Clinical and Genetic Correlates of Serum Aldosterone in the Community: The Framingham Heart Study


Background: We investigated the environmental and genetic sources of interindividual variability in serum aldosterone level in a large, community-based sample.

Methods: We examined the relation of serum aldosterone to vascular risk factors, urine sodium, and candidate single nucleotide polymorphisms in 2891 Framingham Offspring Study participants (53.2% women, mean age 59 years) using multivariable linear regression. Multivariable logistic regression was used to identify predictors of high (top quartile) and low (lowest quartile) serum aldosterone values. We estimated heritability of serum aldosterone via variance-component methods and evaluated linkage via a 10-cM-density genome scan.

Results: Clinical variables related to higher serum aldosterone level included female sex, diuretic treatment, and a higher total/high density lipoprotein cholesterol ratio. A high urinary sodium excretion, postmenopausal status (without hormone replacement therapy), increased pulse pressure, and prevalent cardiovascular disease were related to lower serum aldosterone values. Urinary sodium was the strongest correlate of serum aldosterone ($R^2 = 10\%$). Serum aldosterone levels did not differ by genotype in the aldosterone synthase ($CYP11B2$ c.1-344C>T) and the mineralocorticoid receptor ($NR3C2$ c.754A>G) genes. The estimated heritability of serum aldosterone was 0.10. No chromosomal region attained a log-of-the-odds score in multipoint linkage analysis.


Key Words: Aldosterone, sodium, genetics, diuretics, risk factors.


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cell dysfunction. Clinical studies have highlighted that elevated serum aldosterone and plasma renin levels are associated with left ventricular remodeling, hypertension, and cardiovascular disease (CVD). Clinical trials have also demonstrated that aldosterone blockade lowers morbidity and mortality in post–myocardial infarction and in congestive heart failure patients. Thus, it has been suggested that elevation of serum aldosterone relative to dietary sodium intake may be a modifiable CVD risk factor.

Given the emerging role of aldosterone as a CVD risk factor, it is important to understand its relation to established risk factors and to identify additional features that influence serum levels. Information regarding the potential contributions of clinical and genetic factors to the variability of serum aldosterone is limited; however, such knowledge may be fundamental to understanding the mechanisms by which aldosterone influences susceptibility to CVD. The clinical and environmental correlates of serum aldosterone reported in the literature include age, sex, dietary sodium intake, ethnicity, hypertension, and obesity. The extent to which these variables account for the total variation in serum hormone levels is unclear. In addition, studies evaluating the genetic contribution to serum aldosterone levels have yielded inconsistent results.

The Framingham Study is a large, community-based sample consisting of individuals from multiple extended families who have been well characterized for CVD and its risk factors. Thus, our objectives were the following: 1) to describe the clinical correlates of serum aldosterone; 2) to estimate the genetic contribution to the interindividual variability via a heritability analysis; 3) to conduct a genome-wide linkage analysis using serum aldosterone as a quantitative trait; and 4) to study the relations of specific polymorphisms in mineralocorticoid pathway candidate genes to serum aldosterone levels.

Methods

Study Population

The design and selection criteria of the Framingham Offspring Study have been reported. The 3532 participants who attended the sixth Offspring Study examination (1995 to 1998) were eligible for the present investigation. All participants underwent a routine medical history, physical examination including blood pressure (BP) measurement, anthropometry, and laboratory assessment of CVD risk factors. The Institutional Review Board at Boston Medical Center approved the study, and all participants gave written informed consent.

Participants were excluded from the present investigation if they had missing data on serum aldosterone (n = 157) or urinary sodium measurements (n = 484). After exclusions, 2891 participants (1539 women and 1352 men) remained eligible.

Entire Sample and Reference Sample

The entire eligible sample was used for examining the clinical correlates of serum aldosterone. Additionally, we created a reference sample of apparently healthy individuals within the entire sample by serially excluding participants with the following conditions: prevalent CVD (n = 109); hypertension (systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of antihypertensive medication (n = 1104); obesity (body mass index ≥ 30 kg/m2, n = 369); diabetes mellitus (fasting blood glucose ≥ 126 or hypoglycemic medication, n = 46); current smoking (n = 211); atrial fibrillation (n = 2); and other diuretic use (n = 3). Thus, the reference sample of healthy individuals consisted of 1047 participants (59% women and 41% men).

Measurement of Serum Aldosterone and Urinary Sodium

Serum aldosterone was measured from fasting blood samples with participants in the supine position for about 5 to 10 min before venipuncture. All samples were obtained in the morning, typically between 8 and 9 AM. Participants were instructed to take their medications as usual on the morning of the examination. Venous blood was centrifuged and serum stored at −7°C until measurement. Aldosterone was measured using a radioimmunoassay (Quest Diagnostics, San Juan Capistrano, CA). The assay was highly sensitive (detection to 1 ng/dL) and had an intra-assay coefficient of variation (CV) of 3.8% to 6% (for assay ranges from high concentration to low concentrations, respectively). The interassay CV varied from 4.0% for high concentrations to 9.8% for low concentrations.

Spot urine samples (3 mL) were collected at the time of phlebotomy and then maintained at −20°C until analysis. Urine sodium was measured using an automated ion-electrode method. Samples were analyzed in duplicate with an average intra-assay CV of 0.8%. A modified Jaffe method was used to measure urinary creatinine concentration, with an average intra-assay CV of 1.7% to 3.8%. Urinary sodium excretion is expressed as millimoles of sodium per gram of urinary creatinine (referred to as urine sodium index for simplicity).

Genetic Analyses Sample

The heritability analyses were based on 1443 participants belonging to 478 extended families with at least two members. Of these, 914 participants (48% men) belonging to the 287 largest families underwent a 10-cM–density genome scan by the Mammalian Genotyping Service at the Marshfield Clinic, as previously described.

The candidate single nucleotide polymorphism (SNP) genotype analyses were based on all participants with DNA available and without missing genotypes (n = 2418) for the aldosterone synthase gene (CYB11B2) variant and
n = 2725 for the mineralocorticoid receptor gene (NR3C2) variant).

**Determination of Genotypes**

The nomenclature recommendations of the Human Genome Variation Society are used to describe sequence variants. Specifically, the CYP11B2.c.1-344C>T variant is located 344 bases upstream of the first nucleotide of the closest exon to the marker, position +1 of exon 1 (cDNA accession number NM_000498 and chromosome 8 genomic sequence accession number NT_008127, version 15). The mineralocorticoid receptor SNP typed for this study is similarly named as NR3C2c.754A>G (cDNA accession number NM_000901, chromosome 4 genomic sequence accession NT_016606, version 15). Alternatively, the variants are also described by identification numbers rs1799998 and rs5522 (http://www.ncbi.nlm.nih.gov/SNP). Genomic DNA was extracted from peripheral blood leukocytes, and the CYP11B2.c.1-344C>T and NR3C2c.754A>G genotypes were detected by standard methods.

**Statistical Analyses**

Serum aldosterone levels and urine sodium had a positively skewed distribution and were naturally log transformed to promote normality. We constructed stepwise multivariable linear regression models (SAS REG procedure; SAS Institute, Cary, NC) to identify clinical covariates associated with log aldosterone. Separate models were constructed in the reference sample of healthy participants and in the overall sample. Age and sex were included as covariates in all models. For analyses of the reference sample, additional covariates included pulse pressure, body mass index, heart rate, urine sodium index, and total/high density cholesterol (HDL) cholesterol ratio. For analyses of the overall sample model, additional covariates included diabetes mellitus, current smoking, hypertension, hypertension treatment (including diuretic use), diuretic use, menopausal status (premenopausal, postmenopausal with hormone replacement therapy [HRT], postmenopausal without HRT), prevalent CVD, and atrial fibrillation. A P value <.05 was the significance criterion for covariates to enter and stay in the stepwise logistic models.

**Heritability and Linkage Analyses**

A heritability estimate for serum aldosterone was obtained by variance-components methods using SOLAR. Multi-point quantitative trait linkage analyses were conducted with log aldosterone residuals from the fully adjusted model using GENEHUNTER.

**Statistical Analysis: Genotypes and Aldosterone Levels**

The χ² test was used to compare observed genotype frequencies with their estimates under Hardy-Weinberg equilibrium. Association analyses tested the null hypothesis that mean serum aldosterone level did not differ by candidate SNP genotype. Multivariable linear regression was performed with SAS PROC REG. Analyses were performed on standardized residuals from two sets of linear regression models with log aldosterone as the dependent variable: 1) models adjusting for age and sex (model 1); and 2) models adjusting for age, sex, and all clinical covariates significantly associated with serum aldosterone including pulse pressure, log urine sodium index, diuretic use, menopausal status, and prevalent CVD (model 2). Confirmatory analyses were run using SAS PROC GENMOD to account for correlation among siblings. A nominal P value <.05 was considered to be significant.

**Results**

The baseline characteristics of the overall study sample and the reference sample are displayed in Table 1. Hypertension was present in 44% of the men and 38% of the women. Mean serum aldosterone level was higher in women than in men.

**Multivariable Correlates of Serum Aldosterone in the Reference Sample and in the Entire Sample**

The multivariable clinical correlates of serum aldosterone are displayed in Table 2. In the reference sample, women had 14% higher adjusted-serum aldosterone values compared with men (P < .0001). Urine sodium and pulse pressure were associated with an 18% and 11% lower serum aldosterone value per standard deviation increment, respectively (P < .0001 for both).

In the broad sample, which included participants with cardiovascular risk factors and disease, the relations among serum aldosterone, female sex, and urine sodium remained statistically significant (P < .0001 for all); the magnitude and strength of the associations were similar to those in the reference sample. Three additional correlates were statistically significant in an analysis of the overall sample. Participants treated with diuretics had a 1.6-fold higher serum aldosterone level (P < .0001). Postmeno-
pausal women who were not receiving HRT and individuals with prevalent CVD had lower serum aldosterone levels ($P = .001$ and $P = .01$, respectively).

In the entire sample, the statistically significant variables together explained 17% of the interindividual variability in serum aldosterone level. Urinary sodium excretion explained the largest proportion, about 10% of the variation in serum aldosterone levels among the participants.

### Clinical Correlates of High and Low Serum Aldosterone Levels in the Entire Sample

The multivariable correlates of values in the highest or lowest quartile of serum aldosterone are displayed in Table 3. The analyses are consistent with the results of linear regression models. Diuretic use was positively associated with serum aldosterone in the highest quartile whereas higher urine sodium index was associated with decreased odds of a value in the highest quartile. Additionally, a higher urine sodium index increased and a high total/HDL cholesterol ratio decreased the odds of being in the lowest quartile. In both the linear and logistic regression models, HDL cholesterol alone was not related to serum aldosterone ($P > .05$).

### Heritability and Linkage

After accounting for age, sex, and all significant covariates in the stepwise linear model, we estimated heritability of serum aldosterone to be 0.10 (SE, 0.06; $P = .04$). A genome-wide linkage analysis was performed on the fully adjusted aldosterone residuals in 914 participants who underwent a genome scan and had serum aldosterone measured. No chromosomal region attained a multipoint log-of-the-odds score >1.

### Relation of Aldosterone Synthase and Mineralocorticoid Receptor SNP Genotypes to Serum Aldosterone Levels

Minor allele frequencies in the $CYP11B2$ c.1-344C>T and $NR3C2$ c.754A>G variants were 47% and 9% respectively and the observed genotype frequencies were in Hardy-Weinberg equilibrium ($P = .63$ and $P = .83$, respectively). In unadjusted and multivariable-adjusted analyses, there were no differences in mean serum aldosterone level across the three genotypes for the two allelic variants (Table 4).
Discussion
Principal Findings

We observed that aldosterone was related to established CVD risk factors in a complex fashion. Clinical variables determining interindividual variation in serum aldosterone included female sex, diuretic treatment, elevated total/HDL cholesterol, which were associated with higher serum aldosterone levels, and high urine sodium index, postmenopausal status without HRT, increased pulse pressure, and prevalent CVD, which were associated with lower serum aldosterone values. The genetic contribution to the variability in aldosterone was modest, with an estimated heritability of 0.10. Given the low heritability, it is not surprising that we did not find any evidence for genetic linkage. We found no association between two allelic variants in mineralocorticoid pathway genes and serum aldosterone level.

Relations of Clinical Covariates to Serum Aldosterone: Comparison With Prior Reports

Most previous reports relating clinical covariates to serum aldosterone have been conducted in clinical research units with small samples of selected individuals. In our large, community-based sample, we have confirmed previous reported associations between aldosterone levels, diuretic treatment, and salt intake. Diuretic use depletes volume and activates the renin–angiotensin–aldosterone neurohormonal axis, thereby raising aldosterone levels. We observed that salt intake, as measured by urine sodium excretion, accounted for the greatest proportion of variation in serum aldosterone. The inverse relation of urine sodium to serum aldosterone is intuitive given the fundamental role of serum aldosterone in renal tubular sodium reabsorption. Our results suggest that defining the appro-

Table 2. Clinical correlates of serum aldosterone levels: stepwise linear regression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β (SE)</th>
<th>Fold change in aldosterone (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference sample (n = 1047)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per SD (9.7 y)</td>
<td>-0.013 (0.016)</td>
<td>0.99 (0.96,1.02)</td>
<td>.42</td>
</tr>
<tr>
<td>Sex, female versus male</td>
<td>0.129 (0.029)</td>
<td>1.14 (1.08,1.21)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Pulse pressure, per SD (15.8 mm Hg)</td>
<td>-0.113 (0.026)</td>
<td>0.89 (0.85,0.94)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Log urine sodium index, per SD (0.7 units)</td>
<td>-0.197 (0.015)</td>
<td>0.82 (0.80,0.85)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Model R² = 0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire sample (n = 2891)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per SD (9.7 y)</td>
<td>-0.015 (0.011)</td>
<td>0.99 (0.96,1.01)</td>
<td>.16</td>
</tr>
<tr>
<td>Sex, female versus male</td>
<td>0.165 (0.034)</td>
<td>1.18 (1.10,1.26)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Log urine sodium index, per SD (0.7 units)</td>
<td>-0.169 (0.009)</td>
<td>0.84 (0.83,0.86)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diuretic treatment</td>
<td>0.451 (0.033)</td>
<td>1.57 (1.47,1.67)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HRT, versus premenopausal</td>
<td>-0.078 (0.038)</td>
<td>0.92 (0.86,1.00)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HRT, versus premenopausal</td>
<td>0.033 (0.040)</td>
<td>1.03 (0.96,1.12)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prevalent CVD</td>
<td>-0.140 (0.051)</td>
<td>0.87 (0.79,0.96)</td>
<td>.01</td>
</tr>
<tr>
<td>Model R² = 0.17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

β = regression coefficient; SE = standard error of β; other abbreviations as in Table 1.
* For three-group comparison between premenopausal women, postmenopausal women without HRT, and postmenopausal women with HRT.

Table 3. Clinical correlates of high and low serum aldosterone levels in the entire sample: logistic regression

<table>
<thead>
<tr>
<th>Serum aldosterone in Q2 or Q3‡</th>
<th>Odds ratio for serum aldosterone in Q4* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic treatment present</td>
<td>4.73 (3.46–6.46)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Log urine sodium index</td>
<td>0.57 (0.52–0.63)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum aldosterone in Q2 or Q3‡</th>
<th>Odds ratio for serum aldosterone in Q1* (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log urine sodium index</td>
<td>1.53 (1.37–1.71)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total/HDL cholesterol ratio</td>
<td>0.86 (0.76–0.97)</td>
<td>.01</td>
</tr>
</tbody>
</table>

HTN = hypertension; Q = quartile; other abbreviations as in Table 1.
* Age- and sex-adjusted residual aldosterone values were divided into quartiles; ‡ Q4 n = 720; § Q2 and 3, n = 1440; Q1, n = 713.
prieteness of a given level of serum aldosterone in relation to the dietary sodium intake in a population may promote our understanding of the role of aldosterone in vascular disease.

Two earlier reports detail an association of low HDL cholesterol with higher plasma aldosterone.\(^3^3\)\(^,\)\(^3^4\) We did not observe such a direct relation between HDL cholesterol and aldosterone. Instead, we observed a modest association between an increased total/HDL cholesterol ratio and decreased the odds of being in the lowest quartile of serum aldosterone. It has been hypothesized that HDL cholesterol may directly affect the sensitivity of the adrenal glomerulosa to aldosterone secretion.\(^3^4\)

In contrast to previous reports in the literature, we did not find that serum aldosterone levels decreased with age, nor did we find that levels increased with body mass index.\(^3^9\)\(^,\)\(^3^5\)\(^,\)\(^3^7\) Both earlier conclusions have been drawn from studies with small numbers of individuals. With more than 2800 participants with ages ranging from 29 to 86 and body mass index ranging from 16 to 56, the present study may offer more robust results regarding these correlates.

An alternative explanation may be that age-associated increases in subclinical renal atherosclerosis may result in renin activation and consequently may mitigate any age-associated reductions in aldosterone. In this context, it is interesting that investigators have demonstrated a lack of decline in plasma renin with age when elderly individuals are examined.\(^3^8\)

In our community-based sample, diabetes was not related to serum aldosterone levels. In clinical case series, an inverse relation of serum aldosterone levels and diabetes (referred to as hyporeninemic hypoaldosteronism or type IV renal tubular acidosis) has been noted, principally in diabetic individuals with nephropathy.\(^3^9\)\(^,\)\(^4^0\)

The present study yielded two additional insights regarding correlates of serum aldosterone. First, women had higher serum aldosterone levels than men. Second, postmenopausal women not taking HRT had lower levels of serum aldosterone. Taken together, these findings suggest that sex hormones may influence mineralocorticoid levels.\(^4^1\)\(^,\)\(^4^2\) Consistent with these observations are the findings that adrenal responsiveness to a sodium restriction or angiotensin II infusion stimulus varies by sex.\(^4^3\) A blunted adrenal response to these stimuli, termed the nonmodulation phenotype, has been demonstrated to be less frequent in women.\(^4^1\)\(^,\)\(^4^4\)

In addition, a sexual dimorphism has been noted for plasma renin activity with men having higher plasma renin activity than women,\(^4^5\) a finding that may suggest that serum aldosterone levels should be higher in men (given that renin is a stimulus for aldosterone release). However, in other samples investigating elderly individuals, women have been reported to have higher plasma renin levels than men.\(^3^8\) The present investigation, with more than 1500 women encompassing a wide age range, may better characterize sex-related differences in serum aldosterone levels in the community. Additional studies are needed to clarify these findings.

An intriguing finding in our study is the inverse cross-sectional relation of serum aldosterone to pulse pressure in our healthy reference sample. Previous studies examining serum aldosterone levels in hypertensive individuals have yielded inconsistent results, with high,\(^4^6\) normal,\(^4^7\) and low,\(^4^8\) values being reported compared with those in non-hypertensive controls. Many prior studies were limited by selection bias (inclusion of patients with varying durations and degrees of BP elevation and confounded by treatment effects) and small sample sizes.

The finding that participants with prevalent CVD had lower aldosterone levels is difficult to interpret given the cross-sectional nature of our study. In a cross-sectional analysis of observational data, indication bias may be a confounder and account for the observed inverse relation. Participants with prevalent CVD tend to have a greater burden of risk factors including hypertension and are more likely to receive treatments that may lower aldosterone level (ie, angiotensin converting enzyme inhibitors). Pro-

### Table 4. Serum aldosterone levels (ng/mL) in relation to single nucleotide polymorphisms in the aldosterone synthase and mineralocorticoid receptor genes

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted*</th>
<th>Multivariable-adjusted model†</th>
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<tbody>
<tr>
<td><strong>CYP11B2c.1-344C&gt;T</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC ((n = 684))</td>
<td>11.4 (11.0, 11.9)</td>
<td>11.5 (11.1, 12.0)</td>
</tr>
<tr>
<td>CT ((n = 1193))</td>
<td>11.4 (11.0, 11.7)</td>
<td>11.3 (11.0, 11.6)</td>
</tr>
<tr>
<td>TT ((n = 541))</td>
<td>11.4 (10.9, 12.0)</td>
<td>11.5 (11.0, 12.0)</td>
</tr>
<tr>
<td></td>
<td>(P = .99)</td>
<td>(P = .58)</td>
</tr>
<tr>
<td><strong>NR3C2c.754A&gt;G</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA ((n = 2257))</td>
<td>11.3 (11.1, 11.6)</td>
<td>11.4 (11.1, 11.6)</td>
</tr>
<tr>
<td>AG ((n = 447))</td>
<td>11.2 (10.7, 11.8)</td>
<td>11.3 (10.7, 11.8)</td>
</tr>
<tr>
<td>GG ((n = 21))</td>
<td>11.2 (8.8, 14.1)</td>
<td>10.7 (8.6, 13.2)</td>
</tr>
<tr>
<td></td>
<td>(P = .90)</td>
<td>(P = .83)</td>
</tr>
</tbody>
</table>

* Aldosterone values are mean (95% confidence interval). For ease of interpretation, data are presented after conversion from log aldosterone units; † Adjusted for age, sex, pulse pressure, log urine sodium index, diuretic treatment, menopausal status, and prevalent cardiovascular disease.
pective follow-up of this cohort for incident CVD events will clarify the true relations between serum aldosterone and CVD risk.

Genetic Contribution to Serum Aldosterone Level

Our finding of a low heritability for the quantitative trait of serum aldosterone level is consistent with prior reports. In a study of 43 sib pairs, Kotchen estimated the heritability of serum aldosterone to be 0.19.20 The SNPs in the aldosterone synthase and the mineralocorticoid receptor genes did not influence mean serum aldosterone levels in our sample. Prior studies have evaluated the relations between the CYP11B2c.1-344C>T variant and serum aldosterone levels with inconsistent results. There are reports of the T allele, the C allele, and neither allele being associated with serum aldosterone levels in our sample. Our study sample of 2418 participants is the largest to date to evaluate the relation between the CYP11B2c.1-344C>T variant and serum aldosterone levels. To our knowledge, no prior published studies have evaluated the relation between the mineralocorticoid receptor variant NR3C2c.754A>G and serum aldosterone levels.

Study Limitations and Strengths

Our study has several limitations. First, we obtained a single measure of serum aldosterone, and it may be questioned if a single reading adequately represents an individual’s mineralocorticoid level. Any “noise” introduced by a single reading would lead us to underestimate associations of serum aldosterone, and this random error may explain our ability to only explain 17% of the variability in aldosterone levels. Nonetheless, we have previously reported modest associations of serum aldosterone with left ventricular remodeling and incidence of hypertension.7,8 Suggesting that even a single measurement of serum aldosterone is informative and a reasonable phenotype to investigate.

Second, we measured serum aldosterone after only 5 to 10 min of supine position in contrast to clinical research unit protocols that obtain measurements after 1 h of rest. Although our procedure might cause slightly higher aldosterone values, longer periods of supine posture before a blood test are impractical in an epidemiologic research setting.

Third, we did not measure urine sodium excretion over a 24-h period. Whereas a 24-h urine specimen might more precisely capture net sodium excretion, a spot urine specimen, especially when indexed for urinary creatinine, has been shown to correlate well with 24-h urinary sodium and with daily sodium intake and is more convenient to obtain.50,51

Fourth, two physiologic regulators of aldosterone secretion, namely, potassium and plasma renin activity, were not available for analysis. Knowledge of serum renin and potassium will help to provide an understanding of their contribution to serum aldosterone level. Part of the interindividual variation in aldosterone level may be due to variability in renin and potassium level.

Fifth, given that our sample was predominantly of white ethnicity, we were unable to comment on previously described ethnic differences in serum aldosterone values.52

Sixth, by virtue of being an observational study, antihypertensive medications and, in particular, diuretics, were nonrandomly assigned; however, we provided models in participants not using medications, which confirmed the relations of aldosterone to sex and urine sodium index. Finally, the observational, cross-sectional design of the study precludes assertions of causal relations between the clinical correlates and aldosterone levels.

Our study has several strengths. These include the following: the large, community-based sample; the use of both a healthy reference sample and an overall sample to identify correlates; the inclusion of clinical and genetic covariates in a single study; and the ability to identify correlates of mean and extreme values.

Conclusion

The strongest determinant of interindividual variability in serum aldosterone was dietary salt intake as assessed by urine sodium. Serum aldosterone level in the community is related to established vascular risk factors in a complex fashion. The genetic contribution to aldosterone level was modest.

References


