

# Ethnicity and Unprovoked Hypokalemia in the Atherosclerosis Risk in Communities Study

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**Background:** Hypertension is more prevalent in the African American population when compared with the European American population in the United States. Unprovoked hypokalemia may lead to hypertension and is associated with several forms of recognized secondary hypertension.

**Methods:** We investigated the association of ethnicity with unprovoked hypokalemia in the second Atherosclerosis Risk in Communities (ARIC) study examination. Hypokalemia was defined as serum potassium  $<3.5$  mmol/L.

**Results:** A statistically significant association was detected between ethnicity and unprovoked hypokalemia (odds ratio = 5.3; 95% confidence interval = 3.6, 7.7)

with unprovoked hypokalemia more prevalent in African Americans both before and after adjustment for important covariates. The unadjusted prevalence for unprovoked hypokalemia was 2.6% for African Americans and 0.5% for European Americans.

**Conclusions:** We found that the prevalence of unprovoked hypokalemia for African Americans in the ARIC cohort was more than five times that for European Americans. These data suggest that an increased awareness of hypokalemia and its etiology may be indicated for African Americans. *Am J Hypertens* 2002;15:594–599 © 2002 American Journal of Hypertension, Ltd.

**Key Words:** Hypokalemia, ethnicity, potassium, hypertension, ARIC.

**N**onpharmacologic or unprovoked hypokalemia is defined as serum potassium  $<3.5$  mmol/L in the absence of potassium-depleting medications.<sup>1</sup> Hypokalemia is a consequence of either decreased total body potassium or redistribution of potassium from the extracellular to intracellular space.

Causes of total body potassium depletion can include low dietary potassium levels, high dietary  $\text{Na}^+/\text{K}^+$  ratio,<sup>2</sup> and excessive potassium loss through a variety of mechanisms including renal potassium excretion, sweating, and excessive ethanol intake. Potassium depletion from increased renal excretion is most commonly associated with potassium-depleting medication and less common with disorders involving excess aldosterone production or intrinsic renal mechanisms.<sup>3</sup> Recent studies have shown that although aldosterone levels are often found to be lower in African Americans, there may be differences between Af-

rican Americans and European Americans with respect to renal mechanisms involving epithelial sodium channel activity.<sup>4,5</sup>

Possible correlates of long-term hypokalemia include some forms of hypertension and arrhythmias. Low dietary potassium intake has also been related to stroke mortality.<sup>6</sup> An association between hypertension, low potassium intake, and high sodium consumption has been reported in several populations and has been particularly noted as a feature in African American populations.<sup>7,8</sup> In addition, there is evidence that in some groups, oral potassium supplementation is generally associated with reductions in blood pressure (BP), and that this reduction may be more pronounced in African Americans.<sup>9</sup> The prevalence of hypertension is higher in the African American population when compared with the European American population in the United States. This difference also generalizes to

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stroke mortality rates in groups of individuals aged <85 years.<sup>10</sup> The detection of a higher prevalence of unprovoked hypokalemia in the African American population would point to areas of research that may lead to better understanding of differences in disease prevalence.

## Patients and Methods

### Study Population

The Atherosclerosis Risk in Communities Study (ARIC) study is a multicenter longitudinal study of the etiology of atherosclerosis, the variation of cardiovascular risk factors, medical care, and disease by ethnicity, sex, and place of residence. The ARIC cohort at baseline consisted of approximately 15,800 participants aged 45–64 years for whom data were taken from 1987 through 1989, with follow up visits at intervals of approximately 3-years. The four ARIC communities include Forsyth County, NC; the northwestern suburbs of Minneapolis, MN; Washington County, MD; and city of Jackson, MS. The ARIC study design and participant response by center have been described in detail elsewhere.<sup>11,12</sup> The data for this study were taken from the first ARIC follow-up examination (or examination 2), which occurred between 1990 and 1993 and included 14,348 returning participants. Examination 2 serum potassium data, along with all available examination 2 risk factors for unprovoked hypokalemia, were used for this study. Serum potassium concentration was measured during the baseline examination, but these data were not used for this study because of differences in baseline examination methods with respect to fist clenching during venipuncture. These protocol differences may have led to differences found in repeated measurements of serum potassium,<sup>13</sup> as well as distribution of serum potassium between study centers. This was corrected before the beginning of examination 2.

Exclusions from this analysis include the following: 42 participants who were not reported as either African American or white; 56 participants with missing serum potassium data from examination 2; 100 participants reporting use of potassium-sparing medications; and 2508 participants reporting potassium-depleting medications. Individuals with unknown or inconsistent medication status from the clinic examination were also excluded among these 2,508 individuals. The total sample size for this study after all exclusions was 11,642.

### Measurements

Blood samples were drawn after a period of  $\geq 12$  h during which participants were instructed to fast. Blood collection and processing as well as laboratory blood chemistry analyses were done according to protocols that have been documented in detail elsewhere.<sup>14</sup> For purposes of adjustment in this study, renal dysfunction is indicated by a serum creatinine value  $>1.6$  mg/dL for men and  $>1.4$  mg/dL for women. Hypokalemia was determined as a

serum potassium level  $<3.5$  mmol/L. Physical activity at baseline was represented by activity in sports and non-sports-related leisure time. The methods for obtaining these two physical activity scales have been reported previously along with instrument reliability and validity measures for the ARIC cohort.<sup>15</sup>

Blood pressure measurements for this study consisted of the average of the last two from a series of three random zero sphygmomanometer readings taken while the participant is seated. Hypertension is indicated by systolic BP of  $\geq 140$  mm Hg, diastolic BP of  $\geq 90$  mm Hg, or self-reported use of hypertensive medications.

Medication information was taken by means of a medication inventory during each clinic visit. Potassium-depleting medications were defined as any medication consisting of or containing a potassium-depleting diuretic. Participants were classified as not reporting the use of potassium-depleting medications if they had a valid medication record and no reported use of any potassium-depleting medications as defined above.

To further reduce the influence of potential misclassification of participant medication status, medication codes and medication names were manually compared for participants classified both as not taking potassium-depleting medication and as having serum potassium  $<3.5$  mmol/L. Two individuals were found to have drug codes for a hypertensive medication that did not include a diuretic, whereas the drug name on file indicated a combination including a diuretic. These individuals were both African American but from two different study centers. These two cases were excluded along with individuals of unknown medication status.

Dietary intake of potassium and sodium at baseline were derived from the ARIC dietary instrument.<sup>16,17</sup> Household income was measured at baseline and for the present study was categorized into four categories (less than \$8,000, \$8,000 to \$15,999, \$16,000 to \$34,999, and more than \$34,999).

### Statistical Analysis

General characteristics of the study population are summarized as means  $\pm$  SD for continuous data and as percentages for categorical data. All univariate contrasts between African Americans and European Americans were based on one-way analysis of variance and  $\chi^2$  tests or Fisher's exact tests where appropriate. Covariate adjusted associations of interest in this study were estimated by means of multiple logistic regression using PROC LOGISTIC from the SAS statistical package (SAS Institute, Cary, NC).<sup>18,19</sup>

### Results

The study population was characterized separately for women and men (Tables 1 and 2). Covariates that could potentially lead to lower serum potassium, including lower dietary potassium intake and evidence of renal dysfunc-

**Table 1.** Characteristics of women not reporting use of potassium-depleting medication by ethnicity, ARIC study 1990–1993

Variable	African American			European American			P Value
	n	Mean or %	SD	n	Mean or %	SD	
Age, years	1425	55.7	5.7	4722	56.6	5.6	.001
BMI, Kg/m <sup>2</sup>	1420	30.2	6.3	4718	26.4	5.1	.001
Dietary K <sup>+</sup> , g	1387	2.3	1.0	4640	2.6	0.9	.001
Dietary Na <sup>+</sup> , g	1387	1.3	0.5	4640	1.4	0.5	.001
Serum K <sup>+</sup> , mmol/L	1425	4.18	0.39	4722	4.19	0.35	.489
Current drinker (%)	1422	27.1		4721	61.9		.001
Current smoker (%)	1423	21.8		4721	21.9		.925
Income <\$16,000 (%)	1270	54.3		4486	13.9		.001
ACE inhibitors (%)	1425	5.0		4722	3.5		.007
K <sup>+</sup> supplements (%)	1425	3.3		4722	1.4		.001
Renal dysfunction (%)*	1425	2.7		4722	0.6		.001
Hypertension (%)†	1416	37.0		4715	18.1		.001
Hypokalemia (%)‡	1425	2.9		4722	0.7		.001

ARIC = the Atherosclerosis Risk in Communities study; BMI = body mass index; ACE = angiotensin converting enzyme.

\* Renal dysfunction defined as serum creatinine >1.6 mg/dL for men and 1.4 mg/dL for women.

† Hypertension defined as systolic blood pressure of  $\geq 140$  mm Hg or diastolic blood pressure of  $\geq 90$  mm Hg or self-reported use of antihypertensive medications during the previous 2 weeks.

‡ Hypokalemia defined as serum potassium <3.5 mmol/L.

tion, were significantly different for both African American men and women. Use of potassium supplements was higher for African Americans, and use of angiotensin converting enzyme (ACE) inhibitors was higher only for African American women when compared with European American women. Mean serum potassium was not significantly lower for African American women. Median serum potassium for European American women (4.1 mmol/L) was lower than for African American women (4.2 mmol/L), as shown in Fig. 1. The distributions of serum potassium for men and women as given in Figs. 1 and 2 reflect

the general tendency of serum potassium to be lower for African Americans for values below the median or 50th percentile, with the first percentile (lowest point on percentile scale) being well below 3.5 mmol/L for African Americans and  $\geq 3.5$  mmol/L for European Americans.

The unadjusted prevalence of unprovoked hypokalemia in African Americans was four to seven times that of European Americans (Tables 1 and 2). Sex-specific regressions with ethnicity as an independent variable and non-pharmacologic hypokalemia as a dependent variable resulted in evidence of significant associations between

**Table 2.** Characteristics of men not reporting use of potassium-depleting medication by ethnicity, ARIC study 1990–1993.

Variable	African American			European American			P Value
	n	Mean or %	SD	n	Mean or %	SD	
Age, years	991	56.0	5.9	4504	57.4	5.7	.001
BMI, Kg/m <sup>2</sup>	985	27.6	4.9	4502	27.4	3.9	.086
Dietary K <sup>+</sup> , g	951	2.4	1.0	4426	2.8	1.0	.001
Dietary Na <sup>+</sup> , g	951	1.4	0.5	4426	1.6	0.6	.001
Serum K <sup>+</sup> , mmol/L	991	4.26	0.42	4504	4.31	0.34	.001
Current drinker (%)	981	50.6		4501	68.6		.001
Current smoker (%)	980	34.1		4502	22.1		.001
Income <\$16,000 (%)	887	40.8		4348	7.2		.001
ACE inhibitors (%)	991	4.5		4504	5.1		.494
K <sup>+</sup> supplements (%)	991	1.8		4504	0.9		.012
Renal dysfunction (%)*	991	4.9		4504	1.3		.001
Hypertension (%)†	986	39.2		4492	24.9		.001
Hypokalemia (%)‡	991	2.2		4504	0.3		.001

Abbreviations as in Table 1.

\* Renal dysfunction defined as serum creatinine >1.6 mg/dL for men and 1.4 mg/dL for women.

† Hypertension defined as systolic blood pressure of  $\geq 140$  mm Hg or diastolic blood pressure of  $\geq 90$  mm Hg or self-reported use of antihypertensive medications during previous 2 weeks.

‡ Hypokalemia defined as serum potassium <3.5 mmol/L.

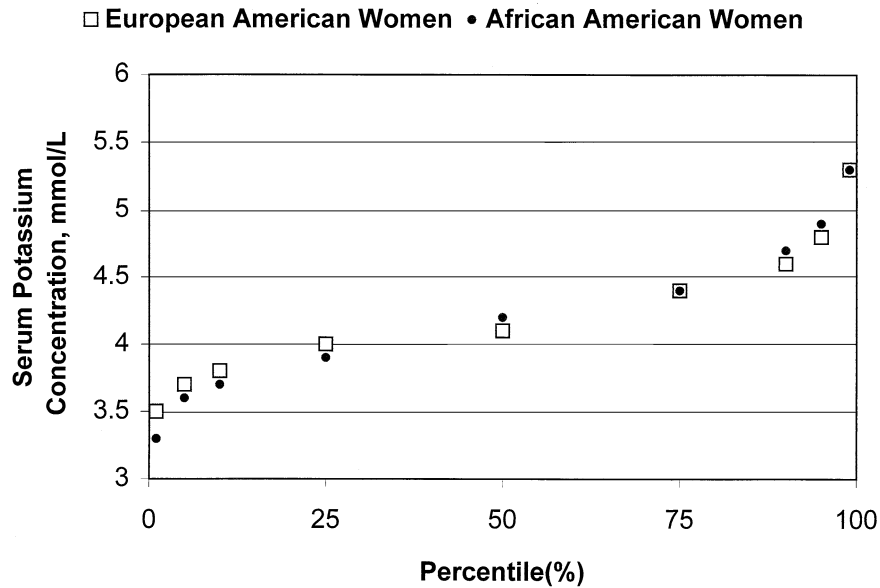


FIG. 1. Serum potassium percentiles for women who did not report use of potassium-depleting medications, by ethnicity.

ethnicity and hypokalemia (Table 3). Significant associations persisted after adjustment for covariates.

Several covariates were significantly related ( $P < .05$ ) to unprovoked hypokalemia in the multiple logistic regressions. For men and women combined, these included body mass index (BMI) below the first quintile (odds ratio [OR] = 3.2; 95% confidence interval [CI] = 1.6 to 6.7,  $P = .0016$ ), annual household income less than \$8,000 (OR = 2.5; 95% CI = 1.3 to 4.5,  $P = .0004$ ), hypercreatinemia (OR = 2.7, 95% CI = 1.1–6.7,  $P = .03$ ), and reported use of potassium supplements (OR = 4.6, 95% CI = 2.1–10.1,  $P < .001$ ).

Physical activity variables were initially included as

covariates in the logistic regressions to account for potential differences in loss of potassium from sweating. The inclusion of these in the analysis did not change the association between ethnicity and hypokalemia for women and appeared to have a nonsignificant inverse association with hypokalemia for men, indicating the possibility of a weak tendency for participants with low potassium to be less active. This is consistent with the clinical consequences of hypokalemia rather than its etiology. For these reasons, physical activity was not included in the regression model.

African American participants from Forsyth County, NC, and the other study centers characterized by a major-

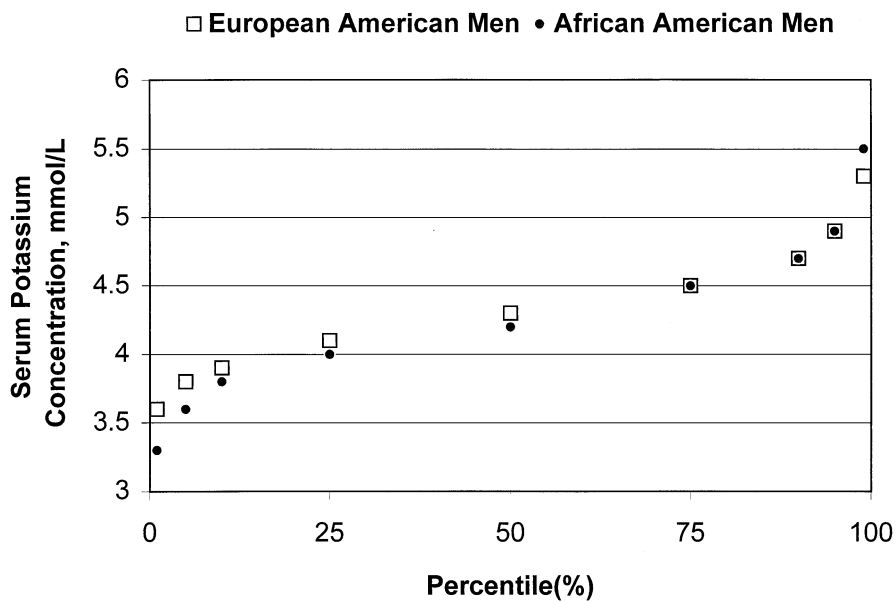


FIG. 2. Serum potassium percentiles for men who did not report use of potassium-depleting medications, by ethnicity.

**Table 3.** Associations between ethnicity and the presence of unprovoked hypokalemia (unadjusted and adjusted for other factors), by sex

Gender	Unadjusted		Adjusted*	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Women	4.6	(2.9, 7.3)	3.0	(1.6, 5.7)
Men	6.8	(3.5, 13.1)	2.9	(1.2, 7.1)
Combined†	5.3	(3.6, 7.7)	2.9	(1.8, 4.9)

CI = confidence interval.

\* Adjusted for age, body mass, dietary potassium and sodium, income, hypercreatinemia, angiotensin converting enzyme inhibitors, potassium supplementation, and ethanol intake.

† Combined estimates also adjusted for sex.

ity of European Americans were included in the general analyses for this article. Although there were too few of these participants to perform a separate multiple regression analysis, it is informative that the patterns in unadjusted prevalence of hypokalemia are similar to the overall study population. The prevalence of unprovoked hypokalemia for African Americans in Forsyth County is 3.8% (10/263), whereas the prevalence for European Americans for the same center is 0.7% (19/2892), which is consistent with differences found in the whole study population.

## Discussion

We have shown that unprovoked hypokalemia is more prevalent in African Americans than in European Americans for this middle-aged population. This cross-sectional association persists after adjustment for risk factors potentially related to ethnicity and hypokalemia status. The consistency of prevalence differences in the overall study population with the Forsyth County center tends to rule out regional differences as an explanation for this result.

Several studies, including results from the ARIC cohort, have reported lower potassium intake in African Americans. Thus, the association reported here could be a consequence of residual confounding from dietary electrolyte intake.<sup>16,20,21</sup>

Other explanations for the results of this study include renal dysfunction or secondary forms of hypertension.<sup>22,23</sup> Given that aldosterone levels are often found to be lower in African Americans, there is no clear evidence to support excess aldosterone secretion as an explanatory mechanism.<sup>4</sup> Recent studies of unrecognized forms of secondary hypertension in some African Americans provide one plausible explanation. These studies point to increased sodium retention in African American individuals that is related to primary renal mechanisms involving epithelial sodium channel activity.<sup>4,5,23</sup>

A potential limitation of this study involves possible underreporting of the use of potassium-depleting medications. One study comparing medication inventory methods to serum levels of medications in an elderly population<sup>24</sup> found that for several drugs including hydrochlorothiazide (HCTZ), rather than underreporting, participants were

more likely to report using the drug in cases in which no serum levels could be detected. However, of 50 participants reporting no use of HCTZ, one participant was found to have measurable serum levels of HCTZ.

We believe that medication-reporting error is an unlikely explanation for the results of this study, as the methods for recording medications were consistent across centers and as individuals with unknown and inconsistent medication status were excluded from this analysis. However, because of higher rates of hypertension and as well as use of hypertension medication in the African American population, and because of the documented potential for underreporting diuretic use in other studies, this limitation cannot be completely ruled out.

This study reports a significant cross-sectional relationship between ethnicity and unprovoked hypokalemia. From a clinical perspective the prevalence of unprovoked hypokalemia is thought to be generally <1%.<sup>1</sup> In this middle-aged African American cohort, the prevalence of unprovoked hypokalemia was >2%. These results clearly indicate the need for increased awareness of unprovoked hypokalemia in African American individuals, along with increased efforts to determine the underlying causes of this disorder.

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## References

- Weiner D, Wingo CS: Hypokalemia—consequence, causes and correction. *J Am Soc Nephrol* 1997;8:1179–1188.
- Young DB: Analysis of long-term potassium regulation. *Endocr Rev* 1985;6:124–144.
- Mandal AK: Hypokalemia and hyperkalemia. *Renal Dis* 1997;81:611–639.
- Pratt JH, Rebhun JF, Zhou L, Ambrosius WT, Newman SA, Gomez-Sanchez CE, Mayes DF: Levels of mineralocorticoids in whites and blacks. *Hypertension* 1999;34:315–319.

5. Ambrosius WT, Bloem LJ, Zhou L, Rebhun JF, Snyder PM, Wagner MA, Guo C, Pratt JH: Genetic variants in the epithelial sodium channel in relation to aldosterone and potassium excretion and risk for hypertension. *Hypertension* 1999;34:631–637.
6. Khaw KT, Barret-Connor E: Dietary potassium and stroke related mortality: a 12 year prospective population study. *N Engl J Med* 1987;316:235–240.
7. Langford HG: Sodium-potassium interaction in hypertension and hypertensive cardiovascular disease. *Hypertension* 1991;17(Suppl I):I155–I157.
8. Kumanyika S, Adams-Campbell L: Obesity, diet, and psychosocial factors contributing to cardiovascular disease in blacks, *in*: Elijah Saunders E (ed): *Cardiovascular Disease in Blacks*. Philadelphia: Davis, Philadelphia, 1991, pp 47–69.
9. Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ: Effects of oral potassium on blood pressure. *JAMA* 1997;277:1624–1632.
10. 1996 Chartbook on Cardiovascular Lung, and Blood Diseases. Bethesda, MD, National Institutes of Health, National Heart, Lung, and Blood Institute, May 1996.
11. ARIC Investigators: The Atherosclerosis Risk in Communities (ARIC) study: design and objectives. *Am J Epidemiol* 1989;129:687–702.
12. Jackson R, Chambless LE, Yang K, Byrne T, Watson R, Folsom A, Shahar E, Kalsbeek W: Differences between respondents and non-respondents in a multicenter community-based study vary by gender and ethnicity. *J Clin Epidemiol* 1996;49:1441–1446.
13. Eckfeldt JH, Chambless LE, Shen YL: Short-term, within person variability in clinical chemistry test results. *Arch Pathol Lab Med* 1994;118:496–500.
14. National Heart, Lung, and Blood Institute: ARIC Manuals of Operation: No. 7, Blood Collection and Processing; No. 10, Clinical Chemistry Determinations; No. 11 Sitting Blood Pressure; No. 12, Quality Assurance. Chapel Hill, NC: ARIC Coordinating Center, School of Public Health, University of North Carolina; 1989.
15. Folsom AR, Arnett DK, Hutchinson RG, Clegg LX, Cooper LS: Physical activity and incidence of coronary heart disease in middle-aged women and men. *Med Sci Sports Exerc* 1997;29:901–909.
16. Shimakawa T, Sorlie P, Carpenter MS, Dennis B, Tell GS, Watson R, Williams OD: Dietary intake patterns and sociodemographic factors in the Atherosclerosis Risk in Communities Study (ARIC). *Prev Med* 1994;23:769–780.
17. Stevens J, Metcalf PA, Dennis BH, Tell GS, Shimakawa T, Folsom A: Reliability of a food frequency questionnaire by ethnicity, gender, age and education. *Nutr Res* 1996;16:735–745.
18. Hosmer DW, Lemeshow S: *Applied Logistic Regression*. John Wiley & Sons, New York, 1989.
19. SAS/STAT Users Guide, 1990, Volume 2, Version 6: SAS Institute, Cary, NC, pp 1071–1126.
20. Elliot P, Dyer A, Stamler R: The INTERSALT Study: results for 24 hour sodium and potassium, by age and sex. *J Hum Hypertens* 1989;3:323–330.
21. Ganguli MC, Grimm RH, Svendsen KH, Flack JM, Grandits GA, Elmer PJ: Higher education and income are related to a better NA:K ratio in blacks: baseline results of the Treatment of Mild Hypertension Study (TOMHS) data. *Am J Hypertens* 1997;10:979–984.
22. Gordon RD, Klemm SA, Tunny TJ, Stowasser M: Primary aldosteronism: hypertension with a genetic basis. *Lancet* 1992;340:159–161.
23. Gadallah MF, Abreo K, Work J: Liddle's syndrome, an underrecognized entity: a report on four cases, including the first report in black individuals. *Am J Kidney Dis* 1995;25:829–835.
24. Smith NL, Psaty BM, Heckbert SR, Russell TP, Cornell E: The reliability of medication inventory methods compared with serum levels of cardiovascular drugs in the elderly. *J Clin Epidemiol* 1999;52:143–146.