# Bone Turnover and Bone Mineral Density Are Independently Related to Selenium Status in Healthy Euthyroid Postmenopausal Women

Antonia Hoeg,* Apostolos Gogakos,* Elaine Murphy, Sandra Mueller, Josef Köhrle, David M. Reid, Claus C. Glüer, Dieter Felsenberg, Christian Roux, Richard Eastell, Lutz Schomburg, and Graham R. Williams

Institute for Experimental Endocrinology (A.H., S.M., J.K., L.S.), Charité-Universitätsmedizin-Berlin, Campus Virchow Klinikum, D-13353 Berlin, Germany; Molecular Endocrinology Group (A.G., E.M., G.R.W.), Department of Medicine, Imperial College London, London W12 0NN, United Kingdom; Biomedizinische Bildgebung (C.C.G.), Diagnostische Radiologie, Universitätsklinikum Schleswig-Holstein, D-24118 Kiel, Germany; School of Medicine and Dentistry (D.M.R.), University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom; Charité-University Medicine Berlin (D.F.), Campus Benjamin Franklin, Center of Muscle and Bone Research, Free University and Humboldt University of Berlin, D-12200 Berlin, Germany; Department of Rheumatology, Paris Descartes University (C.R.), Cochin Hospital, 75014 Paris, France; and Bone Biomedical Research Unit (R.E.), Centre for Biomedical Research, University of Sheffield, Northern General Hospital, Sheffield S5 7AU, United Kingdom

**Context:** Selenium status may have direct effects on bone and indirect effects through changes in thyroid hormone sensitivity.

**Objective:** We hypothesized that variation in selenium status in healthy euthyroid postmenopausal women is associated with differences in bone turnover, bone mineral density (BMD) and fracture susceptibility.

**Design:** The Osteoporosis and Ultrasound Study (OPUS) is a 6-yr prospective study of fracture-related factors.

**Setting:** The study was comprised of a population-based cohort from five European cities.

**Participants:** A total of 2374 postmenopausal women participated. Subjects with thyroid disease and nonthyroidal illness and those receiving drugs affecting thyroid status or bone metabolism were excluded, leaving a study population of 1144.

**Interventions:** There were no interventions.

**Main Outcome Measures:** We measured selenium (micrograms per liter); selenoprotein P (milligrams per liter); free $T_4$ (picomoles per liter); free $T_3$ (picomoles per liter); TSH (milliunits per liter); bone turnover markers; BMD; and vertebral, hip, and nonvertebral fractures.

**Results:** Higher selenium levels were associated with higher hip BMD at study entry ($\beta = 0.072$, $P = 0.004$) and lower levels of bone formation (osteocalcin: $\beta = -0.101$, $P < 0.001$; procollagen type 1 N-terminal propeptide: $\beta = -0.074$, $P = 0.013$) and resorption markers (C-telopeptide of type 1 collagen: $\beta = -0.058$, $P = 0.050$; N-telopeptide of type 1 collagen: $\beta = -0.095$, $P = 0.002$). Higher selenoprotein P was associated with higher hip ($\beta = 0.113$, $P < 0.001$) and lumbar spine BMD ($\beta = 0.088$, $P = 0.003$) at study entry, higher hip BMD after the 6-yr follow-up ($\beta = 0.106$, $P = 0.001$) and lower osteocalcin ($\beta = -0.077$, $P = 0.009$), C-telopeptide of type 1 collagen ($\beta = -0.075$, $P = 0.012$), and N-telopeptide of type 1 collagen ($\beta = -0.110$, $P < 0.001$).

**Conclusion:** Selenium status is inversely related to bone turnover and positively correlated with BMD in healthy euthyroid postmenopausal women independent of thyroid status. (***J Clin Endocrinol Metab* 97: 4061–4070, 2012**)

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* A.H. and A.G. contributed equally to this work.

Abbreviations: BMD, Bone mineral density; BMI, body mass index; Cr, creatinine; DIO, deiodinase; fT3, free $T_3$; fT4, free $T_4$; GPx, glutathione peroxidase; K-W, Kruskal-Wallis test; OPUS, Osteoporosis and Ultrasound Study; PINP, procollagen type I N-terminal propeptide; OC, osteocalcin; s$\beta$CTX, type I collagen C-terminal telopeptide; Se, selenium; SePP, selenoprotein P; uNTX, urinary resorption marker N-terminal telopeptide of type I collagen.

The trace element selenium (Se) is required for development, well-being, and protection against age-related disorders (1). Se bioavailability is dependent on nutrition resulting in variation in Se sufficiency among populations. Europe, including Germany, France, Scotland, and England where this study was conducted, is relatively Se insufficient compared with the United States and Asia (2, 3).

In humans, 25 genes encode selenoproteins (4), in which the amino acid selenocysteine is incorporated during protein translation by a specific tRNA. Although the functions of several selenoproteins are unknown, many have antioxidant activity and eliminate reactive oxygen species (4). The iodothyronine deiodinases (DIO1–3) are selenoenzymes involved in the regulation of circulating and tissue thyroid status and incorporation of selenocysteine is essential for activity (5). DIO1 converts the prohormone $T_4$ to the active hormone $T_3$ or inactivates $T_4$ to $rT_3$ and contributes to iodine homeostasis and the circulating pool of $T_3$. DIO2 is expressed in $T_3$ target tissues in which it activates $T_4$ to control intracellular $T_3$ availability and regulate $T_3$ action. DIO3 protects sensitive tissues from excess thyroid hormone stimulation (5). Normal function of the hypothalamic-pituitary-thyroid axis depends on an adequate supply of iodine and activity of the deiodinases (5).

The importance of Se availability is demonstrated by patients with mutations in *SBP2*, encoding selenocysteine insertion sequence-binding protein-2. Affected individuals display abnormal thyroid hormone metabolism and a multisystem selenoprotein deficiency disorder that includes delayed skeletal development and linear growth (6, 7). The link between Se, thyroid function, and skeletal disease is further evidenced by Kashin-Beck disease, an osteoarthropathy endemic in Se- and iodine-deficient areas of Asia (8). Its etiology may include oxidative damage to cartilage and bone due to Se deficiency or impaired thyroid hormone effects on bone and cartilage because of iodine deficiency. Alternatively, it may result from combined deficiencies of both elements or from other environmental factors (9). Mice with chondrocyte-specific deletion of *Trsp* encoding selenocysteine tRNA exhibit delayed ossification, growth retardation, and chondronecrosis, demonstrating a direct role for selenoproteins in skeletal development (10). Abnormal ossification and growth are seen in rats with hypothyroidism (11) or mice with thyroid hormone receptor deletion (12), whereas mice with the deletion of *Dio2* display brittle bones (13). Dietary supplementation studies in rodents reveal an important role for Se in bone but also identify interactions between Se and iodine (14, 15). In human populations, hypothyroidism and thyrotoxicosis are each associated with an increased risk of fracture (16), and variation in thyroid status across the reference range is associated with changes in bone mineral density (BMD) and fracture risk (17).

Overall, these studies reveal interactions between Se, iodine, and thyroid function. Nevertheless, the exact role of Se in bone development and maintenance is unknown, and effects of Se could involve interactions with thyroid hormones. We hypothesized that variation in Se status is associated with differences in bone turnover, BMD, and fracture susceptibility. To investigate this possibility, we measured Se status in a population of healthy euthyroid postmenopausal women and determined its relationship to bone parameters and thyroid status.

## Subjects and Methods

### Osteoporosis and Ultrasound Study (OPUS)

OPUS is a prospective, population-based European study of postmenopausal women. The study received approval according to the Declaration of Helsinki. Written consent was obtained from all subjects (17).

### Biochemical measurements

Se concentrations were determined by x-ray fluorescence spectroscopy (18). The method was validated with a Seronorm standard (Sero AS, Billingstad, Norway) and was linear over a range of 1:2, 1:5, or 1:10 dilutions. Selenoprotein P (SePP) is a liver-derived Se storage and transport protein and an accurate biomarker of Se status (18). Serum SePP concentrations were determined as described (19). Inter- and intraassay coefficients of variation were less than 10% for Se samples in the concentration range 50–150 $\mu$g/liter and approximately 7% for SePP samples in the range 1.0–3.0 mg/liter.

Serum PTH and 25-hydroxyvitamin D were determined using an Immunodiagnostic Systems (IDS, Boldon, Tyne, & Wear, UK) immunoassay system. Concentrations of TSH, free $T_4$ (fT4) and free $T_3$ (fT3); the bone resorption marker type I collagen C-terminal telopeptide (s$\beta$CTX); the formation markers procollagen type I N-terminal propeptide (PINP), and osteocalcin (OC); and the urinary resorption marker N-terminal telopeptide of type I collagen [uNTX; expressed as a ratio to creatinine (Cr) excretion (uNTX to Cr)] were measured as described (17).

### Physical measurements

Standardized BMD measurement at the hip and lumbar spine was performed by dual-energy x-ray absorptiometry. The incident vertebral, hip and nonvertebral fractures were ascertained, and grip strength and balance were assessed as described (17).

### Study population

fT3, fT4, TSH, Se, and SePP reference ranges were calculated for each decade of age (55–65, 65–75, >75 yr) in 1565 healthy euthyroid postmenopausal women. The 2.5th and 97.5th percentiles were calculated for fT4 and fT3. TSH, Se, and SePP values were ranked and 2.5th and 97.5th percentiles calculated. To analyze the relationships between Se and SePP levels and bone parameters, individuals receiving drugs that interfere with bone

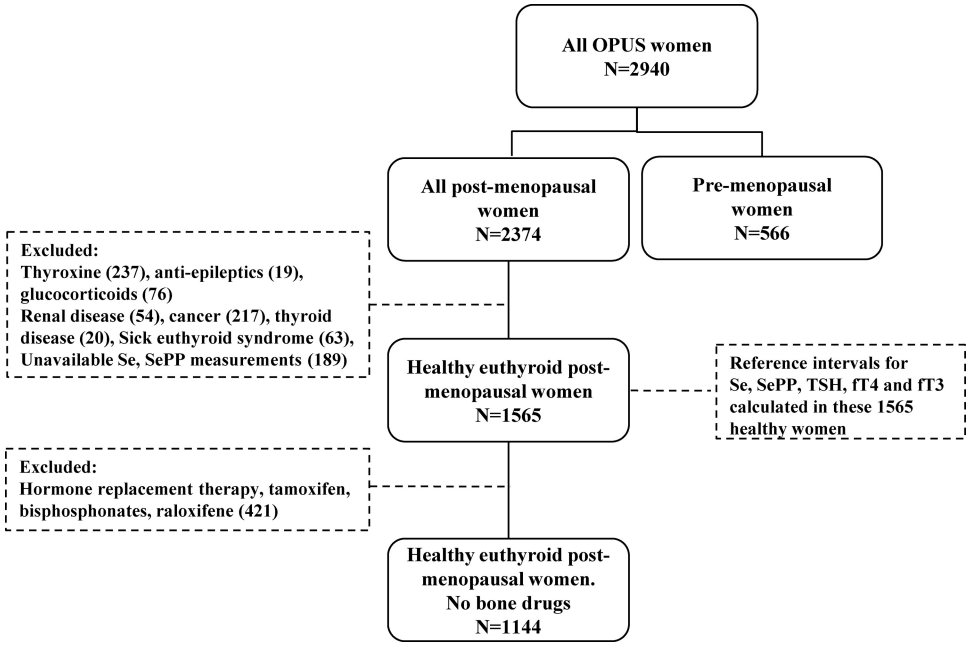


**FIG. 1.** Exclusion criteria to define populations of healthy euthyroid postmenopausal women and those women not receiving drugs affecting bone metabolism.

metabolism were excluded, leaving a final analysis population of 1144 (Fig. 1).

### Statistics

Analyses were performed using SPSS version 15 (SPSS Inc., Chicago, IL). Normal distribution was evaluated using the Kolmogorov-Smirnov test, and nonparametric variables underwent logarithmic transformation after which Se, SePP, TSH, 25-hydroxyvitamin D, PTH, s$\beta$CTX, and uNTX to Cr ratio data sets remained skewed. The whole data set was examined for outlying Se values to exclude subjects likely to be taking Se supplements. Seven individuals with a median Se value of 351 $\mu$g/liter (range 255-1243) were excluded.

Se and SePP levels were grouped into quintiles and the Kruskal-Wallis test (K-W) conducted to explore relationships between Se or SePP and BMD, bone turnover markers, pulse rate, and grip strength. Stepwise regression analysis of relationships between Se or SePP and thyroid status (fT4, fT3, TSH, fT4 to fT3 ratio) was performed.

Odds ratios for vertebral fracture in relation to Se and SePP were determined using unadjusted and adjusted [for the following: 1) 25-hydroxyvitamin D and PTH; 2) age, body mass index (BMI), and BMD; 3) fT3, fT4, and TSH; and 4) all data sets] logistic regression. Incident nonvertebral (including hip) fracture risk was determined by Cox proportional hazards modeling. The independent variable unit of analysis for the odds ratio and hazards ratio was 1 $\mu$g/liter for Se and 1 mg/liter for SePP. Stepwise regression analysis of relationships between Se or SePP and BMD, bone turnover, pulse rate, grip strength, and balance was performed following adjustment for the following: 1) 25-hydroxyvitamin D and PTH; 2) age, BMI, and BMD; 3) thyroid status; or 4) all. Analysis of relationships between thyroid status and BMD, bone turnover, pulse rate, grip strength, and balance was performed following adjustment for age, BMI, and BMD; Se status; or both.

## Results

### Se and thyroid status in healthy postmenopausal women

To define a healthy euthyroid population, subjects were excluded if they were receiving $T_4$ (n = 237), antiepileptic medications (n = 19) or glucocorticoid medications (n = 76); if they had renal disease (n = 54), cancer (n = 217), overt thyroid disease (TSH $>$ 10 mU/liter and fT4 $<$ 9 pmol/liter, or TSH $>$ 10 mU/liter and fT3 $<$ 2.5 pmol/liter, or TSH $<$ 0.1 mU/liter and fT3 $\geq$ 6 pmol/liter) (n = 20); or had evidence of the sick euthyroid syndrome, defined as fT3 less than 2.5 pmol/liter plus one or more of malabsorption, rheumatoid arthritis, bone disease other than

**TABLE 1.** Age-related reference ranges for Se, SePP, and thyroid function tests

| Analyte | All women ≥55 yr | 55–65 yr | 66–75 yr | >75 yr |
|---|---|---|---|---|
| Se ($\mu$g/liter) | 57.10–160.86 | 58.73–160.76 | 55.41–153.71 | 57.43–177.58 |
| SePP (mg/liter) | 1.98–4.85 | 2.02–4.85 | 2.03–4.84 | 1.99–4.80 |
| TSH (mU/liter) | 0.13–3.48 | 0.14–3.55 | 0.18–3.44 | 0.04–3.80 |
| fT4 (pmol/liter) | 9.07–16.62 | 8.83–16.44 | 9.16–16.50 | 9.56–17.00 |
| fT3 (pmol/liter) | 2.11–5.23 | 2.00–5.18 | 2.22–5.22 | 2.23–5.33 |

**TABLE 2.** Baseline characteristics

| | Healthy euthyroid postmenopausal women, no bone-modifying drugs |
|---|---|
| n | 1144 |
| Age (yr) | 67.8 ± 7.0 |
| BMI (kg/m$^2$) | 27.1 ± 4.8 |
| Years since menopause | 18.7 ± 9.0 |
| Se ($\mu$g/liter) | 94.3 (range 54.4–161.2) |
| SePP (mg/liter) | 3.2 (range 2.0–4.9) |
| TSH (mU/liter) | 0.89 (range 0.14–3.64) |
| fT4 (pmol/liter) | 12.8 ± 1.9 |
| fT3 (pmol/liter) | 3.7 ± 0.8 |
| 25-Hydroxyvitamin D (ng/ml) | 19.53 (range 7.35–41.69) |
| PTH (pg/ml) | 39.74 (range 13.38–98.67) |
| Lumbar spine BMD (mg/cm$^2$) | 1021 ± 175 |
| Hip BMD (mg/cm$^2$) | 863 ± 144 |
| OC (ng/ml) | 26.2 ± 10.7 |
| PINP (ng/ml) | 55.3 ± 20.3 |
| s$\beta$CTX (ng/ml) | 0.239 (range 0.011–0.759) |
| uNTX to Cr ratio (nM/mM) | 50.3 (range 18.5–130.1) |
| Grip strength (kg) | 18.5 ± 5.3 |
| Balance (m) | 3.2 ± 2.0 |

osteoarthritis, psoriasis, or asthma (n = 63). One hundred eighty-nine subjects without available measurements of Se or SePP because of insufficient sample volume were excluded. Several subjects fulfilled two or more criteria resulting in an exclusion of 809 subjects from the initial group of 2374 to obtain a population of 1565 healthy euthyroid postmenopausal women (Fig. 1), in which study population reference intervals for Se, SePP, and normal thyroid status were defined (Table 1). There were no differences in years since the menopause, smoking, alcohol consumption, prevalence of osteoarthritis, or a family history of fracture between this healthy euthyroid population and the total population. There was a positive correlation between Se and SePP concentrations (rho = 0.324, $P < 0.001$) (Supplemental Fig. 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Se decreased slightly with age (K-W 8.79; $P = 0.012$), whereas SePP remained constant (K-W 3.08; $P = 0.214$). fT4 and fT3 increased with age (F = 20.27, $P < 0.0001$; F = 4.42, $P = 0.0012$, respectively) and TSH remained constant (K-W 0.047; $P = 0.977$).

### Analysis population

To determine the relationships between Se status and bone parameters, individuals receiving drugs affecting bone metabolism (n = 421) were excluded, to leave a final analysis group of 1144 (Fig. 1 and Table 2). In the analysis population, the following data were unavailable: lumbar spine BMD at entry into the study in four individuals, hip BMD at entry in three, lumbar spine BMD after 6 yr of follow-up in 427, and hip BMD at follow-up in 425. The paired BMD data were thus available in 709 women. 25-hydroxyvitamin D and PTH were unavailable in 13 and 19 individuals, respectively, at entry and in 456 individuals at follow-up. TSH, fT4, and fT3 were unavailable in one individual, pulse rate in 29, balance in 35, grip strength in 187, OC in nine, PINP in nine, s$\beta$CTX in nine, and uNTX to Cr ratio in 45 individuals. Thus, a complete data set was available in 535 individuals (Supplemental Table 1).

### Inverse relationship between Se status and thyroid hormones

After adjustment for age, higher fT4 and fT3 were associated with lower Se (fT4: $\beta = -0.094$, $P < 0.001$; fT3: $\beta = -0.087$, $P = 0.001$) and SePP (fT4: $\beta = -0.129$, $P < 0.001$; fT3: $\beta = -0.172$, $P < 0.001$). There were no associations between Se status and TSH (Se: $\beta = 0.030$, $P = 0.232$; SePP: $\beta = 0.025$, $P = 0.318$). A higher fT4 to fT3 ratio was associated with higher SePP ($\beta = 0.082$, $P = 0.001$) but not Se ($\beta = 0.032$, $P = 0.206$) (Table 3).

### Relationship between Se status and vitamin D and PTH

The 25-hydroxyvitamin D and PTH values were determined at baseline (Table 2) and after 6 yr of follow-up (vitamin D, 20.82 ng/ml, n = 688, range 8.56–46.21; PTH, 40.88 pg/ml, n = 688, range 17.26–106.82). Higher vitamin D was associated with higher Se ($\beta = 0.110$, $P < 0.001$) but not with SePP ($\beta = 0.018$, $P = 0.554$). Higher PTH was associated with lower Se ($\beta = -0.125$, $P < 0.001$) and SePP ($\beta = -0.074$, $P = 0.015$) (Supplemental Table 2).

**TABLE 3.** Relationship between thyroid function tests and Se status

| | fT4 (pmol/liter) | | | fT3 (pmol/liter) | | |
|---|---|---|---|---|---|---|
| | Model $R^2$ | $\beta$-Coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | $\beta$-Coefficient (95% CI) (lower, upper, per SD change) | *P* |
| Se | **0.010** | **−0.101 (−2.045, −0.699)** | **<0.001** | **0.008** | **−0.089 (−4.447, −1.282)** | **<0.001** |
| SePP | **0.017** | **−0.131 (−0.069, −0.031)** | **<0.001** | **0.030** | **−0.173 (−0.200, −0.112)** | **<0.001** |
| Se | **0.012** | **−0.094 (−1.967, −0.604)** | **<0.001** | **0.010** | **−0.087 (−4.353, −1.186)** | **0.001** |
| SePP | **0.017** | **−0.129 (−0.069, −0.030)** | **<0.001** | **0.030** | **−0.172 (−0.199, −0.110)** | **<0.001** |

Statistically significant results are shown in *bold*. CI, Confidence interval.

### Higher hip BMD in women with higher Se and SePP

Individuals with Se levels in the highest quintile had higher hip BMD than women with Se in the lowest quintile at study entry (KW 10.99, $P = 0.027$). Individuals with SePP in the highest quintile also had higher hip BMD at study entry (KW 13.52, $P = 0.009$). Figure 2 shows the quintile plots relating hip and lumbar spine BMD at study entry and after 6 yr of follow-up together with mean changes in BMD in relation to Se and SePP. These plots illustrate the positive association between hip BMD and Se and SePP across the reference range of Se and SePP concentrations and no relationship with lumbar spine BMD. The mean hip and lumbar spine BMD values of women with Se and SePP levels in the lowest and highest quintiles are included in Supplemental Table 3.

### Fracture risk is not related to Se or SePP

During 6 yr of follow-up, there were 43 incident vertebral fractures in 31 individuals and 80 nonvertebral fractures, including seven hip fractures in seven individuals, among the 1144 healthy euthyroid postmenopausal women not receiving drugs affecting bone metabolism in whom data were available. The unadjusted and adjusted logistic regression indicated that Se and SePP were not related to vertebral fracture (Supplemental Table 4). The unadjusted and adjusted Cox proportional hazards analysis revealed the risk of incident nonvertebral fracture (including hip fracture) was not related to differences in Se or SePP. Separate analysis of hip fractures by Cox proportional hazards was not possible because only seven incident fractures were recorded.

### Selenium status is associated with pulse rate, balance, and bone turnover

Pulse rate, grip strength, balance, and bone turnover markers were investigated as possible factors underlying associations between Se status and hip BMD. Individuals with Se in the highest quintile had decreased uNTX to Cr ratio (K-W 13.13, $P = 0.011$) and better balance (K-W 12.29, $P = 0.015$). Individuals with SePP in the highest quintile had lower levels of OC (K-W 14.80, $P = 0.005$), PINP (K-W 10.04, $P = 0.038$), uNTX to Cr ratio (K-W 13.69, $P = 0.008$) and an increased pulse rate (K-W 11.64, $P = 0.020$).

### Adjusted regression

Stepwise regression was performed to investigate relationships between Se and SePP with BMD, bone turnover, and extraskeletal parameters (Table 4). After adjustment for age, BMI, and smoking, higher Se was associated with higher hip BMD at study entry ($\beta = 0.072$, $P = 0.004$). Higher Se was associated with lower markers of bone formation (osteocalcin: $\beta = -0.101$, $P < 0.001$; PINP: $\beta = -0.074$, $P = 0.013$) and resorption (procollagen type 1 N-terminal propeptide: $\beta = -0.058$, $P = 0.050$; uNTX to Cr ratio: $\beta = -0.095$, $P = 0.002$). Associations persisted after adjustment for thyroid status, vitamin D, and PTH. Higher Se was also associated with an increased pulse rate but not other extraskeletal parameters after adjustment for age, BMI, smoking and thyroid status, vitamin D, or PTH (Table 4 and Supplemental Table 5).

After adjustment for age, BMI, and smoking, higher SePP was associated with higher hip ($\beta = 0.113$, $P < 0.001$) and lumbar spine BMD ($\beta = 0.088$, $P = 0.003$) at study entry, with higher hip BMD after 6 yr of follow up ($\beta = 0.106$, $P = 0.001$) and with increased bone loss at the lumbar spine ($\beta = 0.106$, $P = 0.001$). Higher SePP was associated with lower osteocalcin ($\beta = -0.077$, $P = 0.009$), procollagen type 1 N-terminal propeptide ($\beta = -0.075$, $P = 0.012$) and uNTX to Cr ratio ($\beta = -0.110$, $P < 0.001$). Associations persisted after adjustment for thyroid status, vitamin D, and PTH. Higher SePP was also associated with increased pulse rate and grip strength after adjustment for age, BMI, smoking, vitamin D, and PTH, but only the association with grip strength persisted after adjustment for thyroid status (Table 4 and Supplemental Table 5).

### Effects of variation in thyroid status on BMD and fracture risk are independent of Se status

We previously demonstrated that higher fT4 and fT3 levels within the reference range were associated with lower BMD and increased risk of nonvertebral fracture

**TABLE 3.** Continued

| TSH (mU/liter) | | | fT4/fT3 | | | |
|---|---|---|---|---|---|---|
| Model $R^2$ | $\beta$-Coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | $\beta$-Coefficient (95% CI) (lower, upper, per SD change) | *P* | |
| 0.001 | 0.029 (−0.489, 1.860) | 0.253 | 0.001 | 0.030 (−0.642, 2.593) | 0.237 | Unadjusted |
| 0.001 | 0.024 (−0.017, 0.049) | 0.333 | **0.006** | **0.080 (0.028, 0.119)** | **0.001** | |
| 0.004 | 0.030 (−0.458, 1.889) | 0.232 | 0.004 | 0.032 (−0.574, 2.658) | 0.206 | Adjusted for age |
| 0.002 | 0.025 (−0.016, 0.050) | 0.318 | **0.008** | **0.082 (0.029, 0.120)** | **0.001** | |

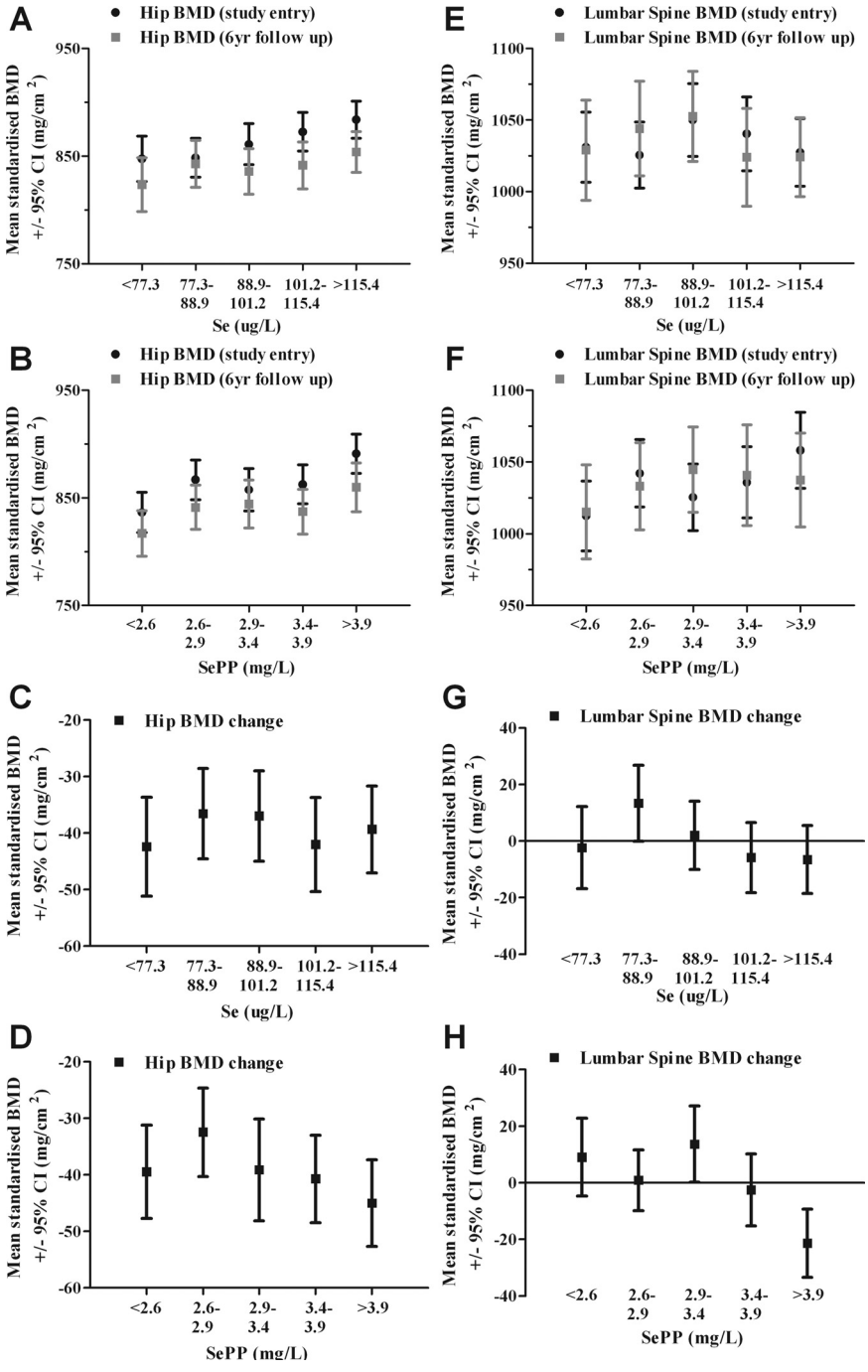


**FIG. 2.** Graphs showing hip (A–D) and lumbar spine (E–G) standardized BMD ± 95% confidence intervals at the time of entry and after 6 yr of follow-up in relation to quintiles of Se (A and E) and SePP (B and F) concentrations and graphs showing mean change in standardized BMD ± 95% confidence intervals in relation to Se (C and G) and SePP (D and H) concentrations.

(17). In the current study, a different analysis population was investigated because Se and SePP measurements were available in only 1565 healthy euthyroid individuals compared with 1754 subjects originally and in 1144 compared with 1278 after exclusion of subjects receiving bone drugs. Analysis of the current study population of 1144 individuals again demonstrated associations between higher fT4 and fT3 levels with hip BMD and nonvertebral fracture risk after adjustment for age, BMI, and smoking (Supplemental Tables 6 and 7). Associations persisted after adjustment for Se and SePP.

## Discussion

These studies demonstrate that variation in Se status is related to BMD and bone turnover in healthy postmenopausal women. There is controversy regarding whether skeletal effects of Se are direct or mediated via interactions with iodine status and thyroid function (8, 9, 15). Use of a rigorously defined healthy euthyroid population, enabling relationships between Se and bone to be investigated without confounding effects of thyroid dysfunction, is a strength of this study. Logistic regression demonstrated that associations between Se status and bone parameters were independent of changes in fT3, fT4, or TSH. Associations between thyroid status and bone parameters were independent of Se status.

Nevertheless, higher Se and SePP levels were associated with extraskeletal parameters including increased pulse rate (Se) and grip strength (SePP). These represent novel associations between Se status and the cardiovascular and musculoskeletal systems that could be direct or may reflect an interaction between Se and the overall nutritional status. Such findings complicate the understanding of the relationship between Se status and bone turnover and BMD.

Se levels correlated with SePP in accord with reliability of SePP as a marker of Se status (18). Se, but not SePP, concentrations fell slightly with age. A study of healthy Chinese (20) reported increases in Se and SePP during the first decade of life until constant levels were maintained in adults. Small increases in Se and SePP with age have been reported in healthy U.S., Portuguese, and German adults (19, 21, 22), but Se was reported to decrease with age in a Finnish population (23). No studies have investigated healthy euthyroid individuals, and reference ranges for Se status in postmenopausal women have not been reported. Nevertheless, the decrease in Se with age, but stability of SePP, is noteworthy, although underlying reasons are un-

clear. A general possibility is that there may be decreasing daily intake of Se-rich foods with age such as meat and seafood. Dietary intake, however, is an unreliable indicator of Se status, particularly because foods are obtained from all over the world, and their Se content is variable and related to source habitat and origin (24). A more specific possibility is that SePP expression includes the translation of both full-length protein and C-terminal truncated isoforms that lack selenocysteine amino acids, resulting in reduced Se transport capacity (25). It is unclear whether SePP biosynthesis is age or gender dependent, but changes in SePP translation could relate to declining estradiol concentrations in postmenopausal women. Such a mechanism would account for the decrease in Se concentration without apparent change in SePP.

Alterations in Se and thyroid status were each associated with bone parameters, but these relationships were mutually exclusive when investigated by logistic regression. Nevertheless, Se and SePP were inversely correlated with fT3 and fT4 and positively correlated with the $T_4$ to $T_3$ ratio. Although interactions between Se status and thyroid hormones have been investigated in epidemiological studies with inconsistent results, randomized intervention trials have not identified effects of Se supplementation on thyroid parameters (26). A study of 41 patients with critical illness, sick euthyroid syndrome, and severe Se deficiency also reported no effect of Se replacement on thyroid hormones (27). Nevertheless, the current finding of an inverse relationship between Se and free thyroid hormones is consistent with a cross-sectional study of 500 iodine-replete Iranian schoolchildren, in which fT4 correlated negatively with Se (28).

Se and SePP were positively associated with changes in BMD and inversely related to bone turnover. The findings are consistent with studies reporting osteopenia in Se-deficient rats (15), but there is a paucity of human data. Only three cross-sectional studies have investigated relationships between Se and BMD. They are limited by inadequate criteria to exclude subjects with confounding factors including thyroid disease, a lack of information on thyroid or iodine status, and a lack of power. A study of 281 Chinese postmenopausal women with marked Se insufficiency found no relationship between Se and BMD in normal and osteoporotic subgroups (29). In 107 Turkish postmenopausal women with similar Se insufficiency, no difference in Se levels among subgroups with normal BMD, osteopenia, or osteoporosis was identified (30), and negative findings were reported in 77 Turkish postmenopausal, Se-deficient osteoporotic women compared with 61 Se-deficient controls (31). No studies have investigated the relationship between Se status and bone turnover. Thus, the current findings identify for the first time that lower levels of Se and SePP within a large population reference range are associated with higher bone turnover and lower BMD in healthy postmenopausal women.

In the context that Se and SePP were positively correlated with BMD, it is reasonable to hypothesize that Se deficiency would be related to fracture susceptibility. However, no association between Se status and fracture risk was identified. Se concentrations in the OPUS population reflect mild Se insufficiency compared with concentrations reported in Se-replete populations (2). In the absence of overt Se deficiency in OPUS, it is not surprising that no relationship between Se status and fracture risk was identified, particularly because only small numbers of incident fractures occurred in the healthy population during 6 yr of prospective follow-up. A larger prospective study will be required to include more fracture events.

There is little information to indicate the mechanisms underlying the relationship between Se status, bone turnover, and BMD. IL-6 and other cytokines play a significant role in the pathogenesis of osteoporosis (32), and Se exerts antiinflammatory actions, mediated in part by inhibitory effects on IL-6 and cytokine activities (33), suggesting a mechanism by which Se could regulate bone turnover. In addition, bone resorption generates a local burden of reactive oxygen species, which may damage bone cells and extracellular matrix, leading to impaired bone remodeling and repair unless they can be adequately eliminated (34). Accordingly, there is evidence to support a critical role for reactive oxygen species in osteoporosis (35). Expression of selenoproteins in bone-resorbing osteoclasts and bone-forming osteoblasts (36, 37) suggests Se status may be a limiting factor that regulates the efficiency of reactive oxygen species clearance. Thus, it is possible that a limiting threshold of Se is required for adequate selenoprotein-mediated antioxidant activity and optimal bone maintenance (38).

Although our study was comprehensive, limitations remain. Although both total Se and SePP were determined in parallel, providing a solid basis for assessment of Se status (18, 39), measures of glutathione peroxidase (GPx) activity in plasma (extracellular GPx-3) or erythrocytes (cellular GPx-1) would provide additional indication of overall antioxidant capacity (24). Such measurements were not possible because only serum samples were available (precluding measurement of GPx1) and these had been thawed previously for other measurements, leading to unreliable activity of GPx3. Se bioavailability is dependent on nutrition, and although diet is an unreliable indicator of Se status (24), it remains possible that the identified relationship between Se status and bone metabolism could reflect an unrelated effect of overall nutrition for which Se may be a biomarker. The OPUS did not include information relating to diet. As discussed (17), blood samples were drawn at the same time of the day to mitigate effects of

**TABLE 4.** Relationship between Se, SePP, BMD, bone turnover, and extraskeletal parameters

| | Se (μg/liter) Unadjusted | | | Se (μg/liter) Adjusted for age, BMI and smoking | | |
|---|---|---|---|---|---|---|
| | Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* |
| BMD | | | | | | |
| At study entry | | | | | | |
| Lumbar spine BMD | 0.000 | 0.003 (−0.389, 0.434) | 0.915 | 0.135 | −0.002 (−0.400, 0.374) | 0.948 |
| Hip BMD | **0.009** | **0.094 (0.195, 0.829)** | **0.002** | **0.304** | **0.072 (0.123, 0.660)** | **0.004** |
| 6-yr follow-up | | | | | | |
| Lumbar spine BMD | 0.000 | −0.015 (−0.684, 0.470) | 0.715 | 0.140 | −0.005 (−0.579, 0.503) | 0.890 |
| Hip BMD | 0.003 | 0.057 (−0.083, 0.650) | 0.129 | 0.307 | 0.036 (−0.130, 0.488) | 0.255 |
| Change in lumbar spine BMD | 0.002 | −0.047 (−0.365, 0.095) | 0.251 | 0.117 | −0.037 (−0.325, 0.113) | 0.342 |
| Change in hip BMD | 0.000 | 0.019 (−0.102, 0.173) | 0.610 | 0.017 | 0.015 (−0.109, 0.167) | 0.683 |
| Bone turnover | | | | | | |
| OC | **0.011** | **−0.103 (−0.065, −0.018)** | **0.001** | **0.042** | **−0.101 (−0.064, −0.017)** | **<0.001** |
| PINP | **0.005** | **−0.073 (−0.101, −0.011)** | **0.014** | **0.021** | **−0.074 (−0.102, −0.012)** | **0.013** |
| sβCTX | **0.004** | **−0.061 (−0.001, 0.000)** | **0.040** | **0.023** | **−0.058 (−0.001, 0.000)** | **0.050** |
| uNTX to Cr ratio | **0.010** | **−0.101 (−0.191, −0.050)** | **0.001** | **0.025** | **−0.095 (−0.185, −0.043)** | **0.002** |
| Extraskeletal parameters | | | | | | |
| Pulse rate | **0.005** | **0.067 (0.003, 0.048)** | **0.024** | **0.026** | **0.076 (0.007, 0.051)** | **0.011** |
| Grip strength | 0.000 | 0.011 (−0.011, 0.015) | 0.745 | 0.100 | −0.100 (−0.014, 0.010) | 0.773 |
| Balance | **0.004** | **0.062 (0.000, 0.009)** | **0.039** | 0.109 | 0.041 (−0.001, 0.007) | 0.151 |
| | **SePP (mg/liter) Unadjusted** | | | **SePP (mg/liter) Adjusted for age, BMI, and smoking** | | |
| | Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* |
| BMD | | | | | | |
| At study entry | | | | | | |
| Lumbar spine BMD | **0.007** | **0.081 (4.286, 32.791)** | **0.011** | **0.142** | **0.088 (6.688, 33.383)** | **0.003** |
| Hip BMD | **0.013** | **0.114 (10.523, 32.187)** | **<0.001** | **0.312** | **0.113 (12.163, 30.364)** | **<0.001** |
| 6-yr follow-up | | | | | | |
| Lumbar spine BMD | 0.004 | 0.064 (−3.746, 32.800) | 0.119 | 0.145 | 0.068 (−1.640, 32.506) | 0.076 |
| Hip BMD | **0.011** | **0.106 (5.717, 30.700)** | **0.004** | **0.317** | **0.106 (7.770, 28.691)** | **0.001** |
| Change in lumbar spine BMD | **0.015** | **−0.123 (−18.444, −3.925)** | **0.003** | **0.128** | **−0.115 (−17.311, −3.537)** | **0.003** |
| Change in hip BMD | 0.003 | −0.051 (−7.962, 1.454) | 0.175 | 0.019 | −0.055 (−8.211, 1.198) | 0.144 |
| Bone turnover | | | | | | |
| OC | **0.006** | **−0.075 (−1.860, −0.241)** | **0.011** | **0.037** | **−0.077 (−1.876, −0.274)** | **0.009** |
| PINP | 0.002 | −0.044 (−2.702, 0.374) | 0.138 | 0.018 | −0.046 (−2.738, 0.333) | 0.125 |
| sβCTX | **0.005** | **−0.073 (−0.043, −0.005)** | **0.014** | **0.025** | **−0.075 (−0.044, −0.006)** | **0.012** |
| uNTX to Cr ratio | **0.012** | **−0.111 (−6.968, −2.146)** | **<0.001** | **0.029** | **−0.110 (−6.929, −2.116)** | **<0.001** |
| Extraskeletal parameters | | | | | | |
| Pulse rate | **0.007** | **0.084 (0.334, 1.846)** | **0.005** | **0.028** | **0.089 (0.396, 1.902)** | **0.003** |
| Grip strength | **0.005** | **−0.074 (−0.951, −0.074)** | **0.022** | **0.106** | **−0.078 (−0.956, −0.121)** | **0.011** |
| Balance | 0.000 | −0.021 (−0.209, 0.101) | 0.494 | 0.108 | −0.028 (−0.222, 0.073) | 0.322 |

Statistically significant results are shown in *bold*. CI, Confidence interval; TFT, thyroid function tests.

diurnal variation. Nevertheless, samples were nonfasting, and direct comparison of bone marker data with other studies using morning fasting samples will continue to be difficult. Furthermore, OPUS did not include information relating to diabetes mellitus. Together with the availability only of nonfasting blood samples, this precluded the exclusion of diabetic individuals. In addition, the OPUS database does not provide information on the use of Se supplements. To prevent confounding effects, individuals with outlying high levels of Se greater than 250 μg/liter were excluded (n = 7). Finally, the study was restricted to postmenopausal women, and further studies are necessary to determine whether the findings apply to other cohorts.

Overall, we demonstrate that variation in Se status within the population reference range in healthy euthyroid postmenopausal women is inversely related to bone turnover and positively correlated with BMD. These relationships were independent of changes in thyroid status. The previously identified relationship between physiological variation in thyroid status and BMD and nonvertebral fracture (17) was independent of changes in Se status. A next step will be to investigate the therapeutic utility of Se supplementation. This could be achieved by conducting a randomized controlled trial of Se supplementation in postmenopausal women with measurement of bone turnover as the end point. Such a trial would need to be short term and cautious because, although Se supplementation could be beneficial in individuals with low Se status, it may have adverse effects in individuals who are replete or have high Se status (40).

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**TABLE 4.** Continued

| Se (μg/liter) Adjusted for TFT | | | Se (μg/liter) Adjusted for age, BMI, smoking, and TFT | | |
|---|---|---|---|---|---|
| Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* |
| 0.007 | −0.002 (−0.424, 0.402) | 0.957 | 0.139 | −0.004 (−0.418, 0.359) | 0.882 |
| **0.022** | **0.083 (0.138, 0.772)** | **0.005** | **0.307** | **0.068 (0.103, 0.642)** | **0.007** |
| 0.013 | −0.016 (−0.689, 0.463) | 0.701 | 0.152 | −0.004 (−0.567, 0.512) | 0.920 |
| 0.026 | 0.042 (−0.156, 0.573) | 0.262 | 0.315 | 0.027 (−0.172, 0.447) | 0.383 |
| 0.023 | −0.043 (−0.351, 0.108) | 0.298 | 0.135 | −0.034 (−0.316, 0.120) | 0.377 |
| 0.005 | 0.013 (−0.114, 0.162) | 0.733 | 0.023 | 0.008 (−0.123, 0.154) | 0.823 |
| **0.015** | **−0.101 (−0.065, −0.018)** | **0.001** | **0.046** | **−0.100 (−0.064, −0.017)** | **0.001** |
| **0.007** | **−0.072 (−0.101, −0.010)** | **0.016** | **0.023** | **−0.073 (−0.102, −0.011)** | **0.015** |
| **0.013** | **−0.058 (−0.001, 0.000)** | **0.052** | 0.031 | −0.057 (−0.001, 0.000) | 0.054 |
| **0.012** | **−0.097 (−0.187, −0.045)** | **0.001** | **0.027** | **−0.093 (−0.182, −0.040)** | **0.002** |
| **0.009** | **0.072 (0.005, 0.049)** | **0.017** | **0.031** | **0.080 (0.008, 0.052)** | **0.008** |
| 0.025 | 0.016 (−0.010, 0.016) | 0.623 | 0.127 | 0.002 (−0.012, 0.130) | 0.956 |
| **0.011** | **0.063 (0.000, 0.009)** | **0.037** | 0.116 | 0.046 (−0.001, 0.008) | 0.112 |
| **SePP (mg/liter) Adjusted for TFT** | | | **SePP (mg/liter) Adjusted for age, BMI, smoking, and TFT** | | |
| Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β-Coefficient (95% CI) (lower, upper, per SD change) | *P* |
| **0.012** | **0.073 (2.124, 31.009)** | **0.025** | **0.146** | **0.083 (5.317, 32.394)** | **0.006** |
| **0.025** | **0.099 (7.577, 29.439)** | **0.001** | **0.314** | **0.108 (10.971, 29.425)** | **<0.001** |
| 0.017 | 0.066 (−3.565, 33.534) | 0.113 | 0.157 | 0.071 (−1.088, 33.550) | 0.066 |
| **0.031** | **0.085 (2.012, 27.128)** | **0.023** | **0.323** | **0.094 (5.508, 26.671)** | **0.003** |
| **0.032** | **−0.106 (−16.963, −2.252)** | **0.011** | **0.144** | **−0.106 (−16.588, −2.641)** | **0.007** |
| 0.009 | −0.060 (−8.605, 0.930) | 0.115 | 0.027 | −0.065 (−8.941, 0.582) | 0.085 |
| **0.011** | **−0.076 (−1.875, −0.236)** | **0.012** | **0.043** | **−0.080 (−1.927, −0.305)** | **0.007** |
| 0.004 | −0.045 (−2.756, 0.362) | 0.132 | 0.020 | −0.047 (−2.795, 0.319) | 0.119 |
| **0.016** | **−0.076 (−0.044, −0.006)** | **0.012** | **0.034** | **−0.080 (−0.046, −0.007)** | **0.007** |
| **0.014** | **−0.106 (−6.770, −1.877)** | **0.001** | **0.029** | **−0.107 (−6.807, −1.922)** | **<0.001** |
| **0.013** | **0.096 (0.468, 1.998)** | **0.002** | **0.034** | **0.099 (0.518, 2.042)** | **0.001** |
| 0.029 | −0.061 (−0.866, 0.015) | 0.058 | 0.130 | −0.057 (−0.811, 0.025) | 0.065 |
| 0.008 | −0.017 (−0.202, 0.112) | 0.574 | 0.114 | −0.018 (−0.198, 0.101) | 0.525 |

Address all correspondence and requests for reprints to: Graham R. Williams, Molecular Endocrinology Group, Imperial College London, 7N2a Commonwealth Building, Hammersmith Campus, Du Cane Road, London W12 0NN, United Kingdom. E-mail: graham.williams@imperial.ac.uk; or Lutz Schomburg, Charité-Universitätsmedizin Berlin, Institut fuer Experimentelle Endokrinologie, Campus Virchow Klinikum (Südring 10), Augustenburger Platz 1, D-13353 Berlin, Germany. E-mail: lutz.schomburg@charite.de.

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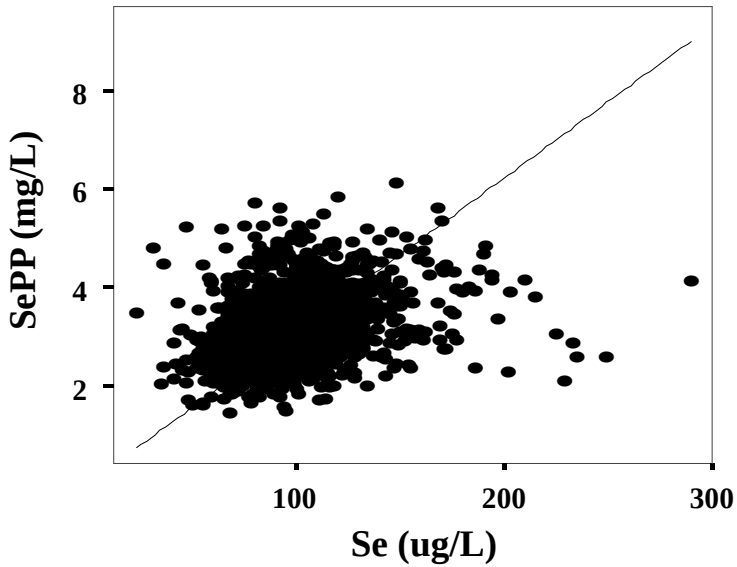
**Supplemental Figure 1**

Graph showing a positive correlation between Se and SePP concentrations (Spearman's rank correlation coefficient rho=0.324, $P<0.001$).


SePP (mg/L)
8
6
4
2
100
200
300
Se (ug/L)

**SUPPLEMENTAL TABLE 1**.
Number of subjects in whom data was available for each variable

| Test variable | Number |
|---|---|
| Lumbar spine BMD at study entry | 1140 |
| Hip BMD at study entry | 1141 |
| Lumbar spine BMD at 6 years follow-up | 717 |
| Hip BMD at 6 years follow-up | 719 |
| Se | 1144 |
| SePP | 1144 |
| TSH | 1143 |
| FT4 | 1143 |
| FT3 | 1143 |
| 25(OH)D at study entry | 1131 |
| 25(OH)D at 6 years follow-up | 688 |
| PTH at study entry | 1125 |
| PTH at 6 years follow-up | 688 |
| Pulse rate | 1115 |
| Balance | 1109 |
| Grip strength | 957 |
| Osteocalcin | 1135 |
| P1NP | 1135 |
| sβCTX | 1135 |
| uNTXCr | 1099 |
| Incident vertebral fracture | 728 |
| Incident hip fracture | 827 |
| Incident non-vertebral fracture | 793 |

**SUPPLEMENTAL TABLE 2. Relationship between 25(OH)D, PTH and Se status**

| | 25(OH)D | | | PTH | | | |
|---|---|---|---|---|---|---|---|
| | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | |
| **Se** | **0.013** | **0.115 (0.152, 0.459)** | **<0.001** | **0.017** | **-0.131 (-0.213, -0.082)** | **<0.001** | **unadjusted** |
| **SePP** | 0.000 | 0.019 (-0.003, 0.006) | 0.529 | **0.005** | **-0.073 (-0.004, 0.000)** | **0.014** | |
| **Se** | **0.016** | **0.110 (0.138, 0.446)** | **<0.001** | **0.019** | **-0.125 (-0.206, -0.074)** | **<0.001** | **adjusted for age** |
| **SePP** | 0.000 | 0.018 (0.003, 0.006) | 0.554 | **0.005** | **0.074 (-0.004, 0.000)** | **0.015** | |

**Statistically significant results are shown in bold. CI, Confidence interval (n=1144).**

**SUPPLEMENTAL TABLE 3.**

| | Se (ug/L) | | SePP (mg/L) | |
|---|---|---|---|---|
| | **Lowest quintile** | **Highest quintile** | **Lowest quintile** | **Highest quintile** |
| | 69.50 (39.46 - 77.06) | 128.43 (115.99 - 205.25) | 2.35 (1.70 - 2.60) | 4.29 (3.89 - 5.61) |
| Se | - | - | **84.41 (46.20 - 149.12)** | **108.86 (59.53 - 190.48)*** |
| SePP | **2.83 (1.89 - 4.56)** | **3.55 (2.17 - 5.06)*** | - | - |
| FT4 | **13.06±1.99** | **12.53±1.85*** | **13.18±1.85** | **12.36±1.92*** |
| FT3 | 3.79±0.84 | 3.61±0.81 | **3.84±0.80** | **3.44±0.79*** |
| TSH | 0.82 (0.11 - 3.36) | 0.91 (0.15 - 4.23) | 0.95 (0.12 - 4.15) | 1.04 (0.19 - 3.79) |
| 25(OH)D | **16.74 (6.67 - 38.97)** | **21.52 (7.87 - 43.61)*** | 17.85 (6.41 - 43.24) | 19.38 (8.05 - 46.75) |
| PTH | **42.90 (16.14 - 127.04)** | **36.74 (11.27 - 78.87)*** | 41.84 (10.35 - 127.67) | 36.74 (15.72 - 87.04) |
| Lumbar spine BMD (study entry) | 1031±175 | 1028±170 | 1013±174 | 1058±186 |
| Hip BMD (study entry) | **848±162** | **884±132 *** | **837±145** | **891±139 *** |
| Lumbar spine BMD (follow-up) | 1029±179 | 1027±160 | 1015±180 | 1040±185 |
| Hip BMD (follow-up) | 824±142 | 854±120 | 817±128 | 860±141 |
| Change in lumbar spine BMD | -2.4±74.3 | -6.6±68.9 | 9.0±75.9 | -21.4±67.7 |
| Change in hip BMD | -42.4±49.7 | -39.4±48.8 | -39.5±50.0 | -45.0±47.6 |

*P≤0.05 highest vs lowest quintile

**SUPPLEMENTAL TABLE 4**. Relationship between Selenium status and fracture

| | Logistic regression model | | | Cox Proportional hazards model | | | | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | | | HR (95% CI) | | | | |
| | Per unit change | Per SD change | *P* | Per unit change | Per SD change | *P* | | |
| **Prevalent vertebral fracture** | 0.99 (0.99 - 1.00) | 0.77 (0.77 - 1.00) | 0.375 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.316 | - | - | - | **Se** | Unadjusted |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.850 | | |
| **Prevalent vertebral fracture** | 1.00 (0.99 - 1.00) | 1.00 (0.77 - 1.00) | 0.316 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.315 | - | - | - | **Se** | Adjusted for 25(OH)D |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.861 | | |
| **Prevalent vertebral fracture** | 1.00 (0.99 - 1.00) | 1.00 (0.77 - 1.00) | 0.376 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.329 | - | - | - | **Se** | Adjusted for PTH |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.824 | | |
| **Prevalent vertebral fracture** | 0.99 (0.79 - 1.23) | 0.99 (0.83 - 1.18) | 0.910 | - | - | - | | |
| **Incident vertebral fracture** | 0.86 (0.53 - 1.39) | 0.89 (0.60 - 1.30) | 0.537 | - | - | - | **SePP** | Unadjusted |
| **Incident non-vertebral fracture** | - | - | - | 1.24 (0.90 - 1.70) | 1.19 (0.92 - 1.53) | 0.184 | | |
| **Prevalent vertebral fracture** | 1.00 (0.80 - 1.24) | 1.00 (0.84 - 1.19) | 0.971 | - | - | - | | |
| **Incident vertebral fracture** | 0.87 (0.53 - 1.41) | 0.90 (0.60 - 1.32) | 0.559 | - | - | - | **SePP** | Adjusted for 25(OH)D |
| **Incident non-vertebral fracture** | - | - | - | 1.24 (0.90 - 1.70) | 1.19 (0.92 - 1.53) | 0.184 | | |
| **Prevalent vertebral fracture** | 1.01 (0.81 - 1.26) | 1.01 (0.85 - 1.20) | 0.953 | - | - | - | | |
| **Incident vertebral fracture** | 0.87(0.54 - 1.41) | 0.90 (0.61 - 1.32) | 0.562 | - | - | - | **SePP** | Adjusted for PTH |
| **Incident non-vertebral fracture** | - | - | - | 1.29 (0.94 - 1.79) | 1.23 (0.95 - 1.59) | 0.121 | | |
| **Prevalent vertebral fracture** | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.771 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.366 | - | - | - | **Se** | Adjusted for age, BMI and lumbar spine BMD |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.688 | | |
| **Prevalent vertebral fracture** | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.650 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.365 | - | - | - | **Se** | Adjusted for age, BMI, lumbar spine BMD and 25(OH)D |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.688 | | |
| **Prevalent vertebral fracture** | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.636 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.369 | - | - | - | **Se** | Adjusted for age, BMI, lumbar spine BMD and PTH |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.600 | | |
| **Prevalent vertebral fracture** | 1.07 (0.85 - 1.34) | 1.06 (0.88 - 1.26) | 0.581 | - | - | - | | |
| **Incident vertebral fracture** | 0.84 (0.51 - 1.39) | 0.87 (0.58 - 1.30) | 0.504 | - | - | - | **SePP** | Adjusted for age, BMI and lumbar spine BMD |
| **Incident non-vertebral fracture** | - | - | - | 1.32 (0.96 - 1.81) | 1.25 (0.97 - 1.62) | 0.092 | | |
| **Prevalent vertebral fracture** | 1.08 (0.86 - 1.36) | 1.06 (0.89 - 1.30) | 0.528 | - | - | - | | |
| **Incident vertebral fracture** | 0.85 (0.52 - 1.41) | 0.88 (0.59 - 1.32) | 0.533 | - | - | - | **SePP** | Adjusted for age, BMI, lumbar spine BMD and 25(OH)D |
| **Incident non-vertebral fracture** | - | - | - | 1.32 (0.96 - 1.82) | 1.25 (0.97 - 1.62) | 0.089 | | |
| **Prevalent vertebral fracture** | 1.08 (0.86 - 1.35) | 1.06 (0.89 - 1.27) | 0.526 | - | - | - | | |
| **Incident vertebral fracture** | 0.85 (0.51 - 1.40) | 0.88 (0.58 - 1.31) | 0.517 | - | - | - | **SePP** | Adjusted for age, BMI, lumbar spine BMD and PTH |
| **Incident non-vertebral fracture** | - | - | - | 1.42 (1.02 - 1.98) | 1.32 (1.02 - 1.73) | 0.037 | | |
| **Prevalent vertebral fracture** | 1.00 (0.99 - 1.00) | 1.00 (0.77 -1.00) | 0.377 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.268 | - | - | - | **Se** | Adjusted for FT3, FT4, TSH |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.703 | | |
| **Prevalent vertebral fracture** | 0.99 (0.79 - 1.24) | 0.99 (0.83 - 1.19) | 0.947 | - | - | - | | |
| **Incident vertebral fracture** | 0.84 (0.52 - 1.38) | 0.87 (0.59 - 1.29) | 0.493 | - | - | - | **SePP** | Adjusted for FT3, FT4, TSH |
| **Incident non-vertebral fracture** | - | - | - | 1.25 (0.90 - 1.73) | 1.20 (0.92 - 1.55) | 0.192 | | |
| **Prevalent vertebral fracture** | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.736 | - | - | - | | |
| **Incident vertebral fracture** | 0.99 (0.98 - 1.01) | 0.77 (0.59 - 1.30) | 0.314 | - | - | - | **Se** | Adjusted for age, BMI, lumbar spine BMD, FT3, FT4, TSH |
| **Incident non-vertebral fracture** | - | - | - | 1.00 (0.99 - 1.01) | 1.00 (0.77 - 1.30) | 0.617 | | |
| **Prevalent vertebral fracture** | 1.06 (0.84 - 1.33) | 1.05 (0.87 - 1.26) | 0.629 | - | - | - | | |
| **Incident vertebral fracture** | 0.83 (0.50 - 1.37) | 0.86 (0.57 - 1.29) | 0.460 | - | - | - | **SePP** | Adjusted for age, BMI, lumbar spine BMD, FT3, FT4, TSH |
| **Incident non-vertebral fracture** | - | - | - | 1.34 (0.96 - 1.86) | 1.26 (0.97 - 1.64) | 0.082 | | |

Units of measure are: Se, ug/liter; SePP, mg/liter. CI, Confidence interval.

**SUPPLEMENTAL TABLE 5. Relationship between Se, SePP and BMD, bone turnover and extraskeletal parameters after adjustment for 25(OH)D and PTH**

| | Se (ug/L) adjusted for 25(OH)D | | | Se (ug/L) adjusted for age, BMI, smoking and 25(OH)D | | | Se (ug/L) adjusted for PTH | | | Se (ug/L) adjusted for age, BMI, smoking and PTH | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* |
| **BMD** | | | | | | | | | | | | |
| ***At study entry*** | | | | | | | | | | | | |
| **Lumbar spine BMD** | 0.003 | -0.004 (-0.442, 0.393) | 0.909 | 0.139 | -0.010 (-0.460, 0.323) | 0.732 | 0.000 | 0.004 (-0.395, 0.442) | 0.911 | 0.135 | -0.005 (-0.426, 0.360) | 0.870 |
| **Hip BMD** | **0.023** | **0.080 (0.118, 0.756)** | **0.007** | **0.317** | **0.059 (0.056, 0.593)** | **0.018** | **0.028** | **0.075 (0.092, 0.731)** | **0.012** | **0.325** | **0.053 (0.025, 0.561)** | **0.032** |
| ***6 years follow-up*** | | | | | | | | | | | | |
| **Lumbar spine BMD** | 0.002 | -0.018 (-0.708, 0.457) | 0.672 | 0.146 | -0.010 (-0.614, 0.469) | 0.793 | 0.000 | -0.016 (-0.704, 0.472) | 0.698 | 0.144 | 0.011 (-0.629, 0.465) | 0.768 |
| **Hip BMD** | 0.014 | 0.044 (-0.147, 0.591) | 0.238 | 0.318 | 0.025 (-0.186, 0.432) | 0.435 | 0.013 | 0.044 (-0.154, 0.590) | 0.250 | 0.319 | 0.022 (-0.200, 0.4220 | 0.485 |
| **Change in lumbar spine BMD** | 0.008 | -0.042 (-0.352, 0.112) | 0.311 | 0.117 | -0.035 (-0.321, 0.119) | 0.367 | 0.002 | -0.048 (-0.373, 0.097) | 0.249 | 0.122 | -0.045 (-0.350, 0.093) | 0.255 |
| **Change in hip BMD** | 0.000 | 0.020 (-0.102, 0.177) | 0.602 | 0.017 | 0.017 (-0.108, 0.171) | 0.655 | 0.000 | 0.019 (-0.104, 0.177) | 0.611 | 0.017 | 0.017 (-0.108, 0.172) | 0.653 |
| **Bone turnover** | | | | | | | | | | | | |
| **Osteocalcin** | **0.012** | **-0.099 (-0.064, -0.016)** | **0.001** | **0.043** | **-0.096 (-0.063, -0.015)** | **0.001** | **0.112** | **-0.061 (-0.047, -0.002)** | **0.033** | **0.153** | **-0.058 (-0.046, -0.001)** | **0.037** |
| **P1NP** | **0.007** | **-0.067 (-0.097, -0.007)** | **0.025** | **0.025** | **-0.068 (-0.097, -0.007)** | **0.024** | 0.030 | -0.052 (-0.085, 0.005) | 0.080 | 0.053 | -0.051 (-0.084, 0.005) | 0.083 |
| **sβCTX** | **0.004** | **-0.062 (-0.001, 0.000)** | **0.039** | **0.023** | **-0.060 (-0.001, 0.000)** | **0.047** | 0.079 | -0.025 (-0.001, 0.000) | 0.397 | 0.100 | -0.023 (-0.001, 0.000) | 0.423 |
| **uNTXCr** | **0.010** | **-0.099 (-0.190, -0.047)** | **0.001** | **0.026** | **-0.093 (-0.183, -0.040)** | **0.002** | **0.030** | **-0.082 (-0.169, -0.027)** | **0.007** | **0.047** | **-0.077 (-0.162, -0.021)** | **0.011** |
| **Extraskeletal parameters** | | | | | | | | | | | | |
| ***At study entry*** | | | | | | | | | | | | |
| **Pulse rate** | **0.005** | **0.067 (0.003, 0.048)** | **0.026** | **0.026** | **0.074 (0.006, 0.050)** | **0.014** | **0.005** | **0.067 (0.003, 0.048)** | **0.028** | **0.027** | **0.072 (0.005, 0.050)** | **0.017** |
| **Grip strength** | 0.008 | 0.000 (-0.013, 0.013) | 0.994 | 0.104 | -0.015 (-0.015, 0.009) | 0.626 | 0.022 | -0.009 (-0.015, 0.011) | 0.779 | 0.112 | -0.022 (-0.017, 0.008) | 0.473 |
| **Balance** | 0.009 | 0.053 (0.000, 0.009) | 0.078 | 0.110 | 0.038 (-0.001, 0.007) | 0.191 | 0.022 | 0.044 (-0.001, 0.008) | 0.144 | 0.114 | 0.032 (-0.002, 0.007) | 0.269 |

| | SePP (mg/L) adjusted for 25(OH)D | | | SePP (mg/L) adjusted for age, BMI, smoking and 25(OH)D | | | SePP (mg/L) adjusted for PTH | | | SePP (mg/L) adjusted for age, BMI, smoking and PTH | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* |
| **BMD** | | | | | | | | | | | | |
| ***At study entry*** | | | | | | | | | | | | |
| **Lumbar spine BMD** | **0.009** | **0.080 (3.955, 32.605)** | **0.012** | **0.147** | **0.087 (6.420, 33.191)** | **0.004** | **0.007** | **0.082 (4.229, 33.046)** | **0.011** | **0.143** | **0.086 (6.280, 33.231)** | **0.004** |
| **Hip BMD** | **0.029** | **0.112 (10.099, 31.726)** | **<0.001** | **0.326** | **0.112 (11.880, 29.978)** | **<0.001** | **0.033** | **0.103 (8.544, 30.235)** | **<0001** | **0.332** | **0.103 (10.273, 28.378)** | **<0.001** |
| ***6 years follow-up*** | | | | | | | | | | | | |
| **Lumbar spine BMD** | 0.005 | 0.065 (-3.671, 33.143) | 0.116 | 0.151 | 0.070 (-1.120, 33.013) | 0.067 | 0.004 | 0.064 (-4.134, 33.010) | 0.127 | 0.148 | 0.064 (-2.625, 31.840) | 0.096 |
| **Hip BMD** | **0.023** | **0.104 (5.361, 30.354)** | **0.005** | **0.328** | **0.105 (7.559, 28.354)** | **0.001** | **0.021** | **0.099 (4.357, 29.588)** | **0.008** | **0.328** | **0.099 (6.447, 27.418)** | **0.002** |
| **Change in lumbar spine BMD** | **0.022** | **-0.125 (-18.661, -4.073)** | **0.002** | **0.129** | **-0.116 (-17.416, -3.608)** | **0.003** | **0.015** | **-0.124 (-18.651, -3.895)** | **0.003** | **0.135** | **-0.120 (-17.848, -3972)** | **0.002** |
| **Change in hip BMD** | 0.003 | -0.051 (-7.989, 1.489) | 0.179 | 0.019 | -0.054 (-8.210, 1.220) | 0.146 | 0.003 | -0.051 (-8.049, 1.508) | 0.179 | 0.019 | 0.054 (-8.223, 1.285) | 0.152 |
| **Bone turnover** | | | | | | | | | | | | |
| **Osteocalcin** | **0.008** | **-0.075 (-1.851, -0.224)** | **0.012** | **0.040** | **-0.076 (-1.867, -0.262)** | **0.009** | 0.111 | -0.051 (-1.490, 0.057) | 0.069 | 0.152 | -0.053 (-1.491, 0.024) | 0.058 |
| **P1NP** | 0.005 | -0.043 (-2.682, 0.408) | 0.149 | 0.022 | -0.045 (-2.712, 0.359) | 0.133 | 0.028 | -0.032 (-2.385, 0.685) | 0.278 | 0.051 | -0.032 (-2.374, 0.667) | 0.271 |
| **sβCTX** | **0.005** | **-0.073 (-0.044, -0.005)** | **0.014** | **0.026** | **-0.075 (-0.044, -0.005)** | **0.012** | 0.081 | -0.053 (-0.036, 0.001) | 0.068 | 0.103 | -0.054 (-0.037, 0.001) | 0.057 |
| **uNTXCr** | **0.013** | **-0.111 (-6.962, -2.112)** | **<0.001** | **0.029** | **-0.110 (-6.919, -2.096)** | **<0.001** | **0.034** | **-0.101 (-6.526, -1.706)** | **0.001** | **0.051** | **-0.100 (-6.470, -1.682)** | **0.001** |
| **Extraskeletal parameters** | | | | | | | | | | | | |
| ***At study entry*** | | | | | | | | | | | | |
| **Pulse rate** | **0.007** | **0.084 (0.328, 1.850)** | **0.005** | **0.028** | **0.089 (0.389, 1.899)** | **0.003** | **0.007** | **0.084 (0.318, 1.849)** | **0.006** | **0.029** | **0.087 (0.359, 1.877)** | **0.004** |
| **Grip strength** | **0.014** | **-0.076 (-0.963, -0.086)** | **0.019** | **0.109** | **-0.079 (-0.963, -0.127)** | **0.011** | **0.029** | **-0.085 (-1.030, -0.154)** | **0.008** | **0.118** | **-0.086 (-1.013, -0.176)** | **0.005** |
| **Balance** | 0.007 | -0.022 (-0.214, 0.098) | 0.464 | 0.110 | -0.029 (-0.224, 0.072) | 0.314 | 0.021 | -0.031 (-0.237, 0.074) | 0.301 | 0.115 | -0.034 (-0.238, 0.059) | 0.236 |

Statistically significant results are shown in bold. CI, Confidence inetrval

**SUPPLEMENTAL TABLE 6. Relationship between thyroid function tests, BMD, bone turnover and extraskeletal parameters**

| | fT4 (pmol/liter) | | | fT3 (pmol/liter) | | | TSH (mU/liter) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Adjusted for age, BMI and smoking | | | Adjusted for age, BMI and smoking | | | Adjusted for age, BMI and smoking | | |
| | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* |
| **BMD:** | | | | | | | | | |
| ***At study entry:*** | | | | | | | | | |
| **Lumbar spine BMD** | 0.136 | -0.036 (-8.742, 2.140) | 0.234 | 0.136 | -0.030 (-18.764, 6.148) | 0.321 | 0.137 | -0.049 (-15.242, 1.295) | 0.098 |
| **Hip BMD** | **0.301** | **-0.050 (-7.483, -0.030)** | **0.048** | 0.301 | -0.040 (-15.758, 1.656) | 0.112 | 0.299 | -0.015 (-7.703, 4.077) | 0.546 |
| ***6 years follow-up:*** | | | | | | | | | |
| **Lumbar spine BMD** | 0.142 | -0.044 (-11.175, 3.002) | 0.258 | 0.143 | 0.051 (-5.232, 26.977) | 0.185 | 0.142 | -0.042 (-24.562, 6.886) | 0.270 |
| **Hip BMD** | **0.312** | **-0.083 (-9.914, -1.382)** | **0.010** | **0.312** | **-0.076 (-22.270, -2.334)** | **0.016** | 0.307 | 0.030 (-3.458, 10.062) | 0.338 |
| **Change in lumbar spine BMD** | 0.115 | 0.001 (-2.852, 2.901) | 0.987 | **0.129** | **0.118 (3.586, 16.557)** | **0.002** | 0.115 | -0.002 (-6.516, 6.244) | 0.967 |
| **Change in hip BMD** | 0.021 | -0.068 (-3.645, 0.176) | 0.075 | 0.017 | -0.029 (-6.219, 2.721) | 0.443 | 0.020 | 0.059 (-0.574, 5.459) | 0.112 |
| **Bone turnover** | | | | | | | | | |
| **Osteocalcin** | 0.032 | -0.011 (-0.389, 0.264) | 0.707 | 0.032 | 0.005 (-0.701, 0.824) | 0.874 | **0.036** | **-0.063 (-1.081, -0.052)** | **0.031** |
| **P1NP** | 0.016 | 0.007 (-0.552, 0.697) | 0.820 | 0.016 | -0.005 (-1.584, 1.334) | 0.866 | 0.017 | -0.040 (-1.667, 0.303) | 0.175 |
| **sβCTX** | 0.021 | 0.033 (-0.004, 0.012) | 0.280 | 0.023 | -0.057 (-0.036, 0.000) | 0.053 | 0.021 | -0.039 (-0.021, 0.004) | 0.191 |
| **uNTXCr** | 0.017 | 0.026 (-0.553, 1.415) | 0.390 | 0.018 | 0.043 (-0.627, 3.965) | 0.154 | 0.016 | -0.011 (-1.833, 1.273) | 0.723 |
| **Extra skeletal parameters:** | | | | | | | | | |
| ***At study entry:*** | | | | | | | | | |
| **Pulse rate** | 0.020 | 0.012 (-0.244, 0.370) | 0.687 | **0.024** | **0.062 (0.042, 1.474)** | **0.038** | 0.020 | -0.017 (-0.625, 0.345) | 0.571 |
| **Grip strength** | **0.105** | **0.068 (0.018, 0.358)** | **0.030** | **0.126** | **0.161 (0.663, 1.446)** | **<0.0001** | 0.102 | -0.039 (-0.443, 0.094) | 0.202 |
| **Balance** | 0.108 | 0.025 (-0.033, 0.087) | 0.382 | **0.114** | **0.078 (0.056, 0.335)** | **0.006** | 0.107 | 0.004 (-0.089, 0.101) | 0.901 |

| | fT4 (pmol/liter) | | | fT3 (pmol/liter) | | | TSH (mU/liter) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Adjusted for age, BMI, smoking, Se and SePP | | | Adjusted for age, BMI, smoking, Se and SePP | | | Adjusted for age, BMI, smoking, Se and SePP | | |
| | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* |
| **BMD:** | | | | | | | | | |
| ***At study entry:*** | | | | | | | | | |
| **Lumbar spine BMD** | 0.144 | -0.025 (-7.798, 3.171) | 0.408 | 0.143 | -0.018 (-16.359, 8.759) | 0.553 | 0.145 | -0.049 (-15.145, 1.339) | 0.101 |
| **Hip BMD** | 0.315 | -0.033 (-6.213, 1.254) | 0.193 | 0.314 | -0.023 (-12.779, 4.670) | 0.362 | 0.314 | -0.019 (-8.110, 3.568) | 0.446 |
| ***6 years follow-up:*** | | | | | | | | | |
| **Lumbar spine BMD** | 0.147 | -0.034 (-10.316, 4.056) | 0.393 | 0.149 | 0.064 (-2.668, 29.916) | 0.101 | 0.147 | -0.044 (-24.936, 6.524) | 0.251 |
| **Hip BMD** | **0.322** | **-0.069 (-9.009, -0.432)** | **0.031** | 0.321 | -0.062 (-20.014, 0.031) | 0.051 | 0.318 | 0.028 (-3.660, 9.782) | 0.372 |
| **Change in lumbar spine BMD** | 0.129 | -0.020 (-30628, 2.173) | 0.622 | **0.139** | **0.102 (2.141, 15.242)** | **0.009** | 0.128 | 0.003 (-6.086, 6.622) | 0.934 |
| **Change in hip BMD** | 0.026 | -0.075 (-3.855, 0.002) | 0.050 | 0.022 | -0.037 (-6.749, 2.280) | 0.332 | 0.024 | 0.059 (-0.580, 5.455) | 0.113 |
| **Bone turnover** | | | | | | | | | |
| **Osteocalcin** | 0.045 | -0.027 (-0.476, 0.180) | 0.376 | 0.044 | -0.009 (-0.880, 0.654) | 0.773 | **0.048** | **-0.059 (-1.037, -0.013)** | **0.045** |
| **P1NP** | 0.022 | -0.003 (-0.658, 0.601) | 0.929 | 0.022 | -0.013 (-1.804, 1.138) | 0.657 | 0.023 | -0.037 (-1.610, 0.358) | 0.212 |
| **sβCTX** | 0.027 | 0.021 (-0.005, 0.011) | 0.494 | **0.032** | **-0.070 (-0.040, -0.004)** | **0.018** | 0.028 | -0.036 (-0.020, 0.005) | 0.225 |
| **uNTXCr** | 0.033 | 0.008 (-0.858, 1.117) | 0.797 | 0.034 | 0.026 (-1.293, 3.316) | 0.389 | 0.033 | -0.006 (-1.699, 1.386) | 0.842 |
| **Extra skeletal parameters:** | | | | | | | | | |
| ***At study entry:*** | | | | | | | | | |
| **Pulse rate** | 0.031 | 0.028 (-0.166, 0.452) | 0.363 | **0.036** | **0.078 (0.231, 1.671)** | **0.010** | 0.031 | -0.021 (-0.655, 0.311) | 0.485 |
| **Grip strength** | 0.110 | 0.059 (-0.008, 0.335) | 0.061 | **0.129** | **0.153 (0.609, 1.400)** | **<0.0001** | 0.108 | -0.038 (-0.439, 0.097) | 0.212 |
| **Balance** | 0.111 | 0.025 (-0.035, 0.086) | 0.402 | **0.117** | **0.077 (0.051, 0.333)** | **0.008** | 0.111 | 0.002 (-0.091, 0.098) | 0.943 |

| | fT4 (pmol/liter) | | | fT3 (pmol/liter) | | | TSH (mU/liter) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Adjusted for Se and SePP | | | Adjusted for Se and SePP | | | Adjusted for Se and SePP | | |
| | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* | Model $R^2$ | β coefficient (95% CI) (lower, upper, per SD change) | *P* |
| **BMD:** | | | | | | | | | |
| ***At study entry:*** | | | | | | | | | |
| **Lumbar spine BMD** | 0.010 | -0.056 (-10.865, 0.630) | 0.081 | 0.008 | -0.025 (-18.755, 8.047) | 0.433 | 0.008 | -0.035 (-13.720, 3.910) | 0.275 |
| **Hip BMD** | **0.028** | **-0.105 (-12.241, -3.547)** | **<0.0001** | 0.020 | -0.051 (-19.450, 1.245) | 0.085 | 0.017 | -0.002 (-7.155, 6.727) | 0.952 |
| ***6 years follow-up:*** | | | | | | | | | |
| **Lumbar spine BMD** | 0.007 | -0.047 (-11.891, 3.258) | 0.263 | 0.010 | 0.067 (-3.041, 31.688) | 0.106 | 0.005 | -0.012 (-19.242, 14.350) | 0.775 |
| **Hip BMD** | **0.030** | **-0.136 (-14.342, -4.338)** | **<0.0001** | **0.020** | **-0.088 (-26.243, -2.398)** | **0.019** | 0.014 | 0.047 (-2.889, 13.129) | 0.210 |
| **Change in lumbar spine BMD** | 0.016 | 0.032 (-1.814, 4.210) | 0.435 | **0.031** | **0.126 (3.856, 17.581)** | **0.002** | 0.016 | 0.007 (-6.064, 7.288) | 0.857 |
| **Change in hip BMD** | 0.008 | -0.065 (-3.569, 0.229) | 0.085 | 0.005 | -0.032 (-6.455, 2.561) | 0.397 | 0.006 | 0.051 (-0.934, 5.102) | 0.176 |
| **Bone turnover** | | | | | | | | | |
| **Osteocalcin** | 0.013 | -0.007 (-0.365, 0.287) | 0.815 | 0.013 | 0.000 (-0.777, 0.768) | 0.991 | **0.017** | **-0.067 (-1.115, -0.082)** | **0.023** |
| **P1NP** | 0.006 | -0.002 (-0.639, 0.602) | 0.954 | 0.006 | -0.013 (-1.792, 1.149) | 0.668 | 0.008 | -0.044 (-1.736, 0.232) | 0.134 |
| **sβCTX** | 0.009 | 0.041 (-0.002, 0.013) | 0.172 | **0.011** | **-0.031 (-0.037, -0.001)** | **0.043** | 0.009 | -0.041 (-0.021, 0.004) | 0.169 |
| **uNTXCr** | 0.018 | 0.022 (-0.609, 1.336) | 0.463 | 0.019 | 0.031 (-1.096, 3.512) | 0.304 | 0.018 | -0.010 (-1.802, 1.286) | 0.743 |
| **Extra skeletal parameters:** | | | | | | | | | |
| ***At study entry:*** | | | | | | | | | |
| **Pulse rate** | 0.010 | 0.036 (-0.119, 0.492) | 0.230 | **0.015** | **0.080 (0.251, 1.694)** | **0.008** | 0.009 | -0.011 (-0.573, 0.397) | 0.722 |
| **Grip strength** | 0.007 | -0.003 (-0.185, 0.169) | 0.931 | **0.023** | **0.128 (0.425, 1.258)** | **<0.0001** | 0.008 | -0.043 (-0.470, 0.093) | 0.188 |
| **Balance** | 0.006 | -0.023 (-0.087, 0.038) | 0.445 | 0.009 | 0.059 (-0.001, 0.295) | 0.052 | 0.006 | -0.015 (-0.124, 0.075) | 0.624 |

**SUPPLEMENTAL TABLE 7.** Relationship between thyroid function tests and fracture

| | Logistic regression model | | | Cox Proportional hazards model | | | | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | | | HR (95% CI) | | | | |
| | **Per unit change** | **Per SD change** | ***P*** | **Per unit change** | **Per SD change** | ***P*** | | |
| **Prevalent vertebral fracture** | 1.06 (0.97-1.16) | 1.12 (0.94-1.33) | 0.208 | - | - | - | | |
| **Incident vertebral fracture** | 0.92 (0.76-1.11) | 0.85 (0.59-1.22) | 0.378 | - | - | - | **fT4** | Unadjusted |
| **Incident nonvertebral fracture** | - | - | - | **0.86 (0.76-0.99)** | **0.75 (0.59-0.98)** | **0.029** | | |
| **Prevalent vertebral fracture** | 0.89 (0.73-1.10) | 0.91 (0.78-1.08) | 0.288 | - | - | - | | |
| **Incident vertebral fracture** | 1.04 (0.67-1.63) | 1.03 (0.73-1.48) | 0.850 | - | - | - | **fT3** | Unadjusted |
| **Incident nonvertebral fracture** | - | - | - | **0.72 (0.55-0.96)** | **0.77 (0.62-0.97)** | **0.024** | | |
| **Prevalent vertebral fracture** | 1.04 (0.93-1.17) | 1.05 (0.92-1.21) | 0.496 | - | - | - | | |
| **Incident vertebral fracture** | 1.19 (0.84-1.67) | 1.23 (0.81-0.85) | 0.333 | - | - | - | **TSH** | Unadjusted |
| **Incident nonvertebral fracture** | - | - | - | 1.16 (0.91-1.47) | 1.19 (0.89-1.59) | 0.240 | | |
| **Prevalent vertebral fracture** | 1.02 (0.95-1.12) | 1.04 (0.91-1.24) | 0.747 | - | - | - | | |
| **Incident vertebral fracture** | 0.92 (0.75-1.12) | 0.85 (0.58-1.24) | 0.392 | - | - | - | **fT4** | Adjusted for age, BMI and lumbar spine BMD |
| **Incident nonvertebral fracture** | - | - | - | **0.86 (0.75-0.99)** | **0.75 (0.58-0.98)** | **0.040** | | |
| **Prevalent vertebral fracture** | 0.83 (0.66-1.04) | 0.86 (0.72-1.03) | 0.100 | - | - | - | | |
| **Incident vertebral fracture** | 1.09 (0.68-1.72) | 1.07 (0.73-1.54) | 0.727 | - | - | - | **fT3** | Adjusted for age, BMI and lumbar spine BMD |
| **Incident nonvertebral fracture** | - | - | - | **0.73 (0.54-0.98)** | **0.78 (0.61-0.98)** | **0.034** | | |
| **Prevalent vertebral fracture** | 1.02 (0.91-1.15) | 1.02 (0.89-1.18) | 0.705 | - | - | - | | |
| **Incident vertebral fracture** | 1.25 (0.88-1.76) | 1.31 (0.86-1.97) | 0.210 | - | - | - | **TSH** | Adjusted for age, BMI and lumbar spine BMD |
| **Incident nonvertebral fracture** | - | - | - | **1.35 (1.03-1.77)** | **1.43 (1.04-1.98)** | **0.032** | | |
| **Prevalent vertebral fracture** | 1.02 (0.93-1.12) | 1.04 (0.87-1.24) | 0.719 | - | - | - | | Adjusted for age, BMI, |
| **Incident vertebral fracture** | 0.90 (0.74-1.11) | 0.82 (0.56-1.22) | 0.327 | - | - | - | **fT4** | lumbar spine BMD, |
| **Incident nonvertebral fracture** | - | - | - | **0.87 (0.75-0.99)** | **0.77 (0.58-0.98)** | **0.048** | | Se and SePP |
| **Prevalent vertebral fracture** | 0.83 (0.67-1.04) | 0.86 (0.73-1.03) | 0.109 | - | - | - | | Adjusted for age, BMI, |
| **Incident vertebral fracture** | 1.06 (0.67-1.70) | 1.05 (0.73-1.53) | 0.797 | - | - | - | **fT3** | lumbar spine BMD, |
| **Incident nonvertebral fracture** | - | - | - | **0.71 (0.83-0.95)** | **0.76 (0.86-0.96)** | **0.023** | | Se and SePP |
| **Prevalent vertebral fracture** | 1.02 (0.91-1.15) | 1.02 (0.89-1.18) | 0.690 | - | - | - | | Adjusted for age, BMI, |
| **Incident vertebral fracture** | 1.27 (0.90-1.81) | 1.33 (0.88-2.04) | 0.173 | - | - | - | **TSH** | lumbar spine BMD, |
| **Incident nonvertebral fracture** | - | - | - | **1.35 (1.02-1.77)** | **1.43 (1.02-1.98)** | **0.034** | | Se and SePP |