Background: Individuals with end-stage renal disease are at higher risk of fractures compared with subjects in the general population. We examined whether elevated albumin-creatinine ratios (ACRs) were associated with nonvertebral fractures in subjects without diabetes or macroalbuminuria.

Methods: A total of 4497 subjects (2267 men and 2230 women) 55 to 74 years old at baseline were followed for a mean of 8.4 years. Measurements of ACR, height, weight, blood pressure, lipids, serum creatinine, and bone mineral density were performed, and information about smoking and drinking habits, physical activity, prevalent diseases, and use of medication was collected before the start of follow-up. Nonvertebral fractures were registered during follow-up.

Results: A total of 135 men and 382 women sustained a new nonvertebral fracture. For a 1-SD higher value for the log-transformed ACR, the relative risk for a fracture was 1.01 in men ($P= .94$, after multiple adjustments) and 1.15 in women ($P=.005$). Women with ACRs in the highest quartile had a 71% higher risk of nonvertebral fractures compared with women with ACRs in the lowest quartile ($P$ value for linear trend over the quartiles, .001). Bone mineral density tended to be lower with higher ACRs in both sexes, but this did not explain the increased fracture risk in women.

Conclusion: Albumin-creatinine ratio was associated with nonvertebral fractures in women without diabetes or macroalbuminuria but not in men.

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The aim of this study was to examine whether ACR, even at low levels, was associated with bone mass and future fractures in subjects without diabetes or macroalbuminuria.
not included. We also excluded 1054 subjects (222 reported diabetes and/or use of medication for diabetes, 9 had missing measurements of albumin or creatinine, 727 had bacteruria or hematuria on any day when urine samples were collected or macroalbuminuria [ACR > 25 mg/mmol], 95 had invalid or missing measurements of BMD, and 1 person sustained a pathological fracture during follow-up). Thus, 4497 subjects (2267 men and 2230 women) were included.

Participants were asked which medication they had used during the last week. Information about smoking habits, prevalent diabetes mellitus, cardiovascular diseases, treatment for hypertension, and physical activity was collected from self-administered questionnaires, and measurements of height, body weight, blood pressure, nonfasting serum lipids, fibrinogen, and white blood cell count were done as described previously. The questionnaires also included questions about previous hip and wrist or forearm fractures. During follow-up, however, fracture incidence was not self-reported but was based on a registry (see the following subsection).

First morning urine samples from 3 consecutive days were used to assess microalbuminuria. Albumin and creatinine levels were measured by turbidimetry on a Cobas Mira S with kits from ABX Diagnostics, Parc Euromedecine, Montpellier, France. The ACR (milligrams for albumin and millimoles for creatinine) was computed, and the mean of the 3 ratios was included in the analyses. The between-assay coefficient of variation for all determinations of albumin level, creatinine level, and the ACR was less than 4% throughout the range of concentrations. Serum creatinine was measured by the HitCo Creatinine Jaffe method with a kinetic colorimetric assay on automated clinical chemistry analyzers (Boehringer-Mannheim, Mannheim, Germany), and estimated glomerular filtration rate (eGFR) was calculated using the abbreviated (4-variable) Modification of Diet in Renal Disease equation. Parathyroid hormone levels were measured by an Immulite intact parathyroid hormone assay (Diagnostic Products Corporation, Los Angeles, California) in a subgroup of 2206 subjects.

Bone mineral density of the distal and ultradistal forearm was assessed as previously described using single x-ray absorptiometry (DTX-100; Osteometer MediTech, Inc, Hawthorne, California). All scans were reviewed to detect and correctly possible artifacts, and systematic BMD differences between the 2 densitometers were adjusted before analysis. A total of 111 subjects had repeated measurements. The median coefficients of variations for 2 scans performed 1 week apart by 2 different operators were 0.79% and 0.98% at the distal and ultradistal sites, respectively.

FRACTURE REGISTRATION AND FOLLOW-UP TIME

Nonvertebral fractures that occurred in the study population were registered from the radiographic archives of the University Hospital of Tromsø, Tromsø, Norway. All fractures are registered at the University Hospital because there is no other radiography service in the city or within 250 km. The only exception to this would be fractures occurring while traveling with no control radiograph after returning home or fractures that were never radiographically examined.

The computerized records in the radiographic archives of the University Hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. Any fracture-coded radiographic examinations among participants were reviewed to ascertain the fracture code; to identify the exact anatomical location of the fracture; to categorize the trauma mechanism as high energetic (fall from a height or traffic accident), low energetic, or pathologic (tumor or metastasis); and to distinguish consecutive fracture cases from one another. A similar registration of fractures in participants in the second and third Tromsø Health Study surveys has been performed, validated, and described by Joakimsen et al.

Follow-up time was assigned from the date of the screening to the date of the first fracture or to the date of censoring (ie, date of migration from Tromsø, death, or end of follow-up [December 31, 2004], whatever came first).

STATISTICAL ANALYSIS

The participants were divided into groups according to quartiles of ACR. Differences between groups at baseline were tested using analysis of covariance, and trends across the quartiles were tested using multiple regression analyses. Multiple regression analyses were also used to examine relationships between ACR and BMD. When ACR was included in an analysis as a continuous variable, the value was logarithmically transformed (log(ACR + 0.1)) before statistical testing was performed.

Survival curves adjusted for age, generated by the Cox analyses, were used to describe the risk of fracture during follow-up as a function of the time. Cox regression analyses were performed to estimate the relative risks (RR) for nonvertebral fractures in relation to ACR (included in the analysis as a log-transformed variable or divided into quartiles).

For each variable listed in Table 1, we tested whether it was related to fracture risk. We tested in sex-specific analyses whether the variable was a significant predictor for fractures when the effects of age and ACR were accounted for. If this variable significantly (P ≤ .05) predicted the risk of nonvertebral fractures in men or women, it was included in the full model. Smoking did not fulfill these criteria but was included in the model because it is an established risk factor for both atherosclerosis and fractures. Thus, in the full model for the association between ACR and fracture risk we adjusted for age, distal forearm BMD, body mass index, height, systolic blood pressure, high-density lipoprotein cholesterol level, eGFR, smoking, and physical activity.

Separate analyses were performed in men and women without high-energetic fractures and in women without previous hip or forearm fractures, in women with an eGFR of 60 mL/min/1.73 m2 or higher, and in women who were not current users of hormone therapy or antihypertensive medication.

The data were analyzed using the Windows 14.0 version of SPSS software (SPSS Inc, Chicago, Illinois). P ≤ .05 (2-sided) was considered statistically significant.

RESULTS

Selected characteristics of the study group by ACRs are presented in Table 1. Albumin-creatinine ratio was positively related to age, blood pressure, smoking, cardiovascular disease, medication for hypertension, white blood cell count, body mass index (men), fibrinogen level (men), eGFR (women), and height (women) and inversely related to serum creatinine level (women), BMD of the forearm, current use of HT, and age at menopause.

ACR AND BMD

In men, BMD of the distal forearm decreased by 2.6 mg/cm2 for each 1-SD increase in the log-transformed ACR when adjusted for age (P = .05) and by 3.5 mg/cm2 with further adjustments for body mass index, height, sys-
In women, the corresponding values were 3.0 mg/cm² (distal forearm) and 1.01 mg/cm² (ultradistal forearm) respectively. The incidence of nonvertebral fracture in men and women were 7.0 and 20.5 per 1000 person-years, respectively. The number of hip, shoulder, wrist, and other fractures were 25, 9, 27, and 74, respectively, among men and 50, 41, 167, and 124, respectively, among women.

Higher ACRs were associated with an increased risk of fracture in women but not in men (Figure and Table 2).

For a 1-SD higher value for the log-transformed ACR, the age-adjusted RR for a fracture was 0.99 in men (P = .94) and 1.17 in women (P = .001). The risks were 0.99 (P = .90) and 1.14 (P = .005), respectively, after further adjustments for distal forearm BMD, and 1.01 (P = .94) and 1.15 (P = .005), respectively, and after additional adjust-ments.
ments for body mass index, height, systolic blood pressure, high-density lipoprotein cholesterol, eGFR, smoking, and physical inactivity. Thus, low BMD or any other of the risk factors did not explain the increased risk.

Women in the highest ACR group had a 71% higher risk of nonvertebral fractures compared with women in the lowest group (P value for linear trend across ACR groups, .001) (Table 2).

Parathyroid hormone (PTH) was measured in 1053 of 2267 men and in 1153 of 2230 women and was significantly associated with log-transformed ACRs in both sexes (P < .001 for men and P = .007 for women). However, in women, the risk of fractures according to ACR was only marginally changed when adjustments for PTH were performed (results not shown).

Fractures may be categorized according to trauma (eg, high- and low-energy fractures—the latter group often denoted as osteoporotic). Exclusion of clearly high-energetic fractures (eg, due to a motor vehicle crash) and fractures of the hands or fingers, feet or toes, and face and skull (less likely to be osteoporotic) (n = 43 for men and n = 72 for women, corresponding to 32% and 19% of the fractures, respectively, in each sex) only slightly influenced the reported associations. In men, there was no relationship, and in women, the RR for a low-energy fracture was 1.80 (95% confidence interval [CI], 1.23-2.61) for ACR group 4 (1.01-24.82 mg/mmol) vs group 1 (0.00-0.38 mg/mmol) (P value for linear trend across ACR groups, .001, after multiple adjustments).

Relatively few subjects (≤5%) reported use of diuretics, steroids, hypnotics-sedatives, or antidepressants or had supplemental calcium intake that may influence BMD or the risk of falling. The association between ACR and fracture risk hardly changed when these factors were included in the regression models (results not shown). None of the women reported use of bisphosphonates at baseline, and 399 received hormone therapy. Present use of hormone therapy was related to ACR (Table 1) but not to fracture risk when included in the age-adjusted model for the association between ACR and fractures. A linear relationship between ACR and fracture risk was found when the analyses were performed excluding those with current hormone therapy use. For a 1-SD higher value for the log-transformed ACR, the RR of a fracture was 1.12 (P = .03) after multiple adjustments. In a separate analysis, we excluded 309 women who had current antihypertensive medication use, and again, a similar linear relationship was found (RR, 1.13; P = .04).

The major part of our study population had normal renal function, and only 165 (7%) of the women had an eGFR lower than 60 mL/min/1.73 m². Excluding these women from the analysis had only minor effects on the results (results not shown).

At baseline, 447 (20%) of the women reported at least 1 previous fracture of the hip or forearm. When these women were excluded, the RR of a new fracture was 1.63 (95% CI, 1.11-2.40) for ACR group 4 (1.01-24.82 mg/mmol) vs group 1 (0.00-0.38 mg/mmol) (P value for linear trend across ACR groups, .005, after multiple adjustments).

In the present population-based study of nondiabetic individuals without macroalbuminuria, increasing levels of ACR were associated with an increased incidence of nonvertebral fractures in women but not in men.

To our knowledge, no previous study has examined the incidence of fractures in relation to ACR in nondiabetic subjects of a general population. The mechanisms behind the relationship in women are still to be determined, but according to Buchanan et al., who found that renal insufficiency was related to low bone mass in el-

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**Figure.** Age-adjusted survival plots for the first nonvertebral fracture in men (A) and women (B). ACR indicates albumin-creatinine ratio (group 1, 0.00-0.38 mg/mmol; group 2, 0.39-0.57 mg/mmol; group 3, 0.58-1.00 mg/mmol; and group 4, 1.01-24.82 mg/mmol).
tery, some of the effect may be mediated by an impaired secretion of 1,25-dihydroxyvitamin D (1,25\([\text{OH}]_2\text{D}\)), which leads to calcium malabsorption. Diminished calcium absorption could increase demands on the skeletal calcium stores. Moreover, when serum calcium level is low, PTH level rises, and this may promote an osteoclast-mediated bone resorption. In our subgroup of participants in whom PTH was measured, we found a relationship between ACR and PTH, but the risk of fractures according to ACR was only marginally influenced after adjustments for PTH.

Several studies have found that ACR is associated with atherosclerosis even in nondiabetic subjects, and 2 recent longitudinal studies (one in our population) have indicated that arterial calcification is a risk factor for fractures. It has been shown that the number of intrasosseous vessels is significantly lower in the femoral heads of patients with fractures of the femoral neck compared with patients with osteoarthritis and that atherosclerotic lesions are more common in the fracture patients. Based on these findings, it has therefore been suggested that atherosclerosis through chronic ischemia may lead to a disturbance of bone remodeling and to a loss of the mechanical properties of the bone. The association between ACR (as a marker on atherosclerosis) and fracture incidence could reflect this relationship.

Low BMD and falls are major risk factors for fractures. Bone mineral density did not explain the increased fracture risk in the present study, and risk of falling was not examined. A recent community-based study showed that elderly persons with chronic kidney disease were at an increased risk of falling, but the relevance of this finding may be questioned with regard to our population, since less than 7% had an eGFR lower than 60 mL/min/1.73 m². Nevertheless, residual confounding by factors for which we have failed to control for could still have influenced our findings.

Scandinavian women have the highest incidence rate of limb fractures in Europe, and we cannot exclude that the relationship between ACR and fracture risk would differ in other populations. The lower incidence of fractures in men compared with women (7.0 and 20.5 per 1000 person-years, respectively) was expected because women have lower peak bone mass, smaller bones, and are more prone to falls. Moreover, the extent of periosteal apposition during aging may be lower and the loss of trabecular connectivity, higher, which again produces a greater deficit in bone strength. In the men in our study, ACR did not predict fractures, but a similar relationship to that in women may have been found in men with weaker bones. The lack of data in the present study, however, precluded such analysis.

The present study has some limitations, and our first concern is related to the possibility of bias. Our study group was large and had a high attendance rate (78% of the eligible population). However, severely ill or disabled individuals are certainly underrepresented. Nevertheless, if this possible selection bias should invalidate our findings with respect to the risk of nonvertebral fractures, the incidence of these fractures would have to be very strongly associated with lower ACRs among the nonparticipants. We believe that this is unlikely and that it is more plausible that nonparticipation may have weakened the true relationship between ACR and fracture.

Table 2. Relative Risks (RRs) for Nonvertebral Fractures in Relation to ACR Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>ACR Group (mg/mmol)</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (0.00-0.38)</td>
<td>2 (0.39-0.57)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>654</td>
<td>503</td>
</tr>
<tr>
<td>No. with fractures</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td>Nonvertebral fractures, RR(^a)</td>
<td>[Reference]</td>
<td>0.92</td>
</tr>
<tr>
<td>Nonvertebral fractures, RR(^b)</td>
<td>[Reference]</td>
<td>0.94</td>
</tr>
<tr>
<td>Nonvertebral fractures, RR (95% CI)(^c)</td>
<td>[Reference]</td>
<td>0.91 (0.57-1.46)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No.</td>
<td>498</td>
<td>577</td>
</tr>
<tr>
<td>No. with fractures</td>
<td>62</td>
<td>68</td>
</tr>
<tr>
<td>Nonvertebral fractures, RR(^a)</td>
<td>[Reference]</td>
<td>1.24</td>
</tr>
<tr>
<td>Nonvertebral fractures, RR(^b)</td>
<td>[Reference]</td>
<td>1.24</td>
</tr>
<tr>
<td>Nonvertebral fractures, RR (95% CI)(^c)</td>
<td>[Reference]</td>
<td>1.28 (0.92-1.80)</td>
</tr>
</tbody>
</table>

Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; NA, not applicable.
\(^a\) Adjusted for age.
\(^b\) Adjusted for age and distal forearm bone mineral density.
\(^c\) Adjusted for age, distal forearm bone mineral density, body mass index, height, systolic blood pressure, high-density lipoprotein cholesterol, estimated glomerular filtration rate, smoking, and physical inactivity.
cent population-based study, only 23% of the participants with a GFR between 30 and 60 mL/min/1.73 m² had detectable albuminuria.33 Our population had predominantly normal renal function, and excluding the women (7%) with an eGFR lower than 60 mL/min/1.73 m² had only a minimal effect on the results. It may seem puzzling that ACR was positively associated with eGFR in women. One reason may be that inactivity (most prevalent in subjects with a high ACR) is related to lower muscle mass, which leads to a decrease in serum creatinine level. The true GFR may therefore be lower than what the eGFR suggests.

Prevalent and incident fractures are closely related, and, unfortunately, we had no information on prevalent fractures other than those of the hip and forearm. However, the results were not notably influenced when subjects with these 2 common fracture types were excluded. We therefore do not believe that the exclusion of subjects with other prevalent nonvertebral fractures would have altered the results substantially.

High-energy fractures as well as fractures of face, skull, hands, and feet are excluded in some studies of osteoporotic fractures. The exclusion of high-trauma fractures in women older than 50 years may, however, result in an underestimation of the contribution of osteoporosis to fractures.34 In the present study, the association between ACR and the risk of fractures was similar after the exclusion of these fracture types.

We conclude that there is a linear relationship between increasing ACR and the risk of nonvertebral fractures in women without diabetes or macroalbuminuria. Although our results show that higher ACRs are associated with lower BMD, factors other than BMD seem to contribute to the increased fracture risk in women.

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Author Contributions: Dr Jørgensen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jørgensen, Jenssen, and Jacobsen. Acquisition of data: Jørgensen, Jenssen, Ahmed, Bjørnerem, and Joakimsen. Analysis and interpretation of data: Jørgensen, Jenssen, Ahmed, Bjørnerem, and Jacobsen. Drafting of the manuscript: Jørgensen, Jenssen, and Jacobsen. Critical revision of the manuscript for important intellectual content: Jørgensen, Jenssen, Ahmed, Bjørnerem, Joakimsen, and Jacobsen. Statistical analysis: Jørgensen, Ahmed, Joakimsen, and Jacobsen. Obtained funding: Jørgensen, Jenssen, and Jacobsen. Administrative, technical, and material support: Jenssen and Joakimsen. Study supervision: Jenssen and Jacobsen.

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Previous Presentation: Preliminary findings of this study have been presented as a poster at the ISN Nexus Symposium on the Bone and the Kidney; October 14, 2006; Copenhagen, Denmark.

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Errors in Abstract, Text, and Table. In the Original Investigation by Jørgensen et al titled “Albuminuria and Risk of Nonvertebral Fractures,” published in the July 9, 2007, issue of the Archives (2007;167[13]:1379-1383), a technical error occurred because a number of fractures had not been included in the database. Among the 2267 men and 2230 women, a total of 215 and 501, respectively (not 135 and 382 as stated in the publication), sustained a new nonvertebral fracture during follow-up. The main result was unchanged after reanalysis, however. Therefore, the “Results” section of the abstract on page 1379 should have read as follows:

“Results: A total of 215 men and 501 women sustained a new nonvertebral fracture. For a 1-SD higher value for the log-transformed ACR, the relative risk for a fracture was 0.96 in men (P=.007, after multiple adjustments) and 1.13 in women (P=.007). Women with ACRs in the highest quartile had a 47% higher risk of nonvertebral fractures compared with women with ACRs in the lowest quartile (P value for linear trend over the quartiles, .002). Bone mineral density tended to be lower with higher ACRs in both sexes, but this did not explain the increased fracture risk in women.”

On page 1381, the first paragraph of the subsection titled “ACR and Fracture Risk” in the “Results” section of the main text should have read as follows: “A total of 215 men (10%) sustained a nonvertebral fracture during 18 941 person-years of follow-up. The mean follow-up time was 8.4 years (range, 13 days–10.3 years). In women, there were 501 fractures (23%) during 18 206 person-years of follow-up, and the mean follow-up time was 8.2 years (range, 7 days–10.3 years). The incidences on nonvertebral fractures, shoulder, wrist, and vertebral Fractures,” published in the July 9, 2007, issue of the ARCH INTERN MED/ VOL 169 (NO. 7), APR 13, 2009 WWW.ARCHINTERNMED.COM

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