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Influence of Urine Creatinine Concentrations on the Relation of Albumin-Creatinine Ratio With Cardiovascular Disease Events: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

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Supplementary Material
Table S1: Correlations among urine measures and eGFR in MESA.
Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

Background—Higher urine albumin-creatinine ratio (ACR) is associated with cardiovascular disease (CVD) events, an association that is stronger than that between spot urine albumin on its own and CVD. Urine creatinine is correlated with muscle mass, and low muscle mass is also associated with CVD. Whether low urine creatinine in the denominator of the ACR contributes to the association of ACR with CVD is uncertain.

Study Design—Prospective cohort study.

Setting & Participants—6,770 community-living individuals without CVD.

Predictors—Spot urine albumin, the reciprocal of the urine creatinine concentration (1/UCr), and ACR.

Outcome—Incident CVD events.

Results—During a mean of 7.1 years' follow-up, 281 CVD events occurred. Geometric means for spot urine creatinine, urine albumin and ACR were 95 ± 2 (SD) mg/dl, 0.7 ± 3.7 mg/dl and 7.0 ± 3.1 mg/g. Adjusted HRs per 2-fold higher increment in each urinary measures with CVD events were similar (1/UCr: 1.07 [95% CI, 0.94-1.22]; urine albumin: 1.08 [95% CI, 1.01-1.14]; and ACR: 1.11 [95% CI, 1.04-1.18]). Urine creatinine was lower in older, female, and low weight individuals. ACR 10 mg/g was more strongly associated with CVD events in individuals with low weight (HR for lowest vs. highest tertile: 4.34 vs. 1.97; p for interaction=0.006). Low weight also modified the association of urine albumin with CVD (p for interaction=0.06), but 1/urine creatinine did not (p for interaction=0.9).

Limitations—We lacked 24-hour urine data.

Conclusions—While ACR is more strongly associated with CVD events among persons with low body weight, this association is not driven by differences in spot urine creatinine. Overall, the associations of ACR with CVD events appear to be driven primarily by urine albumin and less by urine creatinine.

In a variety of patient populations, albuminuria is associated with incident cardiovascular disease (CVD) morbidity and mortality.(1-4) Higher levels of albuminuria, even at levels below the standard definition of microalbuminuria (i.e. <30 mg/g) have consistently been associated with a graded increased risk for CVD events, independent of estimated glomerular filtration rate (eGFR) and other CVD risk factors.(2, 3, 5-7)

Timed urine collections are cumbersome and frequently inaccurate in the out-patient setting, and spot urine albumin-creatinine ratios (ACRs) correlate directly with timed albuminuria measurements. Thus, spot ACR has largely replaced timed urine collections to quantify albuminuria in both clinical and research settings.(8) Urine creatinine is used in the denominator of the ACR to account for variations in urine tonicity.(9),(10) However, creatinine is produced by muscle and the urine creatinine excretion rate is directly correlated with muscle mass. Muscle mass, in turn, is influenced by age, sex, race and nutritional status.(11-15) Higher ACR may therefore result from higher urine albumin excretion, lower urine creatinine excretion potentially due to lower muscle mass, or both concurrently. Because low muscle mass is itself associated with mortality and CVD events,(16, 17) we hypothesized that the association of ACR with CVD events may appear stronger in subgroups with low muscle mass. This may be particularly true when a threshold is used to define albuminuria, such as > 10 mg/g or > 30 mg/g, because modest changes in the denominator could influence the ACR to cross the threshold and lead to diagnosis of albuminuria. Thus, the influence of muscle mass on urine creatinine may have important implications for understanding the prevalence, risk factors, and consequences of kidney disease. For example, a recent large meta-analysis reported that ACR > 30 mg/g was more strongly associated with all-cause mortality in women relative to men.(18) Whether this sex

difference may reflect differential effects of kidney disease, or alternatively differences in muscle mass influencing the denominator of the ACR, is uncertain.

To investigate the influence of urine creatinine on the ACR, we compared the relative strengths of association of urine albumin, the reciprocal of the urine creatinine concentration (1/UCr), and ACR with CVD events in the Multi-Ethnic Study of Atherosclerosis (MESA). We hypothesized that 1/urine creatinine would be positively associated with CVD events, and that this would contribute to a stronger association of ACR with CVD events compared to urine albumin alone. Moreover, we hypothesized that ACR at or above a 10 mg/g threshold (19) would be more strongly associated with CVD events in demographic groups with lower muscle mass, namely older persons, women, those of non-African descent and those with lower body weight.

Methods

Participants

Detailed methods of the MESA study have been previously reported.(20) The study was designed to investigate the correlates of subclinical CVD progression in a longitudinal cohort free of CVD at baseline. Between July 2000 and August 2002, 10,966 individuals were screened, and 6,814 individuals who were between the ages of 45 and 84 years and were free of clinically apparent CVD were deemed eligible and enrolled in MESA from six centers in the Unites States. Participants who were erroneously enrolled and later found to have CVD at baseline (n=5) and those with missing baseline ACR measurements (n=39) were excluded, resulting in 6,770 individuals for this analysis. The Institutional Review Board at each of the participating institutions approved the study and all participants signed informed consent.

Measurements

Urine albumin and urine creatinine—Each participant provided a spot urine sample immediately after arriving at the study site on the morning of his or her baseline study visit. Urinary albumin was determined by nephelometry, using the Array 360 CE Protein Analyzer (Beckman Instruments Inc,.www.beckmancoulter.com). The lowest detectable level was 0.2 mg/dL. Urinary creatinine was measured by the rate Jaffe method, using the Vitros 950IRC instrument (Johnson & Johnson Clinical Diagnostics Inc, www.orthoclinical.com). The range was 0.05-16.5 mg/dL, with a coefficient of variation range of 2.5%-2.9%.

Cardiovascular disease events—Each participant was contacted every 9-12 months by telephone or in person to collect information about hospital admissions, outpatient CVD diagnoses, and deaths. To verify diagnoses, death certificates, medical records, autopsy reports, and interviews with participants were obtained. In cases of out-of-hospital deaths, interviews with physicians, relatives, and friends were conducted. Records were obtained for 98% of hospitalized events and 95% of reported outpatient diagnoses. Two independent physicians reviewed records and classified CVD events by pre-specified criteria. If disagreements regarding diagnosis persisted, a full mortality and morbidity review committee made the final classification. In this analysis, we focused on MESA-defined "hard" CVD events, which included acute myocardial infarction (MI), resuscitated cardiac arrest, coronary heart disease death, stroke or stroke death. Detailed outcomes classification definitions are available.(20a)

Other measurements—Demographic information, health history, medication use, and tobacco use were obtained by questionnaire. Height and weight were measured with

participants wearing light clothing and no shoes. Resting blood pressure was measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida). The mean of the last two measurements was used for analysis. Hypertension was defined as systolic blood pressure 140 mmHg, diastolic blood pressure 90 mmHg, or use of antihypertensive medications. After an overnight (12-hour) fast, a venous blood sample was drawn and analyzed for lipids using a standardized kit (Roche Diagnostics). Diabetes was defined as fasting glucose 126 mg/dL or use of oral hypoglycemic medications or insulin. Cystatin C was measured using a BN II Nephelometer (Dade Behring Inc, Deerfield, Ill, USA) and a particle-enhanced immunonephelometric assay (N Latex Cystatin C; Dade-Behring). The coefficient of variation for this assay is 2.5%. eGFR based on serum creatinine and cystatin C was calculated using the combined CKD-EPI 2012 creatinine–cystatin C equation.(21)

Statistical Analysis

Participants were stratified by age, sex, race/ethnicity, sex specific weight tertiles and CVD risk factors. Urine creatinine, urine albumin, and ACR were compared across groups using the chi square test for categorical variables and linear regression for continuous variables. Correlations between eGFR, urine albumin, urine creatinine, and ACR were calculated using Spearman rank correlations.

Cox proportional hazard models were used to compare the association of each urinary measurement with CVD events. We began by exploring spline functions and quartiles of each predictor, and confirmed that the functional form of the associations of each measure on the log-scale with CVD events was fairly linear. Thus, we log base-2 transformed each measure, to allow evaluation as "per 2-fold higher level", and to facilitate comparisons. Sequential models were evaluated. Model 1 was unadjusted. Model 2 was adjusted for sex, age, race/ethnicity and weight; model 3 was further adjusted for smoking (current, former, never), hypertension, diabetes, total cholesterol, HDL cholesterol, lipid medication use, and eGFR.

A priori, we hypothesized that the association of ACR with CVD would be stronger in groups with lower muscle mass resulting in lower urine creatinine values. To enable comparisons between groups, we used Cox proportional hazard models to determine the association of ACR 10 mg/g versus less with CVD events. We chose to use a cut-point, as low urine creatinine would reclassify some individuals into the higher ACR group even if spot urine albumin concentrations were the same. The ACR 10 mg/g cut-point was chosen because levels below this value are considered optimal according to recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, and because ACR above this threshold have been associated with increased risk of CVD and kidney disease.(19) We then evaluated groups stratified by age (65 years v younger), sex, race/ethnicity (White, Black, Hispanic, Chinese), weight (sex-specific tertiles), diabetes, hypertension, and CKD, and tested for effect modification using multiplicative interaction terms. We observed effect modification by weight. To explore these differences further, associations of urine albumin and 1/urine creatinine were evaluated across weight tertile, and multiplicative interaction terms of urine albumin*weight tertile and urine creatinine*weight tertile were added to the model to determine which component of ACR was principally responsible for driving the observed effect modification.

Statistical analyses were performed with SPSS 16.0.2 software for Windows (SPSS Inc, Chicago, Illinois) and Stata 12.1 for Windows (StataCorp LP, College Station, Texas). P values <0.05 were considered statistically significant for all analyses.

Results

The mean age among the 6770 study participants was 62 ± 10 (standard deviation) years, 53% were female, and the race/ethnic distribution was White (39%), Black (28%), Chinese (12%), and Hispanic (22%). The geometric mean ACR was 7.0 ± 3.1 mg/g, and 281 incident CVD events occurred during a mean follow-up of 7.1 years.

Urine creatinine was lower among women, older individuals, and white and Chinese participants compared to other race/ethnicities, and in persons with lower body weight. Lower urine creatinine was also associated with lower waist-hip ratio, waist circumference, and hip circumference; never smokers; and those with hypertension, without diabetes, or with eGFR<60 mL/min/1.73m^2 (Table 1). Similar to urine creatinine, urine albumin was lower among women, whites, those with lower body weight, waist-hip ratio, waist circumference, and hip circumference; never smokers; and non-diabetic participants. For other variables, the directions of association of urine albumin differed from urine creatinine. Urine albumin was lower in younger persons, non-hypertensives, and those with eGFR 60 mL/min/1.73m^2. Spot ACR was lower among men; younger, white, non-hypertensive, and non-diabetic participants; and those with higher eGFR.

Correlations among the urinary measures were modest (Table SD1, available as online supplementary material). ACR had the strongest correlation with urine albumin (r=0.768; p<0.01) and was only weakly inversely correlated with urine creatinine (r=−0.034). Urine albumin and urine creatinine were modestly correlated (r=0.546: p<0.01), likely reflecting the influence of urine tonicity on both markers. None of the urine measures were strongly correlated with eGFR.

Next we evaluated the respective strengths of associations of 1/urine creatinine, urine albumin, and ACR, with CVD events (Table 2). Both higher urine albumin and ACR were modestly but statistically significantly associated with CVD events in unadjusted and adjusted models. By comparison of the point estimates of hazard ratios, the association was stronger for ACR than urine albumin. The hazard ratio point estimate for the association of 1/urine creatinine with CVD events was similar to that of urine albumin, however it was not statistically significant.

When evaluated as a binary variable, ACR 10 mg/g was associated with CVD events among all participants combined (Table 3). The association was similar irrespective of age, sex, race/ethnicity, diabetes, hypertension, or CKD status (p for interaction for all >0.2). However, we observed that the association was modified by weight (p for interaction = 0.001), and was strongest in the lowest weight tertile, intermediate in the highest weight tertile and weakest in the middle tertile. To explore further, we evaluated urine albumin and urine creatinine by weight tertiles. Similar to ACR, urine albumin was also more strongly associated with CVD events in the lowest vs. highest weight tertile (p for interaction =0.07). In contrast, the associations of 1/urine creatinine with CVD events were similar across the weight tertile groups (p for interaction =0.9; Figure 1). Results were similar in both unadjusted and fully adjusted models (data not shown).

Discussion

In a large multi-ethnic community-living population without CVD at baseline, we found that higher urine ACR and urine albumin were each modestly associated with CVD events after adjustment for relevant covariates. Despite prior studies showing associations of low muscle mass and of low 24-hour urine creatinine excretion with CVD events,(16, 17) spot urine creatinine was not statistically significantly associated with CVD events in this study. Urine creatinine was lower in older, female, and white or Chinese participants, and those with

lower body weight—all likely reflecting lower muscle mass in these groups. Among these factors, only low body weight was found to modify the association of ACR with CVD events. This effect modification appeared to be driven principally by the numerator (urine albumin) rather than by the denominator (urine creatinine).

With the exception of body weight, higher ACR was similarly associated with CVD across subgroups known to differ in muscle mass. Moreover, the associations of urine albumin and ACR with CVD events were generally similar to one another. These data suggest that any bias introduced by spot urine creatinine in the denominator of ACR is likely to be modest in comparison to the stronger relationship of the numerator (urine albumin) with CVD events. Prior studies that had measured both spot and timed urine specimens have reported that the correlations of spot and timed urine creatinine are relatively modest (r=0.38)(22), and the correlation of spot urine creatinine with muscle mass is also relatively modest (r=0.39). (23) This is likely because spot urine creatinine concentration is affected by urine tonicity in addition to muscle mass. The correlation of spot urine creatinine with muscle mass has also been shown to be modest (r=0.39) compared to that of 24 hour urine creatinine excretion rate with muscle mass. Thus, urine tonicity may make spot urine creatinine a less reliable marker of muscle mass than 24-hour urine creatinine, and this may explain the absence of statistically significant associations of urine creatinine with CVD events in this study. Another possibility is that we missed an association of spot urine creatinine with CVD events (i.e. a type II error). We used a large sample size with a substantial number of CVD events. Thus, any missed association would most likely be modest in strength. Future studies with even larger numbers of participants and CVD events would be required to definitively address this possibility.

The association of ACR 10 mg/g with CVD events differed by body weight. Among participants with lower body weight, ACR 10 mg/g was strongly associated with CVD events. Interestingly, those in the middle weight group had the lowest risk, whereas those in the highest weight group were at intermediate risk. The finding that ACR is particularly strongly associated with CVD events in those with low body weight appears robust, given the strong p-value for interaction observed here, and given similar findings in the PREVEND (Prevention of Renal and Vascular Endstage Disease) study participants in a prior study.(22) We had hypothesized that this finding may reflect lower creatinine in the denominator among persons with low body weight artificially increasing the ACR, but this was not confirmed in MESA. Evaluating the numerator and denominator of ACR separately, we found that higher urine albumin was also modified by weight similar to ACR, whereas the association of urine creatinine with CVD events did not meaningfully differ by body weight. The mechanisms responsible remain uncertain, but it may be that people with very low weight have higher subclinical disease burden, potentially resulting in inflammation, (24) endothelial dysfunction and both higher ACR levels and higher risk for CVD.

Both here and in the PREVEND cohort, persons with low body weight had the strongest associations of ACR with CVD events. However, the findings differed for other weight categories. in this study, those in the middle weight group were at lowest risk for CVD, whereas in PREVEND, the high weight group was at lowest risk. Persons in MESA had higher average body weight than those in PREVEND, thus many individuals classified within the middle weight group here would have been classified in the high weight tertile in PREVEND. Future studies will be required to confirm this hypothesis.

The findings presented here confirm many of the findings in the PREVEND study population and extend them in several important ways.(22) In both studies, the association of ACR with CVD events was driven principally by urine albumin rather than urine creatinine, and in both studies, these associations were stronger among persons with lower

body weight. The PREVEND study evaluated a Caucasian European population with a younger mean age than MESA. Thus, the current study extends the findings to an American population, an older age group, and to multiple race/ethnicities. This is important because African-Americans are known to have both higher urine albumin, greater muscle mass and urine creatinine, and higher CVD risk than Caucasians.

Despite these and other strengths, our study also has important limitations. We lacked timed urine collections for comparison, and the urine specimens were not always first morning voids.(25) Imaging measures of muscle mass were not available. Participants were free-living volunteers and generally healthy. Whether results can be generalized to persons with disabilities, hospitalized, or institutionalized individuals, where more marked abnormalities in muscle mass and disease burden are common, is uncertain.

In conclusion, in a multi-ethnic community-living population free of CVD at baseline, urine albumin, rather than 1/urine creatinine, appeared to be the dominant factor driving the association between ACR and CVD events. Effects of lower muscle mass on spot urine creatinine do not appear to be a major source of bias in the association of ACR with CVD events in generally healthy community-living individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Brantsma AH, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT. Extended prognostic value of urinary albumin excretion for cardiovascular events. J Am Soc Nephrol. 2008; 19:1785–1791. [PubMed: 18525003]

2. Appel LJ, Wright JT Jr. Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010; 363:918–929. [PubMed: 20818902]

3. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA. 2001; 286:421–426. [PubMed: 11466120]

4. Roest M, Banga JD, Janssen WM, et al. Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women. Circulation. 2001; 103:3057–3061. [PubMed: 11425768]

5. Arnlov J, Evans JC, Meigs JB, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. Circulation. 2005; 112:969–975. [PubMed: 16087792]

6. Smink PA, Lambers Heerspink HJ, Gansevoort RT, et al. Albuminuria, estimated GFR, traditional risk factors, and incident cardiovascular disease: the PREVEND (Prevention of Renal and Vascular Endstage Disease) study. Am J Kidney Dis. 2012; 60:804–811. [PubMed: 22835901]

7. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011; 79:1341–1352. [PubMed: 21307840]

8. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:S1–266. [PubMed: 11904577]

9. Alstrup K, Graugaard-Jensen C, Rittig S, Jorgensen KA. Abnormal diurnal rhythm of urine output following renal transplantation: the impact of blood pressure and diuretics. Transplant Proc. 2010; 42:3529–3536. [PubMed: 21094810]

10. Shirreffs SM, Maughan RJ. Urine osmolality and conductivity as indices of hydration status in athletes in the heat. Med Sci Sports Exerc. 1998; 30:1598–1602. [PubMed: 9813872]

11. James GD, Sealey JE, Alderman M, et al. A longitudinal study of urinary creatinine and creatinine clearance in normal subjects. Race, sex, and age differences. Am J Hypertens. 1988; 1:124–131. [PubMed: 3401350]

12. Mayersohn M, Conrad KA, Achari R. The influence of a cooked meat meal on creatinine plasma concentration and creatinine clearance. Br J Clin Pharmacol. 1983; 15:227–230. [PubMed: 6849756]

13. Jacobsen FK, Christensen CK, Mogensen CE, Andreasen F, Heilskov NS. Pronounced increase in serum creatinine concentration after eating cooked meat. Br Med J. 1979; 1:1049–1050. [PubMed: 571747]

14. Lambers Heerspink HJ, Brantsma AH, de Zeeuw D, Bakker SJ, de Jong PE, Gansevoort RT. Albuminuria assessed from first-morning-void urine samples versus 24-hour urine collections as a predictor of cardiovascular morbidity and mortality. Am J Epidemiol. 2008; 168:897–905. [PubMed: 18775924]

15. Jacobs DR Jr. Murtaugh MA, Steffes M, Yu X, Roseman J, Goetz FC. Gender- and race-specific determination of albumin excretion rate using albumin-to-creatinine ratio in single, untimed urine specimens: the Coronary Artery Risk Development in Young Adults Study. Am J Epidemiol. 2002; 155:1114–1119. [PubMed: 12048225]

16. Oterdoom LH, Gansevoort RT, Schouten JP, de Jong PE, Gans RO, Bakker SJ. Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population. Atherosclerosis. 2009; 207:534–540. [PubMed: 19535078]

17. Ix JH, de Boer IH, Wassel CL, Criqui MH, Shlipak MG, Whooley MA. Urinary creatinine excretion rate and mortality in persons with coronary artery disease: the Heart and Soul Study. Circulation. 2010; 121:1295–1303. [PubMed: 20212276]

18. Nitsch D, Grams M, Sang Y, et al. Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. BMJ. 2013; 346:f324. [PubMed: 23360717]

19. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011; 80:17–28. [PubMed: 21150873]

20. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol. 2002; 156:871–881. [PubMed: 12397006]

20a. MESA (Multi-Ethnic Study of Atherosclerosis) Web. http://www.mesa-nhlbi.org

21. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012; 367:20–29. [PubMed: 22762315]

22. Carter CE, Gansevoort RT, Scheven L, et al. Influence of urine creatinine on the relationship between the albumin-to-creatinine ratio and cardiovascular events. Clin J Am Soc Nephrol. 2012; 7:595–603. [PubMed: 22383750]

23. Jassal SKWC, Laughlin GA, Barret-Connor E, Riifkin DE, Ix JH. Abstract P1777: Urine Creatinine Based Estimates of Fat Free Mass: The Rancho Bernardo Study: American Heart Association, Epidemiology and Prevention/Physical Activity, Nutrition and Metabolism 2012 Scientific Sessions. New Orleans, Lousiana, Circulation. 2012:AP177.

24. Tsioufis C, Dimitriadis K, Andrikou E, et al. ADMA, C-reactive protein, and albuminuria in untreated essential hypertension: a cross-sectional study. Am J Kidney Dis. 2010; 55:1050–1059. [PubMed: 20189274]

25. Witte EC, Lambers Heerspink HJ, de Zeeuw D, Bakker SJ, de Jong PE, Gansevoort R. First morning voids are more reliable than spot urine samples to assess microalbuminuria. J Am Soc Nephrol. 2009; 20:436–443. [PubMed: 19092125]
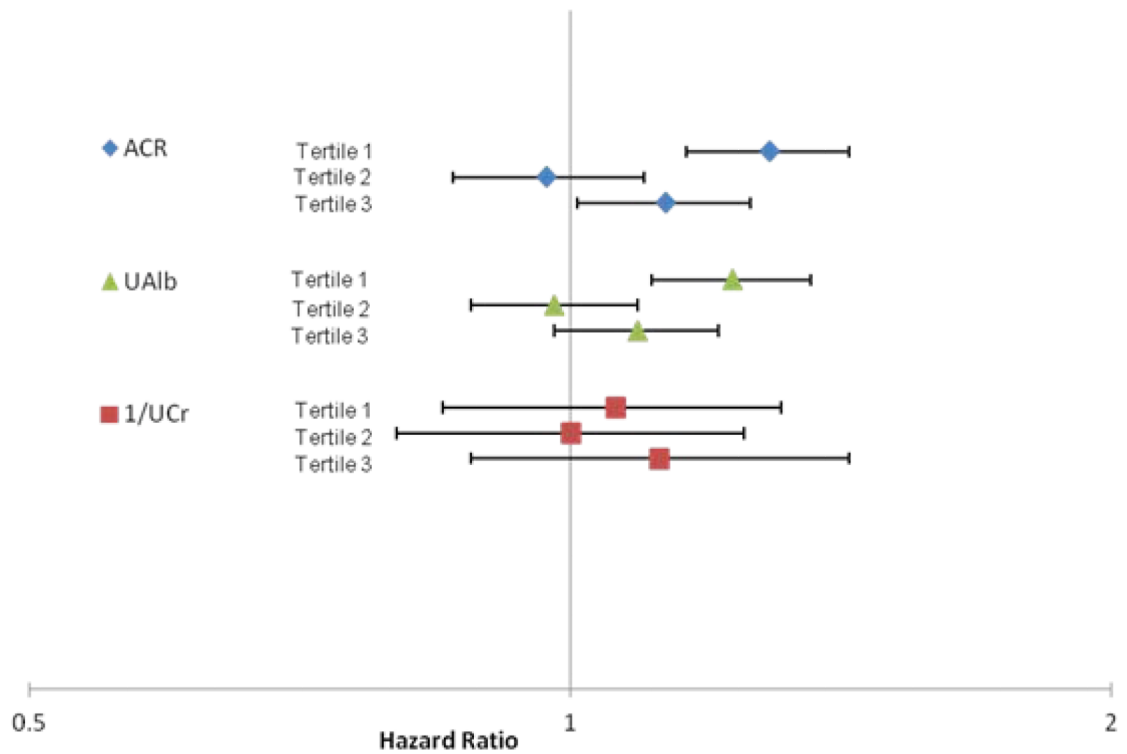
Figure 1.
Unadjusted association, per 2-fold higher value, of spot urine albumin-creatinine ratio (ACR), spot urine albumin concentration (UAlb), and 1/spot urine creatinine concentration (1/UCr) with CVD events by sex-specific weight tertiles. P values for interaction between urinary variable and weight were 0.006 (ACR), 0.06 (UAlb), and 0.9 (1/UCr).

Table 1

Urine creatinine and urine albumin concentrations and ACR

	No. of patients	Urine Cr (mg/dL)	Urine Alb (mg/dL)	Urine ACR (mg/g)
All participants	6770	95 ± 2	0.7 ± 3.7	7.0 ± 3.1
Sex				
Female	3577	79 ± 2	0.6 ± 3.5	7.4 ± 2.9
Male	3193	118 ± 2	0.8 ± 3.8	6.6 ± 3.4
Age				
45-54 y	1929	106 ± 2	0.6 ± 3.3	5.2 ± 2.6
55-64 y	1872	97 ± 2	0.6 ± 3.7	6.4 ± 3.0
65-74 y	2008	90 ± 2	0.7 ± 3.9	8.2 ± 3.3
75-84 y	961	83 ± 2	0.9 ± 3.9	11.0 ± 3.5
Race				
White	2606	83 ± 2	0.5 ± 3.2	5.8 ± 3.8
Chinese	803	88 ± 2	0.8 ± 3.7	8.5 ± 2.6
Black	1873	110 ± 2	0.8 ± 4.0	7.3 ± 3.3
Hispanic	1488	106 ± 2	0.9 ± 3.8	8.3 ± 3.4
Weight $^\wedge$				
Tertile I	2260	85 ± 2	0.6 ± 3.7	7.1 ± 3.0[**]
Tertile II	2243	92 ± 2	0.6 ± 3.6	6.6 ± 3.0[**]
Tertile III	2267	110 ± 2	0.8 ± 3.9	7.3 ± 3.4[**]
Waist-hip ratio				
0.94	3384	87 ± 2	0.5 ± 3.2	6.0 ± 2.7
> 0.94	3386	103 ± 2	0.9 ± 4.0	8.2 ± 3.5
Waist circumference				
97.2 cm	3400	87 ± 2	0.6 ± 3.4	6.4 ± 2.9
> 97.2 cm	3370	104 ± 2	0.8 ± 3.9	7.7 ± 3.4
Hip circumference				
104 cm	3438	90 ± 2	0.6 ± 3.6	6.8 ± 3.0
>104 cm	3332	100 ± 2	0.7 ± 3.8	7.2 ± 3.2
Smoking				
Never	3401	91 ± 2	0.7 ± 3.7	7.1 ± 3.1
Former	2468	96 ± 2	0.7 ± 3.7	6.9 ± 3.1
Current	879	111 ± 2	0.8 ± 3.7	6.9 ± 3.1
Hypertension				
No	3732	99 ± 2	0.5 ± 3.0	5.2 ± 2.4
Yes	3038	91 ± 2	0.9 ± 4.3	10.1 ± 3.7
SBP				

	No. of patients	Urine Cr (mg/dL)	Urine Alb (mg/dL)	Urine ACR (mg/g)
< 140 mm Hg	5015	99 ± 2	0.6 ± 3.3	5.6 ± 2.7
140 mm Hg	1698	85 ± 2	1.0 ± 4.6	12.3 ± 4.0
DBP				
< 90 mm Hg	6431	95 ± 2	0.6 ± 3.6	6.8 ± 3.1
90 mm Hg	310	103 ± 2	1.4 ± 4.6	13.4 ± 4.0
ACEi or ARB use				
No	5743	96 ± 2	0.6 ± 3.4	6.4 ± 2.8
Yes	1024	91 ± 2	1.1 ± 5.1	11.7 ± 4.5
Diabetes				
No	5905	94 ± 2	0.6 ± 3.3	6.1 ± 2.7
Yes	850	102 ± 2	1.8 ± 5.2	17.7 ± 4.8
eGFR				
60 ml/min/1.73m^2	6117	96 ± 2[***]	0.6 ± 3.5	6.5 ± 2.9
<60 ml/min/1.73m^2	598	89 ± 2[***]	1.2 ± 5.6	13.8 ± 5.1

Alb, albumin; Cr,creatinine; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure

Note: Unless otherwise indicated, values are given as geometric mean ± standard deviation.

^
Sex-specific tertiles. Tertile I: F <143 lb, M <169 lb; tertile II: F 143-172 lb, M 169-196 lb; tertile III: F >172 lb, M 196 lb.

**
p=0.021

***
p=0.007; P 0.001 for all comparisons unless otherwise indicated.

Table 2

Association of Urine Albumin, 1/UCr, and ACR with CVD Events

	Model 1[*]	Model 2[**]	Model 3[***]
Urine albumin (mg/dL)	1.22 (1.16, 1.29)[†]	1.18 (1.11, 1.24)[†]	1.08 (1.01, 1.14)[††]
1/UCr (dL/mg)	1.06 (0.94, 1.19)	1.07 (0.94, 1.22)	1.07 (0.94, 1.22)
Urine ACR (mg/g)	1.28 (1.21, 1.35)[†]	1.22 (1.15, 1.29)[†]	1.11 (1.04, 1.18)[††]

Note: Associations (given as HR and 95% CI) are per 2-fold higher.

ACR, albumin-creatinine ratio; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; 1/UCr, reciprocal of urine creatinine concentration.

[*] Unadjusted.

[**] Adjusted for age, sex, race/ethnicity, and weight.

[***] Adjusted for age, sex, race/ethnicity, weight, smoking (current, former, never), hypertension, diabetes, total cholesterol, HDL cholesterol, lipid medication use, and estimated glomerular filtration rate.

[†] $p < 0.001$

[††] $p < 0.05$

Table 3

Association of CVD events with Spot Urine ACR below vs at/above 10 mg/g threshold

	Events/no. at risk		Event Rate[**]		HR (95% CI)		
	ACR <10 mg/g	ACR 10 mg/g	ACR <10 mg/g	ACR 10 mg/g	Unadjusted	Adjusted[*]	p[#]
All participants	154/4921	127/1849	5.1	11.9	2.29 (1.81, 2.90)	1.40 (1.08, 1.80)	
Sex							0.7
Female	62/2550	56/1027	3.9	9.3	2.33 (1.62, 3.34)	1.37 (0.93, 2.01)	
Male	92/2371	71/822	6.4	15.3	2.35 (1.72, 3.20)	1.44 (1.03, 2.03)	
Age							0.8
< 65 y	60/3023	31/778	3.2	6.6	2.04 (1.32, 3.15)	1.38 (0.85, 2.24)	
65 y	94/1898	96/1071	8.4	16.1	1.89 (1.43, 2.52)	1.63 (1.21, 2.19)	
Race							0.2
White	78/2050	43/556	6.1	13	2.11 (1.45, 3.06)	1.18 (0.79, 1.76)	
Black	40/1305	34/568	5.1	10.6	2.05 (1.30, 3.24)	1.36 (0.83, 2.22)	
Hispanic	30/1027	37/461	4.9	14.3	2.86 (1.77, 4.63)	1.61 (0.96, 2.68)	
Chinese	6/539	13/264	1.8	8.3	4.51 (1.71, 11.85)	3.99 (1.43, 11.16)	
Weight[^]							0.001
Tertile I	38/1638	59/622	3.8	16.8	4.34 (2.89, 6.53)	2.21 (1.42, 3.45)	
Tertile II	68/1670	31/573	6.6	9.3	1.38 (0.90, 2.10)	0.81 (0.52, 1.28)	
Tertile III	48/1613	37/654	4.9	9.7	1.97 (1.28, 3.02)	1.49 (0.94, 2.38)	
Diabetes							0.2
No	135/4529	77/1376	4.8	9.5	1.93 (1.46, 2.57)	1.23 (0.91, 1.65)	
Yes	19/381	49/469	8.5	19.1	2.23 (1.32, 3.79)	2.02 (1.17, 3.48)	
Hypertension							0.4
No	68/3096	22/636	3.5	5.8	1.60 (0.98, 2.61)	1.03 (0.61, 1.73)	
Yes	86/1825	105/1213	7.8	15.2	1.91 (1.43, 2.54)	1.55 (1.15, 2.09)	
eGFR							0.4
60 mL/min/1.73 m^2	124/4596	91/1576	4.4	10.0	2.25 (1.72, 2.96)	1.51 (1.13, 2.02)	
< 60 mL/min/1.73 m^2	29/325	34/273	15.4	23.4	1.49 (0.90, 2.45)	0.98 (0.58, 1.67)	

Abbreviations: ACR, albumin-creatinine ratio; CVD, cardiovascular disease; HR=hazard ratio, CI=confidence interval.eGFR, estimated glomerular filtration rate

[^^]Sex-specific tertiles. Tertile I: F <143 lb, M <169 lb; tertile II: F 143-172 lb, M 169-196 lb; tertile III: F >172 lb, M >196 lb.

[**] per 1,000 person-years.

[*] Adjusted for sex, age, race, smoking (current, former, never), hypertension, diabetes, total cholesterol, HDL cholesterol, lipid medication use, eGFR and weight. (Stratifying variables are excluded as covariates. For example, when stratified by age, age is not included as a covariate.)

[#]For interaction, adjusted model.