

## Bimodal Aldosterone Distribution in Low-Renin Hypertension

E. Victor Adlin,<sup>1</sup> Leonard E. Braitman,<sup>2</sup> and Ramachandran S. Vasan<sup>3,4</sup>**BACKGROUND**

In low-renin hypertension (LRH), serum aldosterone levels are higher in those subjects with primary aldosteronism and may be lower in those with non-aldosterone mineralocorticoid excess or primary renal sodium retention. We investigated the hypothesis that the frequency distribution of aldosterone in LRH is bimodal.

**METHODS**

Of the 3,532 attendees at the sixth examination cycle of the Framingham Offspring Study, 1,831 were included in this cross-sectional analysis after we excluded those with conditions or taking medications such as antihypertensive drugs that might affect renin or aldosterone.

**RESULTS**

Three hundred three subjects (17%) had untreated hypertension (SBP  $\geq$ 140 mm Hg or DBP  $\geq$ 90 mm Hg). LRH, defined as plasma renin  $\leq$ 5 mU/L, was present in 93 of those 303 hypertensive subjects (31%). Aldosterone values were adjusted statistically for age, sex, and the

urinary sodium/creatinine ratio. In the subjects with LRH, the adjusted aldosterone distribution was bimodal (dip test for unimodality,  $P = 0.008$ ). The adjusted aldosterone distribution was unimodal in the normal subjects ( $P = 0.98$ ) and in the hypertensive subjects with normal plasma renin ( $P = 0.94$ ).

**CONCLUSIONS**

In this community-based sample of white subjects, those with low-renin hypertension had a bimodal adjusted aldosterone distribution. Subjects with normal-renin hypertension and subjects with normal blood pressure had unimodal adjusted aldosterone distributions. These findings suggest 2 pathophysiological variants of LRH, one that is aldosterone-dependent and one that is non-aldosterone-dependent.

*Keywords:* aldosterone; blood pressure; hypertension; low-renin hypertension; renin.

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Plasma renin is lower than normal in about one-quarter of persons with hypertension.<sup>1-5</sup> Primary aldosteronism (Conn's syndrome) is characterized by low renin as well as by elevated aldosterone levels, and morphologic adrenal abnormalities are common incidental autopsy findings in hypertensive patients. These observations led Conn to suggest that primary aldosteronism might be a common cause of hypertension, responsible for as much as 20% of cases rather than the previously estimated 1% or less.<sup>6</sup> But studies of patients with low-renin hypertension (LRH) consistently failed to find elevated aldosterone levels in more than 1% or 2%, and the cause of the renin suppression in most cases remained unexplained.<sup>1,3-5</sup>

Proposed causes of LRH, in the absence of hyperaldosteronism, include mineralocorticoid excess due to steroids other than aldosterone<sup>7</sup> and extracellular fluid volume expansion caused by primary renal retention of sodium.<sup>8,9</sup> Aldosterone production, largely dependent on renin, would be expected to be low. Indeed low circulating aldosterone levels have been found in many of these disorders.<sup>8,10,11</sup>

Recently a new concept of primary aldosteronism, based on an elevated aldosterone/renin ratio coupled with evidence of nonsuppressible serum aldosterone, even in persons with

normal serum potassium and aldosterone levels, has greatly increased the estimates of the prevalence of primary aldosteronism.<sup>12</sup> A recent review of 18 studies found the median prevalence of primary aldosteronism in persons with hypertension to be 8.9%.<sup>13</sup> Common causes of LRH, then, may be primary aldosteronism or other disorders that cause volume expansion with resulting suppression of renin and aldosterone.

These considerations lead us to propose the following hypothesis: LRH consists of aldosterone-dependent disorders (various forms of primary aldosteronism), and non-aldosterone-dependent disorders; the expected elevation of serum aldosterone levels in the first group of disorders and lowered circulating aldosterone levels in the second group suggest the possibility of a bimodal distribution of serum aldosterone levels in LRH. This study was designed to test that hypothesis.

**METHODS****Participants**

The Framingham Heart Study began in 1948 as a prospective, community-based observational cohort study of 5,209

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men and women. The Framingham Offspring Study, started in 1971, consisted of a cohort of 5,135 individuals who were the children, and their spouses, of the original members of the Framingham Heart Study.<sup>14</sup> At the sixth examination cycle of the Framingham Offspring Study, performed from 1995 to 1998, blood was drawn that was later assayed for serum aldosterone and plasma renin concentrations. Blood pressure was measured, and other data based on medical history, physical examination, and laboratory measurements were collected. Participants in our study are the 3,345 persons, out of a total of 3,532 attendees at examination cycle 6, for whom complete aldosterone, renin, and blood pressure data were available. All patients studied in the Framingham Heart Study and Framingham Offspring Study were considered by the investigators to be white.

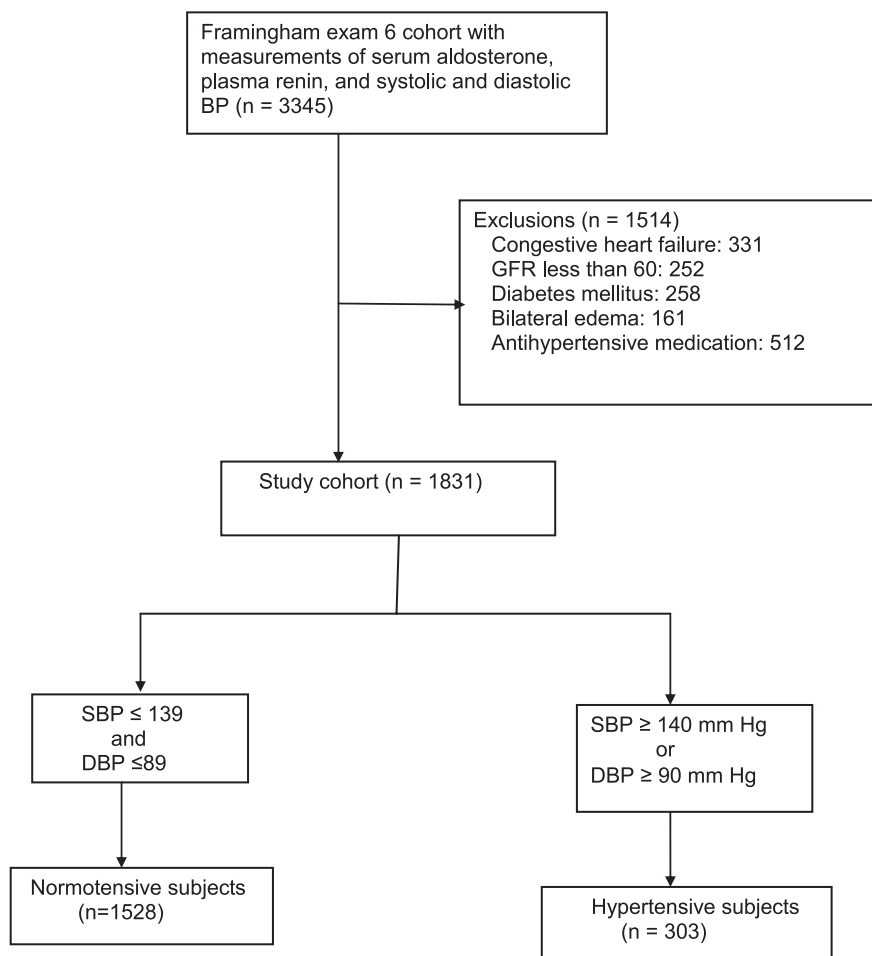
We sought to exclude those subjects who had disorders or were taking medications that would be likely to substantially affect either aldosterone or renin levels. Subjects with congestive heart failure, estimated glomerular filtration rate of <60 ml/minute, diabetes mellitus, or bilateral edema and those using any antihypertensive medication were excluded. Subjects taking diuretics, beta-blockers, angiotensin converting-enzyme inhibitors, calcium-channel blockers, and

alpha-1 adrenergic receptor blockers were excluded. After exclusions, our study sample consisted of 1,831 individuals aged 29–86 years (Figure 1).

### Clinical and laboratory assessment

Blood pressure was measured in the left arm by a Heart Study physician using a mercury column sphygmomanometer and a standardized protocol. Participants rested in the seated position for 5 minutes before blood pressure was measured. Blood pressure was measured twice, and the average of the 2 readings was taken as the blood pressure for the study.

Blood for aldosterone and renin measurement was drawn between 8 AM and 10 AM. Subjects were fasting and ambulatory but remained in a recumbent position for 5–10 minutes before blood was drawn. Specimens were promptly stored at  $-80^{\circ}\text{C}$ . Serum aldosterone was measured by a sensitive radioimmunoassay (Quest Diagnostics, Cambridge, MA).<sup>15</sup> The sensitivity of the assay is <1 ng/dl, with an intra-assay coefficient of variation ranging from 3.8% at high levels to 6.0% at low levels. Corresponding interassay coefficient of variation ranged 4.0%–9.8%.



**Figure 1.** Flow chart showing the derivation of the 1,831 subjects of this study. Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; SBP, systolic blood pressure.

Plasma renin concentration (in milliunits per liter) was measured between June and September 2004 using an immunochemiluminometric assay (Nichols Advantage Direct Renin Assay, Quest Diagnostics Nichols Institute, San Juan Capistrano, CA).<sup>16</sup> Intra-assay coefficient of variation ranged 1.7%–5.3%; interassay coefficient of variation ranged 2.7%–8.2%.

### Statistical analysis

To compare levels of continuous variables in 2 groups, we used independent samples *t* tests, Mann–Whitney–Wilcoxon tests, or permutation tests as appropriate. Fisher exact tests were used to compare proportions. Because the data suggest differences in sex distribution and the urine sodium/creatinine ratio among the groups studied (Table 1), and because age-related differences in aldosterone levels have been reported,<sup>17</sup> we adjusted for these variables. We regressed natural-log-transformed values of aldosterone on age, sex, and the urinary sodium/creatinine ratio and graphed the exponentiated predicted values of natural logarithm of aldosterone (ln(aldo)). Those back-transformed values hereafter will be called adjusted aldosterone. Regression diagnostics were performed for the analysis of hypertensives with low plasma renin ( $\leq 5$  mU/L). These included a normal QQ residual plot and tests for normality of residuals, linearity of ln(aldo), heterogeneity of variance, omitted variables, and multicollinearity. These all showed that the model specification was adequate.

To determine whether the distribution of the aldosterone values (both unadjusted and adjusted) in LRH was bimodal, we used dotplots and the dip test for unimodality.<sup>18</sup> In the dip test, if  $P < 0.05$ , we rejected the null hypothesis of unimodality and concluded that the distribution has  $>1$  mode. Statistical tests were two-sided. All analyses were performed using Stata 11 (StataCorp, College Station, TX).

### RESULTS

Figure 1 shows the exclusion process that resulted in the final sample of 1,831 subjects. One thousand five hundred

twenty-eight persons had normal blood pressure, and 303 had untreated hypertension, as defined in Figure 1.

Figure 2 shows the distribution of renin levels in the normotensive and hypertensive groups. An increased frequency of renin levels in the lower ranges was evident in hypertensive subjects. The median renin concentration was 13 mU/L in the normotensive subjects, compared with 9 mU/L in the hypertensive subjects. There was no evident excess of high renin levels in the hypertensive group, presumably because we excluded many individuals who may have had secondary aldosteronism. Only 1.7% of hypertensive subjects had renin levels above the 97.5 percentile of the normotensive group.

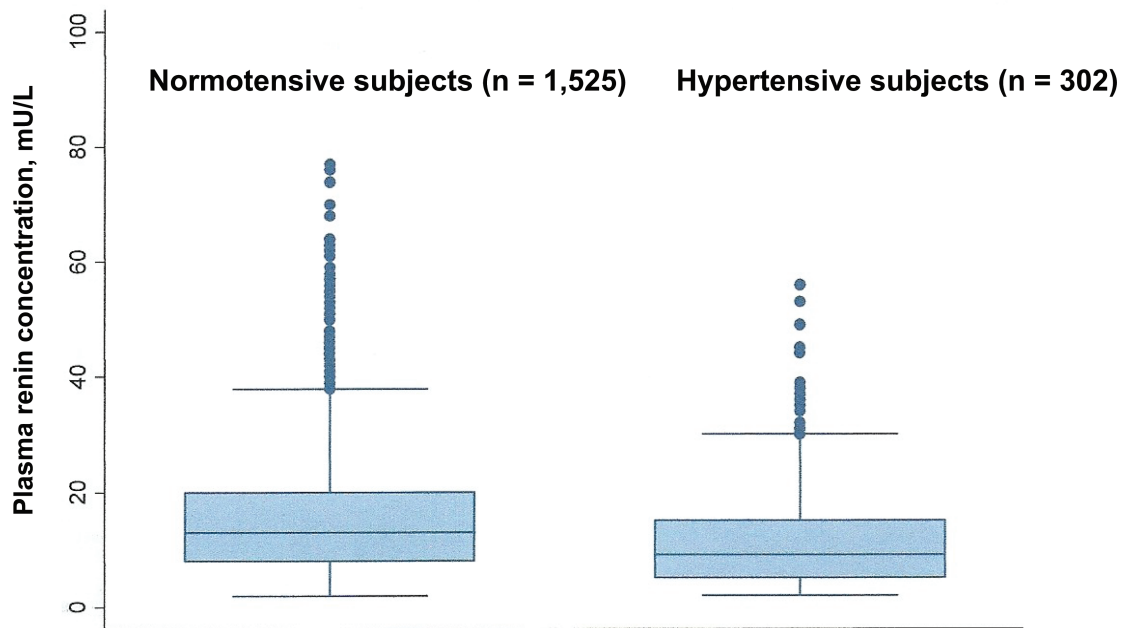
There was no clear criterion for defining LRH. Previous studies<sup>1,4</sup> have shown that consideration only of baseline renin levels fails to identify many persons with renin that is unresponsive to dietary or diuretic-induced salt depletion, a more sensitive indicator of renin suppression. Also, renin values were expressed only as whole numbers, so it was not possible to calculate percentiles (e.g., the 22 hypertensive subjects with a renin value of 2 mU/L could not be ranked individually). For this reason, in examining the distribution of aldosterone levels, we looked at each of the subsets of hypertensive subjects created by using renin values  $\leq 3, 4, 5, 6, 7,$  and  $8$  mU/L as cutoff points to define low renin. These corresponded to low-renin subsets that constituted 14.9%, 21.5%, 30.7%, 36.6%, 44.2%, and 49.5% of the hypertensive subjects, respectively. We selected the cutpoint of renin  $\leq 5$  mU/L for the comparison of demographic and other characteristics of the low-renin and normal-renin hypertensive subjects (Table 1) and for the distribution of aldosterone values in normal-renin hypertensive subjects.

Table 1 shows demographic and other characteristics of the study subjects in 4 groups: normotensive, all hypertensive, low-renin hypertensive, and normal-renin hypertensive.

The distribution of adjusted aldosterone values was unimodal in the normotensive subjects (dip test for unimodality,  $P = 0.98$ ) and in the hypertensive subjects with normal renin, which was defined as plasma renin of  $\geq 6$  mU/L ( $P = 0.94$ ) (Figure 3).

**Table 1.** Demographic, physical examination, and laboratory characteristics of the study subjects

	Normotensive (n = 1,528)	Hypertensive (n = 303)	Hypertensive, renin >5 mU/L (n = 210)	Hypertensive, renin $\leq 5$ mU/L (n = 93)
Age in years, mean (SD)	55.1 (9.0)	60.3 (8.9)	60.1 (9.3)	60.6 (7.9)
Male, No. (%)	707 (46.3)	161 (53.1)	127 (60.5)	34 (36.6)
Body mass index, kg/m <sup>2</sup> , mean (SD)	26.7 (4.4) (n = 1,524)	28.0 (4.9)	28.0 (4.9)	28.0 (4.9)
Systolic blood pressure, mm Hg, mean (SD)	118 (11.5)	152 (13.9)	150.6 (12.5)	154.5 (15.8)
Diastolic blood pressure, mm Hg, mean (SD)	73 (7.7)	85 (9.6)	84.6 (9.6)	84.5 (9.8)
Current smoking, No. (%)	268 (17.5)	50 (16.5)	32 (15.2)	18 (19.4)
Urine sodium/creatinine, mmol/g, mean (SD)	109.8 (71.0) (n = 1,326)	118.0 (73.9) (n = 262)	109.9 (68.8)	136.2 (81.7)
Family history of hypertension, No. (%)	736/1,159 (63.5)	152/221 (68.8)	106/159 (66.7)	46/62 (74.2)



**Figure 2.** Box plots showing the plasma renin concentrations in the normotensive and hypertensive subjects. The horizontal lines above and below the box (whiskers) show the lower and upper values that are the furthest observations within 1.5 times the interquartile range of the lower and upper ends of the box. The mean renin concentration in normotensive subjects was 15.9 mU/L; the mean renin concentration in hypertensive subjects was 12.7 mU/L. The mean difference between normotensive and hypertensive subjects was 3.2 mU/L (95% confidence interval = 1.2–5.0;  $P = 0.001$ ). Four normotensive and 1 hypertensive subject with renin >100 mU/L are not shown.

In the subjects with LRH, which was defined as renin  $\leq 5$  mU/L, the plot of unadjusted aldosterone values appeared as if it might be bimodal, but this possibility was not confirmed by the dip test for unimodality ( $P = 0.11$ ) (Figure 4a). But after adjustment for age, sex, and urinary sodium/creatinine ratio, the aldosterone distribution is clearly bimodal in the dotplot and by the dip test ( $P = 0.008$ ) (Figure 4b).

Figure 5 shows the distribution of adjusted aldosterone values in LRH subsets defined by increasing cutoff points for plasma renin from 3 through 8 mU/L (except for 5 mU/L, which is shown in Figure 4). For the plasma renin with cutoff points of 3, 4, and 5, the separation of adjusted aldosterone values in the low-renin groups is complete (Figure 5). Although there is less separation between the 2 parts of the frequency distributions of adjusted aldosterone as subjects with higher renin levels are added (cutoff points of 6, 7, and 8), those dotplots still suggest the possibility of bimodality.

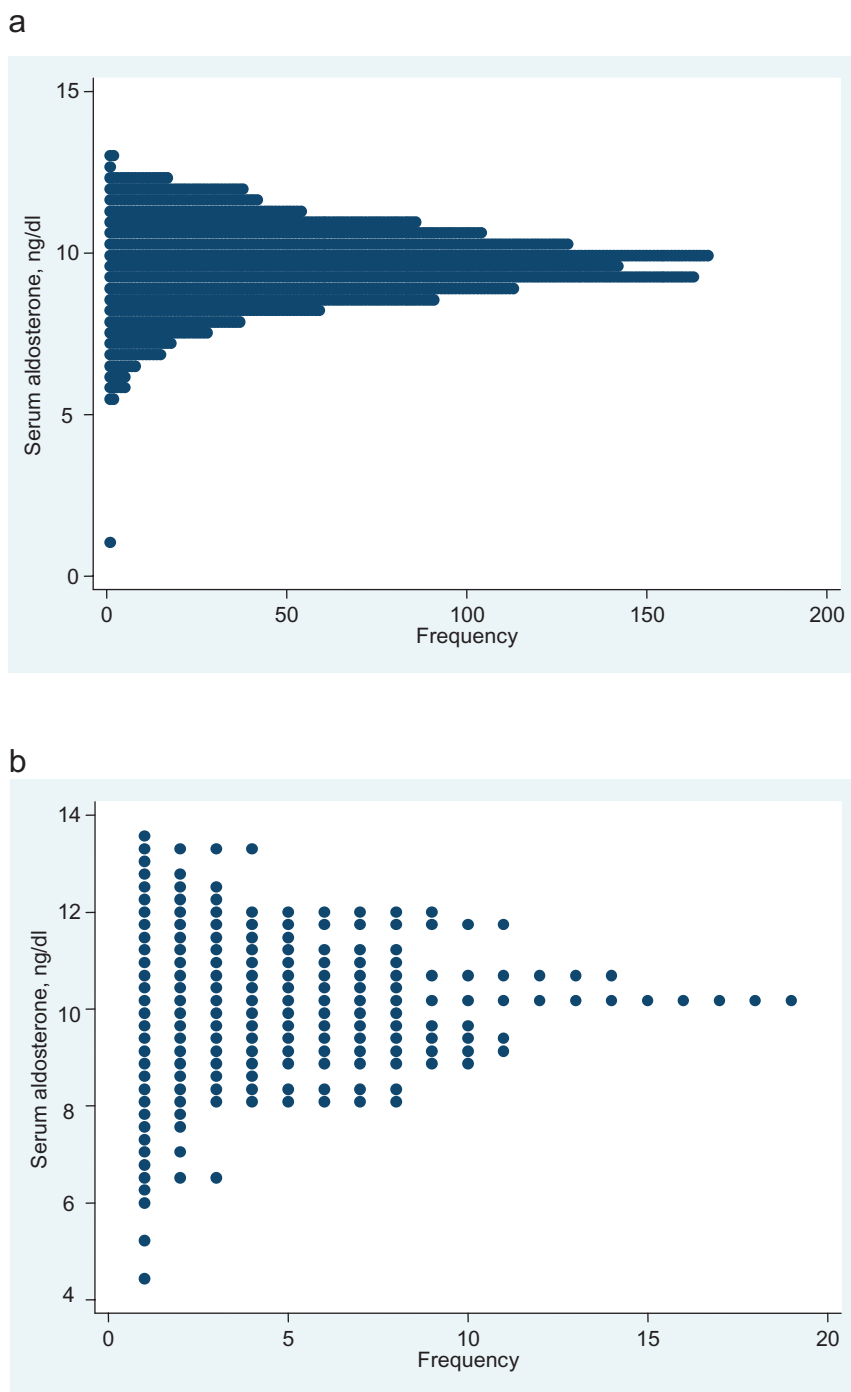
## DISCUSSION

We have analyzed the distribution of serum aldosterone in a community-based sample of 1,831 persons, after excluding those who were taking antihypertensive medications or were believed to have comorbidities likely to affect aldosterone or renin levels. In normotensive subjects and in hypertensive subjects with normal plasma renin concentration, we observed a unimodal distribution of serum aldosterone levels. In the hypertensive subjects with low plasma renin concentration the adjusted aldosterone distribution was bimodal.

The finding of a bimodal aldosterone distribution in LRH may offer clues to the pathophysiology of LRH. High serum aldosterone levels in one group of patients with LRH suggests an aldosterone-dependent form of the disorder, caused by 1 of the several forms of primary aldosteronism; the combination of low renin and high aldosterone is considered pathognomonic of primary aldosteronism.<sup>19</sup>

The finding of a distinct group of LRH patients with lower aldosterone levels suggests a non-aldosterone-dependent form of the disorder. LRH without elevated aldosterone is often referred to as low-renin essential hypertension and is widely believed to result from sodium retention and subsequent expansion of extracellular fluid volume, in most cases of undetermined cause. Mineralocorticoid excess due to steroids other than aldosterone has been suggested by a number of findings, including a low salivary sodium/potassium ratio (an indicator of mineralocorticoid excess)<sup>20,21</sup> and by selective response of the hypertension to a steroid antagonist.<sup>22</sup> A number of mineralocorticoids and mineralocorticoid-related syndromes have been found to cause LRH, but none has been implicated in more than a small number of cases.<sup>5,7</sup> Interest continues in the syndrome of apparent mineralocorticoid excess, in which deficiency of 11 $\beta$ -hydroxysteroid dehydrogenase type 2 causes cortisol to act as a potent mineralocorticoid.<sup>23,24</sup> The activity of this enzyme has recently been found to be decreased in LRH<sup>25</sup> and to be decreased with aging<sup>26</sup> and in salt-sensitivity,<sup>27</sup> both of which are associated with LRH.

Causes other than mineralocorticoid excess that may cause LRH with decreased serum aldosterone levels include

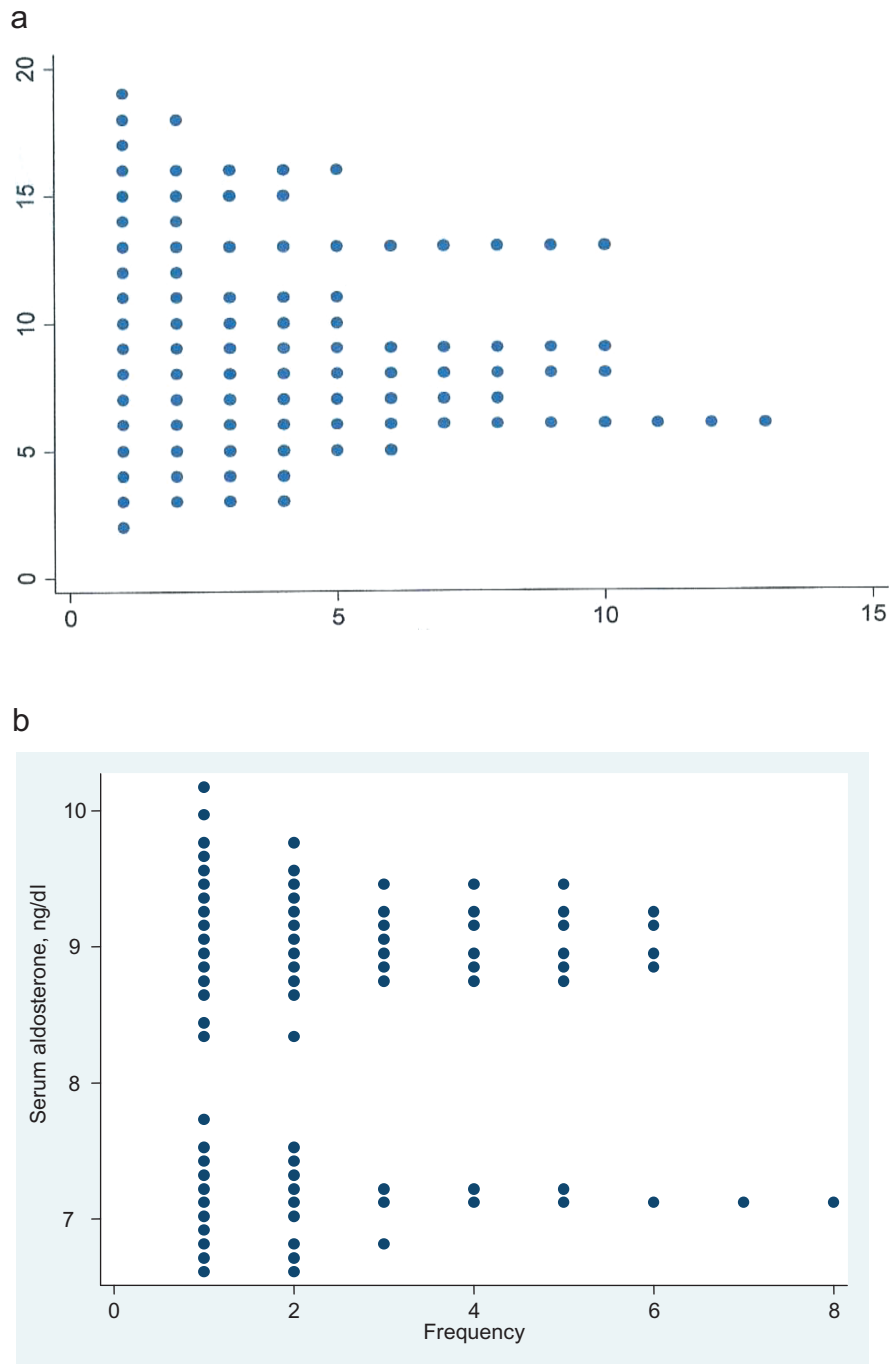


**Figure 3.** Dotplot showing the aldosterone frequency distribution, etc. (a) Aldosterone frequency distribution, adjusted for age, sex, and urine sodium/creatinine ratio, in the 1,326 of the 1,528 normotensive subjects for whom the urine sodium/creatinine ratio was available. Dip test for unimodality,  $P = 0.98$ . (b) Aldosterone frequency distribution, adjusted for age, sex, and urine sodium/creatinine ratio, in the 181 of the 210 subjects with hypertension and plasma renin concentration  $\geq 6$  mU/L, for whom the urine sodium/creatinine ratio was available. Dip test for unimodality,  $P = 0.94$ .

primary renal sodium retention, as in Liddle's syndrome,<sup>8</sup> and perhaps suppression of renin by the effects of arterial hypertension itself.<sup>28</sup> Excess dietary sodium ingestion has been proposed, but there is no evidence that this is an important factor.<sup>29</sup>

It is often stated that serum aldosterone levels are normal in LRH but that the normal levels are inappropriately

elevated in the face of low renin, suggesting a possible role for altered aldosterone responsiveness to angiotensin in the pathogenesis of the hypertension.<sup>30-33</sup> Also, the "normal" serum aldosterone levels in LRH have been cited as evidence that another mineralocorticoid could not be the cause of the hypertension because a lowered aldosterone level would then be expected.<sup>34,35</sup> Our finding that serum aldosterone is



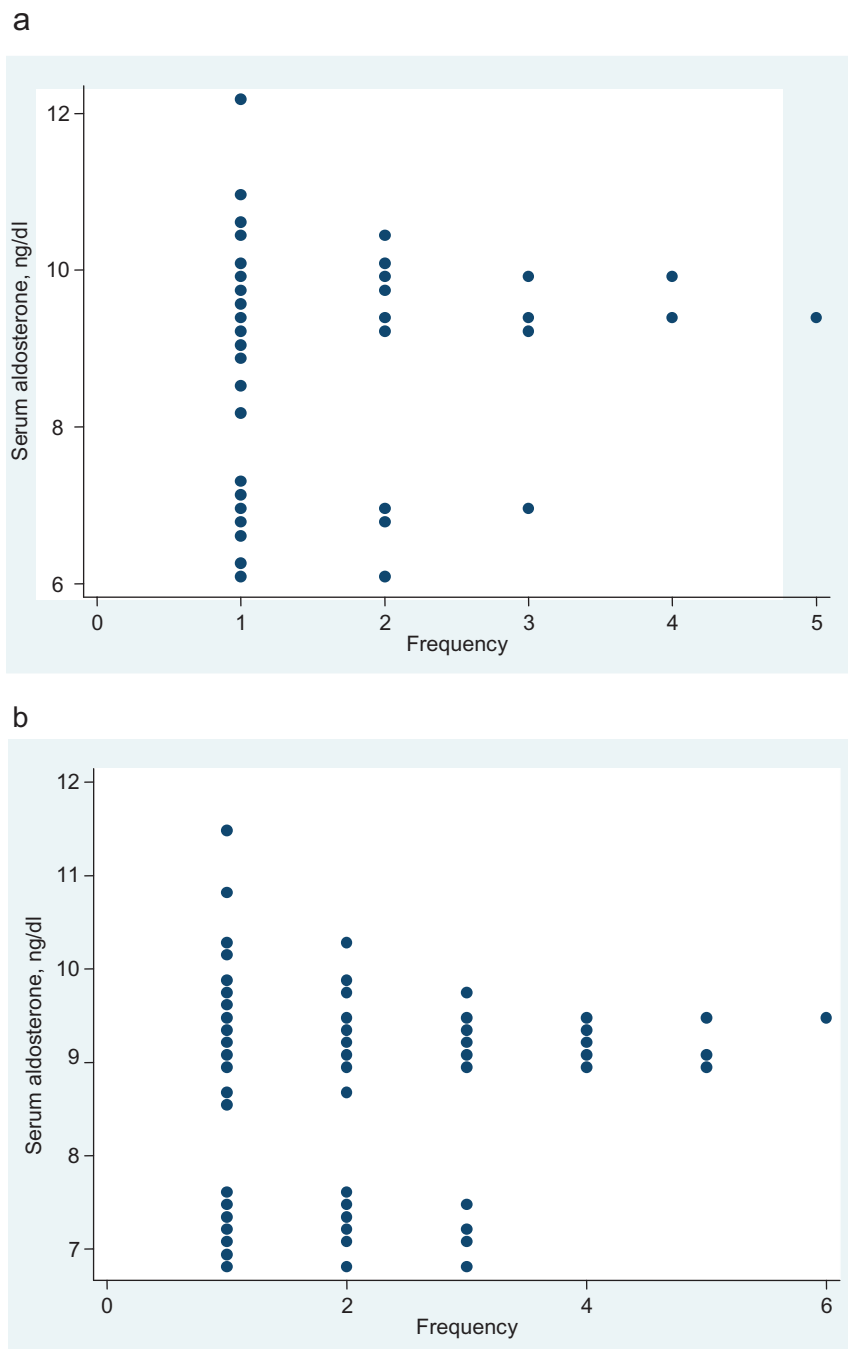
**Figure 4.** Dotplot showing the aldosterone frequency distribution, etc. **(a)** Aldosterone frequency distribution, unadjusted, in 93 subjects with untreated hypertension and plasma renin concentration  $\leq 5$  mU/L. Dip test for unimodality,  $P = 0.11$ . **(b)** Aldosterone frequency distribution, adjusted for age, sex, and urine sodium/creatinine ratio, in the 81 of the 93 subjects with hypertension and plasma renin concentration  $\leq 5$  mU/L, for whom the urine sodium/creatinine ratio was available. Dip test for unimodality,  $P = 0.008$ .

bimodally distributed challenges these notions and is consistent with the idea that a mineralocorticoid other than aldosterone is associated with the lowered aldosterone seen in some cases of LRH.

Studies of the pathophysiology and therapy of LRH frequently consider it to be a single entity, with normal aldosterone levels. Our data suggest that an increase in serum

aldosterone levels in an aldosterone-dependent subset of LRH may be masked by a decrease in aldosterone levels in a non-aldosterone-dependent subset if the aldosterone level is averaged in all individuals with LRH. Future studies of LRH should consider this possibility.

This study has several strengths. The Framingham data are derived from a large, community-based sample that has

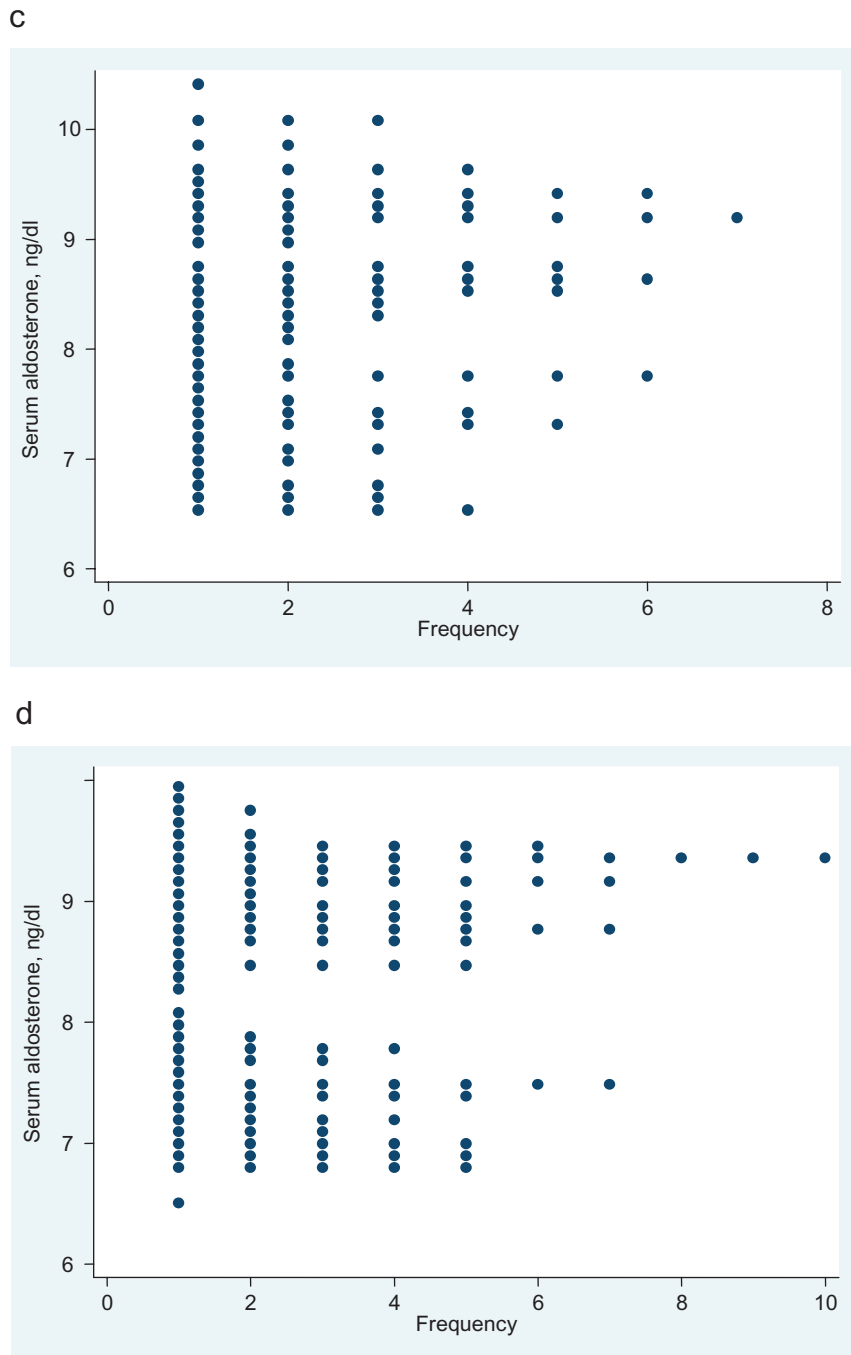


**Figure 5.** Dotplot showing the aldosterone frequency distribution, etc. Aldosterone frequency distribution, adjusted for age, sex, and urine sodium/creatinine ratio. **(a)** Thirty-seven hypertensive subjects with plasma renin concentration  $\leq 3$  mU/L. Dip test for unimodality,  $P = 0.25$ . **(b)** Fifty-five hypertensive subjects with plasma renin concentration  $\leq 4$  mU/L. Dip test for unimodality,  $P = 0.06$ . **(c)** Ninety-six hypertensive subjects with plasma renin concentration  $\leq 6$  mU/L. Dip test for unimodality,  $P = 0.43$ . **(d)** One hundred fifteen hypertensive subjects with plasma renin concentration  $\leq 7$  mU/L. Dip test for unimodality,  $P = 0.06$ . **(e)** One hundred twenty-nine hypertensive subjects with plasma renin concentration  $\leq 8$  mU/L. Dip test for unimodality,  $P = 0.11$ .

been carefully studied under uniform conditions. The numbers were large enough to allow exclusion of many subjects with disorders or taking medications that are known to affect the renin-aldosterone system.

But there are also many limitations. The 2 blood pressure measurements in each participant were obtained on

a single day; the diagnosis of hypertension is therefore much less certain than if the measurements had been obtained on multiple occasions over a period of time. The subjects of the Framingham Heart Study were exclusively white; our findings cannot be extended to nonwhite individuals, especially in view of the many studies that have

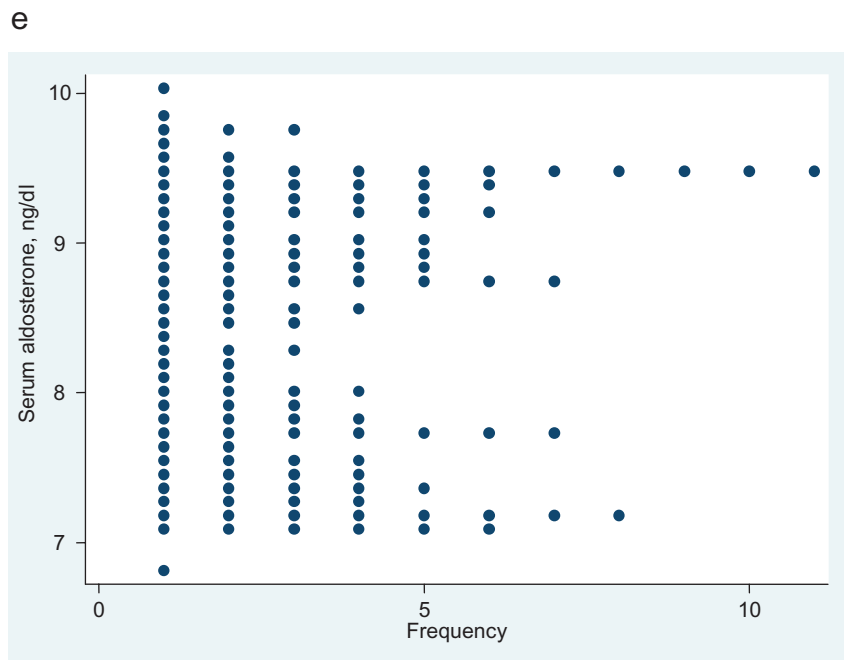


**Figure 5.** (Continued)

showed differences in the prevalence of LRH in black populations. Some disorders that may affect the renin-aldosterone axis, such as Cushing syndrome, hepatic cirrhosis, and nephrotic syndrome could not be excluded because the Framingham data did not identify them. Data on serum and urine potassium levels, which may affect aldosterone, also were not available. LRH is most reliably identified by examining plasma renin levels that have been stimulated by salt restriction or by rapidly acting diuretics,

as well as several hours of upright posture. The renin levels in our study were stimulated only by the upright posture assumed between rising in the morning and the blood drawing between 8 AM and 10 AM; this may have diminished the accuracy of our identification of the LRH cohort. It is likely, however, that these limitations would have biased our findings toward the null hypothesis—that is, would have decreased the likelihood of our finding a bimodal serum aldosterone distribution.





**Figure 5.** (Continued)

These observations, although consistent with the existence of 2 pathophysiologically different variants of LRH, shed no light on the underlying causes of aldosterone-dependent and non-aldosterone-dependent LRH. A prospective study of hormonal and renal factors in an untreated, multiethnic hypertensive population may be needed to further advance our understanding of this common disorder.

#### ACKNOWLEDGMENT

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#### DISCLOSURE

The authors declared no conflict of interest.

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