ORIGINAL ARTICLE

Serum Aldosterone and the Incidence of Hypertension in Nonhypertensive Persons

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ABSTRACT

BACKGROUND

Primary hyperaldosteronism is a well-recognized cause of secondary hypertension. It is unknown whether serum aldosterone levels within the physiologic range influence the risk of hypertension.

METHODS

We investigated the relation of baseline serum aldosterone levels to increases in blood pressure and the incidence of hypertension after four years in 1688 nonhypertensive participants in the Framingham Offspring Study (mean age, 55 years), 58 percent of whom were women. We defined an increase in blood pressure as an increment of at least one blood-pressure category (as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) and defined hypertension as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications.

RESULTS

At follow-up, the blood-pressure category had increased in 33.6 percent of the participants, and hypertension had developed in 14.8 percent. In multivariable models, a 16 percent increase in the risk of an elevation in blood pressure (P=0.002) and a 17 percent increase in the risk of hypertension (P=0.03) were observed per quartile increment in the serum aldosterone level. The highest serum aldosterone quartile, relative to the lowest, was associated with a 1.60-fold risk of an elevation in blood pressure (95 percent confidence interval, 1.19 to 2.14) and a 1.61-fold risk of hypertension (95 percent confidence interval, 1.05 to 2.46). The associations between the serum aldosterone level and blood-pressure outcomes were not significantly affected by adjustment for urinary sodium excretion or left ventricular thickness or internal dimensions.

CONCLUSIONS

In our community-based sample, increased aldosterone levels within the physiologic range predisposed persons to the development of hypertension.

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A substantial body of experimental and clinical evidence implicates mineralocorticoids in the pathogenesis of hypertension.[1] In stroke-prone, spontaneously hypertensive rats, increased vascular and cardiac aldosterone expression and tissue levels of aldosterone antedate the development of hypertension itself.[2,3] All known monogenic forms of hypertension in humans can be traced to defects in renal sodium handling.[4] Primary hyperaldosteronism, the classic example of aldosterone excess, is an important cause of secondary hypertension.[5] Indeed, it has been suggested that primary hyperaldosteronism is more prevalent among hypertensive patients than has previously been recognized,[6] although this point has been contested.[7]

Of great interest is the potential role of aldosterone in the pathogenesis of essential hypertension.[8] Investigators have argued that there is a gray zone in which the differentiation between essential hypertension and primary hyperaldosteronism may be difficult.[9-11] Studies examining serum aldosterone levels in hypertensive persons have yielded inconsistent results: high,[12-14] normal,[15,16] and low[17] values, relative to values measured in nonhypertensive control subjects, have been reported. Many studies have been limited by their cross-sectional design, by selection bias, or by a small sample size. In addition, none have prospectively evaluated the effect of serum aldosterone on the incidence of hypertension.

We hypothesized that a gradient of increasing risk of hypertension may exist within the "normal" range of serum aldosterone and that this risk may vary according to dietary sodium intake.[18] Accordingly, we evaluated the relation of the serum aldosterone level measured at a routine examination to the risk of an increase in blood pressure and the risk of the development of hypertension in a large, community-based sample.

METHODS

PARTICIPANTS

The design and selection criteria of the Framingham Offspring Study have been described previously.[19] Serum aldosterone was measured in 3375 of 3532 attendees (96 percent) at the sixth examination cycle (1995 to 1998). Participants were eligible for the current investigation if they were not hypertensive at this examination, which was considered baseline for purposes of the current investigation. Of 3375 eligible participants, 1687 were excluded from the present investigation, for the following reasons: hypertension (defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications) (1407 persons)[20]; use of cardiac medications (100); prevalent heart failure or recognized myocardial infarction (43); atrial fibrillation (7); a serum creatinine level above 2.0 mg per deciliter (177 μmol per liter) (1); absence at the seventh examination (115); missing data on covariates at baseline (9); or missing data on blood pressure or covariates at the seventh examination (5). After the exclusions, 1688 persons (mean age, 55 years), 58 percent of whom were women, remained eligible. All the participants provided written informed consent, and the institutional review board at the Boston Medical Center approved the study protocol.

BASELINE DATA

At the baseline examination, all the participants underwent a routine physical examination, anthropometry, electrocardiography, and laboratory assessment of vascular risk factors. Each participant had fasted overnight and had rested in a chair for at least five minutes before blood pressure was measured. While the participant remained seated, a physician measured the systolic and diastolic blood pressures twice in the left arm with a mercury-column sphygmomanometer and a cuff of the appropriate size, according to a standardized protocol.[20] The average of the two readings was considered the blood pressure at that examination. Persons were categorized into three groups according to their baseline blood pressure: optimal (systolic less than 120 mm Hg and diastolic less than 80 mm Hg), normal (systolic 120 to 129 mm Hg or diastolic 80 to 84 mm Hg), or high-normal (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg).[20]

Venous blood was drawn (typically between 8 a.m. and 9 a.m.) from each participant after he or she had been in a recumbent position for 5 to 10 minutes. Specimens were immediately stored at −80°C. Serum aldosterone was measured (with blinding to all clinical data) from extracted and fractionated serum with the use of a highly sensitive and specific radioimmunoassay (Quest Diagnostics) with a sensitivity of less than 1 ng per deciliter (28 pmol per liter).[21] The intraassay coefficient of variation ranges from 3.8 percent (at high levels) to 6.0 percent (at low levels), with corre-

sponding interassay coefficients of variation ranging from 4.0 to 9.8 percent.

Spot urine samples (3 ml) were collected at the time of phlebotomy and stored at −20°C until analysis. Urinary sodium excretion was measured by means of an automated ion-electrode method with an average intraassay coefficient of variation of 0.8 percent and was expressed (in millimoles of sodium per gram of urinary creatinine) as the urine sodium index. The level of creatinine in the urine was determined by means of a modified Jaffe method with an average intraassay coefficient of variation ranging from 1.7 percent to 3.8 percent.

At baseline, the participants also underwent routine transthoracic echocardiography. Left ventricular internal dimensions and the thicknesses of the interventricular septum and the left ventricular posterior wall at end diastole were obtained by averaging digitized M-mode measurements in at least three cardiac cycles.[22] The end-diastolic left ventricular wall thickness was calculated as the sum of the septal and posterior wall thicknesses.

BLOOD-PRESSURE OUTCOMES AT FOLLOW-UP

Approximately four years after the baseline examination, participants attended their seventh examination for the Framingham Offspring Study (1998 to 2001), at which time they underwent another routine blood-pressure assessment. We examined the occurrence of two blood-pressure outcomes[23,24]: an increase in blood pressure by one or more categories (as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[20]) and the development of hypertension.

STATISTICAL ANALYSIS

We used sex-pooled multivariable logistic-regression models[25] to examine the association between serum aldosterone levels and the risk of the blood-pressure outcomes during follow-up. The serum aldosterone level was treated both as a continuous variable (natural-log–transformed values because of a positively skewed distribution) and as a categorical variable (in sex-specific quartiles). Separate analyses were performed for each blood-pressure outcome.

The multivariable models were adjusted for the following covariates[23]: age, sex, blood-pressure category, systolic and diastolic blood pressures, heart rate, body-mass index, smoking status, and diabetes mellitus (all of which were defined at baseline), and weight gain at follow-up. Criteria for these covariates have been defined.[26]

Models based on quartiles of the serum aldosterone level were used to test for a linear trend in the risk of the blood-pressure outcomes across quartiles. Multivariable models were also fitted in which the risk of a blood-pressure outcome in each of the three highest quartiles was compared with that in the lowest quartile.

In additional analyses, we tested for effect modification by age, sex, baseline body-mass index, and systolic blood pressure by incorporating several interaction terms in the multivariable models (log-transformed aldosterone value × covariate) for each blood-pressure outcome.

In experimental settings, the effects of aldosterone on the heart are most pronounced in a milieu of increased sodium intake.[27] Data on urinary sodium and urinary creatinine excretion were available for 1459 persons (86 percent of the sample), and the ratio of urinary sodium to urinary creatinine (the urine sodium index) was used as a proxy for dietary sodium intake.[28] All analyses were repeated for this subsample, with adjustment for the urine sodium index and the covariates listed above. To test for effect modification by dietary sodium, we stratified the analyses according to the urine sodium index below (vs. at or above) the sex-specific median.

It is conceivable that increased serum aldosterone is simply a marker of increased left ventricular mass and that it may be related to the development of hypertension by this mechanism.[27,29,30] We repeated all analyses for a subgroup of 1370 participants (81 percent of sample) for whom echocardiographic left ventricular measurements were available. We adjusted for left ventricular wall thickness and diastolic dimensions (incorporated into multivariable models one at a time as dichotomous variables [value below vs. at or above the sex-specific median]). In addition, we stratified our analyses by the sex-specific median values for these variables.

A two-sided P value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the use of SAS statistical software (version 6.12).[31]

RESULTS

STUDY PARTICIPANTS

The baseline characteristics of the participants are shown in Table 1. In more than 40 percent of the

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Men (N=717)	Women (N=971)
Clinical characteristics		
Age (yr)	55±9	56±9
Blood pressure (mm Hg)		
Systolic	121±10	117±12
Diastolic	75±7	71±8
Body-mass index†	28.1±4.3	26.2±4.9
Diabetes (%)	7.0	3.9
Smoker (%)	16.5	17
Heart rate (beats/min)	62±10	64±9
Blood-pressure category (%)‡		
Optimal	41.4	52.7
Normal	29.4	27.4
High-normal	29.2	19.9
Biochemical features		
Serum aldosterone (ng/dl)	10.7±6.1	11.3±6.0
Log-transformed aldosterone§	2.25±0.50	2.29±0.51
Serum creatinine (mg/dl)	1.2±0.2	1.1±0.1
Urine sodium index (mmol/g of creatinine)¶	95±51	117±73

* Plus–minus values are means ±SD. To convert the values for serum aldosterone to picomoles per liter, multiply by 27.74. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Participants were categorized into three groups according to their baseline blood pressure: optimal (systolic less than 120 mm Hg and diastolic less than 80 mm Hg), normal (systolic 120 to 129 mm Hg or diastolic 80 to 84 mm Hg), or high-normal (systolic 130 to 139 mm Hg or diastolic 85 to 89 mm Hg).
§ Data were natural-log–transformed.
¶ Urine sodium index data were available for 619 men and 840 women.

men and women in our sample, the systolic blood pressure was below 120 mm Hg and the diastolic pressure below 80 mm Hg at the baseline examination. The mean values and overall distribution of serum aldosterone levels were similar in men and women. The serum aldosterone level was inversely related to the urine sodium index ($r=-0.36$, $P<0.001$).

SERUM ALDOSTERONE AND THE RISK OF BLOOD-PRESSURE OUTCOMES AT FOLLOW-UP

At follow-up, the blood pressure had increased by one or more categories in 568 participants (33.6 percent), and new-onset hypertension had developed in 250 (14.8 percent). In unadjusted analyses, the proportion of participants with an increase in blood-pressure category or with hypertension was higher in the second, third, and fourth quartiles of serum aldosterone level than in the first (lowest) quartile (Table 2). Figure 1 shows that the age- and sex-adjusted four-year rates of the blood-pressure outcomes increased across the quartiles of serum aldosterone level.

In multivariable models, the log aldosterone value was directly associated with an increase in blood pressure and the development of hypertension (Table 3). The risk of an increase in blood-pressure category or of hypertension increased in the second to fourth quartiles relative to the first (lowest) quartile, and the results were statistically significant in the fourth quartile (Table 3). The highest quartile of serum aldosterone level, relative to the lowest quartile, was associated with a 1.60-fold

Table 2. Serum Aldosterone Levels and the Incidence of Blood-Pressure Outcomes at Four Years.

Aldosterone Quartile	Mean Aldosterone Level (Quartile Range)		Mean Baseline Blood Pressure		Increase in Blood Pressure*	Hypertension†
	Men	Women	Systolic	Diastolic		
	ng/dl		*mm Hg*		*percent*	
First (lowest)	5.6 (2.0–7.0)	5.5 (2.0–7.0)	120	72	29.3	12.1
Second	8.5 (8.0–9.0)	8.5 (8.0–9.0)	119	73	33.4	14.9
Third	11.2 (10.0–13.0)	11.5 (10.0–13.0)	119	73	34.7	15.8
Fourth (highest)	19.1 (14.0–72.0)	18.9 (14.0–60.0)	117	73	37.7	16.8

* An increase in blood pressure was defined as an increment of at least one blood-pressure category (as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).
† Hypertension was defined as a systolic pressure of 140 mm Hg or higher, a diastolic pressure of 90 mm Hg or higher, or the use of antihypertensive medications.

risk of an increase in blood pressure and a 1.61-fold risk of hypertension. In models in which trend was evaluated across quartiles of the serum aldosterone level, a 16 percent increase in the risk of increased blood pressure and a 17 percent increase in the risk of hypertension were observed per quartile increment in serum aldosterone (Table 3).

The effects of serum aldosterone on the risk of hypertension or an increase in blood pressure did not vary significantly with age, sex, systolic blood pressure, or body-mass index (P>0.10 for all interactions).

EFFECT OF ADJUSTMENT FOR URINE SODIUM INDEX

In a subsample of persons for whom urinary sodium data were available, an increase in blood-pressure category or the development of hypertension was observed across quartiles of the serum aldosterone level (data not shown). The associations between the serum aldosterone level and the increases in blood pressure and the development of hypertension were not changed in multivariable models (data not shown). These relations were maintained on additional adjustment for the urine sodium index (odds ratio for increased blood pressure per quartile increment in aldosterone, 1.14 [95 percent confidence interval, 1.03 to 1.27]; odds ratio for hypertension per quartile increment in aldosterone, 1.12 [95 percent confidence interval, 0.96 to 1.30]). Of note, in models based on the log aldosterone value, the urine sodium index was not significantly associated with the blood-pressure category or with the incidence of hypertension (odds ratio for increased blood pressure per unit change in log-transformed urine sodium index, 0.86 [95 percent confidence interval, 0.72 to 1.04]; P=0.13; odds ratio for hypertension per unit change in log-transformed urine sodium index, 0.90 [95 percent confidence interval, 0.70 to 1.17]; P=0.44).

We also analyzed subgroups of persons according to whether their urine sodium index was below the sex-specific median value for urine sodium index or at or above it. The association of serum aldosterone with both an increase in blood pressure and the development of hypertension was strengthened for persons whose urine sodium index was at or above the median, whereas it became statistically nonsignificant for those whose value was below the median (Table 4). However, formal testing showed that the interaction was not statistically significant.

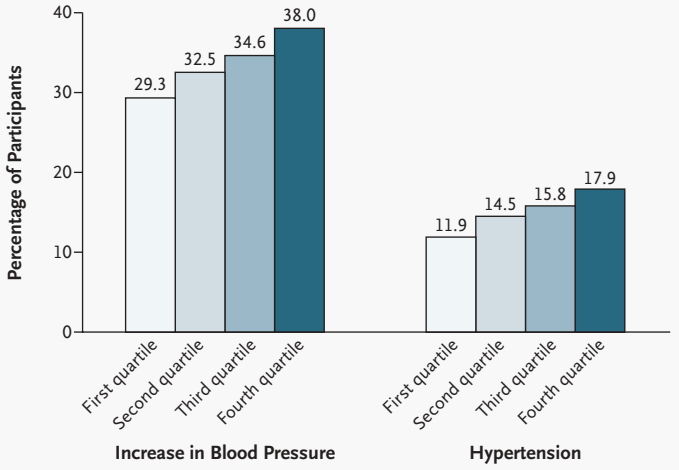

Figure 1. Age- and Sex-Adjusted Rates of Blood-Pressure Outcomes at Four Years According to Quartile of Serum Aldosterone Level.

An increase in blood pressure was defined as an increment of at least one category according to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications.

EFFECT OF ADJUSTMENT FOR ECHOCARDIOGRAPHIC LEFT VENTRICULAR MEASUREMENTS

In analyses restricted to a subsample with echocardiographic left ventricular measurements, the associations between the serum aldosterone level and increases in blood pressure and the development of hypertension persisted after adjustment for ventricular wall thickness (odds ratio for increased blood pressure per quartile increment in aldosterone, 1.17 [95 percent confidence interval, 1.05 to 1.30]; odds ratio for hypertension, 1.15 [95 percent confidence interval, 0.98 to 1.35]) and after adjustment for left ventricular diastolic dimensions (odds ratio for increased blood pressure per quartile increment in aldosterone, 1.19 [95 percent confidence interval, 1.07 to 1.33]; odds ratio for hypertension, 1.21 [95 percent confidence interval, 1.03 to 1.42]). In analyses stratified according to the median left ventricular wall thickness and diastolic dimensions (Table 4), the relations between the quartile of the serum aldosterone level and the blood-pressure outcomes were stronger in the subgroups with a wall thickness below the median and in those with diastolic dimensions above the median. However,

Table 3. Risk of an Increase in Blood Pressure and the Development of Hypertension According to Baseline Serum Aldosterone Level.*

Aldosterone	Increase in Blood Pressure†		Hypertension‡	
	Adjusted Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)	P Value
Log-transformed aldosterone level (per 1-SD increase)§	1.17 (1.05–1.31)	0.005	1.20 (1.03–1.41)	0.023
Sex-specific aldosterone quartile				
First (lowest)	1.00 (reference)		1.00 (reference)	
Second	1.15 (0.84–1.58)	0.37	1.19 (0.76–1.87)	0.45
Third	1.26 (0.94–1.68)	0.12	1.31 (0.86–1.99)	0.21
Fourth (highest)	1.60 (1.19–2.14)	0.002	1.61 (1.05–2.46)	0.03
Trend across quartiles	1.16 (1.06–1.27)	0.002	1.17 (1.02–1.34)	0.03

* Odds ratios were adjusted for age, sex, baseline blood-pressure category, systolic blood pressure, diastolic blood pressure, heart rate, body-mass index, percentage weight gain, diabetes, and smoking status. CI denotes confidence interval.
† An increase in blood pressure was defined as an increment of at least one blood-pressure category (as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).
‡ Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications.
§ For the natural-log–transformed aldosterone level, 1 SD=0.50.

formal testing showed that the interaction was not statistically significant.

DISCUSSION

Prehistoric humans consumed a sodium-restricted, fruit-and-vegetable diet that was rich in potassium.[32] The obligatory loss of sodium through sweating in an arid environment and the possibility of catastrophic volume losses due to diarrhea or hemorrhage necessitated the evolution of physiologic mechanisms for sodium and water conservation and potassium excretion — in other words, the renin–angiotensin–aldosterone system.[32] However, it is unclear whether human beings have biologic feedback mechanisms to lower aldosterone levels in the face of the high salt intake prevalent in industrialized societies.[33] Thus, it is conceivable that an adaptive response essential to survival in a low-sodium environment could turn maladaptive in contemporary society. We tested the possibility that interindividual variations in serum aldosterone levels may contribute to the risk of hypertension in the community, and we found that the serum aldosterone level was related directly to blood-pressure outcomes in both sexes. Increased risks of development of hypertension and of an increase in blood pressure were evident especially among the study participants whose serum aldosterone level was in the fourth (highest) quartile, relative to those whose level was in the first quartile.

The association between the serum aldosterone level and blood-pressure outcomes remained robust after adjustment for the urine sodium index. In contrast, the urine sodium index itself was not related to increases in blood pressure or the development of hypertension. An enormous body of evidence links dietary sodium intake to blood pressure levels and hypertension.[14,34] We had very limited power, however, to detect small changes in blood pressure in relation to baseline urinary sodium.

Although subgroup analyses suggest that the serum aldosterone level is associated with blood pressure and hypertension only among people with higher sodium intake, the absence of a statistically significant effect modification by urinary sodium precludes definitive conclusions. A larger sample would be required to investigate effect modification by sodium intake. Such a possibility is supported by observations made in Yanomamo Indians, who consume a very-low-salt diet and have markedly elevated serum aldosterone levels yet have little or no blood-pressure elevation.[35]

Increasing aldosterone levels within the physiologic range may predispose persons to hypertension through several mechanisms. Aldosterone promotes renal sodium retention,[1] potentiates the

Table 4. Subgroup Analysis of the Risk of an Increase in Blood Pressure and the Development of Hypertension According to Serum Aldosterone Levels at Baseline.*

Subgroup	Adjusted Odds Ratio for an Increase in Blood Pressure (95% CI)†		P Value for Interaction	Adjusted Odds Ratio for Hypertension (95% CI)‡		P Value for Interaction
According to urinary sodium§	Below median	At or above median		Below median	At or above median	
Trend across sex-specific aldosterone quartile	1.09 (0.94–1.26)	1.23 (1.05–1.44)	0.31	1.01 (0.82–1.25)	1.22 (0.98–1.53)	0.21
Log-transformed aldosterone (per 1-SD increase)	1.08 (0.91–1.27)	1.24 (1.03–1.49)	0.30	0.98 (0.77–1.25)	1.30 (1.00–1.71)	0.12
According to left ventricular wall thickness¶	Below median	At or above median		Below median	At or above median	
Trend across sex-specific aldosterone quartile	1.24 (1.06–1.45)	1.12 (0.97–1.30)	0.41	1.31 (0.99–1.73)	1.13 (0.93–1.38)	0.78
Log-transformed aldosterone (per 1-SD increase)	1.27 (1.04–1.53)	1.12 (0.96–1.32)	0.40	1.56 (1.10–2.20)	1.15 (0.92–1.44)	0.40
According to left ventricular diastolic dimensions‖	Below median	At or above median		Below median	At or above median	
Trend across sex-specific aldosterone quartile	1.20 (1.03–1.41)	1.22 (1.05–1.42)	0.89	1.22 (0.95–1.56)	1.24 (1.00–1.55)	0.90
Log-transformed aldosterone (per 1-SD increase)	1.17 (0.97–1.41)	1.26 (1.06–1.49)	0.52	1.18 (0.88–1.58)	1.40 (1.09–1.80)	0.38

* Odds ratios were adjusted for age, sex, baseline blood-pressure category, systolic blood pressure, diastolic blood pressure, heart rate, body-mass index, percentage weight gain, diabetes, and smoking status. For the log-transformed aldosterone level, natural-log transformation was used, 1 SD=0.50. CI denotes confidence interval.

† An increase in blood pressure was defined as an increment of at least one blood-pressure category (as defined by the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).

‡ Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications.

§ Data on the urine sodium index were available for 619 men (median index, 89 mmol per gram of creatinine) and 840 women (median index, 102 mmol per gram of creatinine).

¶ Data on the left ventricular wall thickness were available for 541 men (median thickness, 1.9 cm) and 829 women (median thickness, 1.7 cm).

‖ Data on left ventricular diastolic dimensions were available for 532 men (median diameter, 5.0 cm) and 818 women (median diameter, 4.5 cm).

actions of angiotensin II,[36] impairs endothelial function,[37] and reduces vascular compliance.[38] In addition, aldosterone may promote hypertension through central nervous system mechanisms.[39] Since mineralocorticoid receptors are widely distributed throughout the vasculature, the myocardium, and the central nervous system, serum levels of aldosterone may underestimate its true effects on blood pressure.

An alternative explanation for the observed association is that some of the study participants had subclinical hyperaldosteronism at baseline and that hypertension subsequently developed and was detected at follow-up. The observed trend for increased risks of the blood-pressure outcomes from the second quartile of aldosterone upward makes this possibility unlikely. We did not measure plasma renin or serum potassium levels at the index examination to rule out this possibility. Although plasma renin levels may have provided additional insights, it is noteworthy that the utility of the plasma aldosterone–renin ratio for the diagnosis of primary hyperaldosteronism has been questioned.[40] Although serum potassium was not measured at the index examination, we have previously reported an absence of an association between serum potassium and longitudinal changes in blood pressure.[24]

Strengths of the current investigation include the examination of a large, community-based sample of nonhypertensive persons; the standardized assessment of blood pressure; the independent evaluations of blood pressure and aldosterone, with blinding of each to the other; and the multivariable analyses with adjustment for several factors known to influence both serum aldosterone levels and blood pressure.

Several limitations should be acknowledged. We used spot specimens of urine, rather than 24-hour collections, to measure urinary sodium and calcu-

late an index of dietary sodium intake. This choice was necessitated by the constraints inherent in a large epidemiologic investigation. We did not obtain blood samples after an hour of rest, as described in clinical protocols for measurement of serum aldosterone. Furthermore, the 24-hour urinary excretion of aldosterone metabolites may reflect the endogenous secretion of aldosterone more appropriately than the aldosterone level in a single specimen of blood.[41] Future studies would be strengthened by measurements of serum potassium, plasma renin, and serum aldosterone after an hour of rest and by assessment of 24-hour urinary excretions of sodium, potassium, and aldosterone.

Another limitation of the study is the variability of blood-pressure measurements.[42] Such variability renders error-prone the stratification of people into hypertensive and nonhypertensive categories on the basis of measurements made on a single occasion. Our multivariable analyses are also limited by the noninclusion of several variables known to influence the incidence of hypertension, such as alcohol consumption, physical activity, dietary intake of potassium, and measures of insulin resistance.[20] Taken together, all the aforementioned limitations will bias the results toward the null hypothesis — that is, that there is no association between serum aldosterone and longitudinal changes in blood pressure. Because most of the study participants were white, the extent to which the findings can be generalized to other racial groups is limited. Further research is warranted to determine ethnic variations in pressor responses to serum aldosterone.[35]

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