile

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
Total 25(OH)D (ng/ml; mean ± SD)	15.1 ± 3.7	22.3 ± 1.6	27.0 ± 1.4	34.8 ± 5.2	<0.001
Baseline Characteristics					
Number (% cohort)	221	219	226	222	
Age (years; mean ± SD)	74.5 ± 6.2	73.6 ± 5.9	73.9 ±5.8	73.0 ± 5.4	0.06
Race					
Caucasian (n, %)	188 (23)	203 (25)	206 (26)	209 (26)	
Other (n, %)	33 (40)	16 (20)	20 (24)	13 (16)	0.006
BMI (kg/m²)	28.3 ± 4.0	27.4 ± 3.6	27.2 ± 3.5	26.7 ± 3.3	<0.001
Height					
Current Height in cm (mean ± SD)	173.1 ± 7.2	174.5 ± 6.9	173.6 ± 6.8	174.9 ± 6.5	0.02
Weight					
Current Weight in kg (mean ± SD)	85.0 ± 14.0	83.7 ± 13.8	82.2 ± 12.1	81.8 ± 11.6	0.03
Smoking status					
Current smokers (n,%)	10 (33)	10 (33)	8 (27)	2 (7)	
Past smokers (n, %)	138 (26)	127 (24)	130 (24)	141 (26)	
Never smoked (n,%)	73 (23)	82 (25)	88 (27)	79 (25)	
Total Pack years (mean ± SD)	32.8 ± 27.7	30.2 ± 28.2	30.1 ± 24.9	29.5 ± 25.9	0.73
Alcohol Consumption (drinks/week in the last year)					
none (n, %)	77 (27)	75 (26)**	75 (26)	61 (21)	
1-<7 drinks (n, %)	80 (23)	84 (25)**	96 (28)	82 (24)	
7 or more (n, %)	64 (25)	59 (23)**	55 (21)	79 (31)	0.17
Physical Activity (PASE score; mean ± SD)	134.7 ± 75.2	146.9 ± 65.4	147.3 ± 64.0	157.7 ± 67.4	0.01
Reported Health Status for Age					
Good/Excellent (n, %)	175 (23)	190 (25)	195 (25)	205 (27)	
Very Poor/Poor/Fair (n, %)	46 (37)	29 (24)	31 (25)	17 (14)	0.001
Fracture History					
Non-trauma Fracture since age 50 (n,%)	43 (28)	39 (25)	31 (20)	43 (28)	0.34
Diagnosis of Osteoporosis (n, %)	9 (23)	8 (21)	11 (28)	11 (28)	0.9 [b]
Diagnosis of Arthritis (n, %)	102 (25)	103 (25)	103 (25)	105 (25)	0.98
Ever used osteoporosis medication (n, %)	3 (10)	8 (28)	8 (28)	10 (35)	0.25 [b]
Season of Baseline visit[a]					
Winter (Jan-Mar; n,%)	58 (36)	46 (28)	39 (24)	20 (12)	
Spring (Apr-June; n,%)	87 (28)	82 (26)	76 (24)	69 (22)	
Summer (Jul-Sept; n,%)	32 (13)	49 (21)	64 (27)	93 (39)	
Fall (Oct-Dec; n, %)	44 (25)	42 (24)	47 (27)	40 (23)	<0.001
Latitude of Clinic Site (n, %)[a]					
High (Minneapolis 44°, Pittsburgh 40° and Portland 45°)	149 (31)	116 (24)	113 (24)	96 (20)	
Low (Birmingham 33°, Palo Alto 37°, and San Diego 32°)	72 (17)	103 (25)	113 (27)	126 (30)	<0.001

[a] Latitudes and seasons as previously described in Orwoll E et al. J Clin Endocrinol Metab 2009 April; 94(4): 1214-1222.

[b] Fisher's exact method used

**One participant refused to answer

Table 2: Distribution of dimensions of the femoral neck within 25(OH)D quartiles with adjustments for age, race, latitude, season, weight and BMI in men ages 65 and older

Outcome Measures	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Femoral Neck Measures (n)	221	219	226	222	
Cross-Sectional Area (cm^2)					
Adjusted Mean	12.39	12.42	12.49	12.5	0.42
95% CI	(12.16, 12.62)	(12.17, 12.66)	(12.25, 12.74)	(12.24, 12.77)	
Adjustment + PTH	12.42	12.42	12.49	12.49	0.61
95% CI	(12.18, 12.66)	(12.18, 12.67)	(12.24, 12.73)	(12.22, 12.75)	
Integral Volume (cm^3)					
Adjusted Mean	20.66	20.59	20.49	20.42	0.35
95% CI	(20.27, 21.05)	(20.17, 21.00)	(20.08, 20.90)	(19.98, 20.87)	
Adjustment + PTH	20.65	20.58	20.49	20.43	0.38
95% CI	(20.25, 21.04)	(20.17, 21.00)	(20.09, 20.90)	(19.99, 20.87)	
Cortical Volume (cm^3)					
Adjusted Mean	9.02	9.06	9.21	9.39	0.008
95% CI	(8.80, 9.24)	(8.27, 9.29)	(8.98, 9.44)	(9.14, 9.64)	
Adjustment + PTH	9.03	9.06	9.21	9.39	0.01
95% CI	(8.81, 9.25)	(8.83, 9.29)	(8.98, 9.44)	(9.14, 9.64)	
Medullary Volume (cm^3)					
Adjusted Mean	11.64	11.53	11.28	11.03	0.006
95% CI	(11.29, 11.98)	(11.16, 11.89)	(10.92, 11.64)	(10.64, 11.43)	
Adjustment + PTH	11.62	11.52	11.28	11.04	0.01
95% CI	(11.26, 11.97)	(11.15, 11.89)	(10.92, 11.65)	(10.65, 11.44)	
Percent Cortical Volume					
Adjusted Mean	44.19	44.41	45.34	46.52	<0.001
95% CI	(43.24, 45.14)	(43.41, 45.42)	(44.34, 46.34)	(45.44, 47.59)	
Adjustment + PTH	44.27	44.44	45.33	46.49	<0.001
95% CI	(43.30, 45.23)	(43.43, 45.44)	(44.33, 46.32)	(45.41, 47.57)	

Table 3: Distribution of vBMD of the femoral neck within 25(OH)D quartiles adjusted for age, race, latitude, season, weight and BMI in men ages 65 years and older

Outcome Measures	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Femoral Neck Measures (n)	221	219	226	222	
Integral BMD (g/cm³)					
Adjusted Mean	0.289	0.289	0.3	0.308	<0.001
95% CI	(0.281, 0.298)	(0.281, 0.298)	(0.292, 0.309)	(0.298, 0.318)	
Adjustment + PTH	0.29	0.29	0.3	0.308	<0.001
95% CI	(0.282, 0.299)	(0.281, 0.298)	(0.292, 0.309)	(0.299, 0.317)	
Cortical BMD (g/cm³)					
Adjusted Mean	0.528	0.525	0.534	0.54	0.03
95% CI	(0.519, 0.515)	(0.515, 0.534)	(0.525, 0.544)	(0.529, 0.550)	
Adjustment + PTH	0.522	0.517	0.526	0.531	0.07
95% CI	(0.509, 0.535)	(0.504, 0.531)	(0.513, 0.539)	(0.518, 0.545)	
Trabecular BMD (g/cm³)					
Adjusted Mean	0.075	0.075	0.084	0.084	0.006
95% CI	(0.069, 0.081)	(0.068, 0.082)	(0.078, 0.091)	(0.077, 0.091)	
Adjustment + PTH	0.075	0.075	0.084	0.084	0.008
95% CI	(0.068, 0.081)	(0.068, 0.082)	(0.078, 0.091)	(0.077, 0.091)	

Table 4: Distribution of dimensions of the femoral neck within total intact PTH quartiles with adjustment for age, race, latitude, season, weight, and BMI in men ages 65 and older

Outcome Measures	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Femoral Neck Measures (n)	222	220	224	222	
Cross-Sectional Area (cm^2)					
Adjusted Mean	12.52	12.53	12.43	12.32	0.13
95% CI	(12.27, 12.77)	(12.28, 12.78)	(12.19, 12.67)	(12.08, 12.56)	
Adjustment + 25(OH)D	12.52	12.54	12.44	12.34	0.18
95% CI	(11.27, 12.76)	(12.29, 12.80)	(12.20, 12.69)	(12.10, 12.59)	
Integral Volume (cm^3)					
Adjusted Mean	20.34	20.78	20.5	20.62	0.53
95% CI	(19.93, 20.76)	(20.36, 21.20)	(20.10, 20.90)	(20.22, 21.01)	
Adjustment + 25(OH)D	20.35	20.77	20.49	20.59	0.65
95% CI	(19.93, 20.76)	(20.35, 21.19)	(20.09, 20.89)	(20.18, 20.99)	
Cortical Volume (cm^3)					
Adjusted Mean	9.3	9.04	9.15	9.09	0.3
95% CI	(9.06, 9.53)	(8.80, 9.28)	(8.92, 9.38)	(8.87, 9.31)	
Adjustment + 25(OH)D	9.28	9.07	9.18	9.15	0.64
95% CI	(9.05, 9.51)	(8.83, 9.31)	(8.95, 9.41)	(8.93, 9.38)	
Medullary Volume (cm^3)					
Adjusted Mean	11.05	11.74	11.35	11.53	0.18
95% CI	(10.68, 11.42)	(11.37, 12.12)	(11.00, 11.71)	(11.17, 11.88)	
Adjustment + 25(OH)D	11.07	11.7	11.31	11.44	0.42
95% CI	(10.70, 11.44)	(11.32, 12.07)	(10.95, 11.67_	(11.07, 11.80)	
Percent Cortical Volume					
Adjusted Mean	46.07	43.98	45.09	44.6	0.12
95% CI	(45.06, 47.09)	(42.95, 45.01)	(44.11, 46.07)	(43.63, 45.57)	
Adjustment + 25(OH)D	45.98	44.17	45.26	44.97	0.44
95% CI	(44.97, 46.99)	(43.14, 45.20)	(44.28, 46.25)	(43.98, 45.97)	

Table 5: Distribution of vBMD of the femoral neck within PTH quartiles with adjustment for PTH, age, race, latitude, season, weight, and BMI in men ages 65 and older

Outcome Measures	**Quartile 1**	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-trend**
Femoral Neck Measures (n)	222	220	224	222	
Integral vBMD (g/cm^3)					
Adjusted Mean	0.306	0.289	0.295	0.292	0.06
95% CI	(0.298, 0.315)	(0.280, 0.298)	(0.286, 0.303)	(0.284, 0.301)	
Adjustment + 25(OH)D	0.306	0.291	0.296	0.295	0.24
95% CI	(0.297, 0.314)	(0.282, 0.299)	(0.287, 0.305)	(0.287, 0.304)	
Cortical vBMD (g/cm^3)					
Adjusted Mean	0.542	0.529	0.528	0.526	0.01
95% CI	(0.533, 0.552)	(0.519, 0.539)	(0.519, 0.538)	(0.517, 0.535)	
Adjustment + 25(OH)D	0.542	0.530	0.529	0.528	0.05
95% CI	(0.532, 0.552)	(0.520, 0.540)	(0.520, 0.539)	(0.518, 0.538)	
Trabecular vBMD (g/cm^3)					
Adjusted Mean	0.080	0.076	0.079	0.080	0.89
95% CI	(0.074, 0.087)	(0.069, 0.083)	(0.073, 0.086)	(0.073, 0.086)	
Adjustment + 25(OH)D	0.080	0.077	0.080	0.081	0.56
95% CI	(0.073, 0.087)	(0.070, 0.084)	(0.073, 0.086)	(0.074, 0.088)	

Table 6: Distribution of dimensions of the femoral shaft within 25(OH)D quartiles with adjustment for age, race, 25(OH)D, latitude, season, weight and BMI in men ages 65 and older

Outcome Measures	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Femoral Shaft Measures (n)	200	196	205	202	
Cross-Sectional Area (cm^2)					
Adjusted Mean	9.12	9.18	9.32	9.24	0.25
95% CI	(8.93, 9.32)	(8.98, 9.38)	(9.12, 9.52)	(9.02, 9.45)	
Adjustment + PTH	9.11	9.17	9.32	9.23	0.22
95% CI	(8.92, 9.31)	(8.97, 9.38)	(9.12, 9.52)	(9.02, 9.45)	
Cortical Area (cm^2)					
Adjusted Mean	6.06	6.15	6.38	6.28	0.003
95% CI	(5.92, 6.20)	(6.01, 6.30)	(6.24, 6.53)	(6.13, 6.44)	
Adjustment + PTH	6.06	6.15	6.38	6.28	0.003
95% CI	(5.92, 6.20)	(6.01, 6.30)	(6.24, 6.53)	(6.13, 6.44)	
Medullary Area (cm^2)					
Adjusted Mean	3.06	3.02	2.94	2.95	0.21
95% CI	(2.91, 3.22)	(2.86, 3.19)	(2.77, 3.10)	(2.77, 3.13)	
Adjustment + PTH	3.06	3.02	2.93	2.95	0.24
95% CI	(2.90, 3.21)	(2.85, 3.19)	(2.77, 3.10)	(2.77, 3.13)	
Integral BMD (g/cm^3)					
Adjusted Mean	1.01	1.01	1.03	1.03	0.16
95% CI	(0.99, 1.03)	(0.99, 1.03)	(1.01, 1.05)	(1.00, 1.05)	
Adjustment + PTH	1.01	1.01	1.03	1.03	0.18
95% CI	(0.99, 1.03)	(0.99, 1.03)	(1.01, 1.05)	(1.00, 1.05)	
Percent Cortical Area					
Adjusted Mean	67.01	67.3	68.83	68.43	0.03
95% CI	(65.76, 68.27)	(65.98, 68.62)	(67.53, 70.13)	(67.01, 69.84)	
Adjustment + PTH	67.08	67.34	68.84	68.44	0.04
95% CI	(65.81, 68.36)	(66.01, 68.66)	(67.54, 70.14)	(67.03, 69.86)	

APPENDIX A: Additional Background

Fractures in Older Men

Fractures due to bone fragility are currently a major cause of morbidity and mortality among the senior population of the United States[1]. Hip fractures, while representing 14% of all fractures, cost $17 billion, 72% of the cost burden of fractures in 2005, as well as having some of the greatest morbidity and mortality of all fracture types [2 3 4 5 6]. Among hip fractures, an estimated 39% occur in men, who have greater morbidity and mortality across all types of fracture[7 8].

Hip fractures most commonly occur due to a combination of decreased bone strength and the amount of force applied to the bone. Bone strength, in terms of distribution of components within the bone, overall skeletal dimensions, and density, is made up of variables which can be measured and provide possible sites of intervention. In the hip, fracture risk is currently predicted by guidelines based on 2-dimensional DXA measures calculating bone mineral density (BMD)[9]. As a two-dimensional estimate, BMD results may be skewed by bone size, and variations among sex and race can also contribute to error in estimating fracture risk through BMD measurement. Subsequently, the elderly may experience hip fractures at BMD levels higher than those categorized as osteoporotic. Quantitative computed tomography (QCT) is a three-dimensional imaging technique that provides information on the distribution of bone into cortical and medullary compartments, through volumetric density measurements of cortical and trabecular bone and skeletal dimensions[10 11 12 13 14 15 16 17]. It provides an alternative method for evaluating bone composition that is not limited by two-dimensional estimation. However, while clinical correlates of two-dimensional BMD are well-described, correlates of volumetric BMD and skeletal measures are not well known. QCT is not currently used as a routine screening tool due to higher cost and radiation exposure, but as a research tool it has the potential to provide important insight into skeletal structural changes.

Previous investigators have used the QCT measures contained in the MrOS study to describe important relationships of volumetric measures to age, ethnicity, and sex hormone levels[18 19 20]. Specifically, cortical volume in the femoral neck was shown to decrease significantly with age, while on the other hand medullary volume increased significantly. QCT has also demonstrated significant variation across race, including greater mean cortical thickness in the femoral shaft in African American and Asian men. Using QCT measurements in this population may similarly allow the identification of structural differences among patients with and without vitamin D deficiency, and the relationship to parathyroid (PTH) levels, increasing knowledge about the mechanisms behind the contributions of vitamin D to fracture prevention.

Vitamin D

Vitamin D is a hormone critical to the process of calcium homeostasis[21]. The majority of vitamin D in humans is synthesized from 7-dehydrocholesterol on exposure to sunlight, specifically UVB light. Vitamin D may also be obtained from the diet, including sources such as fish and fortified foods. These forms of vitamin D, 25(OH)D3, can then be converted to the physiologically active form of vitamin D, $1,25(OH)_2D3$, by the enzyme 25-hydroxyvitamin D- 1-α-hydroxylase (1-OHase). Classically, this conversion is known to take place in kidney, however recent studies have found that other sites including colon, skin, and osteoblasts also contain this enzyme and have the potential to activate vitamin D. When calcium levels in serum are below physiological requirements, $1,25(OH)_2D3$ acts on the vitamin D receptor (VDR) in small intestine to increase the absorption of calcium and phosphate from the diet. If this does not produce adequate calcium levels, it also acts on VDRs in osteoblasts to cause their maturation to osteoclasts, resulting in the breakdown of bone to release calcium to the circulation. VDRs are also present in kidney cells, allowing $1,25(OH)_2D3$ to potentiate the activation of additional vitamin D.

Vitamin D deficiency is a highly prevalent problem, particularly in the northern United States. In clinical practice, vitamin D supplementation is encouraged for the treatment of osteoporosis in conjunction with calcium. Inadequate vitamin D has been identified as a risk factor for increased fracture incidence[22]. It has been shown that vitamin D plays an important role in maintaining skeletal integrity by promoting calcium absorption through diet and preventing PTH-mediated calcium resorption of bone[23 24 25]. Serum 25-OH vitamin D has been shown to be the most accurate measure of available vitamin D stores, and therefore a measure of adequate vitamin D levels[26]. Positive associations between increasing vitamin D levels, as reflected by serum 25-OH vitamin D assay, and higher two-dimensional BMD in older men have been previously described[23]. However, other studies have suggested that the associations observed between vitamin D level and BMD are completely explained by the effects of PTH[27]. Differences in the regions affected with vitamin D level (cortical versus trabecular bone) have also been described, suggesting another important component to the changes observed in BMD.

Parathyroid Hormone

Vitamin D levels categorized as "inadequate" are typically defined by the point at which PTH levels rise, resulting in secondary hyperparathyroidism[28 29 30 31]. The biological action of vitamin D on bone metabolism is closely linked with the actions of PTH, as PTH further promotes conversion of 25-OH vitamin D to $1,25(OH)_2D3$, resulting in the activation of osteoclasts and increasing bone turnover and the release of calcium. In addition PTH can activate osteoclast resorption via receptors on osteoblast cells[32]. However, PTH levels can be affected by factors other than vitamin D level, such as renal function or impaired calcium absorption, and it has been shown to increase with age in older men[33 34 35]. $1,25(OH)_2D3$ inhibits PTH via negative feedback, and in renal failure secondary hyperparathyroidism is caused through several pathways[36]. Targeted PTH treatment independent of vitamin D supplementation has also been used to decrease fracture risk and increase BMD[37]. As a result, it is important to distinguish not

only what changes in skeletal dimensions are associated with declining vitamin D levels, but whether these changes seen with decreasing levels of vitamin D are directly correlated to or are independent of changes in PTH levels.

APPENDIX B: Description of Variables

Baseline Visit Datasets	**Variable Name**	**Measurement**	**Description**
Exposure Variables			
OH1		**Assay**	
Total 25(OH)Vitamin D	OHVDTOT	Morning fasting serum at baseline (Liquid chromatography/Mass Spectrometry assay)	Continuous (ng/mL)
Total 25_OH Vitamin D3	OHVD3		Continuous (ng/mL)
Total 25_OH Vitamin D2	OHVD2		Continuous (ng/mL)
Total Intact PTH	OHPTTI	Morning fasting serum at baseline (Immunoradiometric assay)	Continuous (pg/mL)
Outcome Variables			
QH1		**QCT Scan**	
Femoral Neck Cross-Sectional Area (cm^2)	QHFNCSA		Continuous
Femoral Neck Integral Volume (cm^3)	QHFNIVOL		Continuous
Femoral Neck Cortical Volume (cm^3)	QHFNCVOL		Continuous
Femoral Neck Medullary Volume (cm^3)	QHFNMVOL		Continuous
Femoral Neck Trabecular Volume (cm^3)	QHFNTVOL		Continuous
Femoral Neck Integral BMD (g/cm^3)	QHFNIBMD		Continuous
Femoral Neck Cortical BMD (g/cm^3)	QHFNCBMD		Continuous
Femoral Neck Trabecular BMD (g/cm^3)	QHFNTBMD		Continuous
Femoral Shaft Cross Sectional Area (cm^2)	QHFSCSA		Continuous
Femoral Shaft Cortical Area (cm^2)	QHFSCAR		Continuous
Femoral Shaft Medullary Area (cm^2)	QHFSMAR		Continuous

Participant Characteristics			
Age	GIAGE1	What is your age?	Numerical Entry (years)
Race	GIWHITE	Which of the following best describes your racial background? White / Nonwhite (including Black or African American/Asian/Hispanic or Latino/American Indian or Alaska Native/Native Hawaiian or Pacific Islander)?	Yes=1/No=0
Height (mm)	HWHGT	Measured at Baseline Visit	Numerical Entry
Weight (kg)	HWWGT	Measured at Baseline Visit	Numerical Entry
BMI	HWBMI	Calculated from baseline visit measures	(kg/m^2)
Smoking Status	TURSMOKE	Baseline Visit Questionnaire	Pack-years
Alcohol Consumption	Alcuse	Generated from TUDRPRWK	none, 1-7 drinks, or 7 or more drinks/week
Physical Activity	PASCORE	Calculated PASE score	PASE score
Reported Health Status for Age	QLCOMP	(Calculated) From QLHEALTH: Compared to other people your own age, how would you rate your overall health?	Good/Excellent(1) vs Poor/Very Poor/Fair(0)
Non-Trauma Fractures Since Age 50	Fxover50	Calculated from FFNTGT50	None (FFNTGT50 =0) / 1 or more
Inability to rise ≥ 1 time unassisted from a chair	Chairst	Created from NFSTAND1	Stands without arms (NFSTAND1 = 1) / Requires Assistance
Diagnosis of Osteoporosis	MHOSTEO	Has a doctor or other health care provider ever told you that you had or have osteoporosis, sometimes called thin or brittle bones?	Yes/No
Diagnosis of Arthritis	MHARTH	Has a doctor or other health care provider told you that you have arthritis or gout?	Yes/No
Ever Used Osteoporosis Medication	MUMEDOST	Have you ever taken medicine to treat osteoporosis, Paget's disease or other bone diseases?	Yes/No
Season of Baseline Visit	Seas	Generated from variable EFDATE	Winter (Jan-Mar), Spring (Apr-June), Summer (Jul-Sept), Fall (Oct-Dec)
Latitude of Clinic Site	Lat	Generated from Variable SITE	Latitudes as previously described [4]. High: Minneapolis 44°, Pittsburgh 40° and Portland 45°, Low: Birmingham 33°, Palo Alto 37° and San Diego 32°.

APPENDIX C: Analytic Cohort Characteristics by PTH quartile

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
PTH (total intact; mean ± SD)	19.17 ± 3.10	26.65 ± 1.82	34.07 ± 2.68	52.31 ± 15.41	<0.001
Baseline Characteristics					
Number (% cohort)	222	220	224	222	
Age (years; mean ± SD)	73.36 ± 5.86	72.68 ± 5.34	73.35 ± 5.48	75.51 ± 6.37	<0.001
Race					
Caucasian (n, %)	205 (92.34)	205 (93.18)	204 (91.07)	192 (86.49)	
Other (n, %)	17 (7.66)	15 (6.82)	20 (8.93)	30 (13.51)	0.07
BMI (kg/m²)	26.71 ± 3.22	27.29 ± 4.01	27.63 ± 3.37	28.02 ± 3.85	0.001
Height					
Current Height in cm (mean ± SD)	173.98 ± 6.62	174.70 ± 6.63	174.05 ± 7.28	173.40 ± 7.00	0.27
Weight					
Current Weight (mean ± SD)	80.94 ± 11.37	83.41 ± 13.79	83.86 ± 12.32	84.48 ± 13.91	0.02
Smoking status					
Current smokers (n,%)	7 (23.33)	10 (33.33)	11 (36.67)	2 (6.67)	
Past smokers (n, %)	129 (24.07)	133 (24.81)	133 (24.81)	141 (26.31)	
Never smoked (n,%)	86 (26.71)	77 (23.91)	80 (24.84)	79 (24.53)	0.27
Total Pack years (mean ± SD)	26.98 ± 22.97	29.29 ± 25.36	35.77 ± 30.54	30.27 ± 26.45	0.04
Alcohol Consumption (drinks/week in					
none (n, %)	65 (22.57)	65 (22.57)	79 (27.43)	79 (27.43)**	
1-<7 drinks (n, %)	84 (24.56)	85 (24.85)	87 (25.44)	86 (25.15)**	
7 or more (n, %)	73 (28.40)	70 (27.24)	58 (22.57)	56 (21.79)**	0.41
Physical Activity (PASE score; mean	153.38 ± 68.00	145.70 ± 64.95	152.37 ± 74.99	135.07 ± 64.28	0.02
Reported Health Status for Age					
Good/Excellent (n, %)	195 (25.49)	190 (24.84)	191 (24.97)	189 (24.71)	
Fair/Poor/Very Poor (n, %)	27 (21.95)	30 (24.39)	33 (26.83)	33 (26.83)	0.83
Fracture History					
Previous Fracture since age 50 (n,%)	31 (19.87)	39 (25.00)	44 (28.21)	42 (26.92)	0.4
Diagnosis of Osteoporosis (n, %)	7 (17.95)	7 (17.95)	13 (33.33)	12 (30.77)	0.37 [b]
Diagnosis of Arthritis (n, %)	120 (25.26)	129 (27.16)	107 (22.53)	119 (25.05)	0.15
Ever used osteoporosis medication (n,	8 (27.59)	7 (24.14)	7 (24.14)	7 (24.14)	0.99
Season of Baseline visit[a]					
Winter (Jan-Mar; n,%)	51 (31.29)	31 (19.02)	44 (26.99)	37 (22.70)	
Spring (Apr-June; n,%)	71 (22.61)	85 (27.07)	73 (23.25)	85 (27.07)	
Summer (Jul-Sept; n,%)	54 (22.69)	62 (26.05)	62 (26.05)	60 (25.21)	
Fall (Oct-Dec; n, %)	46 (26.59)	42 (24.28)	45 (26.01)	40 (23.12)	0.44
Latitude of Clinic Site (n, %)[a]					
High (Minn 44°, Pitt 40°, Portland 45°)	113 (23.84)	109 (23.00)	121 (25.53)	131 (27.64)	
Low (Birm 33°, Palo Alto 37°, SD 32°)	109 (26.33)	111 (26.81)	103 (24.88)	91 (21.98)	0.19

[a] Latitudes and seasons as previously described in Orwoll E et al. Vitamin D Deficiency in Older Men. J Clin Endocrinol Metab 2009

[b] Fisher's exact method used

**One participant refused to answer

APPENIX D: Model Selection

Least square means by vitamin D quartile based on the final model (age, BMI, height, race, latitude, season) and the final model with PASCORE, total intact PTH, or reported health status adjusted for in the association between baseline serum 25(OH)D and the measures of the femoral neck.

Least Square Means	**Serum 25(OH)D quartile**					
Dependent Variable	(3.1-19.7 ng/mL)	(19.7-24.9 ng/mL)	(24.9-29.6 ng/mL)	(29.7 - 55.8ng/mL)	**p-value**	**Model R^2**
CSA						
Model 1	12.39	12.42	12.49	12.5	<0.001	0.21
+PASCORE	12.4	12.42	12.49	12.5	<0.001	0.21
+OHPTTI	12.42	12.42	12.49	12.49	<0.001	0.22
+ Reported health status	12.38	12.42	12.49	12.51	<0.001	0.21
Integral Volume						
Model 1	20.66	20.59	20.49	20.42	<0.001	0.73
+PASCORE	20.65	20.58	20.49	20.43	<0.001	0.73
+OHPTTI	20.65	20.58	20.49	20.43	<0.001	0.73
+ Reported health status	20.81	20.78	20.69	20.65	<0.001	0.73
Cortical Volume						
Model 1	9.02	9.06	9.21	9.39	<0.001	0.59
+PASCORE	9.03	9.06	9.21	9.39	<0.001	0.59
+OHPTTI	9.03	9.06	9.21	9.39	<0.001	0.59
+ Reported health status	9.09	9.15	9.3	9.50	<0.001	0.59
Medullary Volume						
Model 1	11.64	11.53	11.28	11.03	<0.001	0.56
+PASCORE	11.62	11.52	11.28	11.04	<0.001	0.56
+OHPTTI	11.62	11.52	11.28	11.04	<0.001	0.56
+ Reported health status	11.72	11.63	11.39	11.16	<0.001	0.56
Percent Cortical Volume						
Model 1	44.19	44.41	45.34	46.52	<0.001	0.1
+PASCORE	44.25	44.43	45.35	46.49	<0.001	0.1
+OHPTTI	44.27	44.44	45.33	46.49	<0.001	0.1
+ Reported health status	44.25	44.48	45.41	46.60	<0.001	0.1

Least Square Means	Serum 25(OH)D quartile					
Dependent Variable	(3.1-19.7 ng/mL)	(19.7-24.9 ng/mL)	(24.9-29.6 ng/mL)	(29.7 - 55.8 ng/mL)	**p-value**	**Model R^2**
Cortical BMD						
Model 1	0.528	0.525	0.534	0.540	0.007	0.03
+PASCORE	0.529	0.525	0.534	0.540	0.008	0.03
+OHPTTI	0.530	0.525	0.534	0.539	0.003	0.03
+ Reported health status	0.527	0.523	0.533	0.538	0.009	0.03
Trabecular BMD						
Model 1	0.075	0.075	0.084	0.084	<0.001	0.09
+PASCORE	0.075	0.075	0.084	0.084	<0.001	0.09
+OHPTTI	0.075	0.075	0.084	0.084	<0.001	0.09
+ Reported health status	0.076	0.077	0.086	0.086	<0.001	0.09
Integral BMD						
Model 1	0.289	0.289	0.300	0.308	<0.001	0.10
+PASCORE	0.290	0.289	0.300	0.308	<0.001	0.10
+OHPTTI	0.290	0.290	0.300	0.308	<0.001	0.10
+ Reported health status	0.290	0.290	0.301	0.309	<0.001	0.10

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