The Influence of Serum Uric Acid on Bone Mineral Density, Hip Geometry, and Fracture Risk: The Rotterdam Study

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Context: The role of uric acid (UA) in skeletal metabolism remains to be unraveled.

Objective: We prospectively investigated the association between UA, bone mineral density at the femoral neck (FN-BMD), hip bone geometry parameters, and incident fracture risk and examined whether the associations were modified by age and vitamin C intake.

Participants and Setting: Data of 5074 participants of The Rotterdam Study, a prospective population-based cohort.

Exposure: Serum UA was assessed at baseline.

Main Outcomes and Measures: FN-BMD was measured at baseline, and at second, third, and fourth visits of the Rotterdam Study. Hip bone geometry parameters were measured at baseline and at the second and third visits.

Results: Serum UA levels (per SD increase) were positively associated with FN-BMD ($\beta = 0.007$ g/cm^2; 95% confidence interval [CI] = 0.002–0.01), thicker cortices ($\beta = 0.002$ cm; 95% CI = 0.0003–0.002), lower bone width ($\beta = -0.013$ cm; 95% CI = −0.23 to −0.003), and lower cortical buckling ratio ($\beta = -0.19$; 95% CI = −0.33 to −0.06). The effects of UA on FN-BMD and cortical buckling ratio tended to become stronger over time. Hazard ratios and 95% CIs per SD increase of baseline UA levels for the development of any type of incident fractures, nonvertebral fractures, and osteoporotic fractures were 0.932 (0.86–0.995), 0.924 (0.856–0.998), and 0.905 (0.849–0.982), respectively. These associations were more prominent in older individuals (age, >65 y) and in participants with high intakes of vitamin C (> median).

Conclusions: Higher levels of serum UA are associated with higher BMD (at the expense of thicker cortices and narrower bone diameters) and may be a protective factor in bone metabolism. However, interactions with age and vitamin C may be present. **(*J Clin Endocrinol Metab* 101: 1113–1122, 2016)**

Uric acid (UA) is the final breakdown product of purine metabolism, and therefore it has been traditionally viewed as a metabolic by-product, which in excess may cause gouty arthritis and renal stones (1). Furthermore, UA is recently regarded as a risk factor for cardiovascular diseases (2). However, UA accounts for approximately

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; FN, femoral neck; HBGP, hip bone geometry parameter; HR, hazard ratio; UA, uric acid.

half of the antioxidant properties of human plasma (3). Higher serum levels of UA may play physiologically beneficial roles because of their antioxidant properties and free radical scavenging capacity (4) and have been correlated with the slow progression of Parkinson's disease, Huntington's disease, and mild cognitive impairment (5, 6).

The effect of UA in skeletal metabolism remains to be unraveled. Experimental and clinical studies have shown that oxidative stress or low circulating levels of antioxidants have detrimental effect on bone metabolism (7). On the other hand, UA levels have been associated with metabolic syndrome (8), diabetes (9), and obesity (10), conditions that have been shown to exert both beneficial and detrimental influences on bone outcomes (11). Recent literature suggests that UA may actually be beneficial for bone metabolism. In a cross-sectional cohort of 1705 older men, Nabipour et al (12) showed that higher serum UA levels were associated with higher bone mineral density (BMD) and lower prevalence of vertebral and nonvertebral fractures. Also, two recent studies showed that UA is a protective factor against incident osteoporotic and nonvertebral fractures in cohorts consisting of men only (13, 14). However, evidence remains unclear on whether this relationship is also present in women and how UA relates longitudinally with BMD and incident fractures.

In the present study, we investigated the association between UA, BMD at the femoral neck (FN-BMD), hip bone geometry parameters (HBGPs), and incident fracture risk in both men and women using a longitudinal design. Because UA increases with advancing age (15) and vitamin C intake increases UA excretion, and therefore lowers the plasma levels of UA (8, 15), we evaluated whether these associations were modified by age and vitamin C intake.

Subjects and Methods

The Rotterdam Study is a population-based cohort study, including 7983 participants age 55 years and older living in Ommoord, a district of Rotterdam. The rationale and design of the Rotterdam Study is described elsewhere (16). The Rotterdam Study started in the early 1990s, and periodical examinations were performed every 3 to 5 years. In addition, participants were continuously followed for vital status and medical outcome, obtaining information regularly from the municipal health authorities in the Rotterdam area. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, and written informed consent was obtained from all participants.

Measurements

Uric acid

Values of serum UA were obtained from baseline (1990–1992) nonfasting blood samples that were centrifuged for 10 minutes at 3000 rotations per minute. Subsequently, the serum was stored at −20°C for 1 week, until UA activity was determined with a Kone Diagnostica reagent kit and a Kone autoanalyzer. To check the calibration, three control samples were included for every 10 samples. If the average values of the control samples of each run (100 samples) were not within 2.5% of the true value, the run was repeated. Day-by-day variation had to be within 5% (17).

Skeletal assessments

FN-BMD (g/cm^2) at baseline (1990–1992) and at the second (1993–1995) and third visits (1997–1999) was measured by dual-energy x-ray absorptiometry (DXA) using a Lunar DPX-L densitometer (Lunar Radiation Corp) (18) and analyzed with DPX-IQ version 4.7d software, whereas at the fourth visit (2002–2004), FN-BMD was measured by using a GE Lunar Prodigy bone densitometer (General Electric). Hip structural analysis (19) was used to measure HBGP from the DXA scans of the femur narrow neck region in the three visits of the Rotterdam Study as described previously (20). All events, including incident fractures and death, were reported by general practitioners in the research area (covering 80% of the cohort) by means of a computerized system. Research physicians regularly followed participant information in the general practitioners' records outside the research area and made an independent review and encoding of all reported events. Subsequently, a medical expert reviewed all coded events for the final classification using the guidelines for International Classification of Diseases (ICD)-10. Additional information on hip fractures was gathered through the Dutch National Hospital Registration System. An osteoporosis expert reviewed all coded events for final classification. Subjects were followed from their baseline visit until January 1, 2007, or until a first fracture or death occurred.

Assessment of covariates

See Appendix 1 in the Supplemental Data.

Population for analysis

Serum UA and FN-BMD

Of 5150 individuals with available information on serum UA, 1077 participants were excluded because FN-BMD was not measured at baseline (1990–1993), leaving 4073 participants for the cross-sectional analysis on serum UA and FN-BMD. Among them, 781 participants did not have any follow-up measurement and were therefore excluded from the longitudinal analysis, leaving 3292 participants for inclusion (Supplemental Figure 1).

Serum UA and hip bone geometry

There were 1828 participants who did not have measures of HBGP at baseline. Hence, 3322 participants were included in the cross-sectional analysis on serum UA and hip bone geometry. Among them, 604 participants did not have HBGP measured at both the second and third visits, therefore leaving 2718 participants for the longitudinal analysis (Supplemental Figure 1).

Serum UA and fracture risk

Data on fracture follow-up were not available for 76 participants. Therefore, 5074 men and women were enrolled in the final analysis and were observed for occurrence of incident

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fractures comprising a follow-up of 10.9 years (Supplemental Figure 1).

Statistical analysis

Intraclass correlation coefficient was used to assess the within-subject correlations of the repeated measures of FN-BMD and HBGP in the same individual. To examine the cross-sectional association between serum UA (per SD increase) and FN-BMD and HBGP, linear regression models were fitted in generalized estimated equations. We used exchangeable correlation structure to adjust for the within-subject correlations due to the repeated measurements of FN-BMD and HBGP in the same individual (see Table 2). Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated from the Cox proportional hazard regression models to test the association of UA (per SD or per quintile) with risk of fracture. Associations were first examined in our base model (model 1), which included age, gender, height, weight, and estimated glomerular filtration rate (eGFR). The multivariable model adjustment (model 2) included the factors from the base adjustment model plus smoking status, Dutch Health Diet Index, physical activity, prevalent diabetes mellitus, prevalent cardiovascular disease, history of hip or knee surgery, diuretic drug use, hormone replacement therapy, corticosteroid drug use, drugs for other musculoskeletal diseases, thyroid therapy, anti-gout drug use, serum phosphate, serum total calcium, and energy-adjusted dietary intake of vitamin C. Models for FN-BMD and HBGP were additionally adjusted for the type of DXA scans. To examine the longitudinal effect of UA on FN-BMD and HBGP, the cross-product (interaction) between UA and a time variable t (t = 1, 4, and 8 for HBGP analysis; and 1, 4, 8, and 13 for FN-BMD analysis) was tested in the multivariable model, and the estimates and 95% CI values were reported. We tested for possible nonlinear effects by adding a quadratic term of serum UA in the multivariable model. To test for effect modification, product terms of serum UA with gender, age, body mass index (BMI), or dietary intake of vitamin C were added as independent variables to the multivariable models. Analysis stratified by gender, age (≤65 or 65+ y), or by median BMI and vitamin C intake was performed in case of significant effect modification. Because FN-BMD was not cross-calibrated between the first three measures and the fourth, we repeated all analyses excluding the fourth measure. Furthermore, diabetes mellitus has been shown to affect UA levels; therefore, a sensitivity analysis was performed excluding subjects with type 2 diabetes mellitus. Also, we measured serum UA levels after 8 years in a subgroup of study participants and observed high correlations with baseline UA measure (partial Pearson correlation = 0.70; intraclass correlation = 0.82), supporting internal consistency and validity. To adjust for potential bias associated with missing data, we used a multiple imputation procedure (n = 5 imputations). Rubin's method was used for the pooled regression coefficients (β) and 95% CIs. A P value $< .05$ was considered as statistically significant, but to account for multiple testing, we adjusted the P value from .05 to .005 by applying the Bonferroni correction for the number of outcomes studied (n = 10). All

Table 1. Baseline Characteristics of Subjects in Each of the Three Study Populations

	Fracture	FN-BMD	Hip Geometry
n	5074	4073	3322
Serum UA, μmol/L	324.0 ± 82.3	321.0 ± 78.9	319.5 ± 77.5
Age, y	70.3 ± 9.1	68.6 ± 7.8	68.2 ± 7.7
Women, %	61.5	59.7	59.3
Height, cm	166.1 ± 9.2	166.7 ± 9.1	167.0 ± 9.1
Weight, kg	72.7 ± 11.9	73.3 ± 11.6	73.4 ± 11.4
BMI, kg/m^2	26.3 ± 3.8	26.4 ± 3.7	26.3 ± 3.1
Smoking status, %			
Current	22.9	24.6	24.7
Never or former	77.1	75.4	75.4
Physical activity, min/wk	2543 ± 1176	2550 ± 1180	2623 ± 1164
Dutch Healthy Diet Index	48.0 ± 10.1	47.9 ± 10.1	47.9 ± 10.1
Vitamin C intake, mg/d	112 ± 53.5	119 ± 52.1	116 ± 50.1
Serum calcium, mmol/L	2.4 ± 0.2	2.4 ± 0.2	2.4 ± 0.2
Serum phosphorous, mmol/L	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
Glomerular filtration rate, mL/min/1.73 m^2	76.9 ± 17.4	77.9 ± 16.7	77.8 ± 16.2
Diabetes mellitus, %	11.1	10.2	10.2
Cardiovascular disease, %	32.7	29.1	27.9
Hip and knee operations, %	9.7	9.1	8.9
Diuretic use, %	10.3	14.4	13.1
Hormone replacement therapy, %	1.3	1.4	1.4
Corticosteroids, %	2.0	2.0	1.9
Thyroid drug use, %	2.4	2.1	1.9
Anti-gout preparation, %	0.6	0.6	0.6
Other drugs for disorders of the musculoskeletal system, %	0.2	0.2	0.2
All fractures, %	25.6	25.5	25.5
Vertebral fractures, %	5.0	5.6	5.5
Nonvertebral fractures, %	22.8	22.3	22.3
Osteoporotic fractures, %	23.4	23.1	22.8
Hip fractures, %	6.9	6.2	5.9

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analyses were done using SPSS statistical software, version 20.0 (SPSS Inc).

Results

Table 1 shows the selected characteristics of study participants according to the outcome of interest. There was no significant difference between study groups with regard to serum UA levels or fracture incidence. Table 2 shows the FN-BMD and HBGP characteristic and the within-subject correlations between measures. A within-subject correlation coefficient of 0.91 was observed between the first and second measurements of FN-BMD and of 0.87 between the first and third measurements of FN-BMD. Anthropometric, lifestyle, and other characteristics of the excluded participants did not differ substantially from the participants included in the study (data not shown).

Association with FN-BMD and hip bone geometry

After adjustment for potential confounders, in the cross-sectional analysis, serum UA levels were associated with higher FN-BMD (per SD increase, $\beta = 0.007$; $P = .0001$). Also, serum UA levels were associated with thicker cortices (per SD increase, $\beta = 0.002$; $P = .014$), lower bone width (per SD increase, $\beta = -0.013$; $P = .008$), and lower cortical buckling ratio (per SD increase, $\beta = -0.192$; $P = .005$) (Table 3). The longitudinal analysis revealed that the effect of serum UA levels on FN-BMD (per SD increase in UA, there was an annual increase of 0.0003 [95% CI = 0.000–0.001]; $P = .03$, in FN-BMD) and cortical buckling ratio (there was an annual decrease of 0.05 [95% CI = −0.05 to −0.002]; $P = .048$; on cortical buckling ratio per SD increase in serum UA levels) tended to become stronger over time (Table 3), whereas no change on the effect of UA on cortical thickness and bone width over time was observed (*P*-interaction UA with the time variable > 0.05; data not shown). No association was observed between serum UA and section modulus with serum UA levels in both cross-sectional and longitudinal analysis (Table 3). No significant quadratic term was detected for any of the associations ($P > .05$) (data not shown).

Effect modification by gender, age, BMI, and dietary intake of vitamin C

No effect modification by sex, age, or dietary intake of vitamin C was found for the association between serum UA and FN-BMD (*P*-interaction > 0.05) (Table 3). Among HBGPs, effect modification by sex was found only for the associations between serum UA and bone width (*P*-interaction = 0.013) and section modulus (*P*-interaction = 0.008). After stratification by sex, an inverse association was found between serum UA and bone width in women (per SD increase, $\beta = -0.024$; $P < .001$), whereas

Table 2. BMD at FN and Hip Bone Geometry Characteristics and the Within-Subject Correlations Between Follow-Up Measurement Visits

		r		
	Mean ± SD	**2nd Visit or Round**	**3rd Visit or Round**	**4th Visit**
FN-BMD, g/cm^2				
1st visit (n = 4073)	0.86 ± 0.14	0.0.95	0.94	0.92
2nd visit (n = 2916)	0.86 ± 0.14		0.95	0.93
3rd visit (n = 2052)	0.86 ± 0.15			
4th visit (n = 1664)	0.85 ± 0.14			
Cortical thickness, cm				
1st visit (n = 3322)	0.13 ± 0.03	0.84	0.77	
2nd visit (n = 2387)	0.14 ± 0.03		0.74	
3rd visit (n = 1827)	0.14 ± 0.04			
Bone width, cm				
1st visit (n = 3322)	3.19 ± 0.32	0.84	0.83	
2nd visit (n = 2387)	3.09 ± 0.36		0.84	
3rd visit (n = 1827)	3.11 ± 0.38			
Section modulus, cm^3				
1st visit (n = 3322)	1.12 ± 0.34	0.92	0.89	
2nd visit (n = 2387)	1.16 ± 0.36		0.87	
3rd visit (n = 1827)	1.15 ± 0.39			
Cortical buckling ratio				
1st visit (n = 3322)	13.95 ± 3.50	0.77	0.72	
2nd visit (n = 2387)	12.84 ± 4.22		0.77	
3rd visit (n = 1827)	13.33 ± 4.64			

Abbreviation: *r*, interclass correlation coefficient.

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Table 3. Association of Serum UA (μmol/L) With FN-BMD

	Continuous	*P* Value
FN-BMD, g/cm^{2a}		
Model 1	0.007 (0.002 to 0.011)	.002
Model 2	0.007 (0.004 to 0.013)	.001
Cortical thickness, cm		
Model 1	0.001 (0.0003 to 0.002)	.016
Model 2	0.002 (0.0003 to 0.002)	.014
Bone width, cm		
Model 1	−0.014 (−0.024 to −0.005)	.003
Model 2	−0.013 (−0.023 to −0.003)	.008
Section modulus, cm^3		
Model 1	0.002 (−0.007 to 0.012)	.63
Model 2	0.004 (−0.006 to 0.013)	.48
Cortical buckling ratio[b]		
Model 1	−0.184 (−0.313; −0.055)	.005
Model 2	−0.192 (−0.327; −0.058)	.005

Data are expressed as β (95% CI). Model 1: age, gender, height, weight, eGFR, time when the measurements were performed. Model 2: model 1 plus smoking status, Dutch Healthy Diet Index, physical activity, prevalent diabetes mellitus, prevalent cardiovascular disease, history of hip or knee surgery, diuretic drug use, hormone replacement therapy, corticosteroid drug use, thyroid therapy, anti-gout drugs, serum phosphate, serum total calcium, and dietary intake of vitamin C.

FN-BMD, *P*-interactions: with gender, $P = .11$; with age, $P = .09$; with vitamin C intake, $P = .96$. Cortical thickness, *P*-interactions: with gender, $P = .87$; with age, $P = .17$; with vitamin C intake, $P = .22$. Bone width, *P*-interactions: with gender, $P = .013$; with age, $P = .84$; with vitamin C intake, $P = .21$. Section modulus, *P*-interactions: with gender, $P = .008$; with age, $P = .21$; with vitamin C intake, $P = .45$. Cortical buckling ratio, *P*-interactions: with gender, $P = .49$; with age, $P = .00023$; with vitamin C intake, $P = .51$.

[a] Inclusion of the interaction between UA and the time variable in the multivariable model revealed that: interaction UA × time variable: $\beta = 0.0003$; 95% CI = 0.000–0.001; $P = .03$.

[b] Inclusion of the interaction between UA and the time variable in the multivariable model revealed that: interaction UA × time variable: $\beta = 0.05$; 95% CI = −0.05 to −0.002; $P = .048$.

no association was found in men ($P = .89$) (Figure 1A). In contrast, no significant associations between serum UA and section modulus were detected in either sex (Figure 1B). Also, a significant interaction term with age was observed for the association between UA and cortical buckling ratio (*P*-interaction < 0.001). After stratification by age, an inverse association was observed between UA and cortical buckling ratio only among subjects > 65 years old (per SD increase, $\beta = -0.23$; $P = .02$) (Figure 1C). No effect modification by age was found for other HBGPs (Table 3). Similarly, no effect modification by dietary intake of vitamin C was observed (Table 3). No effect modification by BMI was found for the association of UA with bone parameters (all *P* values $> .05$).

Fracture free survival analysis

During the follow-up, 1297 subjects developed any type of fracture, 1156 developed nonvertebral fractures, and 254 developed clinical vertebral fractures, whereas 1185 and 348 individuals developed osteoporotic and hip fractures, respectively. After adjustment for potential confounding, the HRs per SD increase of baseline serum UA levels for the development of any type of incident fractures, nonvertebral fractures, and osteoporotic fractures were: 0.925 (95% CI = 0.86–0.995; $P = .035$), 0.924 (95% CI = 0.856–0.998; $P = .045$), and 0.905 (95% CI = 0.838–0.977; $P = .01$), respectively (Table 4). No association was found between serum UA and incident vertebral fractures or incident hip fractures (Table 4). No significant quadratic relationship between serum UA and the risk for any type of fractures or fracture subtypes was found ($P > .05$) (data not shown).

Effect modification by gender or age

No effect modification by sex was observed for serum UA and any fracture outcome. However, effect modification by age was observed for the association between serum UA and any type of fractures (*P*-interaction = 0.01) and vertebral fracture (*P*-interaction = 0.01) (Table 4). After stratification by age, there was an inverse association between serum UA and any fracture risk among subjects $>$ 65 years old (HR = 0.91; 95% CI = 0.84–0.99; $P = .03$), whereas no association was found in participants ≤ 65 years old (HR = 0.96; 95% CI = 0.83–1.11; $P = .61$) (Figure 2A). No association was observed between serum UA and the risk for vertebral fractures in either age group after stratification by age (Figure 2B).

Effect modification by dietary intake of vitamin C

Effect modifications by dietary intake of vitamin C were observed only for the association of serum UA with the risk of any type of fractures (*P*-interaction = 0.01),

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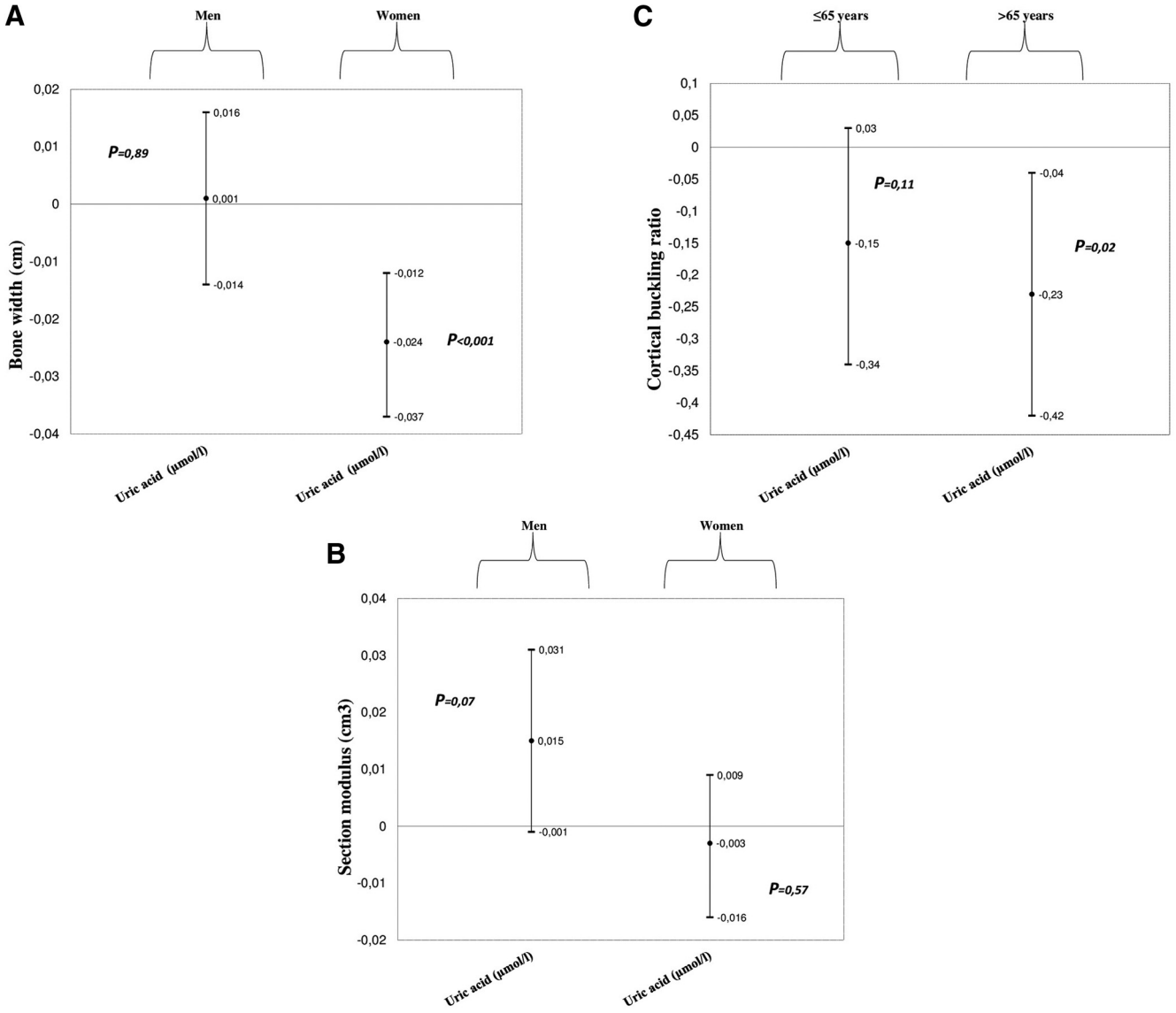

Figure 1. The association between serum UA (µmol/L) and HBGPs by gender and age.

nonvertebral fractures (*P*-interaction = 0.02), or osteoporotic fractures (*P*-interaction = 0.01) (Table 4). After stratification by median vitamin C intake, serum UA was associated with a lower risk of developing any type of fracture (HR = 0.865; 95% CI = 0.778–0.962; *P* = .008), nonvertebral fractures (HR = 0.873; 95% CI = 0.78–0.997; *P* = .018), or osteoporotic fractures (HR = 0.849; 95% CI = 0.761–0.949; *P* = .004) among participants with higher intakes of vitamin C, whereas no associations were observed among subjects with low intake of vitamin C (Figure 2, C–E).

Sensitivity analysis

Exclusion of the fourth measurement of FN-BMD or of the subjects with prevalent diabetes mellitus from our analysis did not affect our results (data not shown). Moreover, after we applied the Bonferroni correction, the association of serum UA with FN-BMD and HBGP remained significant in all study participants as well as the association of serum UA with risk of developing any type of fracture and osteoporotic fractures in participants with higher intakes of vitamin C.

Discussion

In this large prospective study, higher serum UA concentrations were associated with higher BMD at the femoral neck, thicker cortices, and lower bone width and cortical buckling ratio after adjustment for potential confounders. In addition, we noted that high serum UA was associated with a lower risk of incident osteoporotic fracture risk. Also, we showed that age and vitamin C intake differences modify these relationships.

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Table 4. Association of Serum UA (μmol/L) With Fracture Risk*

	RR, 95% CI	*P* Value
All fractures		
No. of events/total participants, n	1297/5074	
Model 1	0.932 (0.870–0.998)	.043
Model 2	0.925 (0.860–0.995)	.035
Nonvertebral fractures		
No. of events/total participants, n	1156/5074	
Model 1	0.933 (0.868–1.003)	.061
Model 2	0.924 (0.856–0.998)	.045
Vertebral fractures		
No. of events/total participants, n	254/5074	
Model 1	0.911 (0.777–1.069)	.26
Model 2	0.932 (0.786–1.105)	.42
Osteoporotic fractures		
No. of events/total participants, n	1185/5074	
Model 1	0.913 (0.849–0.982)	.014
Model 2	0.905 (0.838–0.977)	.010
Hip fractures		
No. of events/total participants, n	348/5074	
Model 1	0.897 (0.797–1.022)	.10
Model 2	0.896 (0.78–1.029)	.12

Model 1: age, gender, height, weight, eGFR, index time. Model 2: model 1 plus smoking status, Dutch Healthy Diet Index, physical activity, prevalent diabetes mellitus, prevalent cardiovascular disease, history of hip or knee surgery, diuretic drug use, hormone replacement therapy, corticosteroid drug use, thyroid therapy, anti-gout drugs, serum phosphate, serum total calcium, and dietary intake of vitamin C.

All fractures, *P*-interactions: with gender, $P = .84$; with age, $P = .01$; with vitamin C intake, $P = .014$, Nonvertebral fractures, *P*-interactions: with gender, $P = .77$; with age, $P = .46$; with vitamin C intake, $P = .024$. Vertebral fractures, *P*-interactions: with gender, $P = .61$; with age, $P = .01$; with vitamin C intake, $P = .23$. Osteoporotic fractures, *P*-interactions: with gender, $P = .77$; with age, $P = .077$; with vitamin C intake, $P = .013$. Hip fractures, *P*-interactions: with gender, $P = .53$; with age, $P = .12$; with vitamin C intake, $P = .80$.

Our results on serum UA and BMD are similar to those reported by Nabipour et al (12) and Sritara et al (21). They found that higher serum UA levels in men were associated with higher BMD. Also, the positive association between UA and BMD was observed in women by Makovey et al (22). They showed that higher serum UA was associated with less annual loss of BMD at the lumbar spine, forearm, and total body, but not at the hip (22). Moreover, Ahn et al (23) observed that in 7502 healthy postmenopausal women, higher serum UA levels were also associated with higher bone mass, lower bone turnover, and lower prevalence of vertebral fractures. Although the evidence shows an association between UA and bone health, a recent study reported no causal effect of UA on BMD (24). However, several issues may have comprised their approach in assessing causality (eg, use of a weak instrument, pleiotropic effect of the genetic variants, and lack of a sufficiently powered setting). Furthermore, yet another study reported no association between UA and FN-BMD in the general population, which can be due to differences in the study settings, eg, cross-sectional design, the relatively young population included in the study, and inclusion of different ethnic groups in the study population (25). As shown in our study, UA may have a protective effect mainly in older individuals who are at higher risk for bone loss. Also, the levels of UA and its effect on health may vary across different ethnicity groups (26). From this perspective, future prospective studies are required to discern the reasons underlying the conflicting results. Likewise, larger scale studies with sufficient power will also be needed to ultimately establish whether serum UA levels have a causal effect on bone.

UA is a biomarker commonly measured to diagnose gout. Also, UA is regarded as a risk factor for cardiometabolic diseases due to stimulation of smooth muscle cell proliferation, increased inflammation, and increased endothelial dysfunction (8, 27). However, there is growing evidence indicating that higher serum levels of UA may have beneficial effects because of its role as an antioxidant and cytoprotectant. UA accounts for a substantial part of the antioxidative capacity of the plasma (28) and is capable of scavenging intracellular free radicals during metabolic stress such as nitric oxide, peroxyl radicals, and hydroxyl radicals (29). Given this, it is also plausible that high UA levels may exert a protective effect in bone metabolism. Oxidative stress seems to attenuate osteoblastogenesis and bone formation (30), and it has been associated with bone mass (31). Moreover, an in vitro study demonstrated that UA treatment decreased osteoclastogenesis and reduced the production of reactive oxygen radicals in osteoclast precursors (32).

To our knowledge, the present study is the first to show that serum UA levels are associated with favorable hip bone geometry and also with a reduction in incident fracture risk of nonvertebral and osteoporotic-fracture risk. We did not find an association between serum UA and hip or vertebral fractures, which may be due to the low number of cases. So far, most of the studies on the topic are cross-sectional and used as primary endpoint BMD or prevalent fracture without evaluating the association with hip bone geometry or incident fractures. Very recently, two longitudinal studies showed that in men, UA is associated with a reduction in incident osteoporotic and nonspine fractures, but not with incident hip fractures (13, 14). These results are consistent with ours and further support the hypothesis that UA may act as a protective factor against metabolic bone diseases not only in men but also in women.

Also, a novel finding of this study is the role that age may play in the effect of UA on musculoskeletal outcomes and the synergetic effect of UA and vitamin C. Although this is the first study to note the interaction between age and UA on bone, a similar interplay of age and UA has

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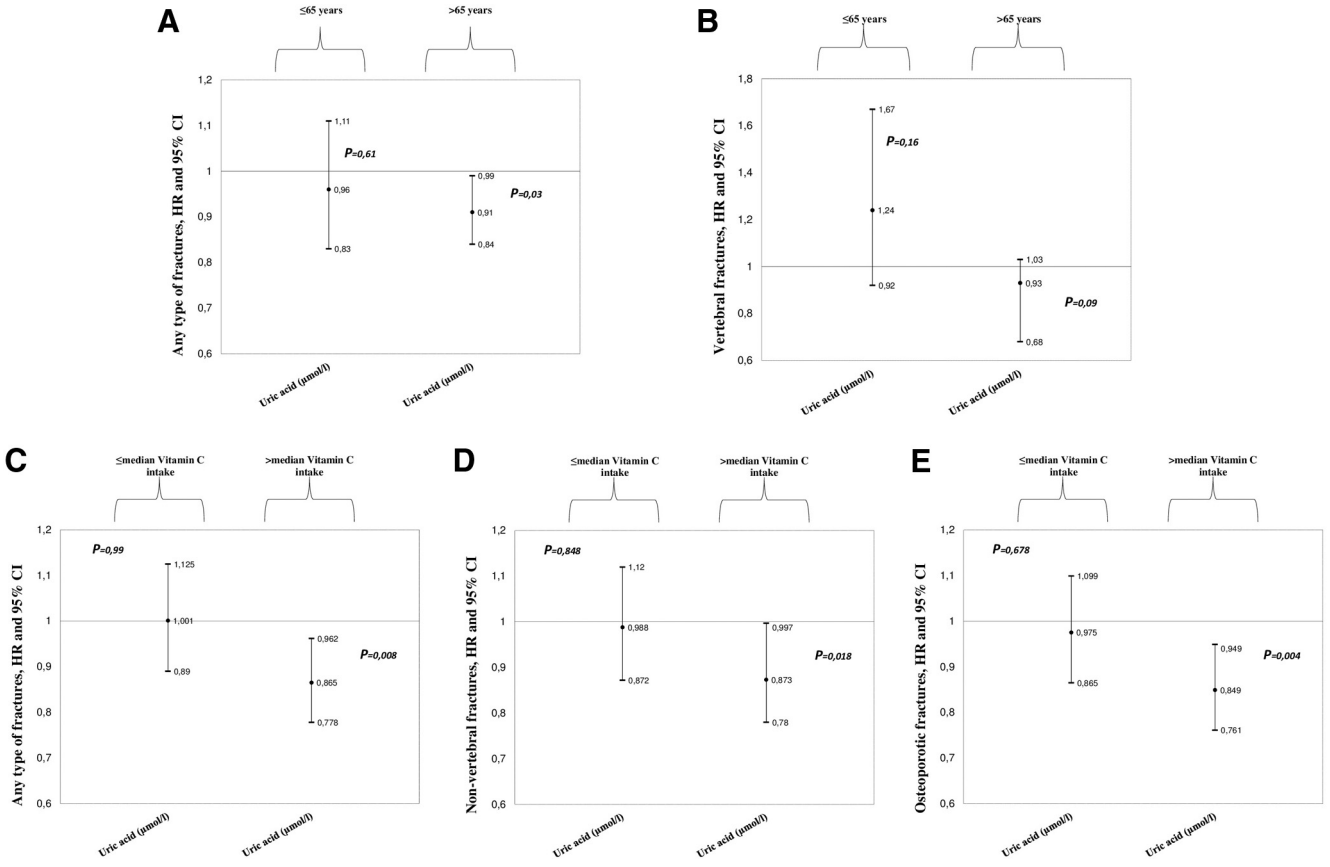

Figure 2. The association between serum UA (μmol/L) and fracture risk by age and intake of vitamin C.

been reported before for other health outcomes, eg, blood pressure (15, 33). Levels of UA increase with age (15), which may explain why the effect of UA on bone is more prominent in older individuals. In contrast, supplemental vitamin C intake has been reported to have an uricosuric effect by increasing renal fractional clearance of UA, inhibiting UA synthesis, and thus lowering the plasmatic levels of UA (34). Under this contention, vitamin C would tend to lower the beneficial effect of UA on bone. In contrast, in the current investigation, we observed a synergistic effect of vitamin C and UA. However, recent evidence shows that vitamin C intake from diet, in contrast to vitamin C supplementation, is not associated with lower serum UA levels, but to the contrary, it can be positively associated with UA levels (35). High vitamin C intake is associated with lower bone loss and may have a protective role for bone health due to its antioxidant properties (36). Therefore, vitamin C from diet may strengthen the effect of UA on bone. Another explanation for the apparent paradox may also be the switch from antioxidant to prooxidant properties of UA, particularly when it is present in blood at supernormal levels (8). We postulate that vitamin C intake may help to regulate the role of UA as anti- or pro-oxidant. However, in the current investigation, the interplay between UA and vitamin C was observed only for the risk of fractures and not for BMD or hip bone geometry. Therefore, other mechanisms may be involved. Further studies are thus needed to replicate our findings and to shed more light on the interplay between age, vitamin C, and UA on relation to bone health.

This study has several strengths. This is a large, prospective, population-based study of 5074 individuals with a comprehensive follow-up of 10 years on average. In addition, in this setting we had the possibility to adjust for a broad spectrum of anthropometric, dietary, clinical, biochemical, and biophysical bone-related confounders. Also, it is the first prospective study to use BMD and hip bone geometry measures in multiple time points. Additionally, to our knowledge, this is the first study on the topic to enroll both men and women. Moreover, our cohort was recruited from community and not clinical practices such that the sample was not selected for comorbid diseases that could influence serum UA levels or the relation with bone parameters. However, there are also shortcomings. We only report results on older individuals and those of Dutch-Northern European background, which is the reason these results are not generalizable to younger individuals or individuals of very distinct ethnical background. Furthermore, blood levels of major endogenous components, exogenous antioxidants (eg, vitamins C and

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E), and antioxidant enzymes were not examined, which can differ from the dietary intake of these nutrients. We did not have PTH or NTX N-terminal telopeptide of type 1 collagen (a sensitive marker of overall bone resorption) measures in our study, which has been reported to correlate with UA, and therefore, we could not determine these associations to be worthy of further investigation. Moreover, we did not have measures of BMD at the total hip or lumbar spine, which could have strengthened our results. Lastly, selection bias may be present due to missing data on bone measurements. However, using a selected source population for a cohort usually leads to bias toward the null rather than a false-positive association (37).

In conclusion, in this large, prospective, population-based cohort of elderly men and women, serum UA levels were shown to have a protective effect on BMD, favorable configuration of hip bone geometry, and lower fracture risk. Additional studies are warranted to establish causality and the precise mechanisms of action and to give more insight into the interplay of UA with age and intake of vitamin C as determinants of bone health and disease.

Acknowledgments

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The contributions of the authors were as follows: T.M., E.A.L.d.J., J.C.K.-d.J., A.G.U., A.H., A.D., M.C.Z., O.H.F., and F.R. participated in the manuscript conception, statistical analyses, data interpretation, manuscript writing and revision. A.H. designed the Rotterdam Study and participated in data interpretation, manuscript writing and revising. All authors read and approved the final manuscript.

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