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Aldosterone, Renin, Cardiovascular Events, and All-Cause Mortality Among African Americans

The Jackson Heart Study

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ABSTRACT

OBJECTIVES This study examined the association of aldosterone and plasma renin activity (PRA) with incident cardiovascular disease (CVD), using a composite endpoint of coronary heart disease, stroke, and/or heart failure and mortality among African Americans in the Jackson Heart Study.

BACKGROUND There is a paucity of data for the association of aldosterone and PRA with incident CVD or all-cause mortality among community-dwelling African Americans.

METHODS A total of 4,985 African American adults, 21 to 94 years of age, were followed for 12 years. Aldosterone, PRA, and cardiovascular risk factors were collected at baseline (from 2000 to 2004). Incident events included coronary heart disease and stroke (assessed from 2000 to 2011) and heart failure (assessed from 2005 to 2011). Cox models were used to estimate hazard ratios (HRs) for incident CVD and mortality, adjusting for age, sex, education, occupation, current smoking, physical activity, dietary intake, and body mass index.

RESULTS Among 4,160 participants without prevalent CVD over a median follow-up of 7 years, there were 322 incident CVD cases. In adjusted analyses, each 1-U SD increase in log-aldosterone and log-PRA were associated with HR of 1.26 (95% confidence intervals [CI]: 1.14 to 1.40) and 1.16 (95% CI: 1.02 to 1.33) for incident CVD, respectively. Over a median of 8 years, 513 deaths occurred among 4,985 participants. In adjusted analyses, each 1-U SD increase in log-aldosterone and log-PRA were associated with HRs of 1.13 (95% CI: 1.04 to 1.23) and 1.12 (95% CI: 1.01 to 1.24) for mortality, respectively.

CONCLUSIONS Elevated aldosterone and PRA may play a significant role in the development of CVD and all-cause mortality among African Americans. (J Am Coll Cardiol HF 2017;5:642–51) © 2017 by the American College of Cardiology Foundation.

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Cardiovascular disease (CVD) remains the most common cause of morbidity and mortality among African Americans in the United States (1). The renin-angiotensin-aldosterone system (RAAS) plays an important role in the pathogenesis of hypertension, a major risk factor for CVD (2). Inappropriate RAAS activation has been hypothesized to explain some of the racial disparities observed in the incidence of hypertension, left ventricular hypertrophy, and heart failure (HF) (3). In particular, the higher rate of hypertension-related complications among African Americans, including HF and death, may be attributed to greater RAAS activity (3).

To date, studies evaluating the association of aldosterone and incident or recurrent CVD and mortality predominantly among non-Hispanic whites (NHWs) revealed positive associations in participants with acute myocardial infarction (4), coronary artery disease (5–7), advanced HF (8,9), and among community-dwelling adults (10). In contrast, a multiethnic study of individuals with chronic renal insufficiency revealed an association of aldosterone with incident HF but not with atherosclerotic events or mortality (11). Prospective studies assessing the association of renin with CVD and mortality, mainly including NHWs, have yielded inconsistent results (12–15).

The association between components of the RAAS (aldosterone and plasma renin activity [PRA]) and incident CVD or all-cause mortality in African Americans remains unclear. We examined these associations among community-dwelling African Americans in the JHS (Jackson Heart Study).

METHODS

STUDY PARTICIPANTS. The JHS is a prospective cohort study of 5,301 African American adults, 21 to 94 years of age from the tricounty area of metropolitan Jackson, Mississippi. The baseline examination was performed from 2000 to 2004, with 2 subsequent follow-up examinations from 2005 to 2008 and 2009 to 2013. The design of the study has been described elsewhere (16). The JHS was approved by the institutional review boards of the participating institutions, and informed consent was obtained from all participants. For this analysis, participants were excluded if they had missing data for exposures, outcomes, or important covariates including aldosterone (n = 52), systolic blood pressure (n = 17), diabetes status (n = 61), education (n = 20), smoking status (n = 40), alcohol use (n = 26), body-mass index (n = 5), waist circumference (n = 2), adiponectin (n = 83), and were lost to follow-up (n = 57 in incident CVD analyses and n = 65 in all-cause mortality analyses). Participants with a supraphysiological serum aldosterone concentration of >2,774 pmol/l (100 ng/dl; n = 2) were excluded. In the incident CVD analysis, participants with CVD at baseline were excluded (n = 776). After these exclusions, 4,160 and 4,985 participants were included in the incident CVD and all-cause mortality longitudinal analyses, respectively.

EXPOSURE: ALDOSTERONE AND PRA. Fasting blood samples were drawn with the participant in the supine position and processed using a standardized protocol. Plasma and serum were prepared from samples by sedimentation in a refrigerated centrifuge within 2 h of blood collection; samples were stored at −70°C and sent to central laboratories (University of Minnesota) (16,17). Serum aldosterone was measured by radioimmunoassay (Coat-a-count aldosterone, Siemens, Munich, Germany), and the intra-assay coefficients of variation were 8.7% and 6.2% for low and high concentrations, respectively. Plasma renin activity was measured at baseline by using immunoradiometric assays of PRA in units of ng/ml/h (n = 2,252), with intra-assay coefficients of variation of 8.0%.

OUTCOMES. Outcomes were incident CVD (coronary heart disease [CHD], stroke, and/or HF) and all-cause mortality. Methods for ascertaining cardiovascular events and deaths in the JHS cohort have been described previously (18). Briefly, CVD events were ascertained through a combination of active and passive surveillance. Annual follow-up included interviews with participants and next of kin to ascertain health events, such as cardiac events, and hospitalizations or death through questionnaires completed by physicians and medical examiners or coroners and reviewed by the medical record abstraction unit to generate diagnostic information. These diagnoses were reviewed and adjudicated by trained medical personnel. Cardiovascular illness hospitalizations were identified and adjudicated as described previously (18). Hospitalization data were obtained from the hospital discharge index from all catchment area hospitals and annual follow-up data. Data from non-catchment area hospitals were obtained after patient consent. Death certificates from state vital statistic offices were surveyed for potential CVD events. The self-reported data from annual follow-up were reconciled with the hospital discharge index data. The primary diagnoses based on International Classification of Diseases-9th Revision-Clinical

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

HbA_{1c} = hemoglobin A_{1c}

HF = heart failure

LDL = low-density lipoprotein

NHW = non-Hispanic white

PRA = plasma renin activity

RAAS = renin-angiotensin-aldosterone system

Modification codes were reviewed and adjudicated by trained medical personnel. We tracked the occurrence of CHD and stroke between 2000 and 2011, and HF hospitalizations between 2005 and 2011.

COVARIATES. Covariates included demographics, occupation (management or professional versus other levels), level of education (≥bachelor's degree versus <bachelor's degree attained), use of tobacco (current smoking versus not smoking), use of alcohol (in the past 12 months versus no alcohol), medical conditions, and current prescription medication usage. Body mass index (BMI) was measured in units of weight (kg)/height^2 (m). Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive therapy.

Physical activity and dietary intake were categorized according to the American Heart Association 2020 CV health guidelines as poor, intermediate, or ideal health, as described previously (19,20). Daily sodium intake (mg/day) was assessed using a validated food frequency questionnaire (21).

Glucose and glycosylated hemoglobin (HbA_{1c}) concentrations were measured as previously described (20). Diabetes was defined based on 2010 American Diabetes Association guidelines ($HbA_{1c} \geq 6.5\%$, fasting glucose ≥ 126 mg/dl, taking diabetes medications, or self-reported physician diagnosis) (22). Fasting serum low-density lipoprotein (LDL [mg/dl]) was assayed using standard techniques (17). Estimated glomerular filtration rate (eGFR) was derived using the Chronic Kidney Disease Epidemiology Collaboration equation (ml/min/1.73 m^2) (23).

STATISTICAL ANALYSIS. Due to their non-normal distributions, aldosterone and PRA were log-transformed. To evaluate for dose-response relationships, aldosterone and PRA were divided into medians. Baseline characteristics of participants are presented according to medians of log-transformed aldosterone, using one-way analysis of variance for normally distributed continuous variables, Mann-Whitney *U* and Kruskal-Wallis tests for non-normally distributed continuous variables, and the chi-square test for categorical variables.

Time of incident CVD or all-cause mortality was defined based on the adjudicated date. We censored data for participants at the time of study participation drop out or the end of study follow-up (December 30, 2011). Cox proportional hazards modeling was used to estimate hazard ratios (HRs) with inclusion of exposures as continuous (each 1-U increase in SD) or categorical variables (median). Based on prior analyses, covariates were selected a priori (10,20), multivariate modeling was performed with sequential adjustment as follows:

- Model 1 was adjusted for age, sex, education, current occupation status, smoking, physical activity, dietary intake, alcohol use, and body-mass index (kg/m^2);
- Model 2 was Model 1 plus systolic blood pressure, LDL, hemoglobin A_{1c};
- Model 3 was Model 2 plus eGFR.

We assessed the shape of the association of aldosterone and PRA with incident CVD and mortality, using cubic spline regression with 4 knots to explore potential nonlinear relationships. We performed a series of sensitivity analyses by, first, limiting the analyses to participants not taking medications that antagonized the RAAS including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor blockers, and statins; and second, examining the association between log-aldosterone and log-PRA by individual incident CVD outcome (CHD, stroke, and HF). We tested for effect modification by age, sex, hypertension, diabetes, and BMI by inserting multiplicative interaction term models and using the likelihood ratio test. The proportional hazards assumption was assessed using Schoenfeld residuals, and no significant violations were noted. Statistical significance was defined as 2-sided alpha <0.05. Analyses were performed using Stata version 13.1 software (Statacorp, College Station, Texas).

RESULTS

During a median follow-up period of 7.3 years, 322 cases of incident CVD (among 4,160 participants without prevalent CVD at baseline) and 513 deaths (among 4,985 participants with and without CVD at baseline) occurred. **Table 1** shows the profile of participants across medians of baseline log-aldosterone. Participants in upper median aldosterone had a more adverse cardiovascular risk profile, including higher baseline BMI, waist circumference, systolic blood pressure, diastolic blood pressure, glucose, HbA_{1c}, and lower eGFR than participants in the lower median aldosterone category. Incidence rates of CHD, stroke, HF and combined CVD were higher in the upper compared to the lower median (all comparisons: $p < 0.05$).

ASSOCIATION OF ALDOSTERONE AND PRA WITH INCIDENT CARDIOVASCULAR DISEASE. Every 1-U SD increase in log-aldosterone was associated with a 26% (95% CI: 1.14 to 1.40) higher risk of CVD, after adjustments for socioeconomic variables and

TABLE 1 Characteristics of Participants in the Jackson Heart Study by Medians of Log-Aldosterone at Baseline

	All (N = 4,985)	Lower Median (n = 2,544)	Upper Median (n = 2,441)	p Value*
Age, yrs	55.2 ± 12.8	55.3 ± 12.9	55.1 ± 12.8	0.591
Females	63.2	67.1	59.2	<0.001
Education ≥bachelor's degree attained	32.6	32.2	33.0	0.534
Occupation: management/professional	35.7	36.1	35.3	0.550
Current smoking	13.1	13.1	13.2	0.915
Current alcohol intake	46.2	45.4	47.0	0.238
Poor AHA physical activity*	49.0	49.0	48.9	0.162
Poor AHA dietary intake*	60.6	62.1	59.0	0.080
Dietary sodium intake total, mg/day†	3,447 ± 1,521	3,433 ± 1,507	3,462 ± 1,536	0.527
Body mass index, kg/m^2	31.8 ± 7.2	31.4 ± 7.4	32.1 ± 7.1	0.001
Waist circumference, cm	100.7 ± 16.2	99.2 ± 16.1	102.3 ± 16.0	<0.001
Systolic blood pressure, mm Hg	127 ± 18	126 ± 18	128 ± 19	<0.001
Diastolic blood pressure, mm Hg	79 ± 11	78 ± 10	80 ± 11	<0.001
Hypertension‡	60.0	51.9	68.4	<0.001
Glucose, mg/dl (n = 4,976)	102 ± 38	99 ± 33	105 ± 42	<0.001
HbA_{1c}, % (n = 4,899)	6.0 ± 1.3	5.9 ± 1.2	6.1 ± 1.4	<0.001
Type 2 diabetes mellitus, %§	21.6	19.5	23.9	<0.001
eGFR (CKD-EPI), ml/min per 1.73 m^2 (n = 4,976)	94 ± 22	98 ± 20	91 ± 23	<0.001
LDL, mg/dl (n = 4,584)	127 ± 36	124 ± 35	129 ± 37	<0.001
Non-parametric variables, median (IQR)				
Aldosterone (ng/dl)	4.4 (2.6–7.2)	2.6 (1.9–3.5)	7.3 (5.7–10.1)	0.001
PRA, ng/ml/h‖	0.5 (0.2–1.1)	0.4 (0.2–0.8)	0.6 (0.3–1.7)	0.001
Adiponectin, ng/ml	4,234 (2,685–6,748)	4,658 (2,923–7,219)	3,814 (2,435–6,118)	0.001
Crude incidence rates per 1,000 person-yrs (95% CI)				
Incidence of coronary heart disease¶	5.1 (4.4–5.8)	4.2 (3.4–5.2)	6.0 (5.0–7.2)	0.019
Incidence of stroke#	3.6 (3.1–4.3)	2.7 (2.1–3.5)	4.6 (3.8–5.7)	0.002
Incidence of heart failure**	6.5 (5.5–7.5)	5.5 (4.3–6.9)	7.5 (6.1–9.2)	0.042
Incidence of combined CVD††	10.9 (9.8–12.2)	8.5 (7.2–10.1)	13.5 (11.7–15.5)	<0.001
Incidence of all-cause mortality‡‡	12.5 (11.4–13.6)	11.6 (10.2–13.2)	13.4 (11.9–15.1)	0.13

Values are mean ± SD or % unless otherwise indicated. p Values were calculated using chi-square (categorical variables), ANOVA (parametric continuous variables), and Kruskal-Wallis tests (non-parametric continuous variables). *AHA ideal physical activity and dietary intake recommendations were defined by AHA "2020" guidelines. Physical activity was considered ideal if participant achieved ≥150 min/week of moderate intensity or ≥75 min/week of vigorous intensity physical activity. Dietary intake was considered ideal if participant met 4 of 5 of the following recommendations: ≥4.5 cups/day fruits and vegetables; ≥2, 3.5-oz. servings of fish per week (preferably oily fish); ≥3 1-oz-equivalent servings/day of fiber-rich whole grains; <1,500 mg/day sodium; and ≤450 kcal (36 oz)/week sugar-sweetened beverages (19). †n = 4,507 with dietary sodium intake calculated from Jackson Heart Study Food Frequency Questionnaire (lower and upper halves: n = 2,296, n = 2,211, respectively). ‡Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive therapy. §Diabetes was defined based on 2010 American Diabetes Association guidelines (i.e., HbA_{1c} ≥6.5%, fasting blood glucose ≥126 mg/dl, taking diabetes medications or presented with a self-reported physician diagnosis) (22). ‖n = 2,250 participants with plasma renin activity at baseline (log-aldosterone lower and upper 50%: n = 1,118, n = 1,132, respectively). ¶n = 4,642, incidence rate per 1,000 person-yrs (overall 192 coronary heart disease events, log-aldosterone lower 50%: n = 80 events, upper 50% n = 112 events). #n = 4,770 participants, incident rate per 1,000 person-yrs (overall 142 stroke events, log-aldosterone lower 50%: n = 54 events, upper 50% n = 88 events). **n = 4,120, incident rate per 1,000 person-yrs (overall 162 heart failure events, log-aldosterone lower 50%: n = 69 events, upper 50% n = 93 events). ††n = 4,160, incident rate per 1,000 person-yrs (overall 322 cardiovascular events, log-aldosterone lower 50%: n = 129 events, upper 50% n = 193 events). ‡‡Incident rate per 1,000 person-yrs (overall 513 deaths, aldosterone lower 50%: n = 244 deaths, upper 50% n = 269 deaths).

AHA = American Heart Association; CKD-EPI = Chronic Kidney Disease Epidemiology collaboration equation (shown); CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein; PRA = plasma renin activity.

cardiovascular risk factors including BMI (Table 2). This association remained significant with full adjustment for cardiovascular risk factors including LDL, systolic blood pressure, HbA_{1c}, and eGFR (Model 3). When the upper median of aldosterone was examined as a categorical variable, it was associated with a 59% higher risk of CVD than the lower median (Model 1) and remained significant after full adjustment (Model 3). The shape of the association of aldosterone with incident CVD unadjusted and fully adjusted using cubic splines revealed a nonlinear association (Figure 1). Log-aldosterone was additionally positively associated with the individual outcomes of incident stroke, CHD, and HF (Online Tables 1 to 3).

Similar findings were seen for log-PRA, each 1-U SD increase in log-PRA was associated with an 16% higher risk of incident CVD; full adjustments for cardiovascular risk factors modestly attenuated the significance of this finding (in Model 3, the HR: 1.16 [95% CI: 0.99 to 1.35]). When findings were examined as a

TABLE 2 Association of Log-Aldosterone and Log-Renin With Incident Cardiovascular Disease (CHD, Stroke, and Heart Failure) Over 7 Yrs

	Lower Median	Upper Median	Continuous (per 1-U SD)
Log-aldosterone	n = 2,131	n = 2,029	n = 4,160
Median aldosterone, ng/dl (IQR)	2.6 (1.9-3.4)	7 (5.5-9.6)	4.3 (2.5-6.9)
Cardiovascular disease cases	129	193	322
Rate per 1,000 person-yrs (95% CI)	8.5 (7.2-10.1)	13.5 (11.7-15.5)	10.9 (9.8-12.2)
Unadjusted hazard ratio (95% CI)*†	1.00 (referent)	1.55 (1.24-1.94)	1.25 (1.12-1.38)
Model 1 hazard ratio (95% CI)	1.00 (referent)	1.59 (1.27-1.98)	1.26 (1.14-1.40)
Model 2 hazard ratio (95% CI)	1.00 (referent)	1.41 (1.11-1.81)	1.18 (1.05-1.32)
Model 3 hazard ratio (95% CI)	1.00 (referent)	1.31 (1.02-1.68)	1.13 (1.00-1.27)
Log-plasma renin activity	n = 918	n = 901	n = 1,819
Median plasma renin activity, ng/ml/h (IQR)	0.2 (0.2-0.3)	1 (0.6-2.0)	0.4 (0.2-1.0)
Cardiovascular disease cases	86	105	191
Rate per 1,000 person-yrs (95% CI)	11.9 (9.7-14.8)	15.0 (12.4-18.1)	13.4 (11.7-15.5)
Unadjusted hazard ratio (95% CI)*†	1.00 (referent)	1.18 (0.88-1.56)	1.15 (1.00-1.31)
Model 1 hazard ratio (95% CI)	1.00 (referent)	1.24 (0.93-1.65)	1.16 (1.02-1.33)
Model 2 hazard ratio (95% CI)	1.00 (referent)	1.27 (0.92-1.76)	1.20 (1.03-1.39)
Model 3 hazard ratio (95% CI)	1.00 (referent)	1.21 (0.87-1.67)	1.16 (0.99-1.35)

*Cox proportional hazards model = hazard ratio is per 1-U SD increase in log-aldosterone or log-plasma renin activity for continuous analysis. †Unadjusted hazard ratio = log-aldosterone n = 4,160 with 322 cases of incident CVD: log-plasma renin activity n = 1,819 with 191 cases of incident CVD. Model 1 = age, sex, education, current occupation status, smoking, physical activity (AHA Life's Simple 7), dietary intake (AHA Life's Simple 7), alcohol use and body-mass index (kg/m^2) (log-aldosterone n = 4,160 with 322 cases of incident CVD: log-plasma renin activity n = 1,819 with 191 cases of incident CVD). Model 2 = Model 1 plus systolic blood pressure, low-density lipoprotein, and hemoglobin A_{1c} (log-aldosterone n = 3,805 with 267 cases of incident CVD: log-plasma renin activity n = 1,665 with 162 cases of incident CVD. Model 3 = Model 2 plus estimated glomerular filtration rate (CKD-EPI) (log-aldosterone n = 3,798 with 266 cases of incident CVD: log-plasma renin activity n = 1,661 with 161 cases of incident CVD).

CHD = coronary heart disease; IQR = interquartile range; other abbreviations as in Table 1.

categorical variable, they were in a similar direction but were nonsignificant.

Excluding participants taking RAAS antagonists, including ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and statins, strengthened the continuous and categorical positive associations with log-aldosterone and incident cardiovascular disease, but attenuated the association of log-PRA with incident CVD (Online Table 4).

ASSOCIATION OF ALDOSTERONE AND PRA WITH ALL-CAUSE MORTALITY. A 1-U SD increase in log-aldosterone was associated with a 13% higher risk of mortality with Model 1 adjustments and was mildly attenuated after adjustment for systolic blood pressure, LDL, and HbA_{1c} and fully attenuated after additional adjustment for eGFR (Table 3). Similar findings were seen for categorical results, although they were nonsignificant.

A 1-U SD increase in log-PRA was associated with a 12% higher risk of all-cause mortality, which remained significant after full adjustment. The upper median of log-PRA was associated with a 53% higher risk of all-cause mortality in the fully adjusted model. Evaluation of the continuous association of PRA with all-cause mortality unadjusted and fully adjusted using cubic splines revealed a similar positive association (Figure 2).

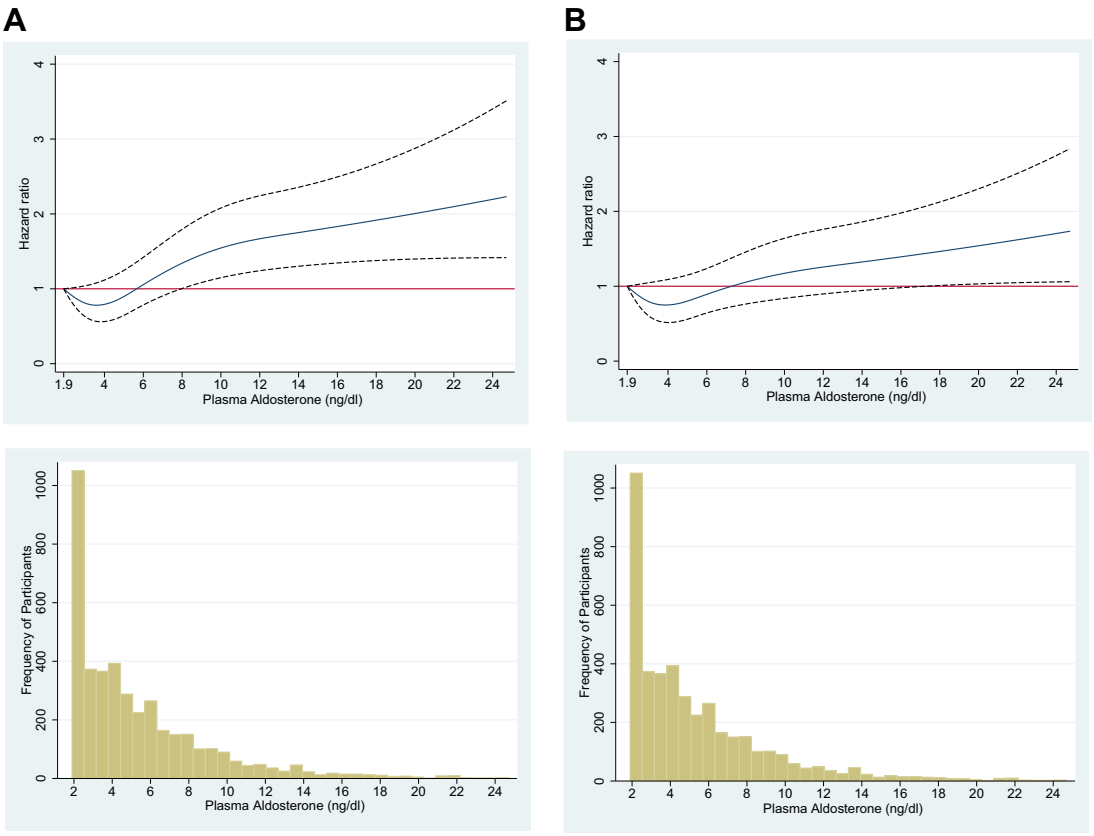
Excluding participants taking RAAS antagonists, including ACE inhibitors, ARBs, mineralocorticoid receptor antagonists, and statins, did not significantly alter these findings (Online Table 5). We found no evidence of effect modification by age, sex, hypertension, diabetes, or BMI in the association between log-aldosterone and incident CVD or all-cause mortality (Online Table 6).

DISCUSSION

In this prospective study of African Americans, higher aldosterone and PRA were nonlinearly associated with higher risks of CVD and all-cause mortality, independently of established cardiovascular risk factors. The use of RAAS antagonists did not affect the relationship between aldosterone and CVD or aldosterone and PRA with all-cause mortality. We found no evidence of effect modification by age, sex, hypertension, diabetes, or BMI. These results suggest that aldosterone and PRA are important in the pathophysiology of CVD and all-cause mortality among African Americans. Our findings combined with those of prior studies indicate that the relative value of aldosterone and PRA may be more important than the absolute value among African Americans. Among participants not receiving hypertension treatment in the MESA (Multi-Ethnic Study of Atherosclerosis), aldosterone and PRA were significantly lower in African Americans than in NHWs (24), but lower aldosterone-to-renin ratio was associated with lower blood pressure only among NHWs (24). This finding of a low state of renin among African Americans is consistent with that of other studies (25,26), whereas results for aldosterone have been mixed with African American normotensive subjects, favoring lower aldosterone (27-29) and African American hypertensive subjects favoring elevated aldosterone (29-31). Consistent with these findings, a study of African Americans and NHWs including aldosterone, PRA, and blood pressure measurements (during childhood and adulthood) found, that although levels of PRA and aldosterone were lower in African Americans, blood pressure was positively associated with plasma aldosterone in African Americans but not NHWs. Furthermore, administration of 9-α fludrocortisone (synthetic steroid with mineralocorticoid receptor activity) increased blood pressure in African Americans but not NHWs (32).

ALDOSTERONE, CVD, AND MORTALITY. To our knowledge, the current report is the largest community-based study of the effects of components

FIGURE 1 **Associations of Aldosterone Examined as a Continuous Variable With Cardiovascular Events**



The cubic spline regression with 4 knots (referent 1.9) estimates the hazard ratio of serum aldosterone up to 99th percentile with incident cardiovascular. **Dotted lines** represent 95% confidence intervals. Below each spline is the histogram of the distribution of serum aldosterone concentration. **(A)** Unadjusted and **(B)** fully adjusted (age, sex, education, current occupation status, smoking, physical activity, dietary intake, alcohol use and body mass index, systolic blood pressure, low-density lipoprotein, hemoglobin A_{1c} [HbA_{1c}] and estimated glomerular filtration rate [eGFR]).

of the RAAS. Our study presents novel findings of a positive association of aldosterone with stroke, CHD, HF, and a composite of CVD. These results extend the previous positive association of aldosterone with all-cause mortality seen among community-dwelling NHWs (10). Our results align with those of previous studies of predominantly NHW participants with known CVD (high-risk), reporting positive associations of aldosterone with cardiovascular events and mortality (4–9). The CRIC (Chronic Renal Insufficiency Cohort) study, included 3,866 participants with chronic kidney disease, of whom 1,606 were African American; revealing a positive association of aldosterone with incident HF among African Americans but no association with atherosclerotic events or death (11). However, the CRIC population may not be representative of the general population as chronic kidney disease is a CVD risk factor and a CHD risk equivalent for all-cause mortality (33); hence, people with chronic kidney disease may develop events through pathways independent of aldosterone, especially those in chronic kidney disease stages IV and V. Our cohort is similar to those of prior studies, with a high prevalence of diabetes (19%) and hypertension (55%) but importantly different in that >80% of individuals were without CVD at baseline; hence, participants had less burden of CVD at baseline than those in studies of NHW participants with CVD at baseline and later stage chronic kidney disease patients.

PRA, CVD, AND MORTALITY. Our investigation of the association of PRA with CVD and all-cause mortality is

TABLE 3 Association of Log-Aldosterone and Log-Plasma Renin Activity With All-Cause Mortality Over 8 Yrs

	Lower Median	Upper Median	Continuous (per 1-U SD)
Log-aldosterone	n = 2,544	n = 2,441	n = 4,985
Median aldosterone, ng/dl (IQR)	2.6 (1.9-3.5)	7.3 (5.7-10.1)	4.4 (2.6-7.2)
All-cause mortality cases	244	269	513
Rate per 1,000 person-yrs (95% CI)	11.6 (10.2-13.2)	13.4 (11.9-15.1)	12.5 (11.4-13.6)
Unadjusted hazard ratio (95% CI)*†	1.00 (referent)	1.14 (0.96-1.36)	1.12 (1.03-1.22)
Model 1 hazard ratio (95% CI)	1.00 (referent)	1.18 (0.99-1.41)	1.13 (1.04-1.23)
Model 2 hazard ratio (95% CI)	1.00 (referent)	1.11 (0.91-1.34)	1.09 (0.99-1.20)
Model 3 hazard ratio (95% CI)	1.00 (referent)	1.01 (0.83-1.24)	1.04 (0.94-1.14)
Log-plasma renin activity	n = 1,232	n = 1,018	n = 2,250
Median plasma renin activity, ng/ml/h (IQR)	0.2 (0.2-0.3)	1.2 (0.8-2.6)	0.5 (0.2-1.1)
All-cause mortality cases	137	160	297
Rate per 1,000 person-yrs (95% CI)	12.3 (10.4-14.6)	17.7 (15.2-20.7)	14.7 (13.2-16.5)
Unadjusted hazard ratio (95% CI)*†	1.00 (referent)	1.41 (1.13-1.78)	1.14 (1.02-1.26)
Model 1 hazard ratio (95% CI)	1.00 (referent)	1.40 (1.11-1.76)	1.12 (1.01-1.24)
Model 2 hazard ratio (95% CI)	1.00 (referent)	1.59 (1.22-2.06)	1.17 (1.04-1.32)
Model 3 hazard ratio (95% CI)	1.00 (referent)	1.53 (1.18-1.99)	1.14 (1.01-1.29)

*Cox proportional hazards model = hazard ratio is per 1-U SD increase in log-aldosterone or log-plasma renin activity for continuous analysis. †Unadjusted = log-aldosterone n = 4,985 with 513 deaths: log-plasma renin activity n = 2,250 with 297 deaths. Model 1 = age, sex, education, current occupation status, smoking, physical activity (AHA Life's Simple 7), dietary intake (AHA Life's Simple 7), alcohol use and body-mass index (kg/m^2) (log-aldosterone n = 4,985 with 513 deaths: log-plasma renin activity n = 2,250 with 297 deaths). Model 2 = Model 1 plus systolic blood pressure, low-density lipoprotein and hemoglobin A_{1c} (log-aldosterone n = 4,508 with 414 deaths: log-plasma renin activity n = 2,036 with 249 deaths). Model 3 = Model 2 plus estimated glomerular filtration rate (CKD-EPI) (log-aldosterone n = 4,499 with 412 deaths: log-plasma renin activity n = 2,030 with 247 deaths).

Abbreviations as in Tables 1 and 2.

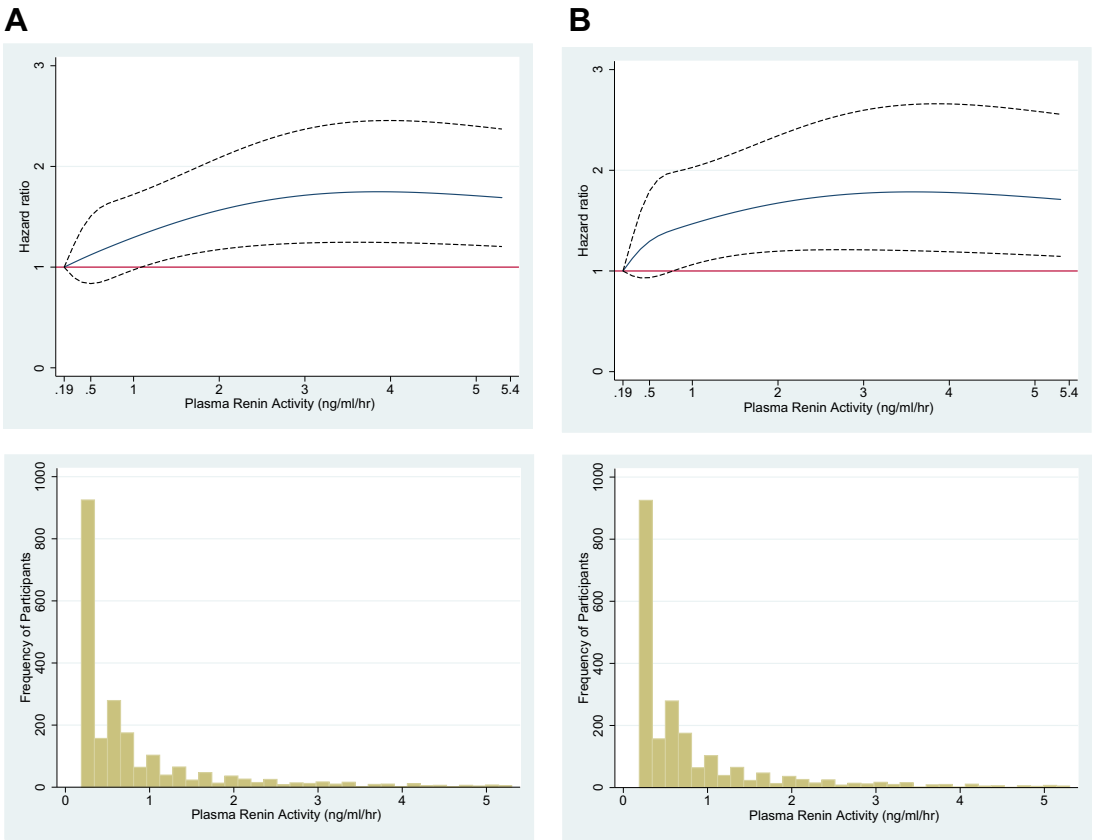
the largest ever conducted among African Americans; thus, having an adequate size to robustly assess the relation of PRA with CVD and all-cause mortality. Our results extend previous findings in smaller, predominantly NHW cohorts, with discrepant findings (12–15). A multiethnic study of 1,717 hypertensive subjects (64% NHW) found an increased risk of CHD with higher renin profile levels (PRA divided by urinary excretion of sodium) but not stroke or mortality (12). These findings were driven by the significant association among NHWs, as the incident event rates for nonwhites was similar for the normal and high renin groups. A study of 803 NHW males, selected independently of blood pressure, found no association between renin and incident CVD (13). In the Framingham Offspring study (mostly NHW), there was an association between renin and greater short-term but not long-term mortality nor incident CVD (14). Lastly, in a study of patients referred for coronary angiography (high risk), there was an association between renin and higher cardiovascular mortality over 10 years among NHWs (15).

MECHANISMS: BLOOD PRESSURE-DEPENDENT AND INDEPENDENT RAAS EFFECTS. The observed effects of aldosterone and renin may be mediated through blood pressure or by more direct effects on the vasculature, myocardium, and central nervous system (34). Aldosterone, through activation of the mineralocorticoid receptor, may exert deleterious effects on the vasculature by decreasing nitric oxide bioavailability, inflammation, smooth muscle proliferation, fibrosis, and calcification, leading to remodeling and atherosclerosis independent of blood pressure (35,36). In the myocardium, formation of reactive oxygen species, inflammation, and coronary vasoconstriction lead to decreased contractility and fibrosis, promoting HF and arrhythmic generation (37,38). Through central nervous system neural actions, aldosterone may promote sodium retention and hypertension (39). In humans, plasma aldosterone is an independent predictor of progression of carotid plaque, left ventricular hypertrophy, and atrial fibrillation, potentially resulting from deleterious effects on the vasculature, myocardium and biological effects of aldosterone and renin including sodium and water retention and hypertension (10,36).

In preclinical models and human trials, the deleterious end organ effects of aldosterone depend upon coexistent high dietary sodium intake (20,40). Recently, high-salt diet was shown to potentiate the negative effects of aldosterone through activation of the rho family member Rac1 (41). African Americans may be more affected by the effects of the RAAS system due to a combination of a high sodium intake (>85% with intake exceeding 2,300 mg/day; mean: 3,500 mg/day in JHS) and high prevalence of salt sensitivity (73% of hypertensive and 36% of normotensive African Americans) (20,42,43). Similar to the preclinical model Dahl salt-sensitive rat, which acutely suppresses aldosterone in response to salt loads but with paradoxical elevation over time (44). Inappropriate activation of the RAAS in African Americans combined with a maladaptive inability to lower aldosterone levels in response to high sodium intake may be a mediator of both the hypertension-mediated effects and direct effects of aldosterone on end-organs including the heart (45). On the contrary, high plasma renin and aldosterone levels with very low sodium intake is not associated with cardiovascular disease, as seen in Yanomamo Indians (46).

STUDY LIMITATIONS. First, the participants in the JHS are from a single metropolitan area in the southeastern United States, possibly limiting generalizability to other African American populations. Second, aldosterone and PRA levels were measured at baseline, and we were not able to account for changes during

FIGURE 2 **Associations of Plasma Renin Activity Examined as a Continuous Variable With All-Cause Mortality**



The cubic spline regression with 4 knots (referent) estimates the hazard ratio of plasma renin activity (ng/ml/h) up to 95th percentile with all-cause mortality. **Dotted lines** represent 95% confidence intervals. Below each spline is the histogram of the distribution of plasma renin activity. **(A)** Unadjusted and **(B)** fully adjusted (age, sex, education, current occupation status, smoking, physical activity, dietary intake, alcohol use and body mass index, systolic blood pressure, low-density lipoprotein, HbA_{1c}, and eGFR). Abbreviations as in Figure 1.

follow-up. Third, we did not have a measurement of 24-h urinary sodium in the full cohort and thus, were unable to assess the impact of dietary sodium intake on aldosterone and PRA. Fourth, the association of PRA with CVD was significantly attenuated after exclusion of participants who were taking RAAS antagonists. This may have been the result of ACE inhibitors, ARBs, or mineralocorticoid receptor antagonists causing elevation in PRA levels (47), which potentially could lead to Type 1 error in our primary analysis. Fifth, statistical associations were interpreted without correction for multiple comparisons, as typical multiple comparison corrections assume tests are independent and are too conservative for correlated hypotheses as have been performed. Therefore, some caution is warranted in the interpretation of our study results. Lastly, we may have underestimated the relation of RAAS elements with cardiovascular disease, as individuals with peripheral vascular disease only, may have remained undetected.

STUDY STRENGTHS. Strengths of the current investigation include the examination of a large, socioeconomically diverse, community-dwelling sample of African Americans with more than a decade of follow-up, standardized assessments of biomarkers, adjudicated outcomes of CVD and mortality, and adjustment for several key factors known to influence both serum aldosterone, PRA, and cardiovascular disease.

CONCLUSIONS

Our study reveals novel associations of aldosterone and PRA with incident CVD and all-cause mortality

among community-dwelling African Americans. It suggests that the RAAS should be considered in the identification of high-risk individuals, to optimize therapeutic or preventive strategies for CVD and mortality in African Americans through a more personalized approach. Further research and clinical trials exploring the impact of current and novel RAAS antagonists in the prevention of CVD, over and above blood pressure and cardiac remodeling in African Americans (i.e., stroke, glucose metabolism, and so on) is paramount given the potential to improve cardiovascular health and reduce racial/ethnic disparities in CVD and mortality.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Higher levels of aldosterone and plasma renin activity are associated with incident cardiovascular disease and all-cause mortality among African Americans.

TRANSLATIONAL OUTLOOK 1: Further research examining the renin-angiotensin-aldosterone system in risk prediction models for cardiovascular disease and mortality among African Americans at all risk strata is warranted.

TRANSLATIONAL OUTLOOK 2: Current Eighth Joint National Committee guidelines recommend initiation of renin-angiotensin aldosterone antagonist (ACE inhibitors and ARBs) after thiazide diuretics or calcium channel blocker therapy among African Americans. Current and novel RAAS antagonists warrant further exploration in their blood pressure-dependent and -independent effects on cardiovascular disease and mortality among African Americans.

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KEY WORDS aldosterone, all-cause mortality, cardiovascular disease, plasma renin activity

APPENDIX For supplemental tables, please see the online version of this paper.