Published in final edited form as:

Osteoporos Int. 2013 December ; 24(12): 2993–3000. doi:10.1007/s00198-013-2389-3.

Albuminuria is associated with hip fracture risk in older adults: the cardiovascular health study

J. I. Barzilay,

Division of Endocrinology, Kaiser Permanente of Georgia, Atlanta, GA, USA. Division of Endocrinology, Emory University School of Medicine, Atlanta, GA, USA. 200 Crescent Center Parkway, Tucker, GA 30084, USA

P. B. Źková,

Department of Biostatistics, University of Washington, Seattle, WA, USA

Z. Chen,

Division of Epidemiology and Biostatistics, The University of Arizona Mel and Enid Zuckerman College of Public Health, Tucson, AZ, USA

I. H. de Boer,

Division of Nephrology, University of Washington, Seattle, WA, USA

L. Carbone,

Division of Connective Tissue Diseases, University of Tennessee Health Science Center and Department of Veterans Affairs Medical Center, Memphis, TN, USA

N. N. Rassouli,

Division of Endocrinology, Kaiser Permanente of Georgia, Atlanta, GA, USA. Division of Endocrinology, Emory University School of Medicine, Atlanta, GA, USA

H. A. Fink, and

Geriatric Research Education and Clinical Center, Veterans Affairs Medical Center, Minneapolis, MN, USA

J. A. Robbins

Department of Medicine, University of California, Davis, Sacramento, CA, USA

J. I. Barzilay: joshua.barzilay@kp.org

Abstract

Summary—The microcirculation plays an important role in bone health. Here, we examine whether albuminuria, a marker of renal microvascular disease, is associated with the risk of hip fracture in older adults (age, 78 years). We find a small independent association in women but not in men.

Introduction—The microvascular circulation plays an important role in bone physiology. Two studies of middle-aged adults have found that albuminuria (≥ 30 mg albumin/g creatinine), a

Correspondence to: J. I. Barzilay, joshua.barzilay@kp.org.

Conflicts of interest: None.

disorder of the renal microvasculature, is associated with fracture risk. Here, we examine whether albuminuria is related to hip fracture risk and reduced hip bone mineral density (BMD) in older adults with a mean age of 78 years.

Methods—From the Cardiovascular Health Study (41 % male), 3,110 adults with albuminuria testing were followed up for incident hip fracture for up to 9.5 years. BMD was performed in a subset of 1,208 participants.

Results—There were 313 hip fractures during follow-up (7.7 % of men; 11.7 % of women). The incidence rate for men, with and without albuminuria, was 1.43 and 0.93/100 person-years of follow-up ($p=0.02$); for women, 1.84 and 1.33 ($p=0.04$). After adjustment for osteoporosis-related factors, frailty and falling, a doubling of albuminuria was significantly associated with hip fracture risk in women (hazard ratio, 1.12, 95 % CI, 1.001–1.25), but not in men. In the subcohort with BMD measurement, increased urine albumin levels were significantly associated with decreased total hip BMD in men (-0.009 g calcium/cm² (-0.017 , -0.001); $p=0.04$), but not in women.

Conclusions—In older women, albuminuria is associated with a small, but statistically significant, increased risk of hip fracture independent of other explanatory factors. No such risk appears to be present in men, although their total hip BMD is lower in association with albuminuria.

Keywords

Albuminuria; BMD; DEXA; Elderly; Hip fracture

Introduction

The microcirculation plays an important role in adult bone health. Endothelial cells from capillaries at sites of bone remodeling release factors associated with mineralization and the coupling of osteoclast and osteoblast function [1]. Disorders of the microcirculation could therefore be associated with bone disease, as evidenced by conditions such as avascular necrosis of the hip. Albuminuria—the excessive excretion of protein in the urine (>30 mg/g creatinine)—is a renal microvascular disorder affecting ~20 % of people ages >69 years and 30–40 % of similarly aged adults with diabetes [2]. Several lines of evidence suggest that there could be an association of albuminuria with osteoporosis and its worst consequence, hip fracture. First, hip fractures are an age-related disorder, as is albuminuria. Second, albuminuria is associated with elevated levels of inflammation factors [3]. Inflammation plays a role in the development of osteoporosis [4], an important risk factor for hip fractures. Third, studies of osteoporotic bone [5, 6] and of hip specimens from people having hip replacement surgery for osteoporotic fractures show impaired microvascular blood flow as compared with hip specimens from people having hip replacement surgery for arthritis [7]. Lastly, the factors most commonly associated with albuminuria—diabetes and hypertension—are also risk factors for fractures [8, 9].

There are two prior investigations of the association of albuminuria and fracture risk. A study from a Scandinavian population cohort identified a significant relationship between albuminuria and nonvertebral fractures in women [10]. That cohort was relatively young (mean age, 63 years) and reported only 75 hip fractures. Risk estimates of hip fracture alone

were not done. A second study [11], also from a relatively young population at high risk for cardiovascular disease, reported an increased risk of hip and pelvis fractures in association with albuminuria. Were albuminuria associated with hip fracture risk, it could inform medical practice as to a role for microvascular disease in fracture risk and possibly could be used for prognostic purposes.

In the present study, we examine a cohort of older individuals who had baseline testing for albuminuria and were followed for incident hip fractures for up to 9.5 years. At baseline, this cohort had a mean age of 78 years, in the range when most hip fractures occur. We determine whether those with albuminuria had a higher risk of hip fracture compared with those without albuminuria. We also examine, in a subcohort that underwent DEXA scanning, the relationship between albuminuria and hip bone mineral density (BMD). We hypothesize that albuminuria is associated with hip fracture risk and with lower hip BMD. Owing to differences in risk factors for hip fractures between men and women, as well as differences in hip BMD and hip fracture rates, and the age at which hip fractures occur, it was decided a priori to conduct analyses separately by gender. This is in keeping with our prior hip fracture studies in the cohort analyzed here [12].

Methods

The cohort for this study was from the Cardiovascular Health Study (CHS) [13]. In brief, a random sample of individuals, 65 years of age, was invited to participate at four sites. Potential participants were excluded if they were institutionalized, were unable to attend clinic visits, or had illnesses expected to lead to early death. Five thousand two hundred one participants were recruited in 1989–1990 and 687 in 1992–1993 to provide additional representation of African-Americans. All participants signed informed consent at study entry. During follow-up, participants were seen in clinic annually and had telephone contact annually at the midpoint between clinic visits.

Study cohorts

In 1996/1997, 4,412 CHS participants had a clinic or telephone visit. Those doing an interview by phone ($n=896$) did not provide urine samples. Another 406 participants who attended the clinic did not provide a urine sample. A total of 3,110 (70.5 %) provided a random urine sample and constitute the analytic cohort. Those who did not provide a urine sample were older, shorter, less heavy, expended less energy, were less often male, and fell more often than those who provided a urine sample. They also had more prior fractures, a history of coronary heart disease (CHD), stroke and diabetes, and reported poorer health (data not shown).

In 1994/1995, 1–2 years prior to urine testing for albuminuria, a subset of the cohort ($n=1,208$) underwent DEXA testing in two of the CHS clinical sites. This subcohort was younger and reported better overall health than the participants who did not have DEXA testing (Appendix).

Demographic and medication information were obtained, including use of alcohol, exercise, and lifestyle activities from which the amount of energy expended per week was derived.

Information regarding past falls was collected. Testing for grip strength and walking speed were performed at the 1996/1997 visit. Grip strength was measured in the dominant arm using an isometric dynamometer. The average of three attempts was used. Walking speed was assessed as the time it took to walk 15 feet. Based on these tests and response to questions regarding exhaustion, each participant's frailty status was determined [14]. Frailty was defined using a phenotype that requires 3 of the following criteria: unintended weight loss of >10 lb in the prior year, self-reported exhaustion most of the time, physical activity in the lowest 20 % of the CHS cohort, weakness as measured by grip strength (lowest 20 % of the CHS cohort), and slowness of walking (lowest 20 % in each sex). Those with one or two criteria were "pre-frail," an intermediate syndrome with increased risk for the development of frailty.

Laboratory and radiologic measures

Laboratory tests (glucose, C-reactive protein (CRP), urine albumin, and creatinine) were performed as previously described [15]. As a measure of renal function, cystatin C (cyst C) levels (in milligrams per liter) were measured from stored samples using a BNII nephelometer (Dade Behring Inc., Deerfield, IL) that utilized a particle enhanced immunonephelometric assay (N Latex Cystatin-C). Estimated cystatin-based glomerular filtration rate (ecGFR) was categorized as above or below $60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$. A CRP level of >3 mg/l was considered elevated.

DEXA Scans (QDR 2000 or 2000+; Hologic, Inc, Bedford, MA) were read blindly at the University of California, San Francisco Reading Center with Hologic software version 7.10.

Outcome variable

Hip fracture ascertainment was done through patient self-report and corroborated from hospital records. Events were defined as incident hip fracture, with follow-up until 30 June 2008. Participants were censored at the time of death. Medicare records of hospitalizations which were coded for hip fractures were also reviewed to identify hip fractures participants did not self report.

Statistical analysis

On account of the small number of hip fractures ($n=12$) among participants with proteinuria (>299 mg/g creatinine), albuminuria was not dichotomized into micro- and macroalbuminuria.

Baseline characteristics of the cohort were computed by albuminuria status and were compared using χ^2 tests for categorical and binary variables and t tests for mean values of continuous variables. Incidence rates of hip fractures were calculated per 100 participant-years. Kaplan–Meier plots were done to illustrate the event curves by albuminuria status. Log rank testing was used to compare the curves.

Cox proportional hazards models were used to model the association of a doubling of urine albumin per gram creatinine and incident hip fracture. The proportional hazards assumptions were examined using graphical and numerical methods based on scaled Schoenfeld

residuals. Urine albumin per gram creatinine was heavily tailed and therefore Winsorized at the 95th percentile and log transformed to base 2. Models were adjusted sequentially: *model 1*, unadjusted; *model 2*, demographic factors (race, age, gender, and clinic site); *model 3*, factors in model 2 plus osteoporosis-related factors, including BMI, smoking status, alcohol use, prevalent coronary heart disease (CHD), hypertension, eGFR, energy used per week (in kilocalories), and inflammation (CRP); and *model 4*, factors in model 3 plus factors related to fracture (frailty status and a history of falling in the year preceding the baseline period).

In the DEXA subcohort, linear regression models were constructed to estimate the associations of a doubling of urine albuminuria with total hip and femoral neck BMD. Adjustments were made for factors known to impact bone density: age, race, smoking status, kilocalories energy expenditure, BMI, eGFR of $<60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$, and diabetes. Analyses were done using R [16].

Results

Baseline characteristics of the cohort

Forty-one percent of the cohort was male (Table 1); 23.7 % of men and 18.9 % of women had albuminuria. As compared with participants without albuminuria, those with albuminuria were older, expended less energy, had a history of falling more often in the past year, and were more likely to be frail or pre-frail. They did not report more fractures prior to the entry visit. Other factors (BMI, alcohol use, and race) differed in relationship with albuminuria between men and women.

Crude outcome rates

Participants with albuminuria had more hip fractures and had them earlier in follow-up than participants without albuminuria (Tables 1 and 2); 98 men (7.7 %) had a hip fracture during a median of 8.04 years of follow-up (interquartile range (IQ), 4.11–11.31 years) and 215 women (11.7 %) had a hip fracture during a median of 9.50 years of follow-up (IQ, 5.42–11.42 years). The incidence rates of hip fracture for men, with and without albuminuria, were 1.43 and 0.93/100 person-years of follow-up, respectively. For women, the incidence rates were 1.84 and 1.33/100 person-years, respectively. For each gender, the log rank test (Fig. 1) shows significantly different event curves based on albuminuria status ($p=0.02$ for men and $p=0.04$ for women).

Adjusted outcome rates

In unadjusted Cox proportional hazard models (Table 3), from time of urine collection to incident hip fracture, a doubling of albuminuria levels was associated with hip fracture risk in men and women (hazard ratio (HR), 1.13 (95 % confidence intervals (95 % CI), 1.02–1.27); HR, 1.15 (95 % CI, 1.05–1.25), respectively). With adjustment for age, race, and clinical site, a doubling of urine albumin per gram creatinine remained significantly associated with hip fracture risk in women (HR, 1.13 (95 % CI, 1.03, 1.24)) and trended to significance in men (HR, 1.11 (95 % CI, 0.99, 1.24)). Adjustment for osteoporotic risk factors attenuated the association of a doubling of albuminuria levels with hip fracture risk

among women. With added adjustment for falling and frailty, a doubling of urine albumin was significantly associated with hip fracture risk (HR, 1.12 (95 % CI, 1.001, 1.26)). Among men, no significant association was found between albuminuria and hip fracture risk in this final multivariate-adjusted model (HR, 1.02 (95 % CI, 0.89, 1.17)).

BMD subcohort

Among men in the DEXA sub-cohort, a doubling of albuminuria (adjusted for age, race, smoking status, kilocalories energy expenditure, BMI, ecGFR, and diabetes) was associated with a lower total hip BMD but not a lower femoral neck BMD (Table 4). There was no association of albuminuria with hip BMD measures in women. Owing to the small number of hip fractures in this group ($n=75$), the association with albuminuria was not examined in this subgroup.

Discussion

In this longitudinal study of older men and women, a doubling of albuminuria level on a baseline examination was associated with a small, but statistically significant, increased risk of incident hip fracture over 9.5 years of follow-up. With adjustment for factors related to osteoporosis, this association was attenuated. When, however, the effects of frailty and a history of falling in the year prior to study entry were adjusted for, albuminuria retained a small, but statistically significant, association with hip fracture risk in women, but not in men. Given the small effect of albuminuria on hip fracture risk, it is not possible to recommend its use for clinical purposes as a marker of hip fracture risk.

The results of this study are similar to those of the other two studies that have examined the relationship of albuminuria with fracture risk. In a population study from Norway [10], a one standard deviation increase in albuminuria resulted in a relative risk of nonvertebral fracture of 1.01 in men ($p=0.94$) and 1.15 in women ($p=0.005$). In the ONTARGET/TRANSCEND Studies [10], which examined people at high risk for CVD, baseline albuminuria predicted an increased risk of hip and pelvic fractures (HR, 1.36 (1.01, 1.84)) in men and women, though the association appeared stronger with macroalbuminuria (HR, 1.71 (1.007, 2.91), $p=0.05$) than with microalbuminuria (HR, 1.28 (.92, 1.78), $p=0.15$). The risk estimates from those studies are similar to those of the current study. In those studies, fractures were examined in people ~15–20 years younger than in our cohort. At such a relatively young age, albuminuria, hip fracture, or both, may differ in character from such factors in the elderly and would not necessarily reflect the same processes. For example, in the population study from Norway, only a small percent of the cohort had microalbuminuria. In our cohort, ~21 % had microalbuminuria. Similarly, in the cohorts from Norway and from ONTARGET/TRANSCEND, hip fractures ($\pm$ pelvic fractures) occurred in ~1.7 and .12 %, respectively, whereas in our cohort hip fractures occurred in ~10 %. Despite these differences, a degree of similarity in risk of hip fracture in relation to albuminuria is present, making our findings believable.

We note that albuminuria was not significantly associated with hip fracture risk after adjustment for osteoporosis risk factors. This suggests that the effect of albuminuria on fracture risk was in part through osteoporosis. It was only after additional adjustment for

frailty and a history of falling that the risk for fracture attained statistical significance in women, though the overall risk estimate remained approximately the same. Women with albuminuria had more frailty and falling than women without albuminuria, and even more than men, with or without albuminuria. The frailty phenotype consists mostly of low grip strength and slow walking, which are factors that predict adverse health outcomes independent of advancing age, chronic disease, and functional limitations [17, 18]. From these findings, one can speculate that albuminuria leads to fracture risk in women through musculoskeletal “senescence,” which is in the causal pathway to fractures. Since menopause is accompanied by loss of muscle mass and strength [19], any adverse impact of albuminuria on the musculoskeletal system can further increase musculoskeletal dysfunction.

Albuminuria was related to a mildly lower total hip BMD in men but not in women. This finding has a parallel in the population study from Norway [9]. In that study, BMD in the distal forearm—a site of trabecular bone—was lower in men ($p=0.01$) with albuminuria, but not in women. Why albuminuria was more strongly associated with BMD in men as compared with women is not certain. It may be speculated that the preceding menopausal state leads to significant loss of BMD in women which overshadows any small effect of albuminuria on BMD in older age. Among older men, who have not experienced a similar period of rapid mineral loss, the impact of increased urine albumin levels on BMD may be more noticeable. Despite this finding, albuminuria was not associated with increased fracture risk in men.

Strengths of this study include information on many aspects of participants’ health, adjustment for many covariates, a high degree of quality control, the use of cystatin to estimate GFR, and prolonged follow-up. The cohort was racially mixed as compared with the homogenous cohort from Norway, an area known for high fracture risk. Three limitations should be noted. First, the participants with albuminuria testing were healthier than those who did not have albuminuria testing. Had sicker individuals been included it is likely that more albuminuria and more fractures would have been detected. Our results are therefore conservative estimates. Second, only one urine specimen was obtained at baseline, a common practice in epidemiological studies, so as to avoid extra cost and burden to participants. Albuminuria levels are known to vary. Because of this variability, we believe that our observations underestimate the true association and are biased to the null. Lastly, the participants with DEXA scanning were healthier relative to those who did not have DEXA scanning. Were sicker individuals examined it is possible that a stronger negative relationship between albuminuria and BMD could have been detected.

In conclusion, we report that albuminuria is associated with a small, independent, increased risk of hip fracture in women. This small effect cannot be used clinically for prognostic purposes. Nonetheless, the findings suggest that microvascular disease contributes to hip fracture risk in older adults.

Acknowledgments

The research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, and N01-HC-45133, grant number U01 HL080295 from the National Heart, Lung, and Blood Institute, with additional contribution from the National

Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at <http://www.chs-nhlbi.org/pi.htm>.

References

1. Parfitt AM. The mechanism of coupling: a role for the vasculature. *Bone*. 2000; 26:319–23. [PubMed: 10787232]
2. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening. Results from NHANES III. *Kidney Int*. 2002; 61:2165–2175. [PubMed: 12028457]
3. Barzilay JI, Peterson D, Cushman M, Heckbert SR, Cao JJ, Blaum C, Tracy RP, Klein R, Herrington DM. The relationship of cardiovascular risk factors to microalbuminuria in older adults with or without diabetes mellitus or hypertension; the Cardiovascular Health Study. *Am J Kidney Dis*. 2004; 44:25–34. [PubMed: 15211434]
4. Redlich K, Smolen JS. Inflammatory bone loss: pathogenesis and therapeutic intervention. *Nat Rev Drug Discov*. 2012; 11:234–250. [PubMed: 22378270]
5. Burkhardt R, Kettner G, Böhm W, Schmidmeier M, Schlag R, Frisch B, Mallmann B, Eisenmenger W, Gilg T. Changes in trabecular bone, hematopoiesis and bone marrow vessels in aplastic anemia, primary osteoporosis, and old age: a comparative histomorphometric study. *Bone*. 1987; 8:157–164. [PubMed: 3606907]
6. Griffith JF, Yeung DK, Tsang PH, Choi KC, Kwok TC, Ahuja AT, Leung KS, Leung PC. Compromised bone marrow perfusion in osteoporosis. *J Bone Miner Res*. 2008; 23:1068–1075. [PubMed: 18302498]
7. Laroche M, Ludot I, Thiechart M, Arlet J, Pieraggi M, Chiron P, Moulinier L, Cantagrel A, Puget J, Utheza G, Mazieres B. Study of the intraosseous vessels of the femoral head in patients with fractures of the femoral neck or osteoarthritis of the hip. *Osteoporos Int*. 1995; 5:213–217. [PubMed: 7492858]
8. Moseley KF. Type 2 diabetes and bone fractures. *Curr Opin Endocrinol Diabetes Obes*. 2012; 19:128–135. [PubMed: 22262002]
9. Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. *Calcif Tissue Int*. 2009; 84:103–111. [PubMed: 19067019]
10. Jørgensen L, Jenssen T, Ahmed L, Bjørnerem A, Joakimsen R, Jacobsen BK. Albuminuria and risk of nonvertebral fractures. *Arch Intern Med*. 2007; 167:1379–1385. [PubMed: 17620531]
11. Barzilay JI, Gao P, Clase K, Mente A, Mann JFE, Sleight P, Yusuf S, Teo KK, on behalf of the ONTARGET/TRANSCEND Investigators. Albuminuria and rapid loss of glomerular filtration rate predict new hip and pelvic fractures: the ONTARGET/TRANSCEND studies. *Clin J Am Soc Nephrol*. 2013; 8:233–240. [PubMed: 23184565]
12. Robbins JA, Biggs ML, Cauley J. Adjusted mortality after hip fracture: from the Cardiovascular Health Study. *J Am Geriatr Soc*. 2006; 54:1885–1891. [PubMed: 17198494]
13. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, O'Leary DH, Psaty B, Rautaharju P, Tracy RP, Weiler PG. Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991; 1:263–276. [PubMed: 1669507]
14. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch Intern Med*. 2007; 167:635–641. [PubMed: 17420420]
15. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem*. 1995; 41:264–270. [PubMed: 7874780]
16. R Development Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing; Vienna: 2009. <http://www.R-project.org>
17. Xue QL, Beamer BA, Chaves PH, Guralnik JM, Fried LP. Heterogeneity in rate of decline in grip, hip, and knee strength and the risk of all-cause mortality: the Women's Health and Aging Study II. *J Am Geriatr Soc*. 2010; 58:2076–2084. [PubMed: 21054287]

18. Chen PJ, Lin MH, Peng LN, Liu CL, Chang CW, Lin YT, Chen LK. Predicting cause-specific mortality of older men living in the Veterans home by handgrip strength and walking speed: a 3-year, prospective cohort study in Taiwan. *J Am Med Dir Assoc.* 2012; 13:517–521. [PubMed: 22459909]
19. Brown M. Skeletal muscle and bone: effect of sex steroids and aging. *Adv Physiol Educ.* 2008; 32:120–126. [PubMed: 18539850]

Appendix

Table 5

Differences between the cohort excluded from DEXA scanning and the cohort with DXA scanning

Characteristic	Total CHS	Excluded Cohort	DEXA Cohort	Difference Between Excluded and DEXA Cohorts
Age (years)	78.61±5.13	78.83±5.31	78.02±4.57	<0.01
BMI	26.9±4.69	26.86±4.81	26.97±4.44	0.49
SBP	136.9±20.69	137.37±20.78	135.96±20.47	0.05
DBP	69.83±11.26	69.96±11.57	69.56±10.61	0.29
Height	163.54±9.56	163.47±9.55	163.66±9.58	0.57
Weight (kg)	72.03±14.69	71.84±15.09	72.41±13.86	0.26
CRP	4.76±8.02	4.68±7.08	4.9±9.53	0.5
Cystatin C	1.16±0.41	1.16±0.41	1.17±0.42	0.6
eGFR	67.66±17.66	68.23±17.7	66.59±17.55	<0.01
Grip (kg)	27.31±9.78	26.9±9.69	28.09±9.91	<0.01
Frailty				0.97
None	1,099 (36.7)	716 (36.5)	383 (37.0)	
Pre frail	1,556 (52.0)	1,020 (52.1)	536 (51.7)	
Frail	340 (11.4)	223 (11.4)	117 (11.3)	
Walk speed	1.13±0.35	1.14±0.36	1.11±0.31	0.01
Creatinine	1.07±0.44	1.05±0.43	1.1±0.45	<0.01
Cholesterol	201.96±39.65	202.06±39.66	201.78±39.63	0.84
Alcohol	1.81±5.16	1.46±4.86	2.66±5.73	<0.01
Kcal/week	1,164.03±1,616.49	1,151.99±1,641.95	1,192.04±1,555.98	0.46
Kcal (chores excluded)	856.23±1,311.36	826.05±1,322.13	926.4±1,283.75	0.02
Male	1,692 (38.3)	1,186 (37)	506 (41.9)	<0.01
Blacks	738 (16.7)	502 (15.7)	236 (19.5)	<0.01
BP (>135 or 85 or med use)	3,096 (78.2)	2,188 (79.5)	908 (75.2)	<0.01
Estrogen use	399 (9.5)	269 (9)	130 (10.8)	0.10
Kidney disease	987 (29.1)	631 (28.5)	356 (30.3)	0.27
Insulin use	137 (3.3)	110 (3.7)	27 (2.2)	0.02
History of stroke	358 (8.1)	282 (8.8)	76 (6.3)	<0.01
History of coronary heart disease	1,165 (26.4)	855 (26.7)	310 (25.7)	0.52
History of hypertension	2,494 (65)	1,751 (66.5)	743 (61.7)	<0.01
Had a fall last year	825 (20)	597 (20.4)	228 (19.1)	0.36

Characteristic	Total CHS	Excluded Cohort	DEXA Cohort	Difference Between Excluded and DEXA Cohorts
Broken arm/hip/leg	116 (2.8)	91 (3.1)	25 (2.1)	0.1
Statin use	373 (8.9)	245 (8.2)	128 (10.6)	0.02
Thyroid hormone use	536 (12.8)	365 (12.3)	171 (14.2)	0.11
Oral hypoglycemic use	332 (7.9)	236 (7.9)	96 (7.9)	1.00
Thiazide use	669 (16)	476 (16)	193 (16)	1.00
Age category				
Up to 75	1,431 (32.4)	1,030 (32.1)	401 (33.2)	<0.01
75–80	1,580 (35.8)	1,087 (33.9)	493 (40.8)	
80 or above	1,402 (31.8)	1,088 (33.9)	314 (26)	
Smoking status				
Never	1,944 (47.7)	1,439 (49.9)	505 (42.5)	<0.01
Former	1,815 (44.6)	1,223 (42.4)	592 (49.8)	
Current	313 (7.7)	222 (7.7)	91 (7.7)	
Glucose status				
Normal	2,651 (76.2)	1,737 (75.5)	914 (77.6)	0.07
IFG	231 (6.6)	146 (6.3)	85 (7.2)	
Diabetes	597 (17.2)	418 (18.2)	179 (15.2)	
Health status				
Excellent	198 (4.6)	135 (4.3)	63 (5.2)	<0.01
Very good	968 (22.3)	658 (21)	310 (25.7)	
Good	1,899 (43.8)	1,343 (42.9)	556 (46)	
Fair	1,027 (23.7)	770 (24.6)	257 (21.3)	
Poor	247 (5.7)	225 (7.2)	22 (1.8)	

Data are reported as group means±standard deviations or counts with percentages

Fig. 1.
Kaplan–Meier plots for time without hip fracture by presence or absence of albuminuria (≤ 30 mg/g creatinine) in men and women

Table 1

Baseline characteristics of the Cardiovascular Health Study cohort categorized by sex and albuminuria (≥ 30 mg/g creatinine) status

	Male		Female	
	ALB ⁻ N=973	ALB ⁺ N=303	ALB ⁻ N=1,488	ALB ⁺ N=346
Demographic factors				
Age (years)	78.05±4.72	79.36±5.33 [*]	77.75±4.63	78.92±5.60 [*]
Race (black; %)	143 (14.7)	42 (13.9)	260 (17.5)	84 (24.3) [*]
BMI (kg/m ²)	26.53±3.91	26.93±3.90	27.30±5.11	26.56±5.32 ^{***}
Smoking status (%)				
Never	295 (30.8)	81 (27.1)	883 (60.6)	176 (53.0) [*]
Former	582 (60.8)	188 (62.9)	480 (32.9)	122 (36.7)
Current	81 (8.5)	30 (10.0)	95 (6.5)	34 (10.2)
Total energy expenditure (kcal/week)	1,362.41±1,643.20	991.10±1,445.57 [*]	671.75±1,055.89	505.25±817.87 [*]
Alcohol intake/week (oz)	3.43±7.40	2.53±5.85 ^{**}	1.21±3.81	0.89±2.89
History (%)				
Hypertension	513 (53.2)	230 (76.2) [*]	947 (63.7)	283 (82.0) [*]
Stroke	67 (6.90)	39 (12.90) [*]	69 (4.6)	35 (10.1) [*]
Coronary heart disease	285 (29.3)	127 (41.9) [*]	262 (17.6)	102 (29.5) [*]
Fall in last year	128 (13.3)	65 (21.7) [*]	306 (20.7)	87 (25.9) ^{****}
Prior fracture (arm, leg, and hip)	17(1.8)	7(2.3)	36 (2.4)	11 (3.2)
Diabetes	133 (14.1)	102 (34.5) [*]	163 (11.3)	93 (28.7) [*]
Frailty (%)				
None	357 (42.6)	71 (29.8) [*]	464 (36.3)	63 (23.5) [*]
Pre-frail	419 (50.0)	132 (55.5)	656 (51.3)	162 (60.4)
Frail	62 (7.4)	35 (14.7)	158 (12.4)	43 (16.0)
Medication use (%)				
Statin	76 (7.8)	35 (11.6)	152 (10.2)	28 (8.1)
Thiazide	129 (13.3)	38 (12.5)	293 (19.7)	66 (19.1)
Thyroid hormone	63 (6.5)	28 (9.2)	254 (17.1)	57 (16.5)
Estrogen therapy	–	–	248 (16.7)	48 (13.9)
Laboratory values				
Cystatin (mg/l)	1.14±0.30	1.45 0.68 [*]	1.09±0.27	1.33±0.59 [*]
ecGFR (ml min ⁻¹ 1.73 m ⁻²)	70.83±17.6	61.8±20.88 [*]	67.15±15.58	62.7±21.4 [*]
ecGFR (<60 ml min ⁻¹ 1.73 m ⁻² (%))	215 (22.8)	129 (44.3) [*]	425 (29.5)	123 (38.9) [*]
CRP (mg/l)	4.5±9.63	6.18±10.84 ^{***}	4.78±6.88	4.87±6.25
Hip fracture				
Time to hip fracture (years)	7.98±3.71	6.01±3.61 [*]	8.73±3.42	6.61±3.67 [*]

	Male		Female	
	ALB ⁻ N=973	ALB ⁺ N=303	ALB ⁻ N=1,488	ALB ⁺ N=346
Number hip fractures	72 (7.4)	26 (8.6)	173 (11.6)	42 (12.1)

Data are reported as group means±standard deviations or counts with percentages. Not all variables have a complete set of values for all participants. Conversion factors for obtaining SI are as follows: C-reactive protein (CRP), 40 nmol/l

*
 $p<0.01$;

**
 $p=0.03$;

 $p=0.02$,

 $p=0.05$

Table 2

Hip fracture rate in CHS participants who had albuminuria testing in 1995/1996 and who were followed up for a mean of 8.0 ± 3.68 years

	Total	No albuminuria	Albuminuria
Men			
Sample size	1,276	973	303
Hip fractures	98	72	26
Person-year follow up	9,585.41	7,764.77	1,820.64
Incidence/100 person-years ^a	1.02	0.93	1.43
Women			
Sample size	1,834	1,488	346
Hip fractures	215	173	42
Person-year follow-up	15,284.10	12,996.35	2,287.75
Incidence/100 person-years ^a	1.41	1.33	1.84

^a Adjusted for age, gender, BMI, and race

Table 3

Hazard ratios for hip fracture by log₂albumin Winsorized at the 95th percentile serially adjusted for factors associated with hip fracture risk

	Men HR (95 % CI)	Women HR (95 % CI)
Model I ^a	1.13 (1.02, 1.27)	1.15 (1.05, 1.25)
Model II ^b	1.11 (0.99, 1.24)	1.13 (1.03, 1.24)
Model III ^c	1.04 (0.92, 1.17)	1.09 (0.98, 1.21)
Model IV ^d	1.02 (0.89, 1.17)	1.12 (1.001, 1.25)

^a Unadjusted

^b Demographic factors: adjusted for age, race, and clinic site

^c Osteoporosis factors: model II plus BMI, smoking status (never, former, and current), alcohol, coronary heart disease, hypertension, ecGFR, kcal expended, CRP (< 3 mg/l), thiazide, statins, thyroid hormone use, and estrogen use in women

^d Fracture factors: model III plus a history of falling and frailty status

Table 4

Linear regression of bone mineral density in the hip and femoral neck with doubling of albuminuria levels that are 95 % Winsorized and log transformed (log₂ transformed albuminuria)

	Men			Women		
	Beta	95 % CI	p value	Beta	95 % CI	p value
Total hip	−0.009	−0.017, −0.001	0.04	−0.001	−0.008, 0.005	0.68
Femoral neck	−0.005	−0.012, 0.002	0.17	−0.0002	−0.006, 0.005	0.87

Values are grams of calcium per square centimeter per doubling of urine albumin per gram creatinine. Values adjusted for age, race, smoking status, kilocalories energy expenditure, BMI, ecGFR, and diabetes