Serum potassium is a predictor of incident diabetes in African Americans with normal aldosterone: the Jackson Heart Study[1,2]

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ABSTRACT

Background: Low-normal potassium is a risk factor for diabetes and may account for some of the racial disparity in diabetes risk. Aldosterone affects serum potassium and is associated with insulin resistance.

Objectives: We sought to confirm the association between potassium and incident diabetes in an African-American cohort, and to determine the effect of aldosterone on this association.

Design: We studied participants from the Jackson Heart Study, an African-American adult cohort, who were without diabetes at baseline. With the use of logistic regression, we characterized the associations of serum, dietary, and urinary potassium with incident diabetes. In addition, we evaluated aldosterone as a potential effect modifier of these associations.

Results: Of 2157 participants, 398 developed diabetes over 8 y. In a minimally adjusted model, serum potassium was a significant predictor of incident diabetes (OR: 0.83; 95% CI: 0.74, 0.92 per SD increment in serum potassium). In multivariable models, we found a significant interaction between serum potassium and aldosterone ($P = 0.046$). In stratified multivariable models, in those with normal aldosterone (<9 ng/dL, $n = 1163$), participants in the highest 2 potassium quartiles had significantly lower odds of incident diabetes than did those in the lowest potassium quartile [OR (95% CI): 0.61 (0.39, 0.97) and 0.54 (0.33, 0.90), respectively]. Among those with high-normal aldosterone (≥9 ng/dL, $n = 202$), we found no significant association between serum potassium and incident diabetes. In these stratified models, serum aldosterone was not a significant predictor of incident diabetes. We found no statistically significant associations between dietary or urinary potassium and incident diabetes.

Conclusions: In this African-American cohort, we found that aldosterone may modify the association between serum potassium and incident diabetes. In participants with normal aldosterone, high-normal serum potassium was associated with a lower risk of diabetes than was low-normal serum potassium. Additional studies are warranted to determine whether serum potassium is a modifiable risk factor that could be a target for diabetes prevention. This trial was registered at clinicaltrials.gov as NCT00415415. *Am J Clin Nutr* 2017;105:442–9.

Keywords: potassium, diabetes risk, racial disparity in diabetes risk, diabetes risk factor, African Americans

INTRODUCTION

African Americans are disproportionately affected by the diabetes epidemic, with a higher incidence and prevalence of diabetes than whites have (http://www.cdc.gov/diabetes/statistics/incidence/fig6.htm). Although African Americans are also disproportionately affected by some of the traditional risk factors for diabetes, particularly obesity, hypertension, and socioeconomic status, these traditional risk factors do not account for all of the race-related disparity in diabetes risk (1, 2). Both serum and dietary potassium are inversely associated with diabetes risk, with lower potassium concentrations being associated with higher risk (3–5). In past studies of biracial cohorts, these associations appear to be stronger in African Americans (4, 6). Serum potassium concentrations are very tightly controlled through homeostatic mechanisms, and are affected by potassium intake, excretion, and hormonal influences (7). In addition, in experimental studies, low serum potassium has been found to have an impact on insulin secretion (8, 9). In previous studies, the influence of diuretic use, which leads to increased potassium excretion, on the association between serum potassium and glucose concentrations or diabetes risk has been assessed (3, 10, 11). Diuretic use can also lead to increased aldosterone concentrations. Aldosterone is a hormone that influences serum potassium concentrations and has been associated with insulin

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resistance, metabolic syndrome, and even diabetes risk (12–15). However, the influence of aldosterone on serum potassium and its association with diabetes risk has not been assessed. In this analysis of the Jackson Heart Study (JHS; NCT00415415), a prospective longitudinal cohort of African-American adults, we sought to confirm the association between potassium measures and incident diabetes, determine whether there is a concentration of serum potassium that may be associated with lower incidence of diabetes, and determine the influence of serum aldosterone concentrations on these associations.

METHODS

The JHS is a community-based prospective cohort study of 5301 African-American adults aged 21–95 y at the time of recruitment from the Jackson, Mississippi, metropolitan area. This cohort was designed to study the prevalence and the incidence of cardiovascular disease risk factors in an African-American population. Participants were recruited beginning in 2000, with baseline data collected between 2000 and 2004. Approximately 30% of the participants had participated in the Atherosclerosis Risk in Communities study, whereas the rest of the cohort was recruited from community-sampling approaches and from families of the Atherosclerosis Risk in Communities study participants (16). Participants came for in-person visits approximately every 4 y and had a telephone follow-up annually, through 2012, for a mean of 8 y of follow-up. At their study visits, participants underwent self-administered and interview-administered questionnaires, anthropometric measurements, and measurement of vital signs, as well as radiologic and laboratory evaluations. Institutional review boards at each of the participating institutions approved the study.

Study participants

We excluded participants from these analyses, sequentially, for the following reasons: if they had diabetes mellitus at baseline or if information regarding diabetes status was missing at baseline (n = 1213); if diabetes status information was missing at follow-up visits (n = 1905); if they had evidence of stage 4 or 5 kidney disease, defined as estimated glomerular filtration rate (eGFR) $<$30 mL/min, serum creatinine $>$1.7 mg/dL (150.28 μmol/L), or self-report of dialysis (n = 24); or if they had implausible serum potassium measures or aldosterone measures (n = 2). A total of 2157 participants were included for further analyses. For analyses involving multivariable models, an additional 792 participants were excluded because of missing covariates.

For analyses that used dietary potassium, we excluded participants who were missing dietary data (n = 158). For analyses that used urinary potassium, we also excluded participants who were missing spot urinary measures (n = 781).

Main exposures: potassium measures

Serum potassium was measured in all participants at the baseline exam only. Spot urine measures were collected at all 3 visits; however, for these analyses, spot urine potassium measures were used from the baseline exam only. For serum and blood measures, participants underwent venipuncture in a fasting state. Blood samples were centrifuged, portioned into aliquots, frozen, and stored at −70°C in a central laboratory. Serum and urinary potassium was measured with a direct electrode potentiometric assay (Vitros 950 or 250 analyzer; Ortho-Clinical Diagnostics) (17). Dietary intake of nutrients, including potassium, was measured in all participants at the baseline exam. Participants completed a 158-item food-frequency questionnaire that was tailored and validated to be culturally appropriate for the population, and which was administered face-to-face by trained African-American interviewers (18, 19).

Outcome: incident diabetes

The outcome of interest was incident diabetes mellitus during the 8 y of follow-up. A diagnosis of diabetes mellitus was defined as having a fasting serum glucose ≥126 mg/dL (6.99 mmol/L) and/or glycated hemoglobin ≥6.5% (48 mmol/mol), and/or the use of antihyperglycemic medications. Glucose was measured on undiluted serum with the use of a glucose oxidase colorimetric assay (Vitros 950 or 250 analyzer; Ortho-Clinical Diagnostics) (17). Glycated hemoglobin was measured on whole blood with the use of HPLC (Tohosh Corporation) (17). Medications and the indications for the use of the medication were assessed at all 3 in-person visits, and medication bottles were viewed and recorded by trained interviewers. Because participants who had diabetes at baseline were excluded, those who were found to have diabetes at either of the 2 follow-up visits were considered to have incident diabetes.

Covariates

For our analyses, all measures of covariates were derived from the baseline exam. Age, sex, and annual household income were self-reported at the baseline in-person visit. Household income was categorized according to relation to the poverty level as follows—poor: ≤1 times the poverty level; lower-middle class: $>$1 to ≤1.5 times the poverty level; upper-middle class: $>$1.5 to ≤3.5 times the poverty level; and affluent: $>$3.5 times the poverty level. Family history of diabetes was also based on self-report and was based on the presence of diabetes in parents or siblings. BMI and waist circumference were measured at baseline with the use of standardized procedures and frequently calibrated equipment. Waist circumference was measured at the level of the umbilicus. Blood pressure was measured with the use of calibrated equipment and a standardized protocol, and was recorded as the mean of 2 blood pressure readings taken 5 min apart and after an initial 5 min of rest. A diagnosis of hypertension was defined as having blood pressure ≥140/90 mm Hg or the use of blood pressure–lowering medications (based on in-person review of medication or self-report). Serum and urinary creatinine were measured with the use of a multipoint enzymatic spectrophotometric assay (Vitros CREA dry reaction slides on a Vitros 950 analyzer; Ortho-Clinical Diagnostics) (20). Serum sodium was measured with the use of a direct electrode potentiometric assay (Vitros 950 or 250 analyzer; Ortho-Clinical Diagnostics) (17). Insulin was measured with the use of a radioimmunoassay (Linco) (17). Aldosterone was also measured at baseline exam, and aldosterone was measured on serum samples by radioimmunoassay (Siemens) (14). Dietary variables were measured from the 158-item food-frequency questionnaire. Based on previous nutrition studies, we selected dietary factors as covariates

that were most indicative of a healthy or unhealthy eating pattern (4). Physical activity was measured with the use of a validated 30-item interviewer-administered survey; for these analyses, physical activity reflects sports and exercise (21).

Statistical analyses

For our primary analyses, we categorized all of the potassium measures of interest into quartiles. We examined baseline characteristics of participants by serum potassium quartiles. We compared characteristics across serum potassium quartiles with chi-square analyses for categorical variables and ANOVA for continuous variables. To assess the associations between potassium measures and incident diabetes, we performed multivariable logistic regression. While using a minimally adjusted model, Model 1, we adjusted only for age, sex, and main exposure. While using a multivariable-adjusted model, Model 2, we adjusted in addition for BMI; waist circumference; serum sodium and creatinine; physical activity; family history of diabetes mellitus; presence of hypertension; systolic blood pressure; use of diuretics; baseline fasting glucose and insulin; income; other dietary factors, including total energy intake, total and saturated fat intake, fiber intake, and dietary sodium intake (dietary analyses only); and urinary creatinine (urinary analyses only). The lowest potassium quartile for each measure was our reference group. For analyses that used serum and urinary potassium, we tested for a possible interaction between aldosterone and potassium. Finding a significant interaction between aldosterone and serum potassium, we conducted stratified analyses by aldosterone concentration. We further adjusted for aldosterone concentration to better determine the influence of aldosterone on the association between serum potassium and incident diabetes (Model 3; serum, urine).

We conducted sensitivity analyses to assess the robustness of our primary findings. Because diuretic use has been associated with increased diabetes risk, is known to influence serum potassium, and can lead to higher aldosterone concentrations, we conducted a sensitivity analysis excluding participants who were taking diuretics at the baseline exam. Because kidney function can also affect serum potassium, we conducted a sensitivity analysis while excluding participants with stage 3 or higher kidney disease (eGFR <60 mL/min) at baseline. For dietary analyses, we further adjusted for total fruit and vegetable intake to determine whether dietary potassium was a significant predictor independent of total fruit and vegetable intake (Model 3; dietary).

Tests of significance were 2-tailed, with an α-level of 0.05. We performed all analyses with the use of R statistical software, version 3.1.2 (22).

RESULTS

Serum potassium and incident diabetes

Baseline characteristics of the 2157 participants included in our analyses, by serum potassium quartile, are shown in **Table 1**. Mean ± SD serum potassium was 4.3 ± 0.4 mmol/L (range: 2.6–5.8 mmol/L). The mean age of these participants was 52 y; 37% of the participants were men; 47% of the participants had a family history of diabetes; mean BMI (in kg/m^2) was 31; and 51% had a diagnosis of hypertension. Compared with participants in the lowest quartile of serum potassium, participants in the highest quartile of serum potassium ($\geq$4.5 mmol/L) had a lower BMI, smaller waist circumference, lower prevalence of hypertension, and lower prevalence of diuretic use. Between the serum potassium quartiles, there were no statistically significant differences in dietary potassium intake or physical activity.

During a mean of 8 y of follow-up, 398 of participants (18.5%) developed diabetes. In minimally adjusted models that were adjusted only for age and sex, serum potassium was a predictor of incident diabetes (OR: 0.83; 95% CI: 0.74, 0.92 per SD increment of serum potassium). Compared with those in the lowest serum potassium quartile, those in the highest serum potassium quartile had a reduced odds of incident diabetes, with an OR (95% CI) of 0.63 (0.47, 0.84) (**Table 2**). After additional adjustment for variables in Model 2, there continued to be a statistically significant association between serum potassium and incident diabetes (Table 2).

We found a statistically significant interaction between baseline serum potassium and aldosterone in their effect on incident diabetes ($P = 0.046$); therefore, with the addition of serum aldosterone in the models, we stratified the cohort based on aldosterone concentration. The overwhelming majority of participants had what would be considered normal concentrations of aldosterone at $\leq$16 ng/dL (0.44 nmol/L). Based on prior cohort studies, we chose aldosterone measures of $<$9 ng/dL (0.25 nmol/L) and $\geq$9 ng/dL (0.25 nmol/L) as cutoffs for the stratified analyses representing normal aldosterone and high-normal aldosterone concentrations, respectively (13, 14). Among those with normal aldosterone concentrations ($n = 1163$), in multivariable models that included adjustment for aldosterone, there was a continued statistically significant association between higher serum potassium and lower odds of incident diabetes. Compared with those in the lowest serum potassium quartile, those in the highest 2 serum potassium quartiles had adjusted ORs (95% CIs) of incident diabetes of 0.61 (0.39, 0.97) and 0.54 (0.33, 0.90), respectively (Table 2). In those with normal serum aldosterone, aldosterone concentration itself was not a significant predictor of diabetes in this model (β: 0.056; 95% CI: -0.027, 0.140; $P = 0.19$). In the small subcohort of participants with high-normal aldosterone ($n = 202$), in multivariable models, there was no significant association between serum potassium and incident diabetes. In addition, as in the previous model, aldosterone was not a significant predictor of incident diabetes (β: 0.092; 95% CI: -0.007, 0.191; $P = 0.07$).

Dietary potassium and incident diabetes

Among the participants included in our analysis, mean ± SD dietary potassium intake was 2542 ± 971 mg/d (range: 671–7443 mg/d). In a minimally adjusted model that adjusted for age, sex, and total energy intake, we found no statistically significant association between dietary potassium quartile and incident diabetes (**Table 3**). After further adjustment for variables in Model 2, there was also no statistically significant association between dietary potassium and incident diabetes (Table 3). Further adjustment for total fruit and vegetable intake did not appreciably change this association (Table 3).

TABLE 1
Baseline characteristics of the 2157 Jackson Heart Study participants by serum potassium quartile[1]

	Serum potassium, mmol/L					
	All[2]	<4.1	4.1 to <4.3	4.3 to <4.5	≥4.5	*P*[3]
Participants, *n*	2157	534	435	485	703	
Age, y	52.37	53.57 ± 11.19	52.43 ± 11.96	50.54 ± 12.35	52.67 ± 11.92	<0.01
Sex, M	799 (37.04)	137 (25.66)	131 (30.11)	197 (40.62)	334 (47.51)	<0.01
Family history of diabetes mellitus	1016 (47.1)	245 (45.88)	213 (48.97)	215 (44.33)	343 (48.79)	0.35
BMI, kg/m^2	31.13 ± 6.87	31.79 ± 6.99	32.13 ± 7.33	31.3 ± 7.13	29.9 ± 6.09	<0.01
Waist circumference, cm	98.13 ± 15.36	98.91 ± 15.92	99.27 ± 15.81	97.85 ± 15.28	97.03 ± 14.62	0.05
Hypertension present	1095 (50.76)	371 (69.48)	218 (50.11)	220 (45.36)	286 (40.68)	<0.01
Diuretic use	544 (25.22)	231 (43.26)	123 (28.28)	91 (18.76)	99 (14.08)	<0.01
Systolic blood pressure, mm Hg	124.03 ± 16.64	127.1 ± 18.23	124.58 ± 16.99	122.13 ± 16.24	122.68 ± 15.04	<0.01
Fasting glucose, mg/dL; mmol/L	89.59 ± 8.87; 4.92 ± 0.49	90.29 ± 9.19; 5.01± 0.51	89.61 ± 8.89; 4.97 ± 0.49	88.6 ± 8.97; 4.92 ± 0.50	89.72 ± 8.48; 4.98 ± 0.47	0.03
Fasting insulin, IU/mL; pmol/L	15.68 ± 8.47; 108.90 ± 58.82	16.24 ± 8.91; 112.79 ± 61.88	16.08 ± 9.01; 111.68 ± 62.57	15.4 ± 7.98; 106.95 ± 55.42	15.2 ± 8.07; 105.56 ± 56.05	0.13
Aldosterone, ng/dL; nmol/L	5.31 ± 3.8; 0.15 ± 0.11	5.72 ± 3.97; 0.16 ± 0.11	5.36 ± 4.25; 0.15 ± 0.12	4.98 ± 3.21; 0.14 ± 0.09	5.19 ± 3.73; 0.14 ± 0.10	0.01
Serum sodium, mmol/L	140.62 ± 2.18	140.69 ± 2.3	140.58 ± 2.15	140.51 ± 2.17	140.66 ± 2.11	0.56
Serum creatinine, mg/dL; μmol/L	0.9 ± 0.19; 68.63 ± 14.49	0.86 ± 0.19; 65.58 ± 14.49	0.87 ± 0.17; 66.35 ± 12.96	0.91 ± 0.19; 69.40 ± 14.49	0.94 ± 0.19; 71.68 ± 14.49	<0.01
Serum potassium, mmol/L	4.29 ± 0.38	3.81 ± 0.2	4.16 ± 0.05	4.35 ± 0.05	4.7 ± 0.21	<0.01
Dietary potassium, mg/d	2542.15 ± 970.51	2507.11 ± 1018.98	2518.54 ± 948.27	2571.84 ± 990.32	2563.59 ± 933.37	0.67
Total fruit servings	0.12 ± 0.07	0.13 ± 0.08	0.11 ± 0.06	0.12 ± 0.07	0.12 ± 0.07	0.1
Total vegetable servings	0.12 ± 0.04	0.12 ± 0.04	0.11 ± 0.04	0.12 ± 0.04	0.12 ± 0.05	0.17
Physical activity						0.56
Poor health	941 (43.63)	244 (45.69)	190 (43.68)	202 (41.65)	305 (43.39)	
Intermediate health	722 (33.47)	167 (31.27)	157 (36.09)	166 (34.23)	232 (33)	
Ideal health	493 (22.86)	123 (23.03)	87 (20)	117 (24.12)	166 (23.61)	
Income						0.01
Poor	197 (9.13)	48 (8.99)	43 (9.89)	47 (9.69)	59 (8.39)	
Lower-middle class	368 (17.06)	113 (21.16)	81 (18.62)	68 (14.02)	106 (15.08)	
Upper-middle class	562 (26.05)	142 (26.59)	108 (24.83)	123 (25.36)	189 (26.88)	
Affluent	696 (32.27)	142 (26.59)	132 (30.34)	170 (35.05)	252 (35.85)	

[1] Values are means ± SDs or *n* (%).
[2] Family history of diabetes mellitus, *n* = 2155; diuretic use, *n* = 1696; systolic blood pressure, *n* = 2156; fasting glucose, *n* = 2085; fasting insulin, *n* = 2070; aldosterone, *n* = 2138; dietary potassium, *n* = 1954; total fruit servings, *n* = 1951; total vegetable servings, *n* = 1951; physical activity, *n* = 2156; and income, *n* = 1823.
[3] Based on chi-square analyses for categorical variables and ANOVA for continuous variables.

TABLE 2
Summary of results from multivariate analyses assessing the association between serum potassium and incident diabetes mellitus over 8 y[1]

	Serum potassium, mmol/L			
	<4.1	4.1 to < 4.3	4.3 to < 4.5	≥4.5
Cases of incident diabetes mellitus,[2] *n* (%)	125 (23.41)	88 (20.23)	72 (14.85)	113 (16.07)
Model 1[3]	1.0 (ref)	0.84 (0.62, 1.15)	0.59 (0.43, 0.82)*	0.63 (0.47, 0.84)*
Model 2[4]	1.0 (ref)	0.91 (0.59, 1.38)	0.57 (0.36, 0.90)*	0.66 (0.44, 1.00)*
Model 3, stratified by normal aldosterone (*n* = 1163)[5]	1.0 (ref)	0.83 (0.51, 1.34)	0.54 (0.33, 0.90)*	0.61 (0.39, 0.97)*
Model 3, stratified by high-normal aldosterone (*n* = 202)[5]	1.0 (ref)	1.97 (0.63, 6.10)	0.84 (0.20, 3.50)	0.89 (0.25, 3.20)
Model 3, nonusers of diuretics (*n* = 935)[5]	1.0 (ref)	0.94 (0.51, 1.72)	0.66 (0.36, 1.21)	0.64 (0.36, 1.11)
Model 3, patients with estimated glomerular filtration rate ≥60 mL/min and normal aldosterone (*n* = 1143)[5]	1.0 (ref)	0.87 (0.54, 1.41)	0.55 (0.33, 0.92)*	0.63 (0.39, 1.00)*

[1] Values are ORs (95% CIs) determined by multivariable logistic regression, unless otherwise indicated. *P*-interaction between serum potassium and aldosterone = 0.046. *Statistically significant.
[2] $P < 0.01$, chi-square analysis.
[3] Adjusted for age and sex.
[4] Adjusted for covariates from Model 1, in addition to BMI, waist circumference, serum sodium and creatinine, physical activity, family history of diabetes mellitus, presence of hypertension, systolic blood pressure, use of diuretics, fasting glucose and insulin, and income.
[5] Adjusted for covariates from Models 1 and 2, in addition to aldosterone.

Urinary potassium and incident diabetes

After applying our exclusions, 1376 participants were included in the analysis that evaluated the association between spot urinary potassium and incident diabetes. In these participants, mean ± SD spot urinary potassium was 56.7 ± 28.0 mmol/L (range: 3.0–166.7 mmol/L). In a minimally adjusted model that adjusted for age, sex, and spot urinary creatinine, we found no significant association between urinary potassium and incident diabetes. We found no significant interaction between aldosterone and urinary potassium. In our multivariable model that adjusted further for the variables in Model 3, there was also no significant association between urinary potassium and incident diabetes (**Table 4**).

Sensitivity analyses of serum potassium and incident diabetes

There were 1152 participants who were not taking diuretics at baseline, 935 of whom had complete data on all model covariates. Among these participants, we found results that were similar to our main analyses; however, the results were no longer statistically significant. In our minimally adjusted model that adjusted for age and sex, there was an inverse association between serum potassium categories and incident diabetes. In this subcohort of participants who were not taking diuretics, we found no statistically significant interaction between aldosterone and serum potassium; therefore, we did not stratify by aldosterone concentration. In our multivariable model, compared with the lowest quartile of serum potassium, those in the highest quartile of serum potassium had an OR (95% CI) of incident diabetes of 0.64 (0.36, 1.11) (Table 2).

There were 1820 people with normal aldosterone and eGFR ≥60; of these, 1143 had complete data on all the model covariates. Among these participants, we found continued inverse associations between serum potassium and incident diabetes, and these results continued to be statistically significant both in our minimally adjusted model and our multivariable-adjusted model (Table 2).

DISCUSSION

Through these analyses, we confirmed the significance of serum potassium on diabetes risk in an African-American adult

TABLE 3
Summary of results from multivariate analyses assessing the association between dietary potassium and incident diabetes mellitus over 8 y[1]

	Dietary potassium, mg/d			
	<1822	1822 to <2410	2410 to <3112	≥3112
Cases of incident diabetes mellitus,[2] *n* (%)	101 (20.7)	87 (17.8)	86 (17.6)	93 (19.0)
Model 1[3]	1.0 (ref)	0.79 (0.56, 1.12)	0.80 (0.54, 1.18)	0.84 (0.51, 1.37)
Model 2[4]	1.0 (ref)	0.77 (0.48, 1.23)	0.74 (0.42, 1.29)	0.84 (0.41, 1.70)
Model 3[5]	1.0 (ref)	0.78 (0.48, 1.25)	0.75 (0.43, 1.33)	0.85 (0.41, 1.76)

[1] Values are ORs (95% CIs) determined by multivariable logistic regression, unless otherwise indicated.
[2] $P = 0.59$, chi-square analysis.
[3] Adjusted for age, sex, and total calorie intake.
[4] Adjusted for covariates from Model 1, in addition to BMI, waist circumference, serum sodium and creatinine, physical activity, family history of diabetes mellitus, presence of hypertension, systolic blood pressure, use of diuretics, fasting glucose and insulin, income, dietary fat intake, saturated fat intake, fiber intake, and dietary sodium intake.
[5] Adjusted for covariates from Models 1 and 2, in addition to total fruit and vegetable intake.

TABLE 4
Summary of results from multivariate analyses assessing the association between spot urinary potassium and incident diabetes mellitus over 8 y[1]

	Urinary potassium, mmol/L			
	<36.1	36.1 to <52.8	52.8 to <74	≥74
Cases of incident diabetes mellitus,[2] *n* (%)	60 (17.5)	57 (16.6)	57 (16.5)	53 (15.4)
Model 1[3]	1.0 (ref)	1.01 (0.66, 1.53)	1.06 (0.68, 1.66)	1.03 (0.63, 1.68)
Model 2[4]	1.0 (ref)	1.07 (0.60, 1.91)	1.41 (0.75, 2.62)	1.69 (0.86, 3.34)
Model 3[5]	1.0 (ref)	1.09 (0.61, 1.94)	1.46 (0.78, 2.74)	1.77 (0.89, 3.53)

[1] Values are ORs (95% CIs) determined by multivariable logistic regression, unless otherwise indicated. *P*-interaction between urinary potassium and aldosterone = 0.8.
[2] $P = 0.9$, chi-square analysis.
[3] Adjusted for age, sex, and urinary spot creatinine.
[4] Adjusted for covariates from Model 1, in addition to BMI, waist circumference, serum sodium and creatinine, physical activity, family history of diabetes mellitus, presence of hypertension, systolic blood pressure, use of diuretics, fasting glucose and insulin, income, and urinary spot creatinine.
[5] Adjusted for covariates from Models 1 and 2, in addition to aldosterone.

cohort. In this cohort, we found that aldosterone may be a significant effect modifier of the association between serum potassium and incident diabetes. However, we found that most of these participants had clinically normal aldosterone concentrations, and that, among participants with normal aldosterone, independent of other diabetes risk factors, high-normal serum potassium was associated with a significantly lower risk of diabetes than was low-normal potassium. In this cohort, we were also able to determine that, among those with normal serum aldosterone concentrations, serum potassium was an independent predictor of incident diabetes, whereas aldosterone was not.

Conditions associated with high aldosterone concentrations, such as primary hyperaldosteronism, have been associated with higher diabetes risk. Subclinically elevated aldosterone has been associated with increased insulin resistance and metabolic syndrome, both of which tend to confer a higher risk of diabetes (12–14, 23–25). In addition, recently, in this cohort, aldosterone has been associated with diabetes risk; however, the effect of serum potassium on this association was not assessed (15). Aldosterone regulates potassium concentrations, and higher concentrations of aldosterone lead to lower concentrations of potassium by increasing renal and urinary excretion of potassium. In past studies that evaluated the association between serum potassium and diabetes risk, to our knowledge, aldosterone measures were not available. Thus, this study extends the literature regarding potassium and diabetes risk by evaluating the impact of aldosterone on this association and by helping to determine whether high aldosterone concentrations could be contributing to a low-normal serum potassium that, in this and other cohorts, has been found to be associated with higher diabetes risk. Interestingly, in this cohort, most participants had serum aldosterone concentrations that were considered to be within a normal range, and aldosterone concentrations were similar between the quartiles of serum potassium. We did, however, find a significant interaction between serum potassium and aldosterone. We found that, among the participants with a normal aldosterone (the majority of the participants), serum potassium was a strong independent predictor of incident diabetes. However, among these participants, aldosterone was not a significant predictor of incident diabetes. The number of participants in the subcohort with a high-normal aldosterone concentration was fairly small. However, among these participants, we found that neither potassium nor aldosterone was a significant predictor of incident diabetes. Likely, the sample size of this subcohort was too small to draw any firm conclusions regarding these associations. However, it could be that aldosterone may be a significant predictor of incident diabetes only at clinically high concentrations, i.e., concentrations higher than observed in this cohort. In the majority of patients with normal aldosterone concentrations, serum potassium may have a direct influence on diabetes risk that is not related to aldosterone.

African Americans continue to be at a higher risk of diabetes than are whites. Traditional risk factors, particularly obesity and socioeconomic status, are very important to address for reducing diabetes risk in African Americans and others; however, both of these are very difficult to change. Based on these analyses, as well as previous analyses, serum potassium is a significant predictor of incident diabetes, and it could be a potentially modifiable risk factor. This may be an especially important risk factor to address for people taking thiazide diuretics, which can reduce potassium concentrations. Thiazide diuretics are the most common class of antihypertensive agents used in this cohort, and they are one of the first-line antihypertensive agents recommended for treatment of hypertension in African Americans (26, 27). Providers may need to target higher serum potassium concentrations in their patients on diuretics.

Based on these analyses, in multivariable models, a serum potassium concentration of ≥4.3 mmol/L seemed to be associated with a lower incidence of diabetes than did a lower serum potassium concentration. Although an observational study cannot prove causality, it can generate hypotheses for further testing. It is possible that relatively simple and inexpensive interventions, alone or in combination, could help people achieve serum potassium concentrations of ≥4.3 mmol/L, and, thus, help reduce their risk of diabetes. Serum potassium and total body potassium concentrations are determined jointly by the balance of potassium intake with potassium excretion, which is primarily in the urine (7). Interventions that might achieve such an increase in potassium concentration could include increasing potassium intake and/or decreasing the amount of potassium excreted in urine. In the United States, dietary potassium intake

is much lower than the Adequate Intake of 4700 mg/d, which is based on optimal health effects of dietary potassium on blood pressure and other medical conditions (7). However, the optimal dietary potassium intake for diabetes risk is unknown. One study in the NHANES database found that <2% of the US population achieved Adequate Intake concentrations of dietary potassium (28). This study also found that African Americans had lower dietary potassium intake than did whites (28). Therefore, a high-potassium diet would seem to be a reasonable intervention to increase total-body and serum potassium, and this may be more relevant to African Americans. Other interventions to increase serum potassium could be the use of potassium supplements and/or the use of potassium-sparing diuretics in patients who require diuretics. These interventions would need to be studied further to determine the adequate doses needed to achieve a meaningful increase in serum potassium concentrations. These types of interventions should also be studied as possible adjunct strategies to reduce diabetes risk and to promote weight loss when appropriate, particularly in African Americans, who face disparate risks of diabetes from low potassium (6, 29).

The strengths of this study include the large size of the African-American cohort, the prospective nature of the data collection, and the measurement of a rich number of variables that can affect the risk of diabetes and other health-related outcomes and can be used in multivariable analyses. However, there are also several limitations to address. Because of missing covariates, we excluded the data from many participants, which limits the generalizability of these findings. The measurements of our main exposures of interest, including potassium measures and aldosterone, and covariates were collected only at the baseline exam and all measures are subject to intraindividual variability, which we did not capture. Based on other studies, and compared with other analytes, the intraindividual variability of serum potassium is relatively small at 5% (30, 31). The measurement of aldosterone, however, is subject to more variability and requires fairly precise conditions for accurate measurement. Aldosterone concentrations are subject to change based on factors that include medication use; recent diet, particularly salt intake; and posture at the time of specimen collection (32). To detect conditions that lead to abnormally high aldosterone concentrations, aldosterone and renin concentrations usually are measured concomitantly, and the aldosterone:renin ratio is used for diagnostic purposes (32). In the JHS cohort, however, it is not clear that the aldosterone measures were drawn under ideal conditions (particularly in regard to time of day and body posture of participants at the time of phlebotomy), and renin measurements were only performed in a subcohort of participants, precluding analyses with aldosterone:renin ratios.

In this cohort, the null associations found between dietary potassium and urinary potassium with incident diabetes differ from the significant inverse association found between serum potassium and incident diabetes. These results are not surprising and are consistent with some other cohort studies that have studied such associations (3, 33). However, these results differ from analyses of the Coronary Artery Risk Development in Young Adults cohort, which did find significant associations between dietary potassium intake and diabetes risk (4). This study found a statistical interaction between race and dietary potassium intake based on diet history, and found, in African-American participants, a significant inverse, although nonlinear, association between dietary intake and diabetes risk (4). This study also collected 24-h urinary measures of potassium in a subcohort of participants, and found a strong and significant inverse association between 24-h urinary potassium, which is considered to be a biomarker for dietary potassium intake, with diabetes risk (4, 7). Diet histories, although a good instrument for measures of dietary intake, are not very accurate; food-frequency questionnaires, administered on only one occasion, are not as accurate as diet histories taken over several days (34–36). In past cohorts, racial and ethnic differences in accuracy of reporting diet history have also been found (37). Twenty-four-hour urinary potassium measures have been found to be a more accurate reflection of dietary potassium intake (7, 38). In this JHS study, however, we had to rely on a one-time administered food-frequency questionnaire, as well as a random urine sample for urinary potassium, neither of which are ideal measures of dietary potassium intake. Therefore, further study with more rigorous measures may be warranted to determine whether there is a significant association between dietary potassium intake and diabetes risk, particularly in African Americans. Further study is also needed to determine whether increasing dietary potassium intake is an appropriate and adequate intervention to increase serum potassium, the latter of which we did find to be significantly associated with diabetes risk.

In conclusion, this study confirms the significance of the association between serum potassium and incident diabetes in this African-American adult cohort. We found that serum aldosterone may modify the association between serum potassium and incident diabetes, but that this association was statistically significant and strong in participants with normal aldosterone, which was the majority of these participants. This study found that, compared with lower concentrations, a serum potassium concentration of ≥4.3 mmol/L was associated with a lower incidence of diabetes; we also found that, in participants with a normal aldosterone concentration, this association was independent of aldosterone. Further study is needed to determine whether, particularly in this high-risk population, interventions designed to achieve a high-normal concentration of serum potassium will help reduce the risk of diabetes.

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