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Evaluation of Measures of Urinary Albumin Excretion in Epidemiologic Studies

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Twenty-four-hour urinary albumin excretion (UAE) is considered the gold standard for determining albumin level in epidemiologic studies, but this measure is inconvenient and often unavailable. Simpler alternatives include the albumin:creatinine ratio (ACR) and urinary albumin concentration (UAC) obtained from a single sample. The authors assessed the strengths and weaknesses of ACR and UAC as alternatives to UAE using albumin measurements from two 24-hour urine samples collected in 1996–1999 from 4,678 participants aged 40–59 years in the International Study of Macronutrients and Blood Pressure (17 population samples from four countries). The authors compared ACR and UAC with regard to correlations with UAE, daily within-person variability, and associations with known predictors of UAE. Rank-order correlations of ACR with UAE were 0.949 and 0.942 for men and women, respectively, versus 0.881 and 0.816 for UAC. Mean within-person coefficients of variation were 34.0–40.0% for the three measures, with the smallest values being observed for UAC. Average correlations with blood pressure were similar for UAE, ACR, and UAC, but the correlation with body mass index was lower for ACR (0.118 for ACR and 0.188 for UAC vs. 0.211 for UAE) because of high correlation between body mass index and creatinine level. Thus, UAC and ACR are acceptable alternatives to the more complex UAE, and the simpler UAC may be preferable to ACR in some respects.

albumins; albuminuria; blood pressure; creatinine; epidemiologic methods

Abbreviations: ACR, albumin:creatinine ratio; CV, coefficient of variation; INTERMAP, International Study of Macronutrients and Blood Pressure.

Albumin excretion and microalbuminuria are currently drawing a great deal of attention in the medical literature. Much of this attention derives from the fact that albumin excretion is a risk factor for kidney failure (1, 2), stroke (3, 4), and cardiovascular and all-cause mortality (3, 5–12), particularly for persons with diabetes and/or hypertension (9–12).

The amount of albumin excreted in the urine over a 24-hour period is considered the "gold standard" for assessing albumin level and defining microalbuminuria (13). However, 24-hour urine collections are cumbersome and subject to error due to inaccurate timing and/or incompleteness. American Diabetes Association guidelines for detection of microalbuminuria permit use of 24-hour collections, timed specimens taken over a period of less than 24 hours, and untimed random specimens (13). For random specimens, results and cutoff points for microalbuminuria must be based on either urinary albumin concentration or the albumin:creatinine ratio (ACR). The American Diabetes Association considers the daily within-person variability of albumin concentration to be too high to permit use of albumin concentration alone in defining microalbuminuria. Thus, researchers have typically used the ACR for defining microalbuminuria (3, 6–9, 14–16) in spot or random collections, although some have also used albumin concentration (4, 17, 18). Use of the ACR is also problematic, however,

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since it requires measurement of creatinine excretion, which varies by gender, age, and ethnicity (5, 19–22). This has led some investigators to propose gender-specific cutoff points for microalbuminuria when using the ACR (5, 19–25). In addition, albumin excretion has been found to be highly variable within individuals, with the within-person coefficient of variation (CV) generally averaging 40–60 percent (26–31). Thus, there are strengths and weaknesses in using 24-hour albumin excretion, ACR, or albumin concentration that are relevant for investigators conducting epidemiologic studies on albumin level and microalbuminuria.

The purpose of this study was to further assess the strengths and weaknesses of the ACR and albumin concentration as alternatives to albumin excretion using albumin measurements from two 24-hour urine collections in men and women in the International Study of Macronutrients and Blood Pressure (INTERMAP). In particular, we examined the following questions: 1) Is ACR or albumin concentration more strongly related to albumin excretion in a 24-hour collection? 2) How does daily within-person variation, as assessed by the within-person CV, compare for 24-hour albumin excretion, ACR, and albumin concentration and for other urinary variables such as sodium, potassium, and creatinine? 3) Are known predictors of albumin excretion, such as blood pressure and body mass index (14–16, 32, 33), more strongly associated with 24-hour ACR or albumin concentration?

MATERIALS AND METHODS

Participants

INTERMAP, begun in 1995, is an ongoing international epidemiologic study on relations of multiple dietary factors to blood pressure. Details on the methods used have been published previously (34). Briefly, INTERMAP involves 4,680 men and women aged 40–59 years from 17 population samples: four in Japan, three in the People's Republic of China, two in the United Kingdom, and eight in the United States. Each sample was selected randomly from a population list, stratified by age and gender, to obtain approximately equal numbers of subjects in each of four gender and 10-year age groups. INTERMAP received institutional review board approval at each field center, the Central Laboratory, and the coordinating centers. All participants provided written informed consent.

Between 1996 and 1999, each participant visited the local INTERMAP research center on four occasions. Two visits were undertaken on consecutive days, with a further two visits made on consecutive days 3–6 weeks later.

Data collection

All data were collected by trained and certified staff. Dietary data were collected at each visit with the 24-hour recall method. Blood pressure was measured twice at each visit with a random-zero sphygmomanometer while the participant was seated. Height and weight without shoes were measured at the first and third visits, and body mass index was calculated as weight divided by height squared (kg/m^2). Data on demographic and other factors were collected by interviewer-administered questionnaire.

Two timed 24-hour urine specimens were collected. Collections were started at the research center on the first and third visits and completed at the center the following day. Urine aliquots were stored frozen at –20° C before and after being shipped frozen to the Central Laboratory, where analyses were performed with strict internal and external quality control. Levels of sodium, potassium, creatinine, urea, magnesium, and calcium were analyzed within 3 years of receipt of aliquots at the Central Laboratory, while albumin was analyzed in aliquots that had been frozen for 3 or more years, with completion in 2002. Urinary sodium and potassium concentrations were measured by emission flame photometry. Standard methods were used for analyses of other urinary variables (35–38). Individual excretion values were calculated as the product of concentrations in the urine and urinary volume corrected to 24 hours.

Among the 4,678 men and women with albumin measurements, there were 2,745 persons for whom one or both albumin concentration values were below the detection limit of the assay (1 mg/liter).

Statistical methods

The American Diabetes Association defines microalbuminuria as excretion of 30–299 mg of albumin in a 24-hour collection, with values ≥300 being defined as macroalbuminuria (13). To derive comparable gender/country-specific INTERMAP cutoffs for ACR and albumin concentration, we divided 30 by each subgroup's mean creatinine excretion and mean urinary volume to obtain ACR and albumin concentration cutoff points for microalbuminuria; we multiplied these by 10 to obtain cutoff points for macroalbuminuria.

To assess associations of ACR and albumin concentration with albumin excretion, we calculated Spearman's rank-order correlations of ACR and albumin concentration with albumin excretion for the 1,933 men and women with albumin concentrations ≥1 mg/liter in both collections and kappa statistics to assess their overall agreement with albumin excretion in classifying all 4,678 INTERMAP participants as having micro- or macroalbuminuria (39). Because the use of INTERMAP-specific cutoff points for micro- and macroalbuminuria defined by ACR and albumin concentration are likely to maximize agreement with 24-hour albumin excretion, we also calculated overall agreement with albumin excretion for 1) the American Diabetes Association cutoffs of 30–299 mg/g for ACR, 2) the gender-specific ACR cutoffs of 17–249 mg/g for men and 25–354 mg/g for women that have been proposed by Warram et al. (20) and used by some investigators (16, 21, 22), and 3) the albumin concentration cutoffs of 16–159 mg/liter suggested by Bakker (19).

Intraindividual variability in albumin excretion is typically assessed by means of the within-person CV (26–31, 40), which is calculated from multiple measurements made in the same individual as 100 × standard deviation/mean (40). Hence, to estimate daily variability for each urinary measure, we calculated each individual's CV for the first collection

TABLE 1. Median values for measures of albumin and creatinine level and urinary volume and derived microalbuminuria cutoff points for albumin:creatinine ratio and urinary albumin concentration, by gender and country, International Study of Macronutrients and Blood Pressure, 1996–2002

Variable	Japan		China		United Kingdom		United States		Total	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
No. of subjects*	254	280	152	208	129	149	315	446	850	1,083
24-hour albumin excretion (mg)	5.40	3.99	4.18	5.22	4.36	4.16	6.58	4.81	5.36	4.48
Albumin:creatinine ratio (mg/g)	3.55	4.00	3.84	6.45	2.73	3.69	3.82	4.49	3.42	4.50
Albumin concentration (mg/liter)	3.33	2.85	2.40	2.95	2.15	2.35	3.00	2.25	2.80	2.55
Creatinine level (g)	1.50	0.99	1.18	0.83	1.72	1.11	1.78	1.13	1.56	1.03
Urinary volume (liters)	1.63	1.47	1.91	1.70	1.89	1.73	2.09	2.00	1.84	1.74
Cutoff point for albumin: creatinine ratio (mg/g)†	19.7	30.4	24.7	34.6	17.9	26.5	16.3	25.5	18.4	28.0
Cutoff point for albumin concentration (mg/liter)‡	18.8	21.3	16.2	18.6	16.6	17.6	15.1	15.7	16.3	17.5

* Number of men or women with albumin concentrations ≥1.0 mg/liter in both urine samples.

† Obtained by dividing 30 mg by mean 24-hour creatinine excretion for all men and women in each country or overall in the total sample of 4,678.

‡ Obtained by dividing 30 mg by mean 24-hour urinary volume for all men and women in each country or overall in the total sample of 4,678.

and the repeat collection and then used the mean and median values among participants to summarize daily within-person variability in INTERMAP. We also computed the Spearman rank-order correlation between the first and repeat measurements for each urinary measure as a further assessment of within-person variation. These analyses were carried out for all 4,678 participants, for the 1,933 participants with albumin concentrations ≥1 mg/liter in both collections, for the 1,709 participants with an average albumin excretion less than 30 mg and an albumin concentration ≥1 mg/liter in both collections, and for the 204 participants with an average albumin excretion of 30–299 mg.

To examine associations of albumin excretion, ACR, and albumin concentration with blood pressure, body mass index, and urinary volume as continuous variables, we calculated Spearman's rank-order correlations separately by country and gender and then computed weighted averages by gender and for men and women combined, with weights equal to sample size. Participants for whom either albumin concentration value was below the detection limit were excluded from these analyses.

We also examined associations of these same variables with microalbuminuria, defined on the basis of each of albumin excretion, ACR, and albumin concentration as described above, using logistic regression with adjustment for age, sex, and INTERMAP sample.

In all analyses except those related to assessment of intraindividual variability of urinary variables, we used the average of all measurements for each variable.

RESULTS

Descriptive statistics

Table 1 presents median values for 24-hour albumin excretion, ACR, albumin concentration, urinary volume, and creatinine level by gender and country for participants with both albumin concentration values ≥1 mg/liter, along with the derived gender/country-specific cutoffs for microalbuminuria based on ACR and albumin concentration. Medians are given rather than means because of the extreme skewness of data distributions for the albumin measures. Within each gender/country subgroup, differences in absolute amounts among albumin excretion, ACR, and albumin concentration generally parallel differences in median urinary volume and median creatinine level—that is, the lower the median creatinine level, the higher the median ACR relative to median albumin excretion and the higher the ACR cutoff for microalbuminuria. Similarly, the higher the median urinary volume, the lower the median albumin concentration and the lower the albumin concentration cutoff for microalbuminuria. The variation in ACR cutoffs for microalbuminuria is large, ranging from 16.3 mg/g to 34.6 mg/g; this reflects the INTERMAP differences in creatinine excretion by gender and country. The variation in albumin concentration cutoffs is much less, ranging from 15.1 mg/liter to 21.3 mg/liter, because of the smaller variation in urinary volume across subgroups.

Associations of ACR and albumin concentration with 24-hour albumin excretion

For participants with albumin concentrations ≥1 mg/liter in both collections, the rank-order correlations of ACR with albumin excretion were 0.949 for men and 0.942 for women, larger than the correlations of 0.881 and 0.816 for albumin concentration with albumin excretion.

Table 2 shows the associations of ACR and albumin concentration with 24-hour albumin excretion based on classification of participants as having micro- or macroalbuminuria. The INTERMAP ACR cutoffs show better agreement with albumin excretion than the INTERMAP albumin concentration cutoffs ($\kappa = 0.935$ and $\kappa = 0.872$, respec-

TABLE 2. Agreement of micro- and macroalbuminuria defined by 24-hour albumin:creatinine ratio and urinary albumin concentration with that defined by 24-hour urinary albumin excretion, International Study of Macronutrients and Blood Pressure, 1996–2002

Albumin measure and cutpoints	Albuminuria category	Urinary albumin excretion						κ
		Normal (<30 mg)		Microalbuminuria (30–299 mg)		Macroalbuminuria (≥300 mg)		
		No.	%	No.	%	No.	%	
ACR*—INTERMAP* (table 1)	Normal	4,424	99.7	9	4.4	0	0.0	0.935
	Microalbuminuria	13	0.3	189	92.6	2	4.4	
	Macroalbuminuria	0	0.0	6	2.9	35	94.6	
Albumin concentration—INTERMAP (table 1)	Normal	4,413	99.5	23	11.1	0	0.0	0.872
	Microalbuminuria	24	0.5	174	85.3	5	13.5	
	Macroalbuminuria	0	0.0	7	3.4	32	86.5	
ACR—Warram et al. (20): men, 17–249 mg/g; women, 25–354 mg/g	Normal	4,410	99.4	7	3.4	0	0.0	0.908
	Microalbuminuria	27	0.6	194	95.1	7	18.9	
	Macroalbuminuria	0	0.0	3	1.5	30	81.1	
ACR—American Diabetes Association (13): 30–299 mg/g	Normal	4,427	99.8	40	19.6	0	0.0	0.857
	Microalbuminuria	10	0.2	161	78.9	9	24.3	
	Macroalbuminuria	0	0.0	3	1.5	28	75.7	
Albumin concentration—Bakker (19): 16–159 mg/liter	Normal	4,406	99.3	22	10.8		0.0	0.855
	Microalbuminuria	32	0.7	173	84.8	6	16.2	
	Macroalbuminuria	0	0.0	9	4.4	31	83.8	

* ACR, albumin:creatinine ratio; INTERMAP, International Study of Macronutrients and Blood Pressure.

tively). The kappa value of 0.908 for the gender-specific ACR cutoffs is only slightly smaller than the value of 0.935 for the INTERMAP ACR criteria. Similarly, the kappa value of 0.855 for the albumin concentration cutoffs suggested by Bakker (19) is only slightly smaller than the value of 0.872 for the INTERMAP albumin concentration criteria. The ACR cutoffs used by the American Diabetes Association yield a kappa value of 0.857 and a sensitivity of 78.9 percent, which is substantially lower than the sensitivities for the other two sets of ACR criteria (i.e., 92.6 percent and 95.1 percent). This is due primarily to the 30 mg/g cutoff's being substantially higher than the cutoffs for INTERMAP men in table 1 and the 17 mg/g for men proposed by Warram et al. (20).

Within-person variability of albumin excretion

Table 3 presents mean and median values for the within-person CVs and the rank-order correlations for the first and repeat measurements of each urinary variable. Based on within-person CVs, the albumin measures show greater within-person variability than the other urinary variables for all participants and each of the three subgroups. Mean CVs for 24-hour albumin excretion, ACR, and albumin concentration are all near 60 percent for all men and all women, 34–40 percent when persons with values below the detection limit are excluded, 33–38 percent among those with values for average albumin excretion in the normal range, and 46–48 percent for men and 78–80 percent for women among those with an average albumin excretion of 30–299 mg. In contrast, mean CVs for the other urinary variables range from 9 percent to 24 percent, with creatinine having the smallest. Median CVs for the albumin measures are also much larger than those for the other urinary variables, with values of 45–50 percent for all men and all women and 26–31 percent after exclusion of persons with values below the detection limit. For the other variables, median CVs range from 6 percent to 20 percent.

Among the albumin measures, the mean and median CVs for albumin concentration are 1–5 percentage points lower than those for albumin excretion and ACR, except for men and women with an average albumin excretion of 30–299 mg, for whom some values are actually larger. Mean and median CVs for albumin excretion and ACR generally differ by less than 1 percent for both men and women.

Mean and median CVs differ little by gender, except for persons with an average albumin excretion of 30–299 mg. Mean and median CVs were also generally similar across the four countries (data not shown). Among persons with both albumin concentration values ≥1 mg/liter, the mean CV for albumin excretion ranged from 31 percent to 38 percent in men and from 29 percent to 41 percent in women.

Rank-order correlations for first and repeat measurements of the albumin measures are similar to those for several other urinary variables for all men and all women. For men with both albumin concentration values ≥1 mg/liter, the correla-

TABLE 3. Intraindividual variability in urinary measures as assessed by mean and median coefficients of variation and Spearman's rank-order correlations, by gender, International Study of Macronutrients and Blood Pressure, 1996–2002

Variable	Mean CV* (%)		Median CV (%)		Rank-order correlation	
	Men	Women	Men	Women	Men	Women
All participants (2,357 men, 2,321 women)						
24-hour albumin excretion	61.7	60.2	48.7	49.7	0.644	0.609
Albumin:creatinine ratio	62.0	60.8	49.2	49.6	0.658	0.604
Albumin concentration	59.6	57.7	47.1	45.2	0.624	0.562
Sodium level	23.7	23.0	19.1	18.7	0.483	0.548
Potassium level	18.0	18.1	14.4	14.7	0.690	0.637
Sodium:potassium ratio	23.0	23.6	19.4	19.5	0.687	0.663
Urea level	15.5	15.4	12.5	12.5	0.593	0.553
Creatinine level	9.9	9.1	6.1	5.7	0.762	0.765
Urinary volume	20.0	18.0	16.5	14.8	0.620	0.707
Albumin concentration ≥1.0 mg/liter (850 men, 1,083 women)						
24-hour albumin excretion	35.7	39.1	28.4	30.7	0.695	0.533
Albumin:creatinine ratio	35.2	40.0	28.0	31.2	0.699	0.516
Albumin concentration	34.0	36.6	26.2	28.2	0.700	0.522
Albumin excretion <30 mg and albumin concentration ≥1.0 mg/liter (726 men, 983 women)						
24-hour albumin excretion	34.8	36.7	27.8	29.4	0.531	0.455
Albumin:creatinine ratio	34.3	37.6	27.4	30.0	0.541	0.442
Albumin concentration	32.8	33.9	25.3	26.1	0.546	0.457
Albumin excretion 30–299 mg (102 men, 102 women)						
24-hour albumin excretion	46.0	78.2	39.4	78.4	0.339	–0.381
Albumin:creatinine ratio	46.5	79.8	39.3	81.3	0.377	–0.320
Albumin concentration	47.8	78.9	42.4	77.6	0.427	–0.236

* CV, coefficient of variation.

tions for albumin excretion, ACR, and albumin concentration of 0.695–0.700 are larger than the correlations for all men for urinary urea, volume, and sodium and similar to the correlations for potassium and sodium:potassium ratio. However, for women with both albumin concentration values ≥1 mg/liter, the correlations of 0.516–0.533 for the three albumin measures are smaller than those for the other variables for all women. Correlations for the albumin measures are smallest among persons with an average albumin excretion of 30–299 mg, ranging from 0.339 to 0.427 for men and being less than zero for women.

Associations of other variables with albumin excretion

Table 4 presents weighted averages of the rank-order correlations of albumin excretion, ACR, and albumin concentration with blood pressure, body mass index, and urinary volume for INTERMAP participants with albumin concentrations ≥1 mg/liter in both collections, as well as odds ratios for associations of these variables with microalbuminuria defined by albumin excretion, ACR, and albumin concentration. We included urinary volume here to assess whether multiplication of the concentration by the 24-hour volume to obtain albumin excretion resulted in stronger associations for volume and albumin excretion than for volume and ACR.

Twenty-four-hour albumin excretion has the largest average correlation with systolic blood pressure in men, while albumin concentration has the largest correlation in women and in men and women combined, with ACR having the smallest average correlations. For men and women combined, weighted averages are 0.289 for albumin excretion, 0.265 for ACR, and 0.293 for albumin concentration. Correlations with systolic pressure were largest in China (0.372–0.474) and smallest in the United Kingdom (0.106–0.172) (data not shown). Twenty-four-hour albumin concentration has the largest correlations with diastolic blood pressure and ACR the smallest. For men and women combined, weighted averages are 0.216 for albumin excretion, 0.188 for ACR, and 0.230 for albumin concentration. Correlations with diastolic pressure were also largest in China (0.369–0.445) and smallest in the United Kingdom (0.043–0.192) (data not shown). Twenty-four-hour albumin excretion has the largest average correlation with body mass index in women and in men and women combined, with albumin concentration having a slightly larger correlation than albumin excretion in men and ACR having substantially smaller correlations, especially in men. Weighted averages

TABLE 4. Average Spearman's rank-order correlations of various albumin measures with blood pressure, body mass index, and urinary volume and odds ratios for microalbuminuria* in relation to these variables, International Study of Macronutrients and Blood Pressure, 1996–2002†

Variable and albumin measure	Men	Women	Total	Odds ratio‡	95% confidence interval
Systolic blood pressure					
24-hour albumin excretion	0.319	0.265	0.289	1.90	1.67, 2.15
Albumin:creatinine ratio	0.299	0.238	0.265	1.90	1.68, 2.16
Albumin concentration	0.304	0.284	0.293	1.90	1.68, 2.16
Diastolic blood pressure					
24-hour albumin excretion	0.235	0.199	0.216	1.71	1.49, 1.97
Albumin:creatinine ratio	0.206	0.173	0.188	1.73	1.51, 1.99
Albumin concentration	0.241	0.222	0.230	1.73	1.50, 1.99
Body mass index					
24-hour albumin excretion	0.181	0.235	0.211	1.47	1.28, 1.69
Albumin:creatinine ratio	0.086	0.143	0.118	1.48	1.29, 1.70
Albumin concentration	0.184	0.191	0.188	1.51	1.31, 1.73
24-hour urinary volume					
24-hour albumin excretion	0.225	0.272	0.251	1.30	1.16, 1.46
Albumin:creatinine ratio	0.206	0.226	0.217	1.25	1.11, 1.41
Albumin concentration	–0.169	–0.221	–0.198	1.07	0.93, 1.22

* Microalbuminuria was defined as 30–299 mg for albumin excretion (n = 204) and by the gender/country-specific cutoff points given in table 1 for albumin:creatinine ratio (n = 204) and albumin concentration (n = 203).

† The rank-correlation analyses included 850 men and 1,083 women with albumin concentrations ≥1.0 mg/liter in both urine samples. For calculation of odds ratios, the analyses included the total sample minus those participants who had macroalbuminuria on the basis of each measure (n = 37, n = 41, and n = 39, respectively).

‡ For each variable, odds ratios were calculated for a one-standard-deviation difference in that variable: 14.6 for systolic blood pressure, 10.0 for diastolic blood pressure, 5.4 for body mass index, and 0.7 for urinary volume.

are 0.211 for albumin excretion, 0.118 for ACR, and 0.188 for albumin concentration. Correlations of body mass index with albumin excretion ranged from 0.305 for women in Japan to 0.090 for men in the United Kingdom, while the correlations with ACR ranged from 0.239 to 0.024 in these same subgroups (data not shown). The smaller correlations of body mass index with ACR reflect the fact that in computing ACR, albumin concentration is being divided by creatinine, a variable strongly related to body mass index.

Twenty-four-hour albumin excretion does not have a substantially larger correlation with 24-hour urinary volume than ACR in men or women. This suggests that multiplying albumin concentration by urinary volume does not markedly increase the correlation with albumin excretion relative to that observed for ACR, since ACR might be expected to be independent of volume unless volume is itself related to albumin excretion. The correlations of albumin concentration with volume are less than zero, which is not unexpected, since on average we would expect the concentration to be higher with lower total volume.

For associations with microalbuminuria, odds ratios are given for a difference of one standard deviation. Participants with macroalbuminuria defined by albumin excretion, ACR, or albumin concentration were excluded from these analyses (37, 41, and 39 participants, respectively). Odds ratios for systolic and diastolic blood pressure and body mass index are the same or nearly the same for all three definitions of microalbuminuria, while the odds ratio for urinary volume is slightly higher for albumin excretion than for ACR, and the odds ratio for albumin concentration and urinary volume does not differ significantly from 1.0. Logistic regression analyses with ACR microalbuminuria defined on the basis of Warram et al.'s (20) criteria and albumin concentration microalbuminuria defined on the basis of Bakker's (19) criteria also gave very similar odds ratios: 1.90 and 1.92, respectively, for systolic pressure, 1.69 and 1.71 for diastolic pressure, 1.46 and 1.52 for body mass index, and 1.26 and 1.05 for urinary volume.

DISCUSSION

The amount of albumin excreted in the urine over a period of 24 hours is considered the gold standard for assessment of albumin level and microalbuminuria (13). However, 24-hour collections are inconvenient, are subject to error due to inaccurate timing and/or incompleteness, and are more costly for epidemiologic studies than alternative types of collections in terms of both supplies and the staff time needed to properly instruct participants and verify completeness. Because of such weaknesses, many studies have evaluated alternative collections (19), including first morning samples (26, 41, 42), morning samples (43–45), random specimens (20, 23,

46, 47), and timed overnight collections (19, 48, 49). Since random and morning specimens are untimed, results and cutoff points for microalbuminuria must be based on either albumin concentration or ACR. However, both ACR and albumin concentration also have weaknesses that may make either measure more or less preferable in a given situation.

The major weakness of ACR is that creatinine excretion is higher in men than in women, varies by ethnicity, and declines with age (5, 19–25), leading to problems in defining appropriate ACR cutoffs for microalbuminuria. While the American Diabetes Association uses a single set of cutoffs to define microalbuminuria for ACR (13), some investigators have proposed gender-specific cutoffs to help alleviate this problem (5, 19–25). The cost of using ACR is also higher than that for albumin concentration because of the added cost of taking creatinine measurements. The primary weakness of albumin concentration is that it is affected by urinary flow rate (19, 26) and is therefore expected to have greater within-person variability than ACR, which is assumed to be affected less by daily variation in creatinine excretion than albumin concentration is by urinary flow rate (19). The American Diabetes Association considers the variability in albumin concentration to be too high to permit its use in defining microalbuminuria (13). When the validities of albumin concentration and ACR as alternatives to albumin excretion have been compared (19, 23, 42, 46–49), those studies that have compared results from a random specimen with 24-hour albumin excretion have generally found ACR to have no clear advantage over albumin concentration (23, 42, 46, 47), while studies that have compared results based on timed overnight collections (19, 48, 49) have favored ACR. However, the results of the latter studies may have been affected by diurnal variation in albumin excretion (5, 26, 50–53), and some investigators consider such collections less sensitive than 24-hour collections (52).

For this report, we used measurements of albumin concentration, ACR, and albumin excretion from two 24-hour urine collections carried out among INTERMAP men and women aged 40–59 years to further assess the relative strengths and weaknesses of ACR and albumin concentration as alternatives to 24-hour albumin excretion. We compared ACR and albumin concentration with regard to associations with albumin excretion, daily within-person variability, and associations with blood pressure and body mass index.

With respect to associations with albumin excretion, rank-order correlations of ACR with albumin excretion were larger for both men and women (0.949 and 0.942, respectively) than were correlations of albumin concentration with albumin excretion (0.881 and 0.816, respectively). When micro- and macroalbuminuria were defined by INTERMAP-specific gender/country cutoffs for both ACR and albumin concentration, ACR showed better agreement with albumin excretion than did albumin concentration ($\kappa = 0.935$ vs. $\kappa = 0.872$). The ACR also showed better agreement with albumin excretion than albumin concentration (i.e., 0.908) when micro- and macroalbuminuria were defined according to the gender-specific cutoffs of 17–249 mg/g for men and 25–354 mg/g for women that were used in several other studies (16, 20–22). When the single albumin concentration cutoff of 16–159 mg/liter suggested by Bakker (19) was used, the rate of agreement with albumin excretion was 0.855, which is similar to the rate of agreement of 0.857 obtained with the American Diabetes Association ACR cutoff of 30–299 mg/g.

In characterizing the daily variability of albumin excretion in individuals, investigators generally use either the mean within-person CV or the median within-person CV, which is typically in the range of 40–60 percent (26–31). Results for INTERMAP participants were consistent with these findings: Mean CVs were almost 60 percent when values below the detection limit were included and 34–40 percent when such values were excluded. While the differences in mean and median CVs among albumin excretion, ACR, and albumin concentration were not large, the smallest values were generally those for albumin concentration. The three urinary albumin measures also had substantially larger mean and median within-person CVs than other urinary variables in INTERMAP, including sodium, potassium, urea, creatinine, and volume. When values below the assay detection limit were excluded, rank-order correlations of first and repeat values for albumin excretion, ACR, and albumin concentration were generally similar and comparable to those of other urinary variables in men but smaller in women.

INTERMAP urine samples were frozen for approximately 3 years at –20° C before being analyzed. Several investigators have reported that long-term freezing at this temperature can affect estimates of concentration, with the impact generally being greater at higher concentrations (54–58). In a study of persons with type II diabetes mellitus, median ACR decreased by 40 percent in urine samples frozen at –20° C for 2 years (56). While within-person CVs for albumin excretion in INTERMAP are consistent with those of other studies, it is likely that they are larger than they might have been if albumin had been measured in fresh urine samples, given the possibility that the loss of measured albumin was differential between the two collections for each person in INTERMAP.

While rank-order correlations of ACR and albumin concentration with systolic and diastolic blood pressure were similar to those for 24-hour albumin excretion, correlations of ACR with body mass index were smaller than those for albumin excretion and albumin concentration. This represents a weakness of ACR for epidemiologic studies that include measures of body size and obesity as key variables, since it raises questions as to whether or not ACR can be used to assess associations of albumin excretion with body mass index and other measures of body size and obesity, and whether investigators in studies that use ACR who wish to adjust for these variables can correctly do so.

Associations of blood pressure and body mass index with micro- and macroalbuminuria were essentially identical whether defined by albumin excretion, the INTERMAP gender/country-specific cutoffs for ACR or albumin concentration, the gender-specific ACR cutoffs proposed by Warram et al. (20), or the single albumin concentration cutoff of 16–159 mg/liter suggested by Bakker (19). This almost certainly reflects the high rate of agreement among the various categorizations, as well as the fact that persons incorrectly classified as microalbuminuric on the basis of ACR or albumin concentration have blood pressure levels

TABLE 5. Comparative strengths and weaknesses of 24-hour urinary albumin excretion, albumin:creatinine ratio, and urinary albumin concentration as measures of albumin level in population research, International Study of Macronutrients and Blood Pressure, 1996–2002

Comparison	Albumin measure		
	24-hour urinary albumin excretion (gold standard)	Albumin:creatinine ratio	Urinary albumin concentration
General comparisons			
Cost of supplies	High	Low	Low
Laboratory tests involved	Albumin	Albumin, creatinine	Albumin
Staff requirements	High	Low	Low
Convenience of collection	Low	High	High
Potential for timing errors	Yes	No	No
Potential for incompleteness	Yes	No	No
Quality control requirements	High	Low	Low
Requirements for defining micro- and macroalbuminuria	Single set of cutoff points	Gender-specific cutoff points, possibly age- and ethnicity-specific also	Single set of cutoff points
Usable literature definitions of micro- and macroalbuminuria	Yes	Yes, if gender-specific; age range not too broad	Yes
INTERMAP* comparisons†			
Average correlation with 24-hour albumin excretion		0.945	0.845
Agreement with micro- and macroalbuminuria defined by 24-hour albumin excretion (κ)		0.935	0.872
Mean within-person coefficient of variation‡ (%)	37.6	37.9	35.5
Average correlation with systolic blood pressure	0.289	0.265	0.293
Average correlation with diastolic blood pressure	0.216	0.188	0.230
Average correlation with body mass index	0.211	0.118	0.188

* INTERMAP, International Study of Macronutrients and Blood Pressure.
† A total of 1,933 men and women were included in all comparisons except that for the kappa statistic.
‡ Weighted average of the sex-specific coefficients of variation presented in table 3.

similar to those of persons incorrectly classified as normoalbuminuric or correctly classified as microalbuminuric.

Limitations of this study include the problem of measuring albumin excretion in urine samples that have been frozen for several years and the issue of whether the similar within-person CVs of ACR and albumin concentration from 24-hour urine samples and the similarity of associations with blood pressure can be expected for other types of urine collection—for example, spot or random collections. The latter concern is lessened by findings that albumin concentration measured in a first morning sample is related to stroke risk (4) and cardiovascular disease risk factors and morbidity (18) and that it correlates as well as or better than ACR with 24-hour albumin excretion in studies measuring albumin concentration and ACR in a spot urine sample following completion of a 24-hour urine measurement (23, 42, 46, 47).

In summary, both albumin concentration and ACR appear to be reasonable alternatives to 24-hour albumin excretion on the basis of their relative strengths and weaknesses and the results presented here (see table 5). However, there are circumstances in which each measure would be favored. In particular, albumin concentration is the better alternative to 24-hour albumin excretion for epidemiologic studies in which measures of body size and obesity are key variables or the cost of creatinine measurement is an important consideration. When these concerns do not apply, ACR appears to be the better alternative to albumin excretion, since it has stronger associations with albumin excretion than albumin concentration. If the study's focus is on microalbuminuria, gender-specific cutoffs such as those proposed by Warram et al. (20) may perform almost as well as those defined specifically for the population under study. However, as Houlihan et al. (24) noted, even gender-specific cutoffs may not be suitable for studies with a broad age range, such as 40–80 years.

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