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Hyponatremia and Fractures: Findings from the Osteoporotic Fractures in Men Study

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Abstract

Hyponatremia may be a risk factor for fracture. To determine the relationship between hyponatremia and fracture we conducted cross-sectional and longitudinal analyses using data from the Osteoporotic Fractures in Men Study (MrOS). The MrOS study enrolled 5122 community dwelling men aged ≥ 65 years from six centers across the United States. We excluded men taking bisphosphonates, those with unknown medication history, those without serum sodium measures, or those with out of range assays for serum sodium. Serum sodium was measured at study entry. Subjects were followed for fractures (nonspine (including hip), hip, and incident and prevalent morphometric) for up to 9 years. We used cox proportional hazards models to analyze the association between serum sodium levels (<135mmol/L versus ≥135mmol/L) and risk of nonspine and hip fractures, with results presented as hazard ratios (HR) and 95% confidence intervals (CI). We examined the association between morphometric vertebral fractures and serum sodium using logistic regression models, presented as odds ratios (OR) and 95% CI. Hyponatremia was observed in 64 men (1.2% of the cohort). After adjusting for age, BMI, study center, and other covariates, we found that, compared to men with serum sodium ≥ 135mmol/L, those with serum sodium <135mmol/L, had an increased risk hip fracture (HR=3.04; 95% CI: 1.37 to 6.75), prevalent (OR=2.46; 95% CI: 1.22 to 4.95) and incident (OR=3.53; 95% CI: 1.35 to 9.19) morphometric spine fractures but not nonspine fractures (OR=1.44; 95% CI: 0.85 to 2.44). Adjusting for bone mineral density did not change our findings. Our data demonstrate that hyponatremia is associated with up to a doubling in the risk of hip and morphometric spine

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fractures, independent of BMD. Further studies, to determine how hyponatremia causes fractures and if correction of hyponatremia decreases fractures, are needed.

Keywords

Fracture risk assessment; DXA; Osteoporosis; Systems biology – bone interactions; General population studies

Introduction

Hyponatremia, typically defined as a serum sodium concentration of less than 135 mmol/L, may be a novel marker for fracture risk. Case control studies report a higher prevalence of hyponatremia among those with fractures compared to those without.[1-3] A recent cross sectional study reports an increased risk of osteoporotic fracture (OR=1.46; 95%CI: 1.05 to 2.04) among those with serum sodium <132mmol/L,[4] while a second cross sectional study demonstrates a doubling in the risk of fracture independent of bone mineral density (OR= 2.06; 95% CI: 1.14 to 3.65).[5]

To date there is only one prospective study that reports on the relationship between hyponatremia and fractures.[6] A secondary analysis of the 5208 elderly men and women participating in the Rotterdam Study reported an increased risk of nonvertebral fractures, by about 30%, among those with hyponatremia (serum sodium < 135 mmol/L; n=399) compared to those without before and after adjustment for other confounders. However, the relationship between vertebral fractures and hyponatremia was less robust; hyponatremia was associated with a higher likelihood of prevalent (OR=1.78; 95%1.04 to 3.06) but not incident vertebral fractures, and only after adjusting for confounders. Further there was no relationship between hip fracture and hyponatremia.

Our study aims to contribute to data concerning hyponatremia and fractures by determining the relationships between hyponatremia and fractures among a cohort of elderly community dwelling men participating in Osteoporotic Fractures in Men Study (MrOS).

Materials and Methods

Subjects

Our study population was men participating in the MrOS study. Details of this study have been published elsewhere.[7, 8] Briefly, it is a prospective study of 5994 community-dwelling men aged 65 years and older, who were able to walk without assistance of another person and did not have bilateral hip replacements at baseline. The primary aim of MrOS is to study healthy aging and fracture risk. Men were enrolled between March 2000 and April 2002 from one of six US clinical centers. Written informed consent was obtained from all participants and the Institutional Review Board at each clinical center approved the protocol.

Our analyses included 5122 men. We excluded 90 men (1.7%) who reporting taking bisphosphonates, 315 men (6%) who had unknown medication history as well as 467 (8%)

participants who did not have serum sodium measures (n=461) or had results that were clearly laboratory error (serum sodium < 20 or >250 mmol/L; n=6).

Serum Sodium Measurements

Fasting serum was obtained at the baseline visit in all men and stored at −70 C. Serum sodium was measured on thawed serum at a central laboratory (Oregon Veterans Administration Clinical Laboratory, Portland, OR, USA) using a Roche COBAS Integra 800 automated analyzer (Roche Diagnostics Corp. Indianapolis, IN). The analyzer was calibrated daily in the clinical laboratory. The interassay coefficient of variation for serum sodium was 2.5%. Hyponatremia was defined as a serum sodium concentration of less than 135mmol/L, the cutoff for the lower end of the normal range.

Bone Mineral Density

Bone mineral density (BMD) was measured at the lumbar spine (L1 to L4), total hip and femoral neck using dual energy x-ray absorptiometry (DXA; Hologic QDR4500; Hologic, Bedford, MA, USA) in all subjects at study entry. Technicians performing the DXA measurements were certified by Hologic training and machine quality control was performed on a daily basis. Further details concerning methods, quality assurance and accuracy of the DXA measurements in MrOS have been reported elsewhere.[9]

Ascertainment of Fractures

Participants were contacted every 4 months by postcard or telephone to inquire about fractures. Follow up for hip and other nonspine fractures was 9 years and these fractures were adjudicated centrally by physician review of medical records and X-ray reports. Prevalent morphometric vertebral fractures were identified from lateral radiographs obtained at study entry. Radiographs were reviewed centrally and prevalent fractures defined using a previously described semi quantitative technique.[10] Incident morphometric fractures were identified by comparing films at baseline and visit two (about 4.5 years later) and were defined as a change in semi quantitative grade of at least one between baseline and follow-up.

In our current analyses we considered 4 categories of fractures: nonspine fractures (including hip fractures), hip fractures, incident morphometric fractures and prevalent morphometric fractures.

Ascertainment of Covariates

All study subjects completed a self-administered questionnaire at baseline. Variables captured included race, education, medical history, falls in the past 12 months, current smoking and alcohol use. Self-rated health was assessed by interviewer administered questionnaire and subsequently dichotomized to fair or poor vs. good or excellent.[11] All medications taken within the last 30 days of the baseline interview were recorded and confirmed by review of the medication container. Medications were classified centrally using the Iowa Drug Information System codes (College of Pharmacy, University of Iowa, Iowa City, IA, USA).[12] Weight was obtained by digital scale or balance beam and height by wall-mounted stadiometer. Body mass index (BMI) was calculated as weight in

kilograms (kg) divided by height in meters squared (m^2). Visual acuity was recorded as number of letter correctly identified by the Bailey- Lovie test corrected for distance.[13] Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine, age and race all obtained at baseline.[14]

Statistical analysis

We examined baseline characteristics by serum sodium (<135mmol/L versus ≥135mmol/L) using t tests for continuous variables and chi-squared tests for categorical variables.

Cox proportional hazards models were used to analyze the association between serum sodium levels (<135mmol/L versus ≥135mmol/L) and subsequent risk of nonspine and hip fractures, with results presented as hazard ratios (HR) and 95% confidence intervals (CI). The association between prevalent and incident morphometric spine fractures and serum sodium was examined using logistic regression models and presented as odds ratios (OR) and 95% CI.

Our base models were minimally adjusted for age, BMI, and study center. We included the following covariates: education, self-perceived health, alcohol intake, falls in the 12 months before baseline, hypothyroidism, diabetes, visual acuity, thiazide diuretic use, non-thiazide diuretic use, hypertension, use of ACE inhibitors, estimated GFR<60ml/min, presence of congestive heart failure. For nonspine and hip fractures we adjusted for total hip BMD and for spine fractures (incident and prevalent morphometric) we adjusted for lumbar spine BMD. Covariates were included based on biologic plausibility, previous literature reporting an association with hyponatremia, or fractures, or both.

We also performed sensitivity analyses to examine the association between serum sodium and fractures after excluding men with serum sodium levels >145mmol/ L; n=204) and we examined the association between fractures including only men (n=4854) with serum sodium levels in the normal range (between 135 and 145 mmol/L). In addition we performed analyses limiting the comparison eunatremic group to white only (n=1393).

Statistical analyses were performed using SAS 9.2 with a p value of <=0.05 considered significant. We did not adjust for multiple comparisons.

Results

Baseline characteristics

Serum sodium measured at baseline was normally distributed; 64 men (1.2%) had serum sodium levels <135mmol, 204 men had levels above 145mmol/L with the remaining 4854 men (95%) between 135 and 145mmol/L (Figure 1). The baseline characteristics of the study subjects by serum sodium (<135mmol/L versus ≥135mmol/L) are shown in Table 1.

Compared to those with serum sodium ≥135mmol/L (men without hyponatremia) subjects with serum sodium <135 mmol/L (men with hyponatremia) were more likely to be older (77 years vs. 74 years), weigh less (76 kg vs. 84 kg), and less likely to report their self-perceived

health as excellent to good (73% vs. 86%). Falls in the past year were more commonly reported in those with hyponatremia (31%) compared to those without (21%). Diuretic use was more commonly reported in men with hyponatremia compared to those without (thiazide: 27% vs. 13%; non thiazide: 22% vs. 9%). BMD at the femoral neck, total hip and lumbar spine was significantly lower in men with hyponatremia (0.74; 0.90 and 1.07 g/cm^2 respectively) compared to those without (0.79; 0.96 and 1.00 g/cm^2). Total hip Z score was also lower in men with hyponatremia (0.04) compared to those without (0.30). Visual acuity was lower in men with hyponatremia (54.5) compared to those without (57.5).

Fractures

Over an average follow-up of 9 years for hip and non-spine fracture and 4.6 years between baseline and visit 2 spine radiographs, 1143 men had a fracture. Of these, there were 788 men with an incident non-spine fracture (17 of these occurred in men with hyponatremia) including 182 men with at least one hip fracture (9 of these in occurred in men with hyponatremia), 357 men with one or more prevalent morphometric spine fractures (12 of these occurred in men with hyponatremia) and 164 men with an incident morphometric spine fracture (6 of these occurred in men with hyponatremia).

Relationship between fractures and serum sodium

After adjusting for age, BMI and study center (the minimally adjusted model), we found that compared to men without hyponatremia, those with hyponatremia had an statistically significant increased risk of nonspine fracture (HR=1.67; 95% CI: 1.02 to 2.69), hip fracture (HR=3.48; 95% CI: 1.76 to 6.87), prevalent (OR=2.78; 95% 1.46 to 5.30) and incident morphometric vertebral fractures (OR=3.36; 95% CI: 1.36 to 8.27) (Table 2).

After adjusting for age, BMI, study center, education, self-perceived health status, alcohol, falls, low thyroid, diabetes, hypertension, congestive heart failure, visual acuity, eGFR < 60ml/min, thiazide and non-thiazide diuretics use, and use of ACE inhibitors (the fully adjusted model), men with hyponatremia had a statistically significant increase in the risk of hip fractures, prevalent and incident morphometric fractures. In the case of nonspine fractures adjusting for multiple confounders only modestly attenuated the point estimate (OR=1.66 in the minimally adjusted model vs. OR=1.44 in the fully adjusted model) but the 95% confidence interval crossed 1.0 (95% CI in the fully adjusted model: 0.85 to 2.44). Additional adjustment for BMD did not alter the HR for hip fractures, the OR for nonspine fractures and modestly decreased the OR for prevalent and incident spine fractures. For example, the risk of hip fracture was 3.04 (95% CI: 1.37 to 6.75) in the fully adjusted model and was 3.07 (1.37 to 6.85) after adjusting for hip BMD. The risk of incident morphometric fractures in men with low sodium was 3.53 (95% CI: 1.35 to 9.19) in the fully adjusted model and decreased to 3.00 (95% CI: 1.14 to 7.91) after adjusting for spine BMD.

Additional Analyses

Excluding men with hypernatremia (serum sodium >145 mmol/L) did not significantly change any of our findings (see Supplemental Table 1). After limiting our analyses to men with serum sodium in the normal range (between 135 and 145mmol/L), there was no association between fractures (nonspine, hip, prevalent morphometric and incident

morphometric) and serum sodium in ether the minimally adjusted or fully adjusted models (see Supplemental Table 2). Limiting our comparator group to white eunatremic men did not significantly change any of our findings (see Supplemental Table 3).

Discussion

We found that, compared to men with serum sodium ≥ 135mmol/L men with serum sodium values <135mmol/L had approximately a 3 fold increase in the risk of hip and incident morphometric spine fractures and a 2½ fold increase in the risk of prevalent morphometric spine fractures. Further, the strength of the relationship between hyponatremia and fractures was not substantially reduced after adjusting for multiple well established fracture risk factors, and in particular, for falls and bone mineral density.

Our results are consistent with previous studies that have reported on associations between hyponatremia and fractures. A case control study identified 513 cases of fractures (mainly hip and femoral neck) after a fall and reported an increased risk of fracture, by about 3 fold in men and women with hyponatremia (<135mmol/L), even after adjusting for medications and medical conditions known to confound that association between fracture and serum sodium.[1] A second case control study reported on the prevalence of hyponatremia (<135mmol/L) among 364 subjects presenting to the emergency department with fractures of the hip/pelvis and femur compared with the incidence of hyponatremia in 364 controls (subjects presenting to the emergency department with non-critical complaints).[3] The incidence of hyponatremia in those with fractures was more than double that of controls. A recent cross sectional study by Arampatzis et al. reported that of 10,823 emergency department admissions among adults (≥50 years) there was an increased risk of osteoporotic fracture (OR= 1.46; 95%CI: 1.05 to 2.04) among individuals with diuretic-induced hyponatremia.[4] A secondary data analysis of 1408 women participating in a study of chronic kidney disease determined that those with hyponatremia (again less than 135mmol/L) had a 2 fold increase risk of fracture (based on self-report) even after adjusting for BMD.[5]

Our analyses showed similar but generally stronger associations between hyponatremia and fracture risk compared to the only other prospective study of the issue; a secondary analysis performed within the Rotterdam Study that included 5208 men and women of which 399 (9%) had a hyponatremia (serum sodium <135mmol/L).[6] In the Rotterdam Study those with hyponatremia there was a 1.4 fold increase in nonvertebral fractures over 7.4 years of follow up and a 1.8 fold increase in prevalent but not incident vertebral fractures or hip fractures. As in our study, adjustment for factors such as disability index and falls did not substantially change the results. Of note, BMD was not associated with low serum sodium in the Rotterdam cohort.

There are several mechanisms by which low serum sodium might contribute to an increase risk of fracture. Hyponatremia, even when mild as in our study, might increase the risk of falls and fall related fractures by causing gait instability and attention deficits.[1, 15] One study reported that the threshold for gait deficits associated with hyponatremia was 134 mmol/L and 132 mmol/L for attention deficits.[15] In our study we noted that 31% of men

with hyponatremia reported falls in the past 12 months compared with 21% of men with serum sodium >135mmol/L. However, adjusting for baseline fall history did not substantially change the relationship between hyponatremia and fracture.

There is growing evidence to suggest that unrecognized complications of hyponatremia include bone loss and osteoporosis, though the mechanisms by which this occurs is not clear. Cellular and animal data suggest that hyponatremia may have a direct effect on bone. Hyponatremia can directly stimulate osteoclastogenesis and osteoclastic resorption without activation of signaling through osteoblasts.[16] Additionally after 3 months of severe hyponatremia, BMD by DXA of the femur in rats demonstrated a 30% reduction in BMD compared with eunatremic controls.[17] Further, micro–computed tomography and histomorphometric analyses in these same rats demonstrated that hyponatremia decreased cortical and trabecular bone components by increasing bone resorption and decreasing bone formation. Consistent with the proof of principle demonstrated in the rat model are cross sectional data from NHANES which demonstrated that mild hyponatremia (mean serum sodium 133.0 ± 0.2 mmol/L) is associated with increased odds of osteoporosis (T-score −2.5 or less) at the hip (odds ratio (OR)=2.85; 95% confidence interval (CI) 1.03-7.86) and femoral neck (OR=2.87 (95% CI)=1.41–5.81). Note that both models were adjusted for age, sex, race, body mass index (BMI), physical activity, history of diuretic use, history of smoking, and serum 25-hydroxyvitamin D [25(OH)D] levels.[17] That said, studies that include models adjusted for BMD still find a significant association between hyponatremia and fracture. In our study, adjusting for BMD slightly decreased the association between hyponatremia and fracture in minimally adjusted models but had a varying effect in the fully adjusted model based on fracture outcome evaluated. For example, there was not a change in the risk of hip fracture in the fully adjusted model – HR=3.05 with and without adjustment for hip BMD while the risk of incident and prevalent morphometric spine fractures decreased slightly after adjusting for spine BMD (e.g. OR=2.48 for prevalent spine fractures and OR=2.26 after adjustment for spine BMD). Finally, it is possible that hyponatremia is a surrogate marker for other causes of fracture. In our study as well as in others, subjects with hyponatremia were older, in poorer health, more likely to report use of relevant medications (such as diuretics, SSRI's) and have concomitant illnesses such as thyroid disease that increase the risk of fractures. However, in our analyses the associations between hyponatremia and fracture risk was not substantially altered by adjusting for many potential confounding factors including falls suggesting that hyponatremia might be associated with bone quality. Thus, assessment of BMD with DXA in mild hyponatraemic subjects may not represent the best available method to address microstructural skeletal alterations.[18]

Our study had some limitations. Most importantly, this was not a randomized trial and as such it is not possible to definitively conclude that low serum sodium causes fractures and that correcting serum sodium will reduce the risk of fractures. The MrOS study is a predominantly Caucasian cohort of healthy ambulatory community dwelling men. This limits generalizability of our findings to women, men of other races and those significant comorbid conditions; indeed in our study only 64 of 5122 men (1.2%) had low serum sodium far less than the 8% that was reported even in the Rotterdam Study. Potential reasons for the difference in prevalence of hyponatremia between the Rotterdam Study and MrOS may be explained by the fact that more than 60% of the Rotterdam Study participants

were females and female gender may be a risk factor for hyponatremia in the elderly even after adjustment for additional confounders.[19] Of note, while other reported co-morbidities and medications were similar between both cohorts it is possible that there were other unmeasured differences between the cohorts that might explain the differences in the prevalence of hyponatremia. Another limitation of our study was the fact that serum sodium was measured only at baseline.

Our findings suggest that hyponatremia, one of the most common electrolyte abnormalities,[20, 21] is associated with up to a doubling in the risk of hip and morphometric spine fractures. The association we observed was strong despite the low prevalence of hyponatremia in our cohort and was not altered by adjusting for fall history or bone mineral density. Further studies are needed to determine if hyponatremia results in an increase in fractures, the mechanism by which this occurs, and whether treatment of hyponatremia reduces the incidence of fractures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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All authors made substantial contributions to conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. SAJ, SA, and DCB initially drafted the work. SAJ and DCB had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors revised it critically for important intellectual content. All authors had final approval of the version to be published and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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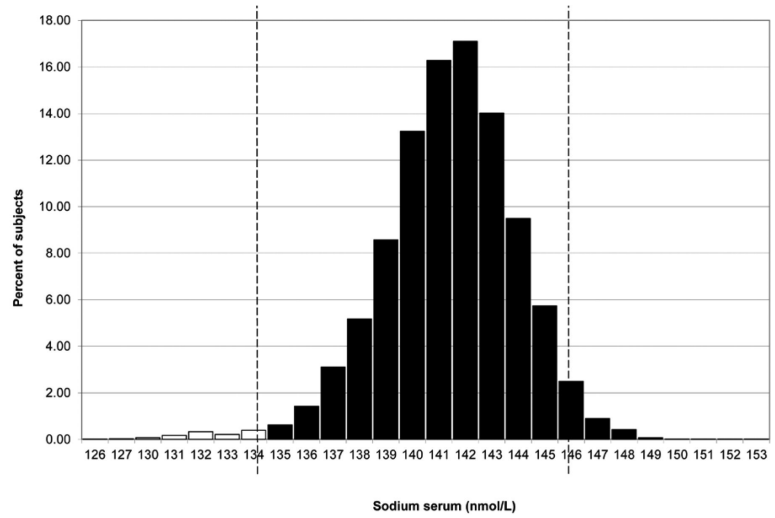

*Dashed lines are the lower and upper ends of the normal range.

Figure 1.
Distribution of serum sodium in study population*

Table 1

Baseline characteristics of study subjects by serum sodium.

	Sodium Levels		p-value
	<135 mmol/L (n=64)	≥ 135mmol/L (n=5058)	
Age, mean (sd)	76.8 (7.0)	73.5 (5.8)	<0.001
BMI, mean (sd)	25.4 (3.3)	27.5 (3.9)	<0.001
Weight, mean (sd)	75.7 (10.9)	83.5 (13.3)	<0.001
Race/ethnicity, n (%)			
White	64 (100.0)	4548 (89.9)	0.12
African American	0	217 (4.3)	
Asian	0	127 (2.5)	
Hispanic	0	106 (2.1)	
Other	0	60 (1.2)	
Education, n (%)			
Less than high school	0 (0.0)	354 (7.0)	0.009
High school	6 (9.4)	926 (18.3)	
College/grad school	58 (90.6)	3778 (74.7)	
Self-perceived health (excellent/good), n (%)	47 (73.4)	4336 (85.8)	0.005
Smoker, n (%)	1 (1.6)	175 (3.5)	0.24
Alcohol, n (%)			
None	14 (24.1)	1805 (40.8)	0.005
1-13 per week	29 (50.0)	2029 (45.8)	
14+ per week	15 (29.9)	592 (13.4)	
Falls past 12 months, n (%)	20 (31.3)	1052 (20.8)	0.04
Low thyroid, n (%)	10 (15.6)	346 (6.8)	0.008
Diabetes, n (%)	1 (16)	573 (11.3)	0.01
Congestive heart failure, n (%)	4 (6.3)	260 (5.1)	0.19
Hypertension, n (%)	37 (57.8)	2223 (44.0)	0.03
Estimated Glomerular Filtration Rate (<60ml/min), n (%)	7 (10.9)	831 (16.4)	0.24
Serum sodium (mmol/L), mean (sd)	132.3 (1.8)	141.5 (2.4)	<0.001
History of spine fractures, n (%)	5 (7.8)	185 (3.7)	0.06
History of nonspine fractures, n (%)	37 (57.8)	2757 (54.5)	0.6
History of hip fractures, n (%)	0 (0.0)	83 (1.6)	0.35
SSRI use, n (%)	3 (4.7)	142 (2.8)	0.16
Thiazide diuretic use, n (%)	17 (26.6)	648 (12.8)	0.002
Non-thiazide diuretic use, n (%)	14 (21.9)	476 (9.4)	0.001
ACE inhibitor use, n (%)	23 (35.9)	979 (19.4)	<0.001
Femoral neck BMD, mean (sd)	0.74 (0.14)	0.79 (0.13)	0.009
Total hip BMD, mean (sd)	0.90 (0.15)	0.96 (0.14)	<0.001
Lumbar spine BMD	1.00 (0.20)	1.07 (0.18)	0.003
Total hip z-score, mean (sd)	0.04 (0.94)	0.30 (0.90)	0.03
Femoral neck z-score, mean (sd)	0.06 (1.01)	0.24 (0.95)	0.13

	Sodium Levels		p-value
	<135 mmol/L (n=64)	**≥ 135mmol/L (n=5058)**	
Visual Acuity	54.5 (6.9)	57.5 (6.7)	0.0004

Table 2

Risk of fractures by serum sodium (<135mmol/L compared with >=135mmol/L). Expressed as HR and 95% CI for nonspine and hip and OR and 95% for spine.

Model	Nonspine (n=788)	Hip (n=182)	Prevalent Morphometric (n=357)	Incident Morphometric (n=164)
Unadjusted	1.94 (1.20 to 3.14)	4.79 (2.45 to 9.36)	3.13 (1.66 to 5.92)	3.97 (1.64 to 9.59)
Minimally adjusted*	1.66 (1.02, 2.69)	3.48 (1.76, 6.87)	2.78 (1.46, 5.30)	3.36 (1.36, 8.27)
Fully adjusted**	1.44 (0.85, 2.44)	3.04 (1.37, 6.75)	2.46 (1.22, 4.95)	3.53 (1.35, 9.19)
Fully adjusted model + BMD***	1.45 (0.86, 2.44)	3.07 (1.37, 6.85)	2.23 (1.08, 4.58)	3.00 (1.14, 7.91)

* adjusted for age, BMI, and study center

** adjusted for age, BMI, study center, education, self-perceived health status, alcohol, falls, low thyroid, diabetes, hypertension, congestive heart failure, eGFR < 60ml/min, thiazide and non-thiazide diuretics, ACE inhibitors, visual acuity

*** for nonspine and hip fractures, baseline total hip BMD was the covariate, and for incident and prevalent morphometric fractures, baseline lumbar spine BMD was used