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ORIGINAL RESEARCH

# Association Between Life's Simple 7 and Biomarkers of Cardiovascular Disease: Aldosterone, Interleukin-6, C-Reactive Protein

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**BACKGROUND:** To promote ideal cardiovascular health, the American Heart Association recommends adhering to Life's Simple 7 (LS7)—achieving healthy targets for body mass index, physical activity, dietary intake, blood pressure, fasting plasma glucose, and cholesterol, along with smoking abstinence. Poorer achievement of LS7 (lower score) has been associated with the development of hypertension and cardiovascular disease. However, less is known about the associations between LS7 and specific biomarkers linked to cardiovascular health: aldosterone, CRP (C-reactive protein), and IL-6 (interleukin-6).

**METHODS AND RESULTS:** We analyzed 379 individuals (age 18–66 years) from the HyperPATH (International Hypertensive Pathotype), who were maintained on ≥200 mEq of sodium daily for 1 week. We calculated a 14-point summative LS7 score according to participants' baseline data. Based on the range of LS7 score in this population (3–14), we classified participants as "inadequate" (3–6), "average" (7–10), and "optimal" (11–14). Regression analyses found that a higher LS7 score group was associated with lower levels of serum and urinary aldosterone ($P_{trend}$<0.001 and $P_{trend}$=0.001, respectively), lower plasma renin activity ($P_{trend}$<0.001), and a blunted increase in serum aldosterone with angiotensin II infusion ($P_{trend}$=0.023). Being in the "optimal" LS7 score group was associated with lower serum CRP ($P_{trend}$=0.001) and IL-6 ($P_{trend}$=0.001).

**CONCLUSIONS:** A higher LS7 score was associated with a lower activity of the renin-angiotensin-aldosterone system and lower levels of the inflammatory markers CRP and IL-6. These findings offer a possible link between ideal cardiovascular health targets and biomarkers known to play a central role in the development of cardiovascular disease.

**Key Words:** aldosterone ■ cardiovascular disease ■ hypertension ■ Life's Simple 7

The development and progression of cardiovascular disease are impacted by both behavioral and biological changes.[1–4] Life's Simple 7 (LS7) are recommendations put forth by the American Heart Association in 2010 for the achievement of better cardiovascular health.[5] The 7 recommendations include smoking abstinence, a healthy body mass index (BMI), a balanced diet, regular physical activity as well as maintaining control of blood pressure, blood sugar, and cholesterol. Since the inception of this framework for considering cardiovascular health, there have been observational studies demonstrating that achievement in a greater number of these recommendations—that is, a higher LS7 score—is associated with lower incidence of cardiovascular disease,[6] incident hypertension,[7,8] and resistant hypertension.[9]

A previous study by Kesireddy et al examined the association between LS7 and serum aldosterone levels.[10] Aldosterone activates the MR (mineralocorticoid

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## CLINICAL PERSPECTIVE

### What Is New?

- In normotensive and hypertensive individuals on controlled sodium diets, better adherence to American Heart Association's Life's Simple 7 recommendations is associated with lower levels of interleukin-6, C-reactive protein, and aldosterone—all mediators of cardiovascular injury.
- Better achievement of Life's Simple 7 is associated with lower activity of the renin-angiotensin-aldosterone system at multiple points—lower plasma renin activity, blunted aldosterone response to infused angiotensin II, and lower serum and urinary aldosterone levels.

### What Are the Clinical Implications?

- Better adherence to the Life's Simple 7 recommendations has a beneficial impact on specific and measurable biomarkers/mediators of inflammation and cardiovascular injury.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **Ang II** | angiotensin II |
| **HyperPATH** | International Hypertensive Pathotype |
| **IL-6** | Interleukin-6 |
| **LS7** | Life's Simple 7 |
| **RAAS** | renin-angiotensin-aldosterone-system |
| **SASSI** | sodium-modulated-aldosterone suppression to stimulation index |

receptor). There is an extensive body of literature linking excess MR activation to cardiovascular disease,[11–14] and multiple clinical trials have shown that MR blockade is efficacious at improving morbidity and mortality in cardiac and renal disease.[15–17]

Using the Jackson Heart Study database, Kesireddy et al found that higher LS7 score was associated with lower serum aldosterone in a Black population.[10] However, the study did not control for dietary sodium intake, which is a key regulator of aldosterone. To better understand the relationship between LS7 and aldosterone, it is important to study the association under controlled dietary sodium. We used the HyperPATH (International Hypertensive Pathotype) consortium database—which consists of a predominantly White population with and without mild hypertension. HyperPATH was designed to study the activity of the renin-angiotensin-aldosterone-system (RAAS). Because dietary sodium intake is a profound regulator of RAAS, individuals were studied on a liberal sodium diet (200 mEq/day of sodium intake for 5–7 days)—when RAAS is suppressed (eg, low serum and urinary aldosterone)—and on a restricted sodium diet (10 mEq/day of sodium intake for 5–7 days)—when RAAS is activated (eg, high serum and urinary aldosterone). Leveraging this unique feature of the data set, in this study, we tested the hypothesis that on a liberal sodium diet, a more ideal cardiovascular health status (higher LS7 score) would be associated with lower aldosterone as compared with those with a less ideal cardiovascular health status (lower LS7 score).

Higher levels of inflammatory biomarkers CRP (C-reactive protein) and IL-6 (interleukin-6) also have been implicated in cardiovascular disease risk.[18–22] Therefore, we also hypothesized that a higher LS7 score would be associated with lower levels of CRP and IL-6.

## METHODS

### HyperPATH Group and Its Protocol

The data that support the findings of this study are available from the corresponding author upon reasonable request. The study included individuals, age 18 to 66 years, who were enrolled as a part of HyperPATH between 1980 and 2011 at 5 international sites: Brigham and Women's Hospital (Boston, Massachusetts), University of Utah Medical Center (Salt Lake City, Utah), Hospital Broussais (Paris, France), Vanderbilt University (Nashville, Tennessee), and University of Virginia (Charlottesville, Virginia; Figure 1). The studies were approved by the institutional review committee and subjects gave informed consent for the deidentified data to be used for future analyses. The protocol for HyperPATH has been previously published in detail.[23,24] In brief, these individuals were previously a part of research protocols investigating the RAAS. Before baseline measurements, there was a 3-month washout period of all direct mediators of RAAS, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, MR antagonists, and a 2-week washout period of calcium-channel blockers, beta-blockers, and diuretic medications. In the HyperPATH protocol, participants were maintained on both liberal sodium diet (200 mEq/day) and restricted sodium diet (10 mEq/day) for at least 5 days each. Participants were admitted to the inpatient clinical research center overnight, where their sodium balance was confirmed with 24-hour urinary sodium collection: >150 mEq sodium/day for the liberal sodium diet and <30 mEq sodium/day for the restricted sodium

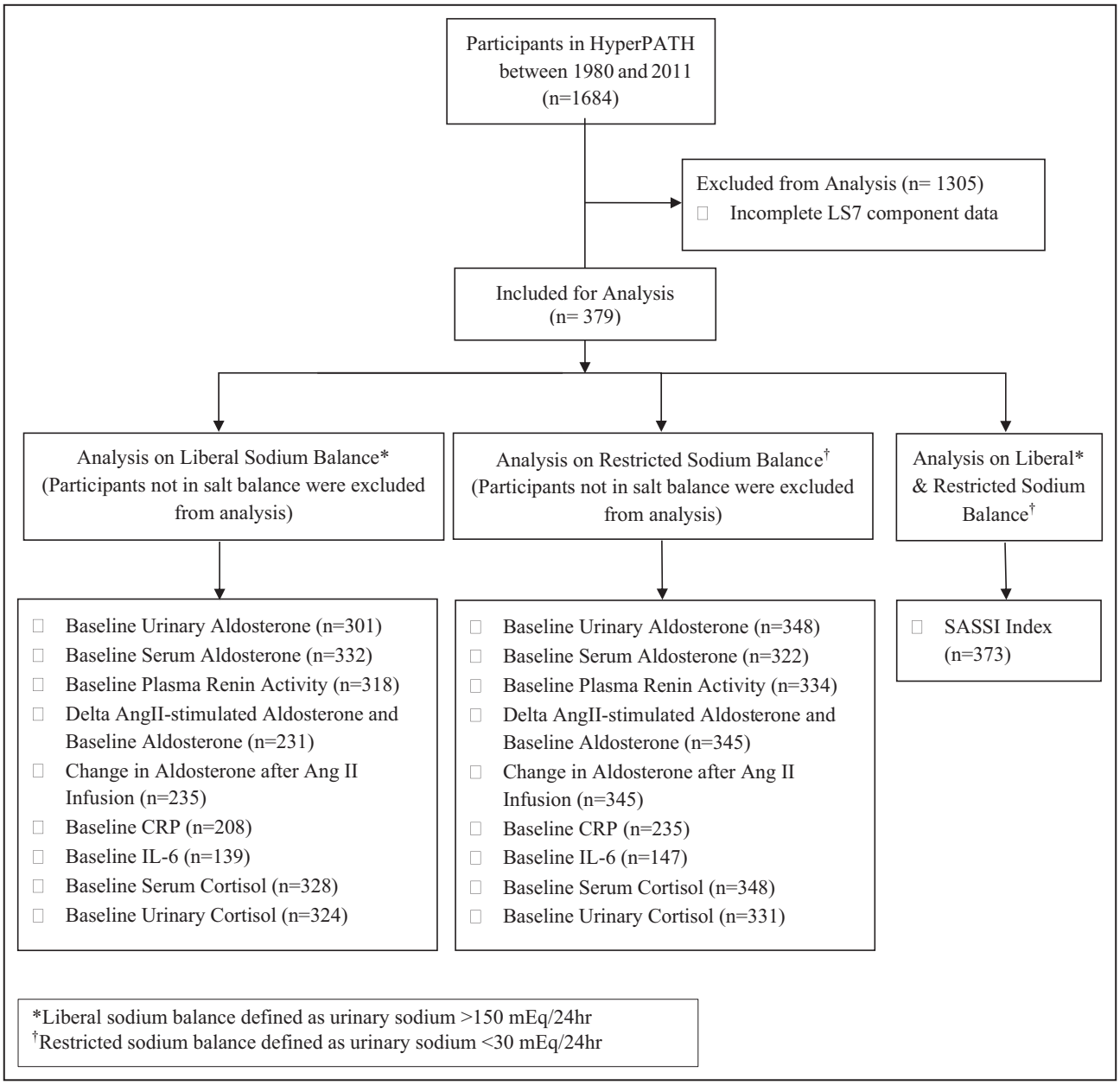


**Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of participants in HyperPATH (International Hypertensive Pathotype) consortium database between 1980 and 2011.**
Individuals with a complete Life's Simple 7 data set were included for analyses. Ang II indicates angiotensin II; CRP, C-reactive protein; IL-6, interleukin-6; and SASSI, sodium-modulated aldosterone suppression-stimulation index.

diet. This analysis included only individuals who were in liberal or restricted sodium balance. Baseline measurements were collected after overnight supine rest, including blood pressure, serum plasma glucose, total cholesterol, serum aldosterone, plasma renin activity, cortisol, CRP, IL-6, and serum electrolytes. Following baseline measurements, participants received an infusion of angiotensin II (Ang II) of 3 ng/kg per minute for 60 minutes, after which vital signs and measurements of serum aldosterone and plasma renin activity were repeated.[24]

## Defining Life's Simple 7

Individuals who did not have complete LS7 data were excluded from analysis. In total, this study included 379 individuals. The definitions of the LS7 variables were adapted from the American Heart Association[5] and categorized as "ideal," "intermediate," or "poor." A numerical value of 2 was assigned for variables that met the criteria for "ideal," 1 was assigned for variables that met the criteria for "intermediate," and 0 was assigned to variables that met criteria for "poor." A summative LS7 score was generated, with

a maximum score of 14. Based on the distribution of the LS7 scores in this population, LS7 summative score categories were designated as inadequate (LS7 score 3–6), average (LS7 score 7–10), and optimal (LS7 score 11–14).

### Blood Pressure

Baseline blood pressure was measured after overnight supine rest at the clinical research centers. Ideal blood pressure was defined as systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg in individuals without hypertension and not on any antihypertensive medications; intermediate blood pressure was defined as systolic blood pressure 120 to 139 mm Hg and diastolic blood pressure 80 to 89 mm Hg or hypertension that was treated to goal; poor blood pressure was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg.

### Fasting Plasma Glucose

Baseline fasting plasma blood glucose was measured after overnight supine fast at the clinical research centers. Ideal plasma glucose was defined as fasting plasma glucose of <100 mg/dL without a history of diabetes and antidiabetic medications, intermediate plasma glucose was defined as 100 to 125 mg/dL or treated to goal; poor was defined as fasting plasma glucose of ≥126 mg/dL.

### Total Cholesterol

Baseline total cholesterol was measured after overnight supine fast at the clinical research centers. Ideal total cholesterol was defined as <200 mg/dL without treatment; intermediate total cholesterol was defined as 200 to 239 mg/dL; a poor total cholesterol was defined as ≥240 mg/dL.

### Smoking

Smoking history was self-reported at screening. Ideal smoking status was defined as a lifetime nonsmoker; intermediate smoking status was defined as former smoker, poor smoking status was defined as current smoker.

### Body Mass Index

BMI was calculated from weight and height at screening. Ideal BMI was defined as <25 kg/m$^2$; intermediate BMI was defined as 25 to 29.9 kg/m$^2$; poor BMI was defined as ≥30 kg/m$^2$.

**Table 1. Baseline Characteristics**

| | Inadequate (LS7 score 3–6) n=95 | Average (LS7 score 7–10) n=238 | Optimal (LS7 score 11–14) n=46 | *P* for trend |
|---|---|---|---|---|
| Demographics | | | | |
| Age, y±SD | 48.3±7.9 | 47.5±9.6 | 43.1±12.6 | 0.015 |
| Female sex, n (%) | 44 (46.3%) | 116 (48.7%) | 23 (50%) | 0.643 |
| Black race, n (%) | 16 (17.2%) | 39 (16.5%) | 4 (8.7%) | 0.340 |
| White race, n (%) | 77 (82.8%) | 190 (79.8%) | 41 (89.1%) | 0.340 |
| Life's Simple 7 components | | | | |
| Smoking score*±SD | 1.2±0.8 | 1.7±0.6 | 1.9±0.2 | <0.001 |
| Exercise score†±SD | 0.5±0.5 | 0.9±0.6 | 1.4±0.6 | <0.001 |
| Salt intake score‡±SD | 0.5±0.6 | 1.1±0.8 | 1.6±0.7 | <0.001 |
| Hypertension, n (%) | 90 (94.7%) | 204 (85.7%) | 27 (58.7%) | <0.001 |
| Systolic blood pressure, mm Hg±SD | 154±21 | 143±20 | 125±19 | <0.001 |
| Diastolic blood pressure, mm Hg±SD | 91±13 | 84±11 | 76±13 | <0.001 |
| Body mass index, kg/m$^2$±SD | 29.8±3.8 | 28.3±4.4 | 23.9±2.4 | <0.001 |
| Diabetes, n (%) | 12 (12.6%) | 9 (3.8%) | 0 (0%) | <0.001 |
| Fasting plasma glucose, mg/dL±SD | 102±19 | 90±11 | 84±11 | <0.001 |
| Total cholesterol, mg/dL±SD | 215±35 | 192±37 | 157±28 | <0.001 |
| On statin, n (%) | 7 (7%) | 20 (8%) | 0 (0%) | 0.633 |

The table summarizes the baseline demographics and Life's Simple 7 (LS7) component variables in the 3 LS7 score categories as the mean (SD) for continuous variables or count (percentage) for categorical variables. *P* for trend was calculated for comparison between the groups.

*Smoking score: 0=current smoker; 1=former smoker; 2=lifetime nonsmoker.

†Exercise score: 0=sedentary; 1=some/moderate exercise level; 2=high exercise level.

‡Salt intake score: 0=little or no effort to control salt; 1=no added salt, avoids salty foods; 2=no added salt, no salty food.

### Physical Activity

Physical activity level was self-reported at screening. Ideal physical activity was defined as a self-reported "high" level of exercise; intermediate physical activity was defined as a self-reported "moderate" or "mild" exercise; poor physical activity was defined as a self-reported "sedentary" lifestyle.

### Diet Score

Comprehensive dietary history was not available for the HyperPATH individuals. A self-reported measurement of salt intake was used as a surrogate. Ideal diet was defined as a self-reported salt intake of "no added salt"; intermediate diet was defined as a self-reported salt intake of "minimal salt"; poor diet was defined as a self-reported salt intake of "no salt limit."

## Statistical Analysis

All statistical analysis was performed using Stata Statistical Software: Release 15 (StataCorp LLC, College Station, TX). Primary analysis included individuals with complete LS7 data and who were in sodium balance. Skewness Kurtosis test was performed on all dependent variables to test for normality. The data presented in Tables 1 and 2 include the mean and SDs for each continuous variable, and the number and percentage of individuals within each group for the categorical variables. *P* for trend was calculated using "nptrend" in Stata, which tests for trend across ordered groups. Trends were defined by the differences across 3 LS7 score categories. The main analysis included multivariable linear regression analyses to analyze the relationship between LS7 score categories and biomarker levels, while controlling for covariates of age, self-identified sex, self-identified race, serum creatinine, and study site (Boston, Massachusetts; Salt Lake City, Utah; Paris, France; Nashville, Tennessee; Charlottesville, Virginia). Covariates were selected a priori and treated as fixed effects. Linear regression analyses were performed for normally distributed continuous variables and logarithmically transformed nonnormally distributed variables. For Figure 2, the Wilcoxon rank-sum test was used to compare the distribution of LS7 scores between male versus female individuals and between White versus Black individuals. Statistical significance was indicated by 2-sided *P* value of <0.05.

# RESULTS

## Study Population

In total, 379 individuals had complete LS7 data in the HyperPATH database (1980–2011) and were included in the analysis: 95 in the inadequate score

**Table 2. Summary of Measurements of Aldosterone and RAAS in the Total Population and After Excluding Primary Aldosteronism**

| | Total population | | | | Excluding primary aldosteronism | | | |
|---|---|---|---|---|---|---|---|---|
| | Inadequate (N=95) | Average (N=238) | Optimal (N=46) | *P* for trend | Inadequate (N=91) | Average (N=234) | Optimal (N=46) | *P* for trend |
| Serum aldosterone, ng/dL | 6.25 (6.25) | 4.74 (3.16) | 3.68 (2.10) | <0.001 | 5.07 (3.0) | 4.43 (2.54) | 3.68 (2.09) | 0.008 |
| Urinary aldosterone, mcg/24 h | 13.87 (9.05) | 10.95 (7.1) | 8.64 (4.27) | <0.001 | 12.37 (7.32) | 10.64 (6.89) | 8.64 (4.27) | 0.002 |
| Plasma renin activity, ng/mL per h | 0.62 (0.55) | 0.47 (0.48) | 0.32 (0.29) | 0.001 | 0.57 (0.48) | 0.47 (0.48) | 0.32 (0.29) | 0.004 |
| Change in aldosterone after angiotensin II infusion, ng/dL | 8.79 (5.28) | 8.91 (6.44) | 6.32 (4.27) | 0.018 | 8.49 (5.05) | 8.91 (6.46) | 6.32 (4.72) | 0.029 |
| Sodium-modulated aldosterone suppression-stimulation index score | 0.48 (0.49) | 0.36 (0.28) | 0.29 (0.20) | 0.007 | 0.43 (0.46) | 0.35 (0.26) | 0.29 (0.20) | 0.044 |

Summary of outcome variables are presented as the mean (SD). *P* for trend was calculated between the 3 groups both in the total population and after excluding individuals who met criteria for primary aldosteronism.
RAAS indicates renin-angiotensin-aldosterone system.

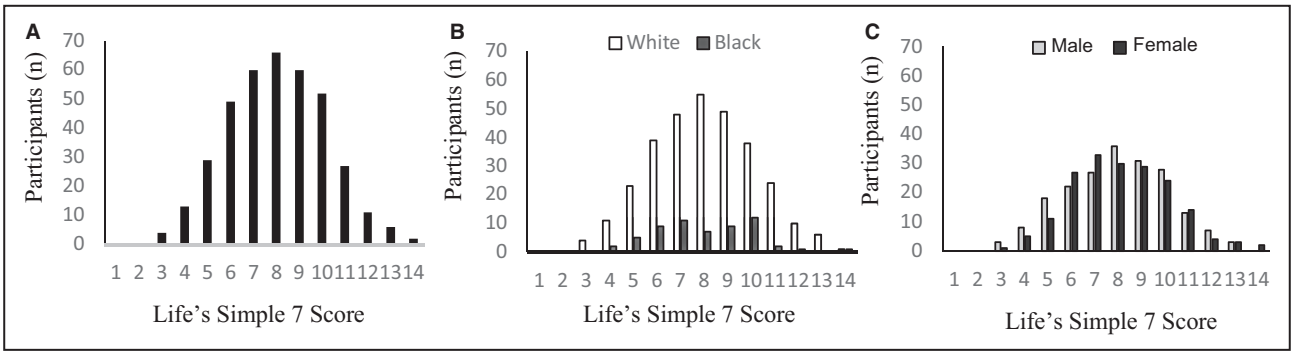


**Figure 2. Distribution of LS7 score.**
**A**, Distribution of LS7 score in overall study population (mean 8.03±2.14). **B**, Distribution of LS7 sScore in White (mean 8.04±2.17) and Black (mean 7.95±2.08) participants (*P*=0.3402). **C**, Distribution of LS7 score in male (mean 7.98±2.18) and female (mean 8.09±2.10) participants (*P*=0.6430). The Wilcoxon rank-sum test was used to compare the distribution of LS7 scores between groups. LS7 indicates Life's Simple 7.

category, 238 in the average score category, and 46 in the optimal score category (Table 1). The percentage of individuals who were women, as well as those who were White or Black, did not significantly differ between the score categories. The mean age of the participants in the optimal LS7 score category was 43.1 years old compared with 47.5 in the average LS7 score category and 48.3 in the inadequate LS7 score category.

The LS7 scores were normally distributed, ranging from 3 to 14, with a mean of 8.03±2.14 in the overall population (Figure 2). There were no significant differences in the distribution of LS7 scores in the White participants (mean 8.04±2.17) versus Black participants (mean 7.95±2.08; *P*=0.6237) or in the men (mean 7.98±2.18) versus women (mean 8.09±2.10; *P*=0.7537).

## Liberal Sodium Diet

### *Aldosterone*

When on a liberal sodium diet (24-hour urinary sodium >150 mEq/L per 24 hours), individuals in the optimal LS7 score category had a significantly lower serum aldosterone as compared with the average LS7 score category (*P*=0.048) and inadequate score category (*P*=0.031; Figure 3). Similarly, those in the optimal LS7 score category had significantly lower urinary aldosterone (*P*=0.006) as well as lower plasma renin activity (*P*=0.007) as compared with those in the inadequate LS7 score category. Notably, there were no significant differences in 24-hour urinary sodium (Figure 3), or serum cortisol, serum creatinine, or serum potassium between the 3 score categories (Table S1).

When on a liberal sodium diet, individuals in the optimal LS7 score category had a blunted increase in aldosterone with Ang II infusion (Ang II-stimulated aldosterone minus baseline aldosterone) as compared with the average and inadequate LS7 score categories (*P*=0.005 and *P*=0.031, respectively; Figure 4).

Ideally, aldosterone is increased on a low sodium diet and decreased on a liberal sodium diet. The ability to modulate aldosterone is captured by a lower sodium-modulated-aldosterone suppression to stimulation index (SASSI), which is the serum aldosterone on a liberal sodium diet divided by serum aldosterone on a restricted sodium diet.[25] Our analysis showed that a higher LS7 score category was associated with a lower SASSI score (Figure 4): the optimal LS7 score group had a significantly lower SASSI score than the inadequate group (*P*=0.005); the average LS7 score group had a significantly lower SASSI score than the inadequate group (*P*=0.008).

In a secondary analysis, we analyzed individuals for evidence of autonomous aldosterone production. There were 8 individuals who met criteria for primary aldosteronism (serum aldosterone ≥15 ng/dL with suppressed plasma renin activity ≤1.0 when on a liberal sodium diet with urinary sodium >150 mEq/L per 24 hours): 4 individuals were in the inadequate LS7 score category, and 4 individuals were in the average LS7 score category; there were no individuals who met criteria for primary aldosteronism in the optimal LS7 score category. Removing these 8 individuals from the data analysis did not change the results of the association between better LS7 score category and lower aldosterone levels (Table 2).

### *CRP and Il-6*

Beyond aldosterone levels, we also found that a higher LS7 score category was associated with lower levels of inflammatory markers of CRP (*P*=0.001). In addition, those in the optimal LS7 score category had lower IL-6 levels when compared with those in the average LS7 score category (*P*=0.026; Figure 5).

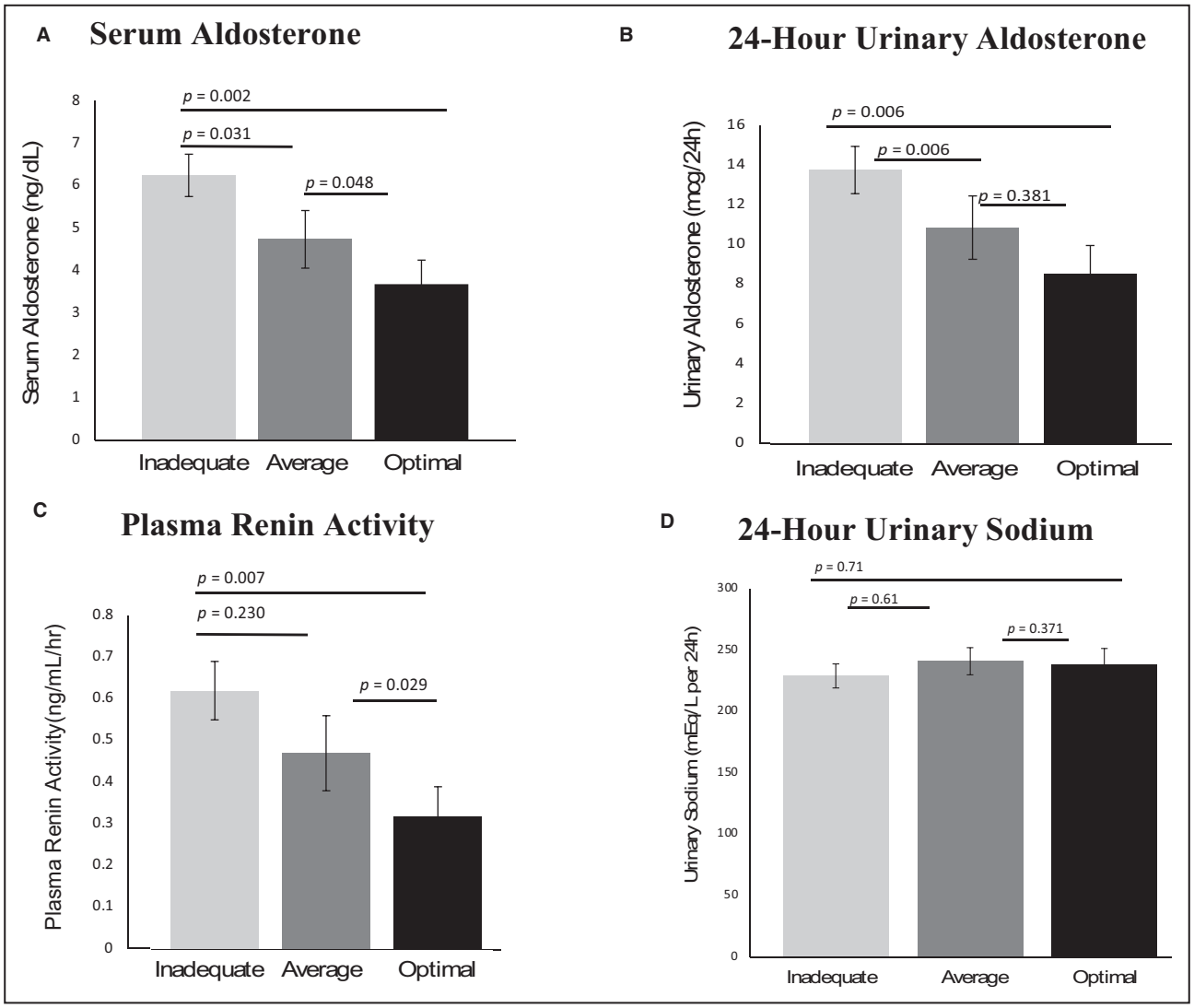


**Figure 3. The association of LS7 score category and serum aldosterone (*P*-trend<0.001) (A), urinary aldosterone (*P*-trend=0.001) (B), plasma renin activity (*P*-trend<0.001) (C), 24-hour urinary sodium (*P*-trend=0.202) (D) on a liberal sodium diet.**
LS7 indicates Life's Simple 7.

## Restricted Sodium Diet

For participants on the restricted sodium diet, we did not find significant differences in the association between LS7 score categories and serum or urinary aldosterone, plasma renin activity, change in aldosterone after Ang II stimulation, or CRP (Table S1). We did see that the optimal LS7 score category was associated with lower IL-6 as compared with the inadequate LS7 score category (*P*=0.017) and the average LS7 score category (*P*=0.026).

# DISCUSSION

Our study found significant associations between a more ideal cardiovascular health status (higher LS7 score category) and lower levels of serum and urinary aldosterone, lower plasma renin activity, lower change in aldosterone after Ang II stimulation, and lower levels of CRP and IL-6 while on a controlled liberal sodium diet. The association between a higher LS7 score and lower serum aldosterone in our study is consistent with the findings by Kesireddy et al in a Black population.[10] We have now demonstrated these results in a predominantly White population. Additionally, given the controlled dietary sodium, we found that these results were not driven by alterations in sodium balance within the study population. Thus, on a liberal sodium diet, maintaining better cardiovascular health is associated with lower levels of IL-6, CRP, and aldosterone—known mediators of cardiovascular disease. Of note, in a forward stepwise regression analysis, we found that it was not one component variable of the LS7 score

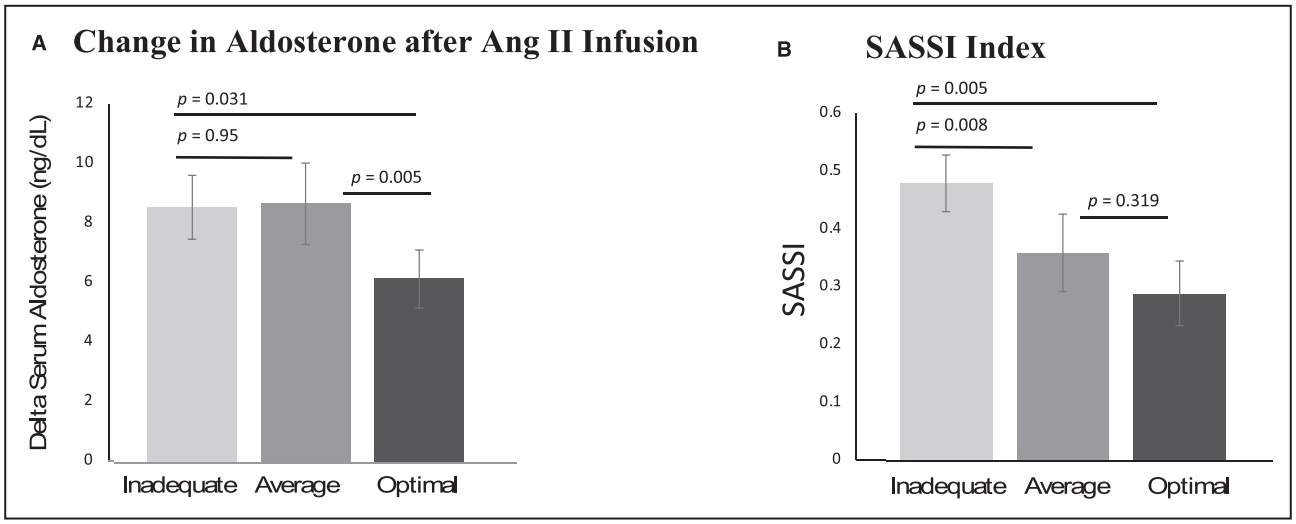


**Figure 4. The association of LS7 score category and the change in aldosterone after angiotensin II (Ang II) infusion (*P*-trend=0.023) (A), and sodium-modulated aldosterone suppression-to-stimulation (SASSI) index (*P*-trend=0.022) (B) on a liberal sodium diet.**
LS7 indicates Life's Simple 7.

that was responsible for the significant differences in the dependent variables between the LS7 score categories (Table S2).

The differences in aldosterone appear to be driven by a downregulation of RAAS with the lowest plasma renin activity in the optimal LS7 score category. Interestingly, although one could have hypothesized that a lower plasma renin activity would lead to lower circulating Ang II levels, and an upregulation of Ang II receptor 1 activity, and thus, an increased aldosterone response to Ang II infusion—we found the opposite was true. Those in the optimal LS7 score category had a blunted aldosterone response to Ang II infusion on a liberal sodium diet. We demonstrated that the differences in aldosterone responsiveness were not attributable to differences in urinary sodium, serum potassium or adrenocorticotropic hormone/cortisol axis activity, which were similar across the 3 LS7 score categories. We exonerated primary aldosteronism as a driver of the differences between the score categories by performing a secondary analysis in which we removed the 8 individuals with primary aldosteronism.

For normal physiology, it is important to be able to increase aldosterone on a low sodium diet and decrease aldosterone on a high sodium diet. Vaidya et al defined the SASSI as the serum aldosterone on

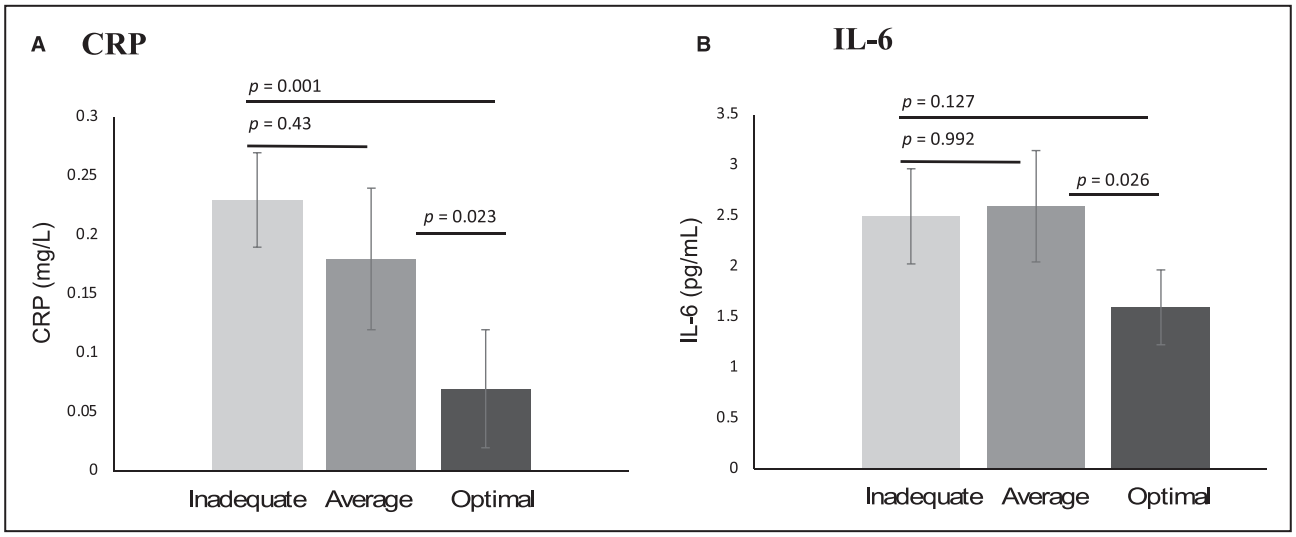


**Figure 5. The association of LS7 score category and C-reactive protein; *P*-trend=0.001) (A), and Interleukin-6 (*P*-trend=0.001) (B) on liberal sodium diet.**
CRP indicates C-reactive protein; IL-6, interleukin-6; and LS7, Life's Simple 7.

a liberal sodium diet divided by serum aldosterone on a restricted sodium diet, with lower SASSI score reflecting more optimal RAAS responsiveness to dietary sodium. In our study, we found that those with a higher LS7 score category had a lower SASSI score suggesting that those with more ideal cardiovascular health are better able to turn off aldosterone on a liberal sodium diet and turn on aldosterone on a restricted sodium diet. This is consistent with the concept that a lower SASSI score is associated with better cardiovascular health. In a cross-sectional analysis of individuals with and without mild hypertension, a lower SASSI score was associated with a smaller number of metabolic syndrome components.[25]

Our findings suggest that greater achievement of LS7 is associated with lower aldosterone levels and a blunted response to Ang II, which are known mediators of cardiovascular disease. It is unclear if the blunted response to Ang II is limited to the adrenal gland. Interestingly, the systolic blood pressure in response to Ang II was not significantly different between the 3 LS7 score categories, suggesting the differences in Ang II responsiveness may not extend to vascular reactivity.

In addition, we found that higher LS7 score was associated with lower levels of IL-6 and CRP, which are mediators of inflammation and cardiovascular injury. Although the mean levels of CRP and IL-6 in all 3 LS7 score categories were within the normal reference range, it is unknown how chronically higher levels of inflammatory makers could affect cardiovascular health.

Lower IL-6 levels were found in the optimal LS7 score category in individuals on both restricted and liberal sodium diets. In contrast, CRP and aldosterone levels were significantly lower in the optimal LS7 score category on the liberal sodium diets, but the levels were similar in the 3 LS7 score categories on the restricted sodium diet. Because the majority of the US population consume a liberal sodium diet under normal conditions,[26] the finding of lower aldosterone, CRP, and IL-6 on the liberal sodium diet is clinically relevant. High sodium intake has been associated with hypertension and increased cardiovascular disease risk.[27,28] The observation that when dietary sodium is restricted, aldosterone and other inflammatory marker levels in the inadequate LS7 score group are not significantly higher than the levels in the optimal LS7 score group suggests that limiting sodium intake could be a potential opportunity for intervention.

There are limitations to the findings of this study. In defining the behavioral LS7 variables (smoking, diet, and exercise), we relied on self-reported data, which are susceptible to bias. In addition, we did not have the full dietary history of the participants. Instead, we used a self-reported average sodium intake measurement as a surrogate variable. The population included in the analyses was predominately White and generally healthy individuals, with and without mild hypertension. Therefore, the results may not be readily extrapolated to the general population. Although the HyperPATH database includes both White and Black individuals, there were not enough Black individuals to perform a subanalysis among Black individuals alone. However, when the analyses were repeated in only the White individuals, our results were maintained indicating that the results were not driven by the Black individuals. Finally, because this is a cross-sectional study, we do not know whether improving LS7 score categories would also improve levels of aldosterone, CRP, and IL-6. Also of note, the American Heart Association recently put forth updated guidelines for cardiovascular health achievement, which now includes an eighth variable of sleep.[29] Because the HyperPATH database did not capture sleep data, we did not include this as a part of our analyses.

## CONCLUSIONS

The findings of this study—higher LS7 achievement is associated with lower levels of aldosterone, IL-6, and CRP—may help to explain the findings of previous studies showing an association between greater LS7 achievement and lower cardiovascular disease risk.[30]

It is known that overactivation of RAAS and increased inflammation contribute to cardiovascular disease. Therefore, a greater understanding of the mechanisms that allow a downregulation of these systems could lead to better biological and behavioral targets that improve cardiovascular health.

## ARTICLE INFORMATION

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### Disclosures

None.

## Supplemental Material

Tables S1–S2

## REFERENCES


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# SUPPLEMENTAL MATERIAL

**Table S1. Analysis of mean difference between LS7 score categories and outcome variables while in restricted sodium balance.**

| | Mean Difference (95% CI) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Continuous** | p-value | **Average vs. Inadequate** | p-value | **Optimal vs. Inadequate** | p-value | **Optimal vs. Average** | p-value |
| **Urinary Aldosterone (mcg/24hr)** | 4.4 (-1.1, 9.0) | 0.113 | 5.2 (-2.9, 13.3) | 0.211 | 8.6 (-2.5, 19.8) | 0.127 | 3.5 (-6.0, 12.9) | 0.473 |
| **Serum Aldosterone (ng/dL)** | -1.6 (-3.6, 0.3) | 0.098 | -0.8 (-3.6, 2.1) | 0.596 | -3.5 (-7.4, 0.4) | 0.080 | -2.7 (-6.0, 0.6) | 0.107 |
| **Plasma Renin Activity (ng/mL/hr)** | -0.4 (-0.9, 0.5) | 0.078 | -0.4 (-1.1, 0.3) | 0.285 | -0.9 (-1.9, 0.1) | 0.078 | -0.5 (-1.3, 0.3) | 0.250 |
| **Change in Aldosterone after AngII-Infusion (ng/dL)** | -0.9 (-3.5, 1.8) | 0.522 | -1.1 (-5.1, 2.9) | 0.599 | -1.7 (-7.2, 3.8) | 0.539 | -0.6 (-5.3, 4.0) | 0.788 |
| **CRP (mg/dL)** | -0.01 (-0.1, 0.1) | 0.769 | -0.05 (-0.2, 0.1) | 0.445 | -0.01 (-0.2, 0.2) | 0.885 | 0.04 (-0.1, 0.2) | 0.641 |
| **IL-6 (pg/mL)** | -0.6 (-1.2, -0.1) | 0.017 | -1.0 (-1.9, -0.1) | 0.026 | -1.4 (-2.4, -0.3) | 0.012 | -0.4 (-1.1, 0.4) | 0.337 |
| **Urinary Cortisol (mcg/hr)** | -0.2 (-7.3, 6.8) | 0.952 | -6.3 (-16.7, 4.0) | 0.231 | 1.2 (-13.0, 15.4) | 0.873 | 7.5 (-5.5, 19.4) | 0.217 |

Analysis of mean difference between Life's Simple 7 (LS7) score categories and measurements of aldosterone, plasma renin activity, change in aldosterone after angiotensin II (AngII) infusion, c-reactive protein (CRP), interleukin-6 (IL-6) and urinary cortisol while in restricted sodium balance (urinary sodium <30 mEq/24hr).

**Table S2. Analysis of the effect of component LS7 and demographic variables on measurements of aldosterone and RAAS.**

| | Serum Aldosterone | 24-Hour Urinary Aldosterone | Plasma Renin Activity | Delta Aldo | SASSI | CRP | IL-6 |
|---|---|---|---|---|---|---|---|
| **Smoking** | 0.636 | 0.295 | 0.544 | 0.477 | 0.581 | 0.001 | <0.001 |
| **Exercise** | 0.009 | 0.001 | 0.009 | 0.288 | 0.414 | 0.75 | 0.007 |
| **Diet** | 0.681 | 0.904 | 0.532 | 0.375 | 0.519 | 0.016 | 0.351 |
| **BMI** | 0.736 | 0.808 | 0.412 | 0.018 | 0.172 | 0.001 | 0.947 |
| **Cholesterol** | 0.93 | 0.862 | 0.163 | 0.959 | 0.4 | 0.707 | 0.505 |
| **Blood Pressure** | <0.001 | <0.001 | 0.006 | 0.096 | 0.047 | 0.912 | 0.434 |
| **Blood Glucose** | 0.4 | 0.829 | 0.977 | 0.86 | 0.335 | 0.944 | 0.388 |
| **Sex** | 0.16 | 0.279 | 0.779 | 0.002 | <0.001 | 0.083 | 0.038 |
| **Race** | 0.144 | 0.958 | 0.002 | 0.004 | 0.051 | 0.199 | 0.454 |
| **Age** | 0.103 | 0.277 | <0.001 | 0.225 | 0.016 | 0.023 | 0.016 |

Forward stepwise regression analyses of each of the seven component variables of Life's Simple 7 (LS7)—along with sex, race, age—and dependent variables in liberal sodium balance show that there is not one single component variable of the LS7 score that is responsible for the differences seen between the LS7 score categories. RAAS = renin-angiotensin-aldosterone-system; Delta Aldo = Angiotensin II-stimulated aldosterone minus baseline serum aldosterone; SASSI = sodium-modulated aldosterone suppression-stimulation index for serum aldosterone; CRP = C-reactive protein; IL-6 = interleukin-6.