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Research Article

Hospitalization Rates in Older Adults With Albuminuria: The Cardiovascular Health Study

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Abstract

Background: Albuminuria is highly prevalent among older adults, especially those with diabetes. It is associated with several chronic diseases, but its overall impact on the health of older adults, as measured by hospitalization, has not been quantified.

Method: We followed up 3,110 adults, mean age 78 years, for a median 9.75 years, of whom 654 (21%) had albuminuria (≥30 mg albumin/gram creatinine) at baseline. Poisson regression models, adjusted for cardiovascular, renal, and demographic factors, were used to evaluate the association of albuminuria with all-cause and cause-specific hospitalizations, as defined by ICD, version 9, categories.

Results: The rates of hospitalization per 100 patient-years were 65.85 for participants with albuminuria and 37.55 for participants without albuminuria. After adjustment for covariates, participants with albuminuria were more likely to be hospitalized for any cause than participants without albuminuria (incident rate ratio, 1.39 [95% confidence intervals, 1.27. 1.53]) and to experience more days in hospital (incident rate ratio 1.56 [1.37, 1.76]). The association of albuminuria with hospitalization was similar among participants with and without diabetes (adjusted incident rate ratio for albuminuria versus no albuminuria: diabetes 1.37 [1.11, 1.70], no diabetes 1.40 [1.26, 1.55]; *p* interaction nonsignificant). Albuminuria was significantly associated with hospitalization for circulatory, endocrine, genitourinary, respiratory, and injury categories.

Conclusions: Albuminuria in older adults is associated with an increased risk of hospitalization for a broad range of illnesses. Albuminuria in the presence or absence of diabetes appears to mark a generalized vulnerability to diseases of aging among older adults.

Keywords: UACR, ICD-9, Diabetes, Hospitalization, Length of hospitalization

Albuminuria (≥30 mg albumin/gram creatinine) is an age-related disorder, reaching its highest prevalence in the general population among people 70–79 years of age (21.2%) (1). Among similarly aged individuals with diabetes, the prevalence is even higher (42.6%) (1). Albuminuria occurs most often in the setting of hypertension and diabetes, which are also disorders of aging (2), and is a risk factor for renal and cardiovascular disease (CVD) (3,4). Endothelial dysfunction of glomerular capillaries underlies its pathogenesis, at least in part (5,6).

We have recently shown that higher urine albumin–creatinine ratio (UACR) and albuminuria in the presence of intact renal function (estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2) are associated with a high risk of hip fractures and cognitive decline (7–10). We have also shown that these disorders are prospectively associated with decreased physical performance, as measured by gait speed and grip strength (11). Taken together, these findings suggest that albuminuria may be an indicator of enhanced physiological aging beyond its known association with cardiovascular risk.

One way to test this hypothesis in an unbiased manner is to examine the rates and types of hospitalization in older adults with or without albuminuria (ie, to conduct a phenome-wide association study). If our hypothesis is correct, then we would expect to find more hospitalizations among people with albuminuria. We would also expect more hospitalizations in certain domains of aging—for example, fractures, heart failure, cancer, and infection. Finally, given the strong association of albuminuria with diabetes, and the adverse effect of diabetes on health, it might be hypothesized that albuminuria and diabetes would have multiplicative effects. In the present study, we test these hypotheses among participants of the Cardiovascular Health Study (CHS), a well-characterized cohort of older American adults with decades of comprehensive follow-up.

Method

CHS is an ongoing longitudinal study of adults aged 65 and older in four U.S. communities drawn from Medicare lists (12). In 1989–1990, 5,201 participants were recruited, followed by an additional 687 African Americans in 1992–1993. All participants gave informed consent upon study entry. Institutional review board approval was received at all clinical sites. From 1989–1990 to 1998–1999, participants were seen in clinic annually and had annual telephone contact between clinic visits.

Hospitalizations were generally ascertained through regular surveys initiated by the field centers or by participants contacting the local site. Investigator-initiated ascertainment occurred primarily during biennial clinic visits and surveillance calls, when participants were asked to provide information on all hospitalizations and outpatient end point diagnoses since the last CHS contact. Secondary sources of events include identification of unreported earlier hospitalizations or outpatient end point diagnoses during the review of medical records for a reported event, and through review of Medicare hospitalization data after 1992 for the present cohort. Follow-up for this study was truncated on June 30, 2015.

Urine Testing

Of the 5,888 original and African American participants, 4,494 were seen in 1996–1997, the baseline year for this study. Of these participants, 3,110 provided spot urine samples in the fasting state for albumin and creatinine levels. Participants without urine testing were older and had more comorbidity than participants with urine testing. Urine albumin was measured soon after collection on the Array 360 CE Protein Analyzer (Beckman Instruments, Fullerton, CA), and urine creatinine on the Ektachem 700 Analyzer (Eastman Kodak, Rochester, NY). Urinary albumin excretion was estimated as the UACR in milligrams albumin per gram creatinine. This method based on a spot urine yields results comparable to those from a 24-hour urine collection (13).

Covariates

Information from the baseline year (1996–1997) was collected on demographics (sex, age, race), smoking status, alcohol intake (drinks/week), medical history, seated blood pressure, and technician-measured height, weight, and waist circumference. Data collection was complete, other than ~2% missing data for smoking status, ~16% missing for frailty status, and ~1.7% for activities of daily living function. Coronary heart disease was centrally adjudicated, as previously described (14). Diabetes and impaired fasting glucose were defined using American Diabetes Association cut points and use of hypoglycemic medication. Renal function was assessed using the CKD-EPI formula based on cystatin C levels (15). We have reported that cystatin C is a stronger predictor of the risk of death and cardiovascular events in older persons than is creatinine (15). Lipid and C-reactive protein levels were measured as previously described (16). Modified Mini-Mental Status scores done at the baseline year are presented.

Outcomes

We predefined categories of causes of hospitalization based on the primary ICD-9 diagnosis code. These included infection (001–139); neoplasms (140–239); endocrine (240–279); blood (280–289); mental (290–319); nervous system (320–389); circulatory (390–459); respiratory (460–519); digestive (520–579); genitourinary (580–629); skin (680–709); musculoskeletal (710–739); symptoms (780–799); injury (800–999); cause of injury (E & V codes). For those categories in which the rate ratios between the presence and absence of albuminuria were statistically significant, we further examined individual diagnosis codes within the given category, restricting to those diagnosed with at least 40 hospitalizations for a given subcategory.

Statistical Methods

We present baseline factors by albuminuria status. For all outcomes, we examined numbers of hospitalizations and, as a secondary measure of burden, the number of hospital days to account for longer hospitalizations reducing the possibility of rehospitalization. Our primary exposure was albuminuria status, but we also examined outcomes per doubling of UACR as a continuous variable using the $\log_2$ transformation. To reduce the influence of outliers, UACR values above the 95th percentile of the distribution were set to the 95th percentile.

We estimate incidence rate ratios for numbers of hospitalizations and number of hospital days by Poisson regression. We estimate rate and rate ratios for numbers of hospitalizations and number of hospital days using quasi-likelihood Poisson regression, with offset for an individual's overall follow-up time. For robustness, we also examined time-to-first hospitalization using Cox models, but because these yielded very similar results, they are not shown here. Sex was considered an effect modifier. Data are presented for the whole group, as well as by sex to account for different disease susceptibilities for illnesses among women and men. Diabetes status was also considered as an effect modifier, and analyses were run separately by diabetes status.

We created sequentially adjusted regression models as follows: M0: age, race, gender, clinic site; M1: additionally for waist circumference, smoking status (current, never, former), diabetes, estimated glomerular filtration rate based on cystatin C levels, previous CVD, $\log_2$(C-reactive protein), total cholesterol, low-density lipoprotein cholesterol, triglycerides, self-reported health (good, very good, excellent versus fair or poor, alcohol (0, ≤7 drinks/wk, >7 drinks/wk), hypertension, hypertension medications, and serum albumin.

We conducted two additional sensitivity analyses of our primary outcomes (ie, all-cause hospitalization rates). First, we tested albumin excretion adjusted for, rather than multiplied by, the inverse of urine creatinine. This was done to examine whether low urine creatinine levels from loss of muscle mass did not artificially increase urine albumin to creatinine ratios. Second, we additionally adjusted our M1 model for cognitive status (Modified Mini-Mental Status score), frailty, and number of impaired activities of daily living to

see whether the impact of albuminuria on hospitalization rates was mediated by these disorders.

Analyses were conducted in R (R Development Core Team (17)).

Results

Table 1 shows baseline characteristics categorized by the presence and absence of albuminuria. There were 654 (21.0%) participants with albuminuria; of whom, 104 had UACR ≥ 300 mg/g creatinine. When compared with participants without albuminuria, those with albuminuria were older and more likely to be male; had higher systolic blood pressure and diastolic blood pressure; were current smokers or had previously smoked; had prevalent CVD, chronic obstructive pulmonary disease, hypertension, frailty, and difficulties with activities of daily living and instrumental activities of daily living; lower Modified Mini-Mental Status scores; and had higher glucose, C-reactive protein, triglyceride, and creatinine levels.

The median follow-up was 9.75 years (interquartile range, 5.38, 14.95), during which time there were 13,089 hospitalizations (Table 2), ranging from 0 to 63 events per participant. The hospitalization rates per 100 participant-years were 41.83 overall, 37.55 for those without albuminuria, and 65.85 for those with albuminuria. Participants accumulated 71,436 hospital days during follow-up, and the corresponding rates of hospitalized days were 228.33, 198.77, and 393.84 per 100 participant-years.

Poisson regression results are given in Table 3. After initial adjustment, participants with albuminuria were 70% more likely to be hospitalized than participants without albuminuria. Further adjustment for other covariates attenuated the results, but participants with albuminuria remained nearly 40% more likely to be hospitalized. Men and women had approximately similar associations of albuminuria with hospitalization rates. Similarly, participants with albuminuria had 90% more hospitalized days than participants without albuminuria on initial adjustment, and 56% with further adjustment.

Analyses were repeated examining UACR as a continuous variable (Table 3, bottom). For every doubling of the UACR, there was a statistically significant ~9% fully adjusted higher rate of hospitalization and ~13% more hospital days.

A multiplicative interaction term between albuminuria and diabetes was not statistically significant (Table 3, middle). The hospitalization rate ratios for albuminuria versus no albuminuria for participants without and with diabetes were similar, and there were no large differences in days of hospitalization comparing those with and without diabetes.

The incident rate ratio (IRR) hospitalization and hospitalization days of albuminuria versus no albuminuria with predefined categories of ICD-9-defined hospitalization are given in Table 4 and Supplementary Table S1, respectively. Almost all ratios were above one. Circulatory diseases had the highest IRR (1.65). Respiratory and endocrine hospitalizations had similar IRR (1.61), while genitourinary diseases (1.39) and injuries (1.30) had lower but statistically significant IRR of hospitalization as well. Circulatory disorders accounted for the largest number of hospitalizations (3,884/13,089 = ~30%) and hospital days. Together the above five categories accounted for 60.6% (7,930/13,089) of hospitalizations. When analyses were repeated using a doubling of UACR (ie, a continuous variable with more power), UACR was additionally associated with a significantly increased IRR for gastrointestinal and musculoskeletal hospitalizations (Supplementary Table S2; accounting for an additional 1,885 admissions; total 75% of all hospital admissions). (The mean number and lengths of hospitalizations per 100 participant-years, respectively, are given in Table 4 and Supplementary Table S1.)

For outcomes with statistically significant associations with a doubling of UACR, we examined which specific diagnoses appeared to account for the class-specific findings (Supplementary Table S4). In these analyses, the common causes of hospitalization significantly associated with albuminuria were diabetes, hypertensive disease, ischemic heart disease, congestive heart failure, occlusion of cerebral arteries, pneumonia, unspecified functional disorder of the intestine, unspecified disorders of male genital organs, acute kidney failure, other diseases of the urinary system, and pelvic fracture. The strongest associations were for diabetes, heart failure, pneumonia, and diseases of the male genital organs.

In sensitivity analyses, we additionally adjusted our M1 model for frailty, cognition, and disability, with little change in observed estimates; the additionally adjusted IRRs were 1.36 (95% confidence interval, 1.19–1.56) for hospitalizations and 1.57 (95% confidence interval, 1.31–1.89) for days hospitalized. Because UACR comprises a ratio, and hence may reflect associations with muscle mass (as estimated by urinary creatinine excretion) rather than urine albumin itself, we repeated our primary analyses analyzing albumin excretion adjusted for urinary creatinine concentration. These confirmed the associations of albuminuria with outcome, with adjusted IRRs of 1.09 (95% confidence interval, 1.07–1.11) for hospitalizations and 1.12 (95% confidence interval, 1.09–1.15) for days of hospitalization per doubling in urine albumin level (Supplementary Table S5).

Discussion

Using incident hospitalization rates as a measure of outcome, we found albuminuria to have a pervasive and deleterious association with the health of older adults across a broad range of diagnoses. Hospitalization rates were 39% higher among people with albuminuria even after adjustment for its key determinants, for example, hypertension and diabetes, and adjustment for concomitant estimated glomerular filtration rate. Circulatory disorders accounted for the largest number of hospitalizations (3,884/13,089 = ~30%) and the highest IRR. Most hospitalizations, however, were not for circulatory disorders, and endocrine and respiratory hospitalizations had similar IRR values. The above findings emphasize the broad impact of albuminuria on the health of older adults.

We hypothesize that albuminuria may not be a renal-specific disorder in this age group (when compared with the young). Rather, it may mark a systemic disorder of the microvasculature (18). Disorders of the microvasculature of the skin (as measured through nail-fold capillaroscopy) (19), brain (abnormal brain white matter and cognitive decline]) (8), lungs (greater FEV1 decline with a doubling of log-transformed UACR) (20), of large blood vessel reactivity (post-occlusive arterial hyperemia) (21), and of the heart muscle [reduced myocardial flow reserve] (22), have been described in association with albuminuria or increased UACR. In contrast to these other measures, albuminuria is easily assessed and hence can be used inexpensively in clinical practice.

Contrary to our hypothesis that diabetes would synergistically worsen the number of hospitalizations in people with albuminuria, we found no material differences in the incident rate ratios of hospitalization or lengths of hospitalization in participants with or without diabetes. This finding is similar to that of the Chronic Kidney

Table 1. Baseline Characteristics of the Cardiovascular Health Study Cohort With Spot Urine Testing in 1996/1997 Overall and Categorized by the Presence or Absence of Albuminuria

	Total Group (*N* = 3,110)	No Albuminuria (*N* = 2,456)	Albuminuria (*N* = 654)	*p* Value
Demographics				
Age (y, *SD*)	78.13 (4.87)	77.86 (4.67)	79.12 (5.46)	<.001
Male (*n*, %)	1,276 (41.0)	971 (39.5)	305 (46.6)	.001
SBP (mm Hg, SD)	137.17 (21.1)	134,76 (19.63)	146.21 (23.82)	<.001
DBP (mm Hg)	69.95 (11.35)	69.50 (10.68)	71.65 (13.45)	<.001
Race (Black; *n*, %)	529 (17.0)	403 (16.4)	126 (19.3)	.10
Education (HS education; *n*, %)	1,461 (47.1)	1,169 (47.7)	292 (44.9)	.21
Alcohol (drinks/wk; *n*, %)				
None	1,762 (57.1)	1,377 (56.5)	385 (59.5)	.28
<7 drinks/wk	1,005 (32.6)	801 (32.9)	204 (31.5)	
≥7 drinks/wk	318 (10.3)	260 (10.7)	58 (9.0)	
Smoking (*n*)	3,047	2,411	636	<.001
Current (*n*, %)	282 (9.3)	202 (8.4)	80 (12.6)	
Former (*n*, %)	1,330 (43.6)	1,034 (42.9)	296 (46.5)	
Never (*n*, %)	1,435 (47.1)	1,175 (48.7)	260 (40.9)	
Clinic (*n*)	3,110	2,456	654	.005
North Carolina (*n*, %)	785 (25.2)	649 (26.4)	136 (20.8)	
California (*n*, %)	875 (28.1)	687 (28.0)	188 (28.7)	
Maryland (*n*, %)	633 (20.4)	474 (19.3%)	159 (24.3)	
Pennsylvania (*n*, %)	817 (26.3)	646 (26.3)	171 (26.1)	
Measures of weight				
Weight (kg, *SD*)	72.49 (14.67)	72.60 (14.50)	72.07 (15.29)	.42
Waist (cm, *SD*)	97.34 (13.25)	97.37 (13.33)	97.21 (12.95)	.78
BMI (kg/m^2, *SD*)	26.95 (4.68)	27.01 (4.68)	26.73 (4.70)	.19
Prevalent HTN and CVD				
HTN (*n*, %)	1,973 (63.7)	1,455 (59.5)	518 (79.4)	<.001
HTN meds (*n*, %)	1,848 (59.5)	1,363 (55.5)	485 (74.3)	<.001
CHD prevalence (*n*, %)	776 (25.0)	544 (22.1)	232 (35.5)	<.001
Prevalent MI (*n*, %)	377 (12.1)	253 (10.3)	124 (9.0)	<.001
Stroke (*n*, %)	210 (6.8)	136 (5.5)	74 (11.3)	<.001
TIA prevalence (*n*, %)	121 (3.9)	73.3 (3.0)	48 (7.3)	<.001
CHF prevalence (*n*, %)	297 (9.5)	174 (7.1)	123 (18.8)	<.001
Medical conditions				
Diabetes (*n*, %)	491 (16.3)	294 (12.3)	197 (31.5)	<.001
COPD (*n*, %)	400 (15.9)	299 (14.8)	101 (20.1)	.004
Number of difficulties with ADL (*n*)	3,056	2,414	642	.004
None (*n*, %)	2,458 (80.4)	1,976 (81.9)	482 (75.1)	
1 (*n*, %)	388 (12.7)	294 (12.2)	94 (14.6)	
2 (*n*, %)	129 (4.2)	88 (3.6)	41 (6.4)	
≥3 (*n*, %)	81 (2.7)	56 (2.3)	25 (3.9)	
Any difficulty with IADL (%)	35.1	33.3	42.2	<.001
Self-reported good, very good, excellent health (%)	75.7	77.9	67.2	<.001
Modified Mini-Mental Test score	91.08 ± 10.37	91.55 ± 10.05	89.30 ± 11.33	<.001
Frailty (*n*)	2,622	2,112	510	
None (*n*, %)	955 (36.4)	821 (38.9)	134 (26.3)	<.001
Pre-frail (*n*, %)	1,369 (52.2)	1,073 (50.8)	296 (58.00)	
Frail (*n*, %)	298 (11.4)	218 (10.3)	80 (15.7)	
Laboratory results				
Glucose (mg/dL, *SD*)	107.42 (32.97)	103.97 (27.71)	120.84 (45.87)	<.001
Log_2 CRP (mg/L, *SD*)	1.34 (1.59)	1.28 (1.58)	1.56 (1.59)	<.001
Log_2 UACR (mg/g, *SD*)	0.36 (1.97)	−0.39 (1.13)	3.17 (1.91)	<.001
Serum albumin (mg/dL)	3.83 (0.30)	3.83 (0.29)	3.84 (0.33)	.42
Serum creatinine (mg/dL, *SD*)	1.08 (0.43)	1.03 (0.29)	1.27 (0.73)	<.001
e_tGFR_{cyst} (mL/min/1.73 m^2, *SD*)	70.02 (19.5)	72.33 (18.42)	61.03 (20.95)	<.001
Total cholesterol (mg/dL)	201.8 (39.8)	202.5 (38.9)	199.2 (43.2)	.09
LDL cholesterol (mg/dL)	128.3 (32.9)	128.6 (32.6)	126.8 (34.1)	.24
Triglycerides (mg/dL)	145.4 (88.9)	141.9 (81.9)	158.6 (10.6)	<.001

Notes: ADL = activities of daily living scale; BMI = body mass index; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFRcyst = estimated glomerular filtration rate based on cystatin C levels; frailty = presence of at least three characteristics (Fried criteria [ref.]): self-reported exhaustion, slow walking, low grip strength, involuntary weight loss, low physical activity; HS = high school; HTN = hypertension; IADL = instrumental activities of daily living scale; LDL = low-density lipoprotein; MI = myocardial infarction; SBP = systolic blood pressure; UACR = urine albumin–creatinine ratio. Numbers in the columns are the number of people from each group with that characteristic.

Table 2. The Number of Hospitalizations and the Number of Days of Hospitalization During Follow-up in the Cardiovascular Health Study Cohort With Spot Urine Testing in 1996/1997, Overall, and Categorized by the Presence or Absence of Albuminuria

	Total	No Albuminuria	Albuminuria
Number of participants/number hospitalizations	3,110/13,089	2,456/9,967	654/3,122
Incidence rates per 100 participant-years (95% CI)	41.83 (40.24, 43.49)	37.55 (36.02, 39.14)	65.85 (60.78, 71.33)
Number of participants/days of Hospitalization	3,110/71,436	2,456/52,763	654/18,673
Hospital days per 100 participant-years (95% CI)	228.33 (215.98, 241.39)	198.77 (186.81, 211.49)	393.84 (354.93, 437.01)

Note: CI = confidence interval.

Table 3. Poisson Regression Models of the Ratio of Hospitalizations and Length of Hospitalization Between Participants With Albuminuria Versus Those Without Albuminuria and by Doubling of Urine Albumin–Creatinine Ratio

	All			Men			Women		
	Rate Ratio	95% CI	*p* Value	Rate Ratio	95% CI	*p* Value	Rate Ratio	95% CI	*p* Value
All									
Hospitalization									
Model 1	1.70	1.56, 1.85	<.001	1.64	1.44, 1.85	<.001	1.75	1.56, 1.96	<.001
Model 2	1.39	1.27, 1.53	<.001	1.36	1.19, 1.57	<.001	1.42	1.25, 1.60	<.001
Hospital days									
Model 1	1.90	1.69, 2.14	<.001	1.85	1.56, 2.20	<.001	1.95	1.66. 2.29	<.001
Model 2	1.56	1.37, 1.76	<.001	1.48	1.23, 1.77	<.001	1.61	1.35. 1.91	<.001
No diabetes									
Hospitalization									
Model 1	1.62	1.47, 1.79	<.001	1.58	1.35, 1.83	<.001	1.65	1.45, 1.89	<.001
Model 2	1.40	1.26, 1.55	<.001	1.43	1.22, 1.69	<.001	1.36	1.18, 1.56	<.001
Hospital days									
Model 1	1.82	1.59, 2.10	<.001	1.79	1.48, 2.16	<.001	1.86	1.52, 2.26	<.001
Model 2	1.56	1.36, 1.79	<.001	1.57	1.29, 1.91	<.001	1.53	1.26, 1.87	<.001
Diabetes									
Hospitalization									
Model 1	1.55	1.29, 1.86	<.001	1.47	1.14, 1.90	.003	1.62	1.25, 2.09	<.001
Model 2	1.37	1.11, 1.70	.003	1.15	0.84, 1.57	.383	1.65	1.21, 2.23	.002
Hospital days									
Model 1	1.69	1.32, 2.17	<.001	1.65	1.13, 2.42	.011	1.75	1.27, 2.41	<.001
Model 2	1.49	1.11, 2.00	.008	1.24	0.77, 2.00	.384	1.79	1.23, 2.61	.003
LOG_2 ACR									
Hospitalization									
Model 1	1.14	1.12, 1.16	<.001	1.13	1.10, 1.16	<.001	1.15	1.13, 1.82	<.001
Model 2	1.09	1.07, 1.12	<.001	1.09	1.06, 1.13	<.001	1.10	1.07, 1.13	<.001
Hospital days									
Model 1	1.18	1.15, 1.21	<.001	1.17	1.13, 1.21	<.001	1.18	1.14, 1.22	<.001
Model 2	1.13	1.10, 1.16	<.001	1.13	1.09, 1.17	<.001	1.13	1.08, 1.17	<.001

Notes: ACR = albumin–creatinine ratio; CI = confidence interval. Models are also categorized by the presence or absence of diabetes mellitus. Model 1 adjusted for age, gender, black race, clinic site. Model 2 further adjusted for waist circumference, smoking status, diabetes, prevalent cardiovascular disease, log2(C-reactive protein), estimated glomerular filtration rate based on cystatin C levels, total cholesterol, low-density lipoprotein cholesterol, triglycerides, self-reported health (excellent, very good, good versus fair, poor), HbA1c, alcoholic drinks per week (0, <7, >7), hypertension, antihypertension mediations, serum albumin.

Disease Consortium, which reported similar relative risks for mortality and renal failure for albuminuria in people with and without diabetes (3). Our result suggests that many of the injurious effects of diabetes on clinical outcomes are magnified in the presence of albuminuria and that in the absence of albuminuria, diabetes may be associated with fewer complications. Population-based studies and randomized clinical trials indirectly confirm this hypothesis. In the population-based Third Health and Nutrition Examination Survey (NHANES III) study, kidney disease (estimated glomerular filtration rate < 60 mL/minute/1.73 m^2 or albumin/creatinine ratio ≥ 30 mg/g) accounted for the increased mortality in association with diabetes (23). In the absence of albuminuria, mortality was not increased in comparison to people without diabetes. Likewise, in an analysis of ~270,000 participants from the Swedish National Diabetes Register, the absence of albuminuria, together with low levels of CVD risk factors, was associated with little to no excess risk of mortality, myocardial infarction, or stroke (24). In a meta-analysis of randomized diabetes clinical trials, the presence of impaired renal function or proteinuria was strongly associated with an increased risk of mortality (25). In their absence, mortality was not markedly increased.

Lastly, we did not observe a significantly increased risk of cancer associated with albuminuria. Cancer is more common with aging. NHANES III reported a modest increased risk (relative risk, 1.20 [95% CI, 1.06–1.36]) of cancer in people with albuminuria (26). We note that our nonsignificant risk estimate of 1.12 is similar to that of the NHANES study, and the confidence interval extends to 1.68. The

Table 4. The Rate Ratio of Hospitalizations for Different Categories of Illness (Based on the ICD-9 Classification) for the Total Cohort and Categorized by Sex Between Those With and Without Albuminuria From the Cardiovascular Health Study

	All (n = 3,110)			Men (n = 1,276)			Women (n = 1,834)		
Category	Rate Ratio	95% CI	p Value	Rate Ratio	95% CI	p Value	Rate Ratio	95% CI	p Value
Infectious (n = 522)	1.24	0.92, 1.68	.15	0.93*[1]	0.52, 1.64	.79	**1.47**	**1.03, 2.10**	**.03**
Neoplasms (n = 621)	1.12	0.74, 1.68	.59	1.45	0.87, 2.43	.16	0.82	0.43, 1.56	.55
Endocrine (n = 487)	**1.61**	**1.16, 2.25**	**.005**	1.18	0.64, 2.18	.60	**1.98**	**1.34, 2.91**	**<.001**
Blood (n = 138)	1.23	0.68, 2.23	.49	0.53*[2]	0.15, 1.87	.23	1.76	0.90, 3.43	.10
Mental (n = 114)	0.88	0.45, 1.72	.71	0.21	0.04, 1.08	.06	1.36	0.60, 3.08	.46
Nervous system (n = 199)	1.08	0.64, 1.83	.77	0.53*[3]	0.19, 1.51	.23	**1.80**	**1.02, 3.16**	**.04**
Circulatory (n = 3,884)	**1.65**	**1.43, 1.91**	**<.001**	**1.66**	**1.34, 2.05**	**<.001**	**1.66**	**1.37, 2.02**	**<.001**
Respiratory (n = 1,538)	**1.61**	**1.28, 2.04**	**<.001**	**1.92**	**1.39, 2.65**	**<.001**	1.36	0.99, 1.87	.06
Digestive (n = 1,267)	1.16	0.92, 1.48	.23	1.11	0.76, 1.60	.60	1.22	0.89, 1.68	.22
Genitourinary (n = 746)	**1.39**	**1.09, 1.77**	**.008**	1.09*[4]	0.74, 1.64	.67	**1.74**	**1.26, 2.38**	**<.001**
Skin (n = 191)	1.06	0.63, 1.78	.83	0.38*[5]	0.12, 1.20	.10	1.63	0.95, 2.80	.08
Musculoskeletal (n = 618)	1.23	0.94, 1.61	.13	1.06	0.67, 1.68	.81	1.30	0.93, 1.82	.13
Symptoms (n = 998)	1.13	0.89, 1.43	.31	1.07	0.75, 1.55	.70	1.18	0.86, 1.60	.30
Injury (n = 1,275)	**1.30**	**1.06, 1.59**	**.01**	**1.42**	**1.00, 2.00**	**.05**	1.19	0.93, 1.53	.17
Cause of injury (n = 121)	1.83	0.67, 5.04	.24	1.44	0.22, 9.46	.71	2.51	0.88, 7.15	.09

Notes: Results are fully adjusted per Model 2, Table 3. Statistically significant results are in bold. The numbers next to the hospitalization category are the number of hospitalizations for that category in the total cohort. Starred results (*) are significant incident rate ratio (IRR) differences between men and women. Rates of incident hospitalization for all participants per 100 participant-years for those without and with albuminuria in each disease category are shown. Significant IRR differences between men and women (*) (1): 0.55 [0.31, 0.99], p = .05 (2); 0.20 [0.05, 0.81], p = .02 (3); 0.33 [0.12, 0.94], p = .04 (4); 0.62 [0.40, 0.98], p = .04; (5) 0.31 [0.10, 0.95], p = .04.

1. Infectious: 1.54 (1.37, 1.73) vs. 2.40 (1.84, 3.14).
2. Neoplasms: 1.94 (1.66, 2.26) vs. 2.26 (1.59, 3.20).
3. Endocrine: 1.22 (1.03, 1.46) vs. 3.42 (2.74, 4.26).
4. Blood: 0.41 (0.36, 0.53) vs. 0.59 (0.38, 0.93).
5. Mental: 0.37 (0.29, 0.47) vs. 0.36 (0.19, 0.67).
6. Nervous system: 0.63 (0.52, 0.77) vs. 0.65 (0.47, 0.92).
7. Circulatory: 10.40 (9.70, 11.54) vs. 23.71 (20.93, 26.85).
8. Respiratory: 4.29 (3.83, 4.80) vs. 8.42 (7.05, 10.04).
9. Digestive: 3.79 (3.42, 4.19) vs. 5.51 (4.61, 6.57).
10. Genitourinary: 2.12 (1.90, 2.37) vs. 3.86 (3.20, 4.66).
11. Skin: 0.55 (0.45, 0.68) vs. 0.93 (0.57, 1.52).
12. Musculoskeletal: 1.93 (1.75, 2.12) vs. 2.26 (1.78, 2.86).
13. Symptoms: 3.00 (2.73, 3.30) vs. 4.24 (3.59, 5.00).
14. Injury: 3.81 (3.51, 4.13) vs. 5.59 (4.60, 6.80).
15. Cause of injury: 0.33 (0.21, 0.51) vs. 0.72 (0.33, 1.58).

NHANES III study had more participants and longer follow-up than did CHS; hence, this association warrants greater study.

The Atherosclerosis Risk in Communities (ARIC) reported on hospitalization rates among 4766 older adults (mean age 75.7 years) using Kidney Disease Improving Global Outcomes (KIDGO) criteria (27). It reported high UACR values to be strongly associated with hospitalization risk. Owing to its methodology of simultaneously using estimated glomerular filtration rate and UACR, we cannot compare our results to those from ARIC. In a report from Kaiser Permanente (28), CVD hospitalization risk rose from normoalbuminuria to microalbuminuria to macroalbuminuria.

This study has several strengths. By using total hospitalization rates, we gauge the association of albuminuria with the health of older individuals in as broad and unbiased a manner as possible. Most studies focus only on mortality and cardiovascular/renal outcomes. The cohort has been closely followed up for many years and is well characterized, enabling us to account for important confounders. Complete data on baseline variables (other than smoking, frailty, and activities of daily living status) were available. Hospital follow-up data are complete. Both African American and Caucasians are studied. We examined results by two effect modifiers: sex and diabetes status. Limitations of the study should be noted. The results of this study are limited to older adults. It is possible that, in the absence of the accumulated effects of aging, the associations of albuminuria with chronic disease outcomes may not be present in younger people. Urine was collected only once; urine albumin levels vary, which may have biased our estimates to or away from the null owing to misclassification. We examined a number of inter-related outcomes, but some types of hospitalization were infrequent, limiting our power. Because of their inter-relationships, we did not formally adjust for multiple comparisons, but as given in Supplementary Table 1, most associations would be significant even with a stringent penalty. Because only ~100 participants had macroalbuminuria, we could not study its effects separately from microalbuminuria. Also, several covariates that we adjusted for could be in the causal pathways to hospitalization (mediation) and were not confounders. Hence, we may have overadjusted our findings. Several outcomes had statistically significant associations with albuminuria, and most IRRs reflected 40% or more increases in hospitalization rate, but the degrees of association may not have been clinically meaningful, particularly for rarer endpoints. We also note that CHS participants without

albuminuria testing (~30% of the total cohort at baseline) were more ill than those who had urine testing. Hence our estimates may be conservative. Finally, CHS is an observational study, so causality cannot be ascribed to our results. Nonetheless, our findings are plausible and robust across several methodological approaches, and it is not clear how an experimental design could directly address this question.

In conclusion, in a population-based cohort of older adults, urine albumin excretion was associated with an increased risk of hospitalization and hospitalized days for many chronic age-associated disorders. Our findings were similar in people with and without diabetes. These findings, combined with the associations of albuminuria with difficulties of activities of daily living and frailty and our prior publication that albuminuria is associated longitudinally with diminishments of gait speed and grip strength (11), suggest that it may be a marker of enhanced physiological aging. This paradigm broadens the view of urine albumin excretion beyond that of being solely a marker of renal disease or even a CVD risk factor, to one that may mark a system-wide disorder of biological aging. Validation of our results would be of interest.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Author Contributions

All authors of this article have participated in the conception and design of the article and are accountable for the integrity and accuracy of the work. All authors have given final approval to submit the article. J.I.B. conceived the original idea and contributed to the design, interpretation, and writing of paper; P.B. involved in the design, data analysis, interpretation, and intellectual content of the paper; M.G.S. is the co-head of the CHS renal group and involved in the design, interpretation, data acquisition, intellectual content of paper; N.B. is co-head of the CHS renal group and contributed to the interpretation, intellectual content of paper, editing; P.G. contributed to the interpretation, intellectual content of paper, editing, design; and K.J.M. involved in the design, data analysis, funding, data acquisition, writing the paper, intellectual content of paper.

Conflict of Interest

None reported.

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