ORIGINAL ARTICLE

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Low-Level Cadmium Exposure Is Associated With Decreased Bone Mineral Density and Increased Risk of Incident Fractures in Elderly Men: The MrOS Sweden Study

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ABSTRACT

One risk factor for osteoporosis that has attracted increasing attention in recent years is exposure to cadmium. The aim of this study was to examine the associations between low-level cadmium exposure, from diet and smoking, and bone mineral density (BMD) and incident fractures in elderly men. The study population consisted of 936 men from the Swedish cohort of the Osteoporotic Fractures in Men (MrOS) study, aged 70 to 81 years at inclusion (years 2002 to 2004), with reliable data on cadmium in urine (U-Cd) analyzed using inductively coupled plasma mass spectrometry in baseline samples. The participants also answered a questionnaire on lifestyle factors and medical history. BMD was measured at baseline using dual-energy X-ray absorptiometry (DXA) in the total body, hip, and lumbar spine. During the follow-up period (until 2013), all new fractures were registered by date and type. Associations between BMD and U-Cd were assessed using multiple linear regression, and associations between incident fractures and baseline U-Cd were analyzed using Cox regression. In both cases, a number of potential confounders and other risk factors (eg, age, smoking, body mass index [BMI], and physical activity) were included in the models. We found significant negative associations between U-Cd and BMD, with lower BMD (4% to 8%) for all sites in the fourth quartile of U-Cd, using the first quartile as the reference. In addition, we found positive associations between U-Cd and incident fractures, especially nonvertebral osteoporosis fractures in the fourth quartile of U-Cd, with hazard ratios of 1.8 to 3.3 in the various models. U-Cd as a continuous variable was significantly associated with nonvertebral osteoporosis fractures (adjusted hazard ratio 1.3 to 1.4 per μg Cd/g creatinine), also in never-smokers, but not with the other fracture groups (all fractures, hip fractures, vertebral fractures, and other fractures). Our results indicate that even relatively low cadmium exposure through diet and smoking increases the risk of low BMD and osteoporosis-related fractures in elderly men. © 2015 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals, Inc. on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: OSTEOPOROSIS; DXA; FRACTURE RISK ASSESSMENT; EPIDEMIOLOGY; DISEASES AND DISORDERS OF/RELATED TO BONE

Introduction

Osteoporosis is a disorder characterized by low bone mineral density (BMD) and a subsequent increased risk of fractures.[1] It is a major public health concern because fragility fractures cause considerable morbidity and mortality, as well as extensive costs for society.[1,2] Osteoporosis is often underdiagnosed and undertreated, especially in men, because it has traditionally been seen as a women's disease.[1] However, in recent years, there has been a growing awareness that osteoporosis is also a major problem for the male population. Therefore, to take preventive measures against osteoporosis and

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osteoporosis-related fractures, it is important to identify risk factors for these conditions both in men and in women. A systematic clinical review and meta-analysis from 2012 revealed statistically significant associations between increased risk for osteoporosis-related fractures in men and high age, low body mass index (BMI), excessive alcohol consumption, current smoking, long-term use of corticosteroids, and history of fractures, falls, hypogonadism, stroke, and diabetes.[3] Parental hip fracture has been found to be a major risk factor for hip fracture in both men and women.[4] A meta-analysis from 2014 revealed a statistically significant inverse association between higher physical activity and total fracture risk; however, this association was type-specific, and remained for wrist and hip fractures but not for vertebral fractures.[5] It is also well known that patients with chronic kidney disease have an increased risk of fragility fractures.[6]

High-level exposure to cadmium has long been considered a risk factor for osteomalacia, osteoporosis, and fractures, most dramatically described as the cause of itai-itai disease in Japan in the 1950s in a population consuming highly contaminated rice.[7] Cadmium can also cause renal damage, initially in the proximal tubules, and in severe cases impaired glomerular function and even renal failure.[8] It accumulates in the kidney and is excreted in urine as a reflection of the body burden.[8,9] Cadmium occurs both naturally in the environment and as a widespread contaminant resulting from industrial and agricultural activities.[8] Humans in the non-smoking general population without occupational exposure to cadmium are exposed mainly through their diet because cadmium is present in most food items. Cadmium is easily taken up by crops grown in contaminated soil; most of the dietary cadmium exposure in European countries comes from cereals, vegetables, nuts, pulses, starchy roots, and potatoes but also from meat.[9] In smokers, inhaled tobacco smoke is often the main source of cadmium exposure. In recent years, studies have indicated that low-level exposure to cadmium, as found in the general population, might also increase the risk of osteoporosis and fractures.[10–15]

The aim of this study was to examine the effects of low-level cadmium exposure, from diet and smoking, on BMD and incident fractures in a cohort of elderly men.

Materials and Methods

Study population

The initial study population consisted of 1010 older men (median age at baseline 75.3 years, range 70.5 to 81.0) in Gothenburg, Sweden. These men formed part of the Swedish cohort of the Osteoporotic Fractures in Men (MrOS) study, a cross-sectional and prospective multicenter study focused on bone metabolism and fractures. The participants were randomly selected from national population registries (men aged 69 to 81 years) and contacted by telephone. They were then invited to participate in the MrOS study by letter. To be included in the study, the men had to be able to walk without assistance, sign an informed consent, and provide information about their lifestyle, medical history, and medication; there were no other exclusion criteria. At baseline (years 2002 to 2004), the participants were physically examined, answered a questionnaire, gave blood and urine samples, and were measured for BMD (see below). In the prospective part of the study, all new fractures during the follow-up period were registered, first in 2009 and then in 2013.

For the present study, we were able to analyze urinary cadmium in baseline samples from 983 men, 44 of whom were then excluded because of very diluted urine samples (urinary creatinine <0.3 g/L). Three more were also excluded: one because he had not answered the questionnaire, one because of missing urinary creatinine, and one because of very high urinary cadmium (9.0 μg/g creatinine), probably owing to contamination or occupational exposure because he had only smoked for 2 years. The remaining 936 men formed the total study group.

The study was approved by the ethics committee at the University of Gothenburg and conducted in accordance with the Declaration of Helsinki.

Assessment of incident fractures

The participants were followed for 8.9 years on average (median 9.8 years) after the baseline examination. The X-ray archives in Gothenburg, and later in a larger area (Västra Götaland Region), were searched regularly for all new fractures. Central Swedish registers covering all citizens were used to identify the participants and the time of death for those who died during the follow-up period. At the end of the follow-up period (December 2013), 363 (38.8%) of the 936 participants were deceased.

All new fractures that occurred during the follow-up period were registered by date and type of fracture. Fractures reported by the participants were only included if they could be confirmed by a physician's review of X-ray reports. Vertebral fractures were only included if clinical symptoms were reported. The risk time for each participant was calculated from the date of the baseline examination to the date of the first fracture, the date of death, or the end of the follow-up time.

We examined incident hip fractures and clinical (symptomatic) vertebral fractures separately, and three other groups of incident fractures were also formed. "Nonvertebral osteoporosis fractures" were defined as fractures in the hip, pelvis, distal radius, and proximal humerus. "All osteoporosis fractures" included clinical vertebral fractures and nonvertebral osteoporosis fractures. The final category was "other fractures," which included all validated fractures minus all osteoporosis fractures.

Assessment of BMD

At baseline, areal BMD (aBMD, g/cm^2) of the total body, total hip including femoral trochanter and femoral neck, and lumbar spine (vertebrae L_1 to L_4), as well as the total fat mass and total lean mass were measured by dual-energy X-ray absorptiometry (DXA) using the Hologic QDR 4500/A-Delphi equipment (Hologic, Waltham, MA, USA). The coefficient of variation (CV) for the aBMD measurements ranged from 0.5% to 3%. Because measurements in the other parts of the MrOS Sweden study were performed with different equipment, a standardized BMD (sBMD) was calculated for total hip, femoral neck, trochanter, and lumbar spine, as previously described.[16]

Assessment of covariates

Pack-years were calculated from smoking data in the questionnaire as the mean number of packs of cigarettes smoked per day multiplied by the number of years the person had smoked. Physical activity was the participant's total daily walking distance (km/d), which was calculated as the combination of self-reported walking outdoors in daily life and walking as a

means of exercise.[16] Information on falls during the previous 12 months was retrieved from the questionnaire. Height and weight were measured at baseline using standard equipment,[16] and BMI was calculated as weight in kilograms divided by height in square meters (kg/m^2). The estimated glomerular filtration rate (eGFR) was calculated using a cystatin C-based formula, as previously described.[17] Cystatin C was measured in serum by the Hitachi Modular P analyzer with reagents and calibrators from Dako A/S (Copenhagen, Denmark) with a total imprecision of 2.1%.[17] Methods for serum levels of total estradiol, total testosterone, free estradiol, free testosterone, sex hormone-binding globulin (SHBG), plasma osteocalcin, and serum N-terminal propeptide of type I procollagen (PINP) have been described previously.[18,19]

Urine samples

Morning urine was collected at baseline and frozen for later analyses. The urine samples were analyzed for cadmium and creatinine in 2012 at the Department of Occupational and Environmental Medicine, Lund University Hospital. Urinary cadmium (U-Cd) was measured by inductively coupled plasma mass spectrometry (Thermo X7, Thermo Elemental, Winsford, UK), in samples diluted 10 times with an alkaline solution and corrected for molybdenum oxide-based interference.[20] U-Cd samples were prepared in duplicate to assess the imprecision (calculated as the CV for duplicate preparations), which was 4.4%. The limit of detection (LOD; calculated as three times the standard deviation of the blank) was 0.05 μg/L. U-Cd concentrations were below LOD in 5 of the 936 men included in the study group, and in these cases, we used the estimate from the analyses (0.01 to 0.03 μg/L). Three quality-control samples were used (Trace Elements Urine, Seronorm AS, Billingstad, Norway, and Interlaboratory Comparison Program for Metals in Biological Matrices, Centre de Toxicologie du Quebec, Quebec, Canada). The results versus recommended values (± standard deviation) were 0.26 ± 0.03 μg/L ($n = 44$) versus 0.26 to 0.36 μg/L; 0.97 ± 0.03 μg/L ($n = 44$) versus 1.01 ± 0.09 μg/L; and 4.9 ± 0.12 μg/L ($n = 44$) versus 5.1 ± 0.26 μg/L, respectively. Analyses of creatinine concentrations in urine were performed using the Jaffé method with a COBAS 6000 instrument (Roche Diagnostics, Rotkreuz, Switzerland) with a LOD of 0.1 mmol/L.

Statistical analysis

Spearman rank correlation analysis was used to assess associations (r_s) between single variables. Differences between groups were compared using a *t* test, ANOVA, chi-square test, and Fisher's exact test. Assuming a nonlinear relationship between U-Cd and BMD, or fracture risk, U-Cd was treated both as a categorized and a continuous variable. Relations between U-Cd and BMD were calculated using multiple linear regression with continuous U-Cd and general linear models with U-Cd quartiles as dummy variables. Associations between baseline urinary cadmium and incident fractures were analyzed in three different models, using Cox proportional hazards regression. Model 1 included only U-Cd, in quartiles or as a continuous variable. Model 2a also included the covariates age, pack-years, BMI, and physical activity. Model 2b was as model 2a but with current smoking instead of pack-years. Model 3 additionally included sBMD of the femoral neck. We calculated hazard ratios with 95% confidence intervals for fractures by quartile of U-Cd, with the lowest quartile as reference, or per 1 μg Cd/g creatinine. Statistical calculations were performed using version 9.4 of the SAS software package.

Results

Baseline characteristics and incident fractures

The main characteristics of the study population are shown in Table 1. The mean U-Cd level was 0.33 (median 0.26, range 0.01 to 6.98) μg/g creatinine. On average, U-Cd concentrations in current smokers were three times as high as in never-smokers (mean U-Cd 0.67, SD 0.67 versus mean 0.22, SD 0.16, μg/g creatinine, $p < 0.001$). U-Cd concentrations in former smokers (mean 0.36 μg/g creatinine, SD 0.46) were also significantly higher than in never-smokers ($p < 0.001$). There were only 8% never-smokers in the 4th quartile of U-Cd compared with 64% in the 1st quartile (Table 1). Only 5 men had U-Cd >2.0 μg/g creatinine; all were current or former smokers who had smoked for 44 to 57 years. Mean U-Cd in those who died during the follow-up period was 0.36 (range 0.07 to 5.1) μg/g creatinine. BMI was somewhat lower in the 4th quartile of U-Cd compared with the 1st (25.9 and 26.6 kg/m^2, respectively, $p = 0.021$). U-Cd was not associated with sex hormones, SHBG, osteocalcin, or procollagen. The total numbers of participants with incident fractures at first and second follow-up, as well as the numbers in each quartile of U-Cd, are shown in Table 2.

Associations between U-Cd and BMD

In univariate analyses, U-Cd (as a continuous variable) was negatively associated with total body BMD ($r_s = -0.16$) and sBMD for total hip, femoral neck, trochanter, and lumbar spine, respectively ($p < 0.05$). In a multiple linear regression model adjusted for age, BMI, pack-years, and physical activity, the associations between continuous U-Cd and BMD were no longer significant (Supplemental Table S1). However, when U-Cd was classified in quartiles, the same model (adjusted for age, BMI, pack-years, and physical activity) showed significantly lower total body BMD, and sBMD for all sites, in the 4th quartile using the 1st quartile as the reference (Table 3). This was also true for BMD in the 3rd quartile for most sites. In never-smokers ($n = 353$), BMD was lowest in the 3rd quartile (Supplemental Table S2).

Associations between U-Cd and incident fractures from baseline to first follow-up in 2009

From baseline (2002 to 2004) to first follow-up (2009), 143 participants experienced at least one fracture (Table 2). In Cox proportional hazard models, hazard ratios (HRs) were between 1.5 and 3.3 in the 3rd and 4th quartiles for all incident fractures, as well as all osteoporosis fractures and nonvertebral osteoporosis fractures (Table 4). The HR for nonvertebral osteoporosis fractures remained significant after adjusting for age, pack-years, BMI, and physical activity (model 2a), and also after adding femoral neck sBMD to the model (model 3: HR = 2.7, $p = 0.044$; Table 4). In a model adjusted for current smoking instead of pack-years, as well as age, BMI, and physical activity (model 2b), the HR in the 4th quartile was also significantly increased for all fractures and all osteoporosis fractures (Table 4). When we analyzed never-smokers separately, the point estimates for the adjusted HRs were increased in the 3rd and 4th quartiles for fractures in all groups except for other fractures, but significant only for all osteoporosis fractures in the 4th quartile (adjusted

Table 1. Characteristics of the Study Cohort at Baseline by Quartiles of Urinary Cadmium

Variable, mean (range) unless otherwise specified	All	Quartiles of urinary cadmium				*p* Value[a]
	(*N* = 936)	Q1 (*n* = 229)	Q2 (*n* = 238)	Q3 (*n* = 230)	Q4 (*n* = 239)	
Cadmium in urine (μg/g creatinine)	0.33 (0.01–6.98)	0.14 (0.01–0.17)	0.21 (0.18–0.25)	0.31 (0.26–0.36)	0.67 (0.37–6.98)	
Age (years)	75.3 (70.5–81.0)	75.2 (70.5–80.9)	75.5 (70.5–81.0)	75.4 (70.5–81.0)	75.0 (70.5–80.9)	0.278
Body weight (kg)	81.2 (48.1–138.3)	82.5 (60.6–138.3)	80.9 (57.5–127.4)	82.1 (54.2–114.5)	79.2 (48.1–126.6)	0.015
Body height (cm)	175.8 (155.0–199.4)	175.9 (156.8–194.0)	175.6 (155.0–194.2)	176.6 (158.8–199.0)	174.9 (158.6–199.4)	0.038
BMI (kg/m^2)	26.3 (16.3–43.7)	26.6 (18.5–43.7)	26.2 (18.8–42.2)	26.3 (17.9–37.2)	25.9 (16.3–39.3)	0.118
Total body fat mass (kg)	18.6 (4.5–38.2)	18.6 (7.7–34.5)	18.9 (6.3–35.0)	18.8 (4.5–38.2)	18.0 (5.7–37.1)	0.352
Total body lean mass (kg)	59.3 (41.8–81.3)	60.4 (42.4–79.6)	59.2 (42.6–78.7)	60.2 (46.3–78.3)	57.7 (41.8–81.3)	<0.001
Smoking status, *N*	910					<0.001
Never-smoker, *n* (%)	353 (39)	144 (64.3)	114 (49.1)	76 (33.9)	19 (8.3)	
Former smoker, *n* (%)	484 (53)	79 (35.3)	115 (49.6)	135 (60.3)	155 (67.4)	
Current smoker, *n* (%)	73 (8)	1 (0.45)	3 (1.3)	13 (5.8)	56 (24.3)	
Pack-years (never/former/current smokers)	13.4 (0–93.0)	4.2 (0–70.5)	7.2 (0–67.5)	14.0 (0–93.0)	28.4 (0–84.0)	<0.001
Medication with corticosteroids, *n* (%)	13 (1)	0 (0)	5 (2.1)	2 (0.87)	6 (2.5)	0.054
Medication against osteoporosis, *n* (%)	5 (0.5)	0 (0)	1 (0.42)	1 (0.43)	3 (1.3)	0.412
Physical activity (km/d)	4.0 (0–22.0)	3.8 (0–14.0)	4.1 (0–16.0)	4.1 (0–17.0)	3.9 (0–22.0)	0.651
Falls during the last year, *n* (%)	140/907 (15)	25/222 (11)	39/233 (17)	29/223 (13)	47/229 (21)	0.032
Calcium intake (mg/d)	929 (60.7–4140)	945 (224–2236)	917 (148–2919)	902 (60.7–2562)	952 (82.5–4140)	0.527
Diabetes (anamnestic/B-glucose >7), *n* (%)	139 (15)	44 (19.7)	36 (15.9)	31 (14.0)	28 (12.3)	0.152
Intact parathyroid hormone (pM)	6.0 (1.3–71.8)	6.3 (1.3–68.8)	5.8 (2.1–19.9)	6.2 (1.9–71.8)	5.8 (1.9–16.2)	0.404
25(OH)-vitamin D (nM)	66.7 (12.0–148)	66.7 (22.0–146)	66.8 (22.0–129)	66.1 (15.0–118)	67.2 (12.0–148)	0.944
eGFR (mL/min/1.73 m^2)	71.3 (18.0–288)	71.0 (18.0–121)	73.0 (29.0–288)	71.1 (31.0–142)	70.2 (22.0–133)	0.457
Total testosterone (nM)	15.5 (0.09–43.9)	15.3 (0.24–43.9)	15.6 (0.09–36.4)	15.7 (0.09–37.3)	15.2 (0.09–37.1)	0.837
Free testosterone (nM)	0.26 (0.001–1.04)	0.26 (0.004–1.0)	0.26 (0.001–0.64)	0.27 (0.001–0.72)	0.26 (0.001–0.66)	0.989
Total estradiol (pM)	77.3 (3.7–202.6)	79.7 (3.7–202.6)	77.4 (3.7–202.6)	77.3 (3.7–177.7)	74.8 (3.7–202.6)	0.399
Free estradiol (pM)	1.3 (0.03–3.7)	1.3 (0.06–3.2)	1.3 (0.04–3.5)	1.3 (0.05–3.6)	1.3 (0.03–3.7)	0.572
SHBG (nM)	47.3 (3.3–269.5)	47.0 (3.3–269.5)	47.2 (3.6–126.7)	47.4 (12.8–164.1)	47.5 (11.9–170.0)	0.997
PINP (ng/mL)	40.8 (4.0–191.3)	41.7 (4.0–183.5)	39.7 (11.0–171.6)	40.8 (15.4–191.3)	41.0 (12.5–94.3)	0.727
Osteocalcin (μg/L)	26.8 (8.0–280.0)	27.9 (8.0–280.0)	26.4 (8.0–88.0)	26.3 (10.0–78.0)	26.5 (9.0–60.0)	0.524
BMD						
Total body BMD (g/cm^2)	1.09 (0.77–1.59)	1.12 (0.86–1.45)	1.10 (0.77–1.59)	1.09 (0.79–1.44)	1.07 (0.83–1.35)	<0.001
Total hip, sBMD, right-left (g/cm^2)	0.96 (0.59–1.65)	1.00 (0.64–1.55)	0.97 (0.62–1.45)	0.96 (0.59–1.53)	0.93 (0.63–1.65)	<0.001
Femoral neck, sBMD, right-left (g/cm^2)	0.85 (0.54–1.50)	0.87 (0.58–1.48)	0.86 (0.57–1.38)	0.85 (0.54–1.50)	0.82 (0.58–1.35)	0.002
Trochanter, sBMD, right-left (g/cm^2)	0.82 (0.49–1.43)	0.85 (0.53–1.38)	0.83 (0.51–1.43)	0.81 (0.51–1.37)	0.78 (0.49–1.39)	<0.001
Lumbar spine L_1 to L_4, sBMD (g/cm^2)	1.12 (0.61–1.95)	1.15 (0.73–1.87)	1.12 (0.72–1.95)	1.11 (0.61–1.73)	1.10 (0.62–1.73)	0.015

eGFR = glomerular filtration rate estimated from cystatin C; SHBG = sex hormone–binding globulin; PINP = N-terminal propeptide of type I procollagen; sBMD = standardized BMD.

[a]ANOVA, chi-square, or Fisher's exact test.

Table 2. Incident Fractures From Baseline Until 2009 and 2013, Respectively, by Quartiles of Urinary Cadmium

Variable	All	Quartiles of urinary cadmium			
	($N = 936$)	Q1 ($n = 229$)	Q2 ($n = 238$)	Q3 ($n = 230$)	Q4 ($n = 239$)
Cadmium in urine (μg/g creatinine), mean (range)	0.33 (0.01–6.98)	0.14 (0.01–0.17)	0.21 (0.18–0.25)	0.31 (0.26–0.36)	0.67 (0.37–6.98)
Participants with incident fractures 2009					
All fractures, *n* (%)	143 (15.3)	24 (10.5)	35 (14.7)	38 (16.5)	46 (19.2)
All osteoporosis fractures, *n* (%)	101 (10.8)	13 (5.7)	24 (10.1)	30 (13.0)	34 (14.2)
Nonvertebral osteoporosis fractures, *n* (%)	53 (5.7)	7 (3.1)	11 (4.6)	15 (6.5)	20 (8.4)
Hip fractures, *n* (%)	24 (2.6)	3 (1.3)	6 (2.5)	5 (2.2)	10 (4.2)
Clinical vertebral fractures, *n* (%)	56 (6.0)	7 (3.1)	15 (6.3)	19 (8.3)	15 (6.3)
Other fractures, *n* (%)	56 (6.0)	14 (6.1)	14 (5.9)	13 (5.7)	15 (6.3)
Participants with incident fractures 2013					
All fractures, *n* (%)	229 (24.4)	46 (20.1)	51 (21.4)	60 (26.1)	72 (30.1)
All osteoporosis fractures, *n* (%)	173 (18.5)	31 (13.5)	36 (15.1)	50 (21.7)	56 (23.4)
Nonvertebral osteoporosis fractures, *n* (%)	101 (10.8)	17 (7.4)	19 (8.0)	29 (12.6)	36 (15.1)
Hip fractures, *n* (%)	58 (6.2)	10 (4.4)	10 (4.2)	17 (7.4)	21 (8.8)
Clinical vertebral fractures, *n* (%)	90 (9.6)	15 (6.6)	21 (8.8)	31 (13.5)	23 (9.6)
Other fractures, *n* (%)	90 (9.6)	22 (9.6)	24 (10.1)	19 (8.3)	25 (10.5)

The numbers and percentages of participants with one or more incident fractures in each quartile of urinary cadmium are given. Nonvertebral osteoporosis fractures are defined as fractures in hip, distal radius, proximal humerus, and pelvis. All osteoporosis fractures also include clinical vertebral fractures.

HR = 3.3, $p = 0.029$ [model 2] and $p = 0.031$ [model 3]; Table 5). When U-Cd was treated as a continuous variable, its effect was significant for nonvertebral osteoporosis fractures in all models (model 3: HR = 1.4 per 1 μg Cd/g creatinine, $p = 0.024$; Supplemental Table S3). In never-smokers, the adjusted HRs were about four times higher for nonvertebral osteoporosis fractures (model 3: HR = 5.9 per 1 μg Cd/g creatinine, $p = 0.009$) and also significant for all osteoporosis fractures (HR = 4.2 per 1 μg Cd/g creatinine, $p = 0.017$) (Supplemental Table S4).

Estimated GFR and falls during the last 12 months were not associated with U-Cd or with sBMD of the femoral neck in the univariate analyses. The HRs were also very similar when we added eGFR or falls to model 2 (data not shown).

In ever-smokers, the point estimates for the HRs were increased, but in the adjusted models these were only significant for all osteoporosis fractures in the 3rd quartile (model 2: HR = 3.5, $p = 0.043$; model 3: HR = 3.5, $p = 0.048$; data not shown). Smoking (pack-years) was only significant for vertebral fractures in ever-smokers ($p = 0.010$; data not shown) in the model with U-Cd, age, pack-years, BMI, physical activity, and BMD. When smoking was not included in the multivariate models, the HR increased for all fractures, all osteoporosis fractures, and clinical vertebral fractures in the 3rd and 4th quartiles of U-Cd.

Associations between U-Cd and incident fractures from baseline to second follow-up in 2013

From baseline (2002 to 2004) to second follow-up (2013), 229 participants experienced at least one fracture (Table 2). In Cox proportional hazard models, U-Cd was related to the risk of all incident fractures, all osteoporosis fractures, and hip fractures in the unadjusted model, comparing the highest quartile of U-Cd with the lowest, but nonsignificant in the multivariate models with pack-years (Table 4). However, the HR for nonvertebral osteoporosis fractures in the 4th quartile remained significant after adjusting for age, pack-years, BMI, and physical activity (model 2a: HR = 2.0, $p = 0.044$; Table 4), and also after adjustment for eGFR (HR = 2.0, $p = 0.047$; data not shown), but not after adding femoral neck sBMD to the model. In the model with current smoking instead of pack-years (model 2b), HR in the 4th quartile was also significant for all fractures and all osteoporosis fractures (Table 4). For all osteoporosis fractures and vertebral fractures, HRs were significantly higher in the 3rd quartile than in the 1st in most models (Table 4). In never-smokers, the adjusted HRs were increased in the 3rd and 4th quartiles for all fracture groups except for other fractures but not significantly so (Table 5).

In ever-smokers, the adjusted HRs in the 4th quartile of U-Cd were somewhat lower for all fracture groups, except for vertebral and other fractures, compared with the total study group, but no HRs were significantly increased (data not shown). When smoking (pack-years) was excluded from the multivariate models, HRs in the 3rd and 4th quartiles increased for all fractures, all osteoporosis fractures, and vertebral fractures but not significantly so.

When U-Cd was treated as a continuous variable, the association was still significant for nonvertebral osteoporosis fractures (adjusted HR = 1.3 per 1 μg Cd/g creatinine, $p = 0.021$ [model 2] and $p = 0.036$ [model 3]; Supplemental Table S3); this was also the case in never-smokers, where the adjusted HRs were more than three times higher (model 2: adjusted HR = 4.8 per 1 μg Cd/g creatinine, $p = 0.021$; model 3: adjusted HR = 4.4,

Table 3. Adjusted Mean BMD by Quartiles of Urinary Cadmium

U-Cd (μg/g creatinine), mean (range)	Q1 ($n = 229$) 0.14 (0.01–0.17)	Q2 ($n = 238$) 0.21 (0.18–0.25)	Q3 ($n = 230$) 0.31 (0.26–0.36)	Q4 ($n = 239$) 0.67 (0.37–6.98)
Total body BMD (g/cm^2)	1.11	1.10	1.09 ($p = 0.019$)	1.07 ($p < 0.001$)
Total hip sBMD (g/cm^2)	0.99	0.97	0.96 ($p = 0.012$)	0.94 ($p < 0.001$)
Femoral neck sBMD (g/cm^2)	0.87	0.86	0.86	0.82 ($p = 0.002$)
Trochanter sBMD (g/cm^2)	0.85	0.83	0.81 ($p = 0.003$)	0.78 ($p < 0.001$)
Lumbar spine L_1 to L_4 sBMD (g/cm^2)	1.15	1.12	1.11 ($p = 0.029$)	1.10 ($p = 0.016$)

sBMD = standardized BMD.

Mean BMD values for quartiles of urinary cadmium, adjusted for age, BMI, smoking (pack-years), and physical activity (daily walking distance) in a general linear model (least squares means). A p value is given if there is a significant effect of cadmium on BMD, with quartile 1 as the reference category.

$p = 0.029$; Supplemental Table S4). HR was also significantly increased in a model adjusted for age, pack-years, BMI, physical activity, and eGFR (HR = 4.4, $p = 0.031$; data not shown) but not in a model including both BMD and eGFR. Adding falls as a covariate (ie, falls during the year before the baseline examination) to model 2 did not change the results substantially (data not shown).

For the group of fractures not related to osteoporosis ("other fractures"), there were no associations between U-Cd and fracture risk in either the univariate or the multivariate analyses (Tables 4 and 5, Supplemental Tables S3 and S4).

Discussion

It has long been known that high-level cadmium exposure can cause osteomalacia, osteoporosis, and fractures, with the first reports coming from Japan in the 1950s.[7] The main objective of this study was to investigate if low-level cadmium exposure, from diet and smoking, affects BMD and fracture risk in elderly men. A preexisting cohort of elderly men was used because it was well characterized and of suitable size and age. In a previous study of the same size conducted on middle-aged Swedish women, the authors had found associations between BMD and U-Cd at the same low cadmium levels as we expected to find in the present cohort.[21] We investigated 936 Swedish men aged >70 years and found an association between relatively low levels of U-Cd and an increased risk of incident nonvertebral osteoporosis fractures from baseline to first and second follow-up. The increased risk remained significant after adjustment for possible covariates such as age, smoking, BMI, and physical activity (HR = 3.0 and 2.0, respectively), and for the first period also in the model including BMD (HR = 2.7), when the 4th quartile of U-Cd was compared with the 1st. The HRs for hip fractures, all osteoporosis fractures, and all fractures were 1.3 to 3.3 in the adjusted models in the 4th quartile of U-Cd, but not significantly different from 1.0. When U-Cd was treated as a continuous variable, the HRs were again significantly increased for nonvertebral osteoporosis fractures (HR = 1.3 to 1.4) but nonsignificant for the other fracture groups. The AIC (Akaike Information Criterion) values from the Cox regression models with U-Cd either as a categorized or as a continuous variable were nearly identical. However, the prevailing theory is that there is a threshold and that very low levels of exposure to cadmium do not increase fracture risk. There were also negative associations between U-Cd and total body BMD and sBMD for total hip, femoral neck, trochanter, and lumbar spine. Significant associations between U-Cd and BMD, or fracture risk, were mainly found in the highest quartiles of U-Cd, supporting the assumption that the relationship is probably nonlinear. These results in elderly men support previous findings from studies conducted mainly among women, as well as results from studies on men with higher exposure or with less reliable measures of cadmium exposure.[11–13,22–26]

There are few prior studies concerning associations between fracture risk and low-level cadmium exposure in men, and only a few have used biomarkers of cadmium to assess exposure. Staessen and colleagues, who investigated 199 men and 307 women in Belgium, found an association between U-Cd and increased risk of fractures in women but not in men (relative risk of 1.73 for fractures in women associated with doubled U-Cd).[27] However, the participants were relatively young (mean age 44 years), and the follow-up time (median 6.6 years) was quite short considering their young age. In addition, only 44 fractures occurred during this period.[27] The young age and the limited number of fractures might explain why no association was detected in these men. In our study, the mean age at baseline was 75 years, and 229 participants had at least one new fracture during the follow-up time. The Swedish OSCAR study, which included 1021 men and women occupationally or environmentally exposed to Cd, revealed a negative relationship between U-Cd and BMD for participants ≥60 years and a significantly increased risk of forearm fracture after the age of 50 years (adjusted HR = 1.18 per 1 nmol Cd/mmol creatinine).[23,24,28] There was also a dose-response relationship between U-Cd and osteoporosis,[23] in agreement with the relationship between U-Cd and BMD found in our study. Mean U-Cd was 0.74 nmol/mmol creatinine (approximately 0.74 μg/g creatinine) for the whole study group and 0.94 nmol/mmol creatinine for those aged >50 years,[28] which is 2 to 3 times higher than in our study. In a study on Swedish women, Engström and colleagues found a negative association between U-Cd and BMD, an increased risk of osteoporosis in relation to U-Cd, and in never-smokers an increased risk of fractures related to U-Cd (odds ratio = 2.06 for first osteoporotic fracture comparing U-Cd ≥0.5 μg/g creatinine with lower levels).[26] Sommar and colleagues found a statistically significant association between cadmium in erythrocytes (Ery-Cd) and an increased risk of hip fractures in a case-control study of 109 cases and 187 controls (81% women), but after adjustment for covariates (BMI, height, smoking, and hormone-replacement therapy in women), the association was only significant in women (odds ratio = 3.33 per 1 μg/L increase in Ery-Cd).[11] However, Ery-Cd is a less certain measure of lifetime exposure to Cd than U-Cd because it is more related to short-term exposure to cadmium. Some previous studies have investigated the relation between estimated cadmium in diet or drinking water and fracture risk in men. In a prospective cohort study of 22,173 Swedish men, multivariable-adjusted dietary cadmium intake was associated with a significantly higher rate of any fracture and in never-smokers also a higher rate of hip fractures.[25] Similarly, a study from

Table 4. Risk (Hazard Ratios and 95% Confidence Limits) of First Fracture by Quartiles of Urinary Cadmium

		Quartiles of urinary cadmium			
Year of follow-up (no. of fractures)	Model	Q1	Q2	Q3	Q4
All fractures					
2009 ($n = 143$)	1	1.0	1.4 (0.8–2.4)	1.7 (1.0–2.8)	1.9 (1.2–3.1)[a]
	2a	1.0	1.3 (0.8–2.2)	1.5 (0.9–2.5)	1.6 (0.9–2.9)
	2b	1.0	1.3 (0.8–2.3)	1.6 (0.9–2.6)	1.9 (1.1–3.2)[a]
	3	1.0	1.4 (0.8–2.4)	1.5 (0.9–2.6)	1.5 (0.8–2.7)
2013 ($n = 229$)	1	1.0	1.1 (0.7–1.6)	1.5 (1.0–2.1)	1.7 (1.2–2.5)[a]
	2a	1.0	1.0 (0.7–1.6)	1.3 (0.9–1.9)	1.4 (0.9–2.2)
	2b	1.0	1.1 (0.7–1.6)	1.4 (0.9–2.1)	1.6 (1.1–2.4)[a]
	3	1.0	1.0 (0.7–1.5)	1.3 (0.9–2.0)	1.3 (0.8–2.0)
All osteoporosis fractures					
2009 ($n = 101$)	1	1.0	1.8 (0.9–3.5)	2.5 (1.3–4.7)[a]	2.6 (1.4–4.9)[a]
	2a	1.0	1.6 (0.8–3.3)	2.1 (1.1–4.1)[a]	1.9 (0.9–4.1)
	2b	1.0	1.7 (0.9–3.4)	2.3 (1.2–4.4)[a]	2.5 (1.3–4.9)[a]
	3	1.0	1.7 (0.8–3.3)	2.0 (1.0–4.0)[a]	1.7 (0.8–3.6)
2013 ($n = 173$)	1	1.0	1.2 (0.7–1.9)	1.8 (1.2–2.8)[a]	2.0 (1.3–3.1)[a]
	2a	1.0	1.1 (0.7–1.8)	1.6 (1.0–2.6)[a]	1.6 (1.0–2.7)
	2b	1.0	1.1 (0.7–1.8)	1.7 (1.1–2.7)[a]	1.8 (1.1–2.9)[a]
	3	1.0	1.1 (0.7–1.8)	1.6 (1.0–2.6)[a]	1.4 (0.8–2.4)
Nonvertebral osteoporosis fractures					
2009 ($n = 53$)	1	1.0	1.5 (0.6–3.9)	2.2 (0.9–5.4)	2.7 (1.2–6.5)[a]
	2a	1.0	1.3 (0.5–3.5)	2.2 (0.9–5.6)	3.0 (1.1–8.1)[a]
	2b	1.0	1.4 (0.5–3.6)	2.1 (0.8–5.2)	3.3 (1.4–8.0)[a]
	3	1.0	1.3 (0.5–3.5)	2.1 (0.8–5.2)	2.7 (1.0–7.3)[a]
2013 ($n = 101$)	1	1.0	1.1 (0.6–2.1)	1.9 (1.0–3.5)[a]	2.3 (1.3–4.1)[a]
	2a	1.0	1.0 (0.5–2.0)	1.7 (0.9–3.2)	2.0 (1.0–4.0)[a]
	2b	1.0	1.1 (0.6–2.1)	1.8 (1.0–3.3)	2.2 (1.2–4.1)[a]
	3	1.0	1.0 (0.5–2.0)	1.6 (0.9–3.1)	1.8 (0.9–3.6)
Hip fractures					
2009 ($n = 24$)	1	1.0	1.9 (0.5–7.5)	1.7 (0.4–7.0)	3.1 (0.8–11.3)
	2a	1.0	1.8 (0.4–7.2)	1.8 (0.4–7.6)	3.3 (0.8–14.2)
	2b	1.0	1.7 (0.4–7.0)	1.7 (0.4–7.0)	3.1 (0.8–12.0)
	3	1.0	1.8 (0.4–7.2)	1.6 (0.4–6.9)	2.9 (0.7–12.5)
2013 ($n = 58$)	1	1.0	1.0 (0.4–2.4)	1.9 (0.9–4.1)	2.2 (1.1–4.7)[a]
	2a	1.0	1.0 (0.4–2.3)	1.6 (0.7–3.6)	2.0 (0.8–4.8)
	2b	1.0	1.0 (0.4–2.3)	1.8 (0.8–4.0)	2.0 (0.9–4.5)
	3	1.0	1.0 (0.4–2.4)	1.5 (0.7–3.5)	1.7 (0.7–4.2)
Vertebral fractures					
2009 ($n = 56$)	1	1.0	2.1 (0.9–5.2)	2.9 (1.2–6.9)[a]	2.1 (0.9–5.2)
	2a	1.0	2.0 (0.8–4.9)	2.3 (0.9–5.5)	1.3 (0.5–3.8)
	2b	1.0	2.1 (0.8–5.1)	2.6 (1.1–6.3)	1.6 (0.6–4.2)
	3	1.0	2.1 (0.8–5.1)	2.2 (0.9–5.4)	1.2 (0.4–3.3)
2013 ($n = 90$)	1	1.0	1.4 (0.7–2.7)	2.3 (1.3–4.3)[a]	1.6 (0.8–3.1)
	2a	1.0	1.4 (0.7–2.7)	1.9 (1.0–3.7)[a]	1.2 (0.6–2.5)
	2b	1.0	1.4 (0.7–2.7)	2.2 (1.2–4.0)[a]	1.4 (0.7–2.8)
	3	1.0	1.4 (0.7–2.7)	1.9 (1.0–3.6)[a]	1.0 (0.5–2.2)
Other fractures					
2009 ($n = 56$)	1	1.0	0.9 (0.4–2.0)	0.9 (0.4–2.0)	1.0 (0.5–2.1)
	2a	1.0	0.9 (0.4–2.0)	0.9 (0.4–2.0)	1.3 (0.5–3.0)
	2b	1.0	0.9 (0.4–1.9)	0.8 (0.4–1.7)	1.2 (0.6–2.5)
	3	1.0	1.0 (0.5–2.2)	1.0 (0.4–2.2)	1.2 (0.5–2.9)
2013 ($n = 90$)	1	1.0	1.1 (0.6–1.9)	0.9 (0.5–1.7)	1.2 (0.7–2.1)
	2a	1.0	1.0 (0.6–1.9)	0.9 (0.5–1.7)	1.2 (0.6–2.4)
	2b	1.0	1.0 (0.6–1.9)	0.8 (0.4–1.6)	1.3 (0.7–2.4)
	3	1.0	1.0 (0.6–1.9)	0.9 (0.5–1.7)	1.2 (0.6–2.3)

Model 1 ($n = 936$): not adjusted. Model 2a ($n = 887$): adjusted for age, smoking (pack-years), BMI, and physical activity (daily walking distance). Model 2b ($n = 903$): as model 2a but with current smoking instead of pack-years. Model 3 ($n = 879$): as model 2a but also adjusted for standardized BMD (femoral neck).

[a] $p < 0.05$.

Table 5. Risk (Hazard Ratios and 95% Confidence Limits) of First Fracture by Quartiles of Urinary Cadmium in Never-Smokers ($n = 353$)

		Quartiles of urinary cadmium			
Year of follow-up (no. of fractures)	Model	Q1	Q2	Q3	Q4
All fractures					
2009 ($n = 50$)	1	1.0	1.2 (0.6–2.4)	1.2 (0.6–2.6)	2.1 (0.8–5.7)
	2	1.0	1.2 (0.6–2.3)	1.2 (0.6–2.6)	2.0 (0.7–5.4)
	3	1.0	1.3 (0.6–2.5)	1.2 (0.6–2.7)	2.0 (0.7–5.6)
2013 ($n = 76$)	1	1.0	1.0 (0.6–1.7)	1.4 (0.8–2.5)	1.7 (0.7–4.0)
	2	1.0	0.9 (0.5–1.7)	1.4 (0.8–2.4)	1.5 (0.6–3.6)
	3	1.0	0.9 (0.5–1.7)	1.4 (0.8–2.5)	1.5 (0.6–3.7)
All osteoporosis fractures					
2009 ($n = 35$)	1	1.0	1.5 (0.6–3.4)	1.6 (0.6–4.0)	3.6 (1.2–10.6)[a]
	2	1.0	1.4 (0.6–3.3)	1.5 (0.6–3.8)	3.3 (1.1–9.9)[a]
	3	1.0	1.4 (0.6–3.3)	1.4 (0.5–3.6)	3.3 (1.1–9.8)[a]
2013 ($n = 56$)	1	1.0	1.1 (0.6–2.1)	1.7 (0.9–3.3)	2.2 (0.8–5.8)
	2	1.0	1.0 (0.5–2.0)	1.7 (0.9–3.3)	1.9 (0.7–5.1)
	3	1.0	1.1 (0.5–2.1)	1.7 (0.8–3.3)	1.9 (0.7–5.1)
Nonvertebral osteoporosis fractures					
2009 ($n = 19$)	1	1.0	1.0 (0.3–3.3)	1.9 (0.6–6.0)	2.3 (0.5–11.6)
	2	1.0	1.0 (0.3–3.2)	1.9 (0.6–5.9)	2.1 (0.4–10.6)
	3	1.0	1.0 (0.3–3.2)	1.8 (0.6–5.8)	2.1 (0.4–10.5)
2013 ($n = 30$)	1	1.0	1.0 (0.4–2.6)	2.0 (0.8–4.7)	1.5 (0.3–7.1)
	2	1.0	1.0 (0.4–2.5)	2.0 (0.8–4.9)	1.4 (0.3–6.3)
	3	1.0	1.0 (0.4–2.7)	2.0 (0.8–5.0)	1.4 (0.3–6.3)
Hip fractures					
2009 ($n = 7$)	1	1.0	1.1 (0.2–7.9)	1.9 (0.3–13.4)	3.0 (0.3–33.7)
	2	1.0	1.1 (0.2–7.8)	1.8 (0.2–12.8)	2.9 (0.2–33.2)
	3	1.0	1.0 (0.1–8.9)	2.1 (0.2–18.3)	3.5 (0.3–43.6)
2013 ($n = 16$)	1	1.0	0.8 (0.2–3.0)	1.7 (0.5–5.4)	1.3 (0.2–10.7)
	2	1.0	0.8 (0.2–3.0)	1.8 (0.5–5.9)	1.2 (0.1–9.7)
	3	1.0	0.9 (0.3–3.5)	1.9 (0.5–6.9)	1.2 (0.1–10.5)
Vertebral fractures					
2009 ($n = 20$)	1	1.0	1.7 (0.6–5.5)	2.0 (0.6–6.9)	4.4 (1.0–18.3)[a]
	2	1.0	1.6 (0.5–5.2)	1.9 (0.5–6.4)	4.0 (0.9–16.9)
	3	1.0	1.7 (0.5–5.2)	1.8 (0.5–6.2)	3.9 (0.9–16.5)
2013 ($n = 31$)	1	1.0	1.2 (0.5–2.8)	1.8 (0.7–4.4)	2.4 (0.6–8.6)
	2	1.0	1.1 (0.4–2.7)	1.7 (0.7–4.3)	1.9 (0.5–7.1)
	3	1.0	1.1 (0.4–2.7)	1.7 (0.7–4.1)	1.9 (0.5–6.8)
Other fractures					
2009 ($n = 22$)	1	1.0	0.7 (0.3–1.9)	0.9 (0.3–2.7)	0.6 (0.1–5.0)
	2	1.0	0.7 (0.3–1.9)	0.9 (0.3–2.7)	0.6 (0.1–5.0)
	3	1.0	0.8 (0.3–2.1)	1.0 (0.3–3.0)	0.7 (0.1–5.2)
2013 ($n = 34$)	1	1.0	1.0 (0.4–2.1)	0.9 (0.4–2.3)	1.0 (0.2–4.3)
	2	1.0	0.9 (0.4–2.1)	0.9 (0.4–2.3)	1.0 (0.2–4.3)
	3	1.0	0.9 (0.4–2.1)	1.0 (0.4–2.4)	1.0 (0.2–4.4)

Model 1: not adjusted. Model 2: adjusted for age, BMI, and physical activity (daily walking distance). Model 3: as model 2 but also adjusted for standardized BMD (femoral neck).

[a] $p < 0.05$.

Norway revealed a positive association between cadmium levels in drinking water and hip fractures in men.[12]

Previous studies (cross-sectional or prospective) have reported associations between Cd and decreased BMD or increased osteoporosis and fractures at U-Cd 0.5-2 μg/g creatinine.[10] In the present study, associations between Cd and BMD or fractures were found both in quartiles 3 and 4. In quartile 3, mean U-Cd was 0.31 μg/g creatinine (range 0.26 to 0.36), and in quartile 4, it was 0.67 μg/g creatinine (range 0.37 to 6.98).

There was a higher percentage of ever-smokers in the 4th quartile compared with the other quartiles, which was expected because smokers generally have higher U-Cd than never-smokers.[8] Because smoking is associated with U-Cd, BMD, and fracture risk, the covariate pack-years was included in the multivariate model as a confounder. However, because most of the body burden of cadmium in smokers usually comes from cigarettes, there is a risk of overadjustment when the covariate pack-years is included in the model. When we used current smoking instead of pack-years in the multivariate models, the HRs in the 4th quartile were generally higher. Nevertheless, pack-years is a better estimate of cumulative smoking. Because we adjusted for pack-years in the multivariate models in our study, most of the effect of cadmium on the HR for incident fractures probably came from dietary cadmium.

Because we believe that the most likely mechanism behind the effect of cadmium on fractures includes decreased bone strength, we used multivariate regression models both with and without BMD. Surprisingly, HRs and confidence intervals were very similar in the two models and only somewhat lower in the model with BMD. Except for nonvertebral fractures at follow-up in 2013 (Table 4), all results that were significant in model 2a were also significant in model 3 (including BMD). The reason for this could be that areal BMD as measured by DXA is just one of many determinants of bone strength and fragility.[29] As discussed by Fonseca and colleagues, osteoporosis (defined as BMD $\leq$ 2.5 SD lower than average in healthy young adults) almost always increases bone fragility, but bone fragility is not always only caused by osteoporosis. The main factors considered to be determinants of bone quality are the morphology of the whole bone, the composition of bone tissue, and the biophysical properties of the different components of bone tissue, for example, crystallinity, mineral crystal size, and type of collagen cross-linking.[29] It is possible that cadmium increases bone fragility by also affecting factors other than aBMD, not measured by DXA. Alternatively, the results could indicate that part of the effect of cadmium on fracture risk is not mediated by direct effect on bone. For example, recent studies have indicated that cadmium may increase the risk of atherosclerosis,[30,31] which might lead to thromboembolism in the brain and thereby dizziness or acute cerebral disease and thus increase the risk of falling.

Because cadmium is known to affect both kidney function and bone, and chronic kidney disease is associated with an increased risk of fractures, we also tested the inclusion of eGFR in the multivariate analysis; however, the fracture risk was substantially unaffected. This was also the case when falls during the last year before baseline were included in the model. The HRs for first fracture in relation to U-Cd were generally lower at the second follow-up, possibly because a longer period of time had elapsed since the collection of baseline data and so these were no longer as relevant. This could be especially true for factors such as smoking status, physical activity, and BMI, which may change considerably over the years. Conversely, we consider U-Cd to be relatively stable, as it mainly reflects the kidney burden and the accumulated lifetime exposure to cadmium[8,32] A possible limitation of the present study is that the participants were relatively old and the effect of cadmium may not be the same in younger age groups. However, the high age of the participants is also a strength because older people are those with the highest incidence of fractures.[2] In addition, cadmium accumulates in the body with increasing age, and its effect on bone might only be evident at a higher age. There is a risk that some fracture data are missing if some of the men have moved to other parts of the country during the follow-up period, but we assume this to be a minor problem considering the high age of the participants.

One further limitation of this study is that Sweden is a country with a high prevalence of osteoporotic fractures,[33] and the results may, therefore, not be generalizable to all countries. One of the strengths is that this is a relatively large cohort study of elderly men, who have been followed prospectively with respect to fractures. Our fracture data are very reliable because they were obtained from X-ray registers. We also used U-Cd, which is considered the best biomarker of long-term cadmium exposure apart from kidney cortex cadmium. The levels of U-Cd were relatively low in our study but only slightly lower than in the US and most European countries. Both ever- and never-smokers were included in the study, which enabled us to compare the effect of cadmium from the diet with the effect of cadmium mainly from smoking. We were also able to adjust for cumulative smoking, calculated as pack-years of smoking, which is a better measure of the effect of smoking than current smoking.

In conclusion, in the present study, we found significant negative associations between U-Cd and BMD, and positive associations with osteoporosis-related incident fractures, in a cohort of elderly Swedish men. The association between fractures and cadmium was also found in never-smokers, who are exposed mainly via their diet, but only at the first follow-up, 5 to 7 years after baseline. These results show that older men with relatively low cadmium exposure through diet and smoking also have an increased risk of low BMD and fractures associated with cadmium. The study provides additional support for the need to reduce the deposit of cadmium in agricultural land and to reduce the smoking of tobacco.

Further research is needed to study the effect of cadmium on determinants of bone quality other than aBMD. There are now newer techniques of imaging, for example, QCT, which give more information about bone quality than standard methods like DXA.

Disclosures

All authors state that they have no conflicts of interest.

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