ISSN 2472-1972

# Fatty Liver Disease, Women, and Aldosterone: Finding a Link in the Jackson Heart Study

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**Context:** Fatty liver disease is one of the most common forms of chronic liver disease. The renin-angiotensin-aldosterone system has been implicated in the pathogenesis of fatty liver.

**Objective:** Determine the relationship between fatty liver and aldosterone in a large cohort study.

**Design:** Community-based, observational cohort study of African Americans.

**Setting:** The original Jackson Heart Study cohort enrolled African American participants from the Jackson, Mississippi, metropolitan area in Hinds, Madison, and Rankin Counties.

**Participants:** Our study population consisted of 2507 Jackson Heart Study participants (1625 women and 882 men) who had liver attenuation measured per computed tomography scans, had aldosterone measurements, and were not taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or mineralocorticoid receptor antagonists.

**Intervention:** There was no intervention.

**Main outcome measure:** Liver attenuation on computed tomography scans.

**Results:** Univariate regression analysis demonstrated a statistically significant correlation between aldosterone levels and liver attenuation. Each doubling of aldosterone was associated with 1.08 Hounsfield unit decrease (95% confidence interval, 1.47 to −0.69, $P < 0.001$). A multivariable model adjusted for body mass index, age, alcohol intake, and homeostatic model assessment of insulin resistance determined that the association was statistically significant only for women.

**Conclusion:** Our data demonstrate a positive association between aldosterone levels and fatty liver in African American women.



**Freeform/Key Words:** aldosterone, fatty liver, women

Hepatic steatosis or fatty liver is one of the most common forms of chronic liver disease throughout the world (1). Fatty liver is most commonly linked to alcohol intake, and in the setting of nonalcoholic fatty liver disease, it is closely associated with obesity, type 2 diabetes mellitus, and hypertension. The current standard of care for the treatment of patients with

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; HU, Hounsfield unit; JHS, Jackson Heart Study; LA, liver attenuation; RAAS, renin-angiotensin-aldosterone system; VAT, visceral adipose tissue.

Received 17 January 2017
Accepted 17 March 2017
First Published Online 22 March 2017

fatty liver focuses on the underlying etiology. In the case of nonalcoholic fatty liver disease, therapy is focused on lifestyle interventions, particularly diet and exercise, whereas pharmacologic therapeutic options are limited (2).

Activation of the renin-angiotensin-aldosterone system (RAAS) has been implicated in the pathogenesis of fatty liver disease and is thought to play a role in liver fibrosis (3). Animal studies have demonstrated that RAAS blockade can prevent hepatic stellate activation, thereby preventing hepatic inflammation and fibrogenesis (4, 5). There is also evidence of crosstalk between RAAS and insulin signaling (6). Insulin signaling plays a central role in nonalcoholic fatty liver disease, and RAAS activation has been demonstrated to worsen insulin resistance (7). Thus, RAAS blockers are being explored as therapeutic options for fatty liver disease. Some randomized controlled trials have already shown some promising effect, but overall the results are conflicting (8).

Although multiple studies have looked at RAAS suppression in fatty liver, there are limited data regarding the association between RAAS and fatty liver in large cohort studies. A better delineation of the interrelationship between RAAS and fatty liver could further our understanding on the potential therapeutic role of the RAAS blockade. To help narrow this gap, we investigated the association of serum aldosterone concentration with fatty liver in the Jackson Heart Study (JHS), a large community-based observational study of African Americans.

## 1. Methods

### *A. Study Sample*

The original JHS cohort enrolled participants from September 2000 to March 2004 and includes 5306 participants between the ages of 21 and 95 years with a mean age of 55 years. Participants were recruited from the Jackson, Mississippi, metropolitan area in Hinds, Madison, and Rankin Counties. Serum aldosterone was measured in the participants in the exam 1 cohort. As part of the second JHS examination (JHS exam 2), a subset of participants underwent multidetector computed tomography (CT) scanning from 2007 to 2010.

A total of 2940 participants from JHS had liver attenuation data (Hounsfield unit, HU). Of this group, participants with aldosterone data available and who were not taking medications affecting RAAS (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists) were included for further analysis (total of 2507 participants). A comparison of the baseline characteristics of the study sample and the remaining JHS cohort is shown in Supplemental Table 1. Overall, the study sample was more insulin sensitive and with a lower prevalence of type 2 diabetes mellitus.

The study protocol was approved by the institutional review board of the participating institutions: the University of Mississippi Medical Center, Jackson State University, and Tugaloo College. All of the participants provided informed consent.

### A-1. Multidetector CT scan protocol for measuring adiposity

The research CT protocol included the heart and lower abdomen using a 16-channel multidetector CT system (Lightspeed 16 Pro; GE Healthcare, Milwaukee, WI). Quality control and image analysis were performed at a core reading center (Wake Forest University School of Medicine, Winston-Salem, NC). The acquired abdominal imaging slices covering the lower abdomen from L3 to S1 were used to quantify visceral adipose tissue (VAT) and subcutaneous adipose tissue. Briefly, 24 contiguous 2.5-mm-thick slices centered on the lumbar disk space at L4 to L5 were used for this analysis; 12 images before the center of the L4 to L5 disk space and 12 images after the disk space were used for quantification of VAT and subcutaneous adipose tissue. The abdominal muscular wall was first manually traced, and the adipose tissue volumes in different compartments were measured by a semiautomatic segmentation technique. Volume Analysis software (Advantage Windows; GE Healthcare) was used to segment and characterize each individual voxel as a tissue attenuation of fat using a

threshold range of −190 to −30 HUs. The VAT volumes were the sum of VAT voxels over 24 slices located within the intra-abdominal cavity. A CT scan was also used to measure fat infiltration in the liver (9). Measurement of liver attenuation (LA) in HUs was performed in the right lobe of the liver of CT scans of the abdomen at the level of the T12 to L1 intervertebral space and was used to quantify fat deposit in the liver. As the amount of liver fat increases, the measured LA decreases based on the HU scale in which fat has negative values. The LA was determined by calculating the mean HUs of three circular regions of interest measuring 100 $mm^2$ in the parenchyma of the right lobe of the liver as previously described (10).

### *B. Laboratory Measurements*

All laboratory measurements were done during exam 1. Venous blood samples were drawn from each participant at baseline examination after at least 8 hours of fasting. Vials of serum were stored at the JHS central repository in Minneapolis, Minnesota, at −80°C until assayed. C-reactive protein (CRP) was measured using immunoturbidimetric CRP-latex assay from Kamiya Biomedical Company (Seattle, WA) following manufacturer's high-sensitivity protocol. The interassay coefficients of variation of control samples, which were repeated in each assay, were 4.5% and 4.4% at CRP concentrations of 0.45 and 1.56 mg/L, respectively. The reliability coefficient for masked quality-control replicates was 0.95 for the CRP assay. Serum aldosterone was measured by radioimmunoassay (Siemens, Malvern, PA). The intra-assay coefficients of variation for aldosterone were 8.7% and 6.2% for low and high aldosterone concentrations, respectively.

HOMA-IR stands for homeostatic model assessment of insulin resistance and is used as an estimate of insulin resistance. This was calculated by multiplying fasting plasma insulin by fasting plasma glucose, then dividing by the constant 22.5: HOMA-IR = (fasting plasma insulin × fasting plasma glucose)/22.5 (11).

### *C. Statistical Analysis*

Univariate regression analysis was performed to investigate the cross-temporal association between LA and several factors, including serum aldosterone concentration, high-sensitivity CRP (hs-CRP), and HOMA-IR. A multivariable model was constructed to investigate the persistence of these independent relationships with LA. Furthermore, stratified models were used to check for the presence of sex-specific differences. Stata version 14 (StataCorp LP, College Station, TX) was used to perform all analyses.

## 2. Results

### *A. Study Participants and Baseline Characteristics*

Of the 2507 JHS participants included in the study, 1625 were women and 882 were men (Table 1). Overall, this was a middle age, obese population [mean age of 54.67 years and body mass index (BMI) of 30.17 $kg/m^2$]. Only 15% of this population had a diagnosis of diabetes, whereas almost half (48%) carried a diagnosis of hypertension. The men in the sample had a statistically significant lower BMI compared with women (28.52 vs 31.45 $kg/m^2$, $P < 0.001$). As has been previously described, men had higher VAT volume and lower subcutaneous adipose tissue. Men also had statistically significant lower leptin (7.8 vs 32.7 ng/mL, $P < 0.001$). In concordance with the BMI differences, women had a higher HOMA-IR (3.03 vs 2.71, $P < 0.001$). Despite the differences in body composition and HOMA-IR, there were no statistically significant differences in diabetes prevalence. Men had a statistically significant higher diastolic blood pressure but received less treatment for blood pressure compared with women. Men had a statistically significant higher alcohol intake compared with women (3.2 vs 0.67 alcoholic drinks per week). We also observed statistically significant higher aldosterone levels in men compared with women (4.0 vs 4.8 ng/dL, $P < 0.001$).

**Table 1. Baseline Characteristics of JHS Participants**

| Characteristic | Overall (n = 2507) | Women (n = 1625) | Men (n = 882) | *P* Value |
|---|---|---|---|---|
| Age (y) | 54.67 (10.96) | 55.22 (10.98) | 53.66 (10.87) | 0.001 |
| BMI (kg/m$^2$) | 30.17 [7.98] | 31.45 [8.78] | 28.52 [5.87] | <0.001 |
| Average number of alcoholic drinks per week | 1.56 (5.47) | 0.67 (3.25) | 3.20 (7.86) | <0.001 |
| Leptin (ng/mL) | 22.60 [28.20] | 32.70 [23.20] | 7.80 [8.30] | <0.001 |
| VAT (cm$^3$)[a] | 810.27 (372.40) | 784.74 (351.00) | 856.88 (404.67) | <0.001 |
| Subcutaneous adipose tissue (cm$^3$)[a] | 2307.92 (1015.25) | 2641.11 (958.97) | 1699.67 (813.35) | <0.001 |
| Fasting total cholesterol (mg/dL) | 200.98 (39.20) | 202.63 (39.24) | 197.89 (38.95) | 0.005 |
| Fasting LDL cholesterol level (mg/dL) | 128.41 (36.63) | 127.47 (36.89) | 130.18 (36.09) | 0.089 |
| Fasting HDL cholesterol level (mg/dL) | 52.18 (14.49) | 55.50 (14.66) | 45.98 (11.93) | <0.001 |
| Fasting triglyceride level (mg/dL) | 89.00 [58.00] | 87.00 [56.00] | 94.00 [64.00] | 0.001 |
| Diabetes (yes/no), n (%) | 369 (15) | 244 (15) | 125 (14) | 0.541 |
| Fasting insulin (plasma IU/mL) | 14.00 [10.00] | 15.00 [10.00] | 13.00 [9.00] | <0.001 |
| Fasting plasma glucose level (mg/dL) | 96.42 (25.84) | 95.89 (25.75) | 97.42 (25.99) | 0.171 |
| NGSP hemoglobin HbA1c (%) | 5.60 [0.70] | 5.60 [0.70] | 5.60 [0.70] | 0.839 |
| Diabetic medication status (yes/no), n (%) | 192 (8) | 135 (9) | 57 (7) | 0.167 |
| HOMA IR (molar units) | 2.92 [2.07] | 3.03 [2.17] | 2.71 [1.84] | <0.001 |
| Hypertension status (yes/no), n (%) | 1200 (48) | 827 (51) | 373 (42) | <0.001 |
| Systolic blood pressure (mm Hg) | 125.79 (15.15) | 125.44 (15.27) | 126.45 (14.91) | 0.112 |
| Diastolic blood pressure (mm Hg) | 75.91 (8.31) | 74.68 (7.94) | 78.16 (8.51) | <0.001 |
| Blood pressure medication status (yes/no), n (%) | 968 (42) | 704 (46) | 264 (33) | <0.001 |
| Concentration of adiponectin (plasma ng/mL) | 4173.68 [3932.97] | 4933.46 [4128.44] | 3090.40 [2775.82] | <0.001 |
| Average LA (HUs)[a] | 59.14 (9.29) | 59.70 (9.12) | 58.11 (9.52) | <0.001 |
| hs-CRP (serum mg/dL) | 0.25 [0.44] | 0.34 [0.53] | 0.15 [0.25] | <0.001 |
| Concentration of aldosterone (serum ng/dL) | 4.30 [4.40] | 4.00 [4.30] | 4.80 [4.30] | <0.001 |

Abbreviations: HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LPL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.
Values are presented as mean (SD) or median [interquartile range] unless otherwise indicated.
[a]CT was performed during exam 2 visit.

### *B. Factors Associated with LA on CT*

In a univariate regression model, men had statistically significant lower liver HU attenuation (Table 2) indicative of higher hepatic steatosis compared with women. As expected BMI, hs-CRP, and HOMA-IR had a strong correlation with LA for both men and women. In the pooled analysis, aldosterone had a strong correlation with LA. Each doubling of the serum aldosterone level was associated with a 1.08-HU decrease in LA [95% confidence interval (CI), −1.47 to −0.69; $P < 0.001$]. The subgroup analysis determined that the association was strongest in women, with each doubling of the serum aldosterone level associated with a 1.11-HU decrease in LA in women (95% CI, −1.44 to −0.62; $P < 0.001$). In men, each doubling of the serum aldosterone level was associated with a 0.77-HU decrease in LA (95% CI, −1.37 to −0.04; $P < 0.05$). We found a statistically significant correlation between LA and alcohol intake only in the overall analysis.

Given the known effect of BMI, alcohol intake, and age on hepatic steatosis, a multivariable analysis adjusted for these variables was performed (12). The analysis showed that the association of LA with aldosterone remained statistically significant, with each doubling of serum aldosterone decreasing the LA by 0.83 HUs (95% CI, −1.18 to −0.47; $P < 0.001$) (Fig. 1). Upon subgroup analysis by sex, it was determined that the correlation of aldosterone with LA was only statistically significant in women such that LA decreased by 0.94 HUs (95% CI, −1.35 to −0.52; $P < 0.001$) with each doubling in serum aldosterone concentration. Similarly, in this analysis, HOMA-IR was found to have a stronger association in women than in men. hs-CRP was statistically significant for the overall group and for women. Further adjustment of the multivariable analysis to include HOMA-IR demonstrated that aldosterone

**Table 2. Factors Associated with LA on CT in Univariate Regression Model**

| Variable | Overall (n = 2507) | Women (n = 1625) | Men (n = 882) |
|---|---|---|---|
| Male (yes/no) | −1.59*** (−2.35 to −0.83) | — | — |
| Menopause status (yes/no) | — | 0.83 (−0.65 to 2.31) | — |
| BMI (kg/m$^2$) | −0.25*** (−0.31 to −0.19) | −0.26*** (−0.32 to −0.20) | −0.40*** (−0.53 to −0.28) |
| Age (y) | 0.03 (−0.00 to 0.07) | 0.02 (−0.02 to 0.06) | 0.04 (−0.01 to 0.10) |
| hs-CRP (mg/dL)$^{log}$ | −0.59*** (−0.79 to −0.38) | −0.79*** (−1.04 to −0.54) | −0.71*** (−1.10 to −0.33) |
| HOMA-IR (molar units)$^{log}$ [b] | −2.75*** (−3.23 to −2.27) | −3.37*** (−3.97 to −2.77) | −2.19*** (−3.00 to −1.38) |
| Concentration of aldosterone (serum ng/dL)$^{log}$ | −1.08*** (−1.47 to −0.69 | −1.11*** (−1.57 to −0.65) | −0.77* (−1.50 to −0.04) |
| Mean number of alcoholic drinks per week | −0.07* (−0.14 to −0.00) | 0.07 (−0.07 to 0.21) | −0.08 (−0.16 to 0.01) |

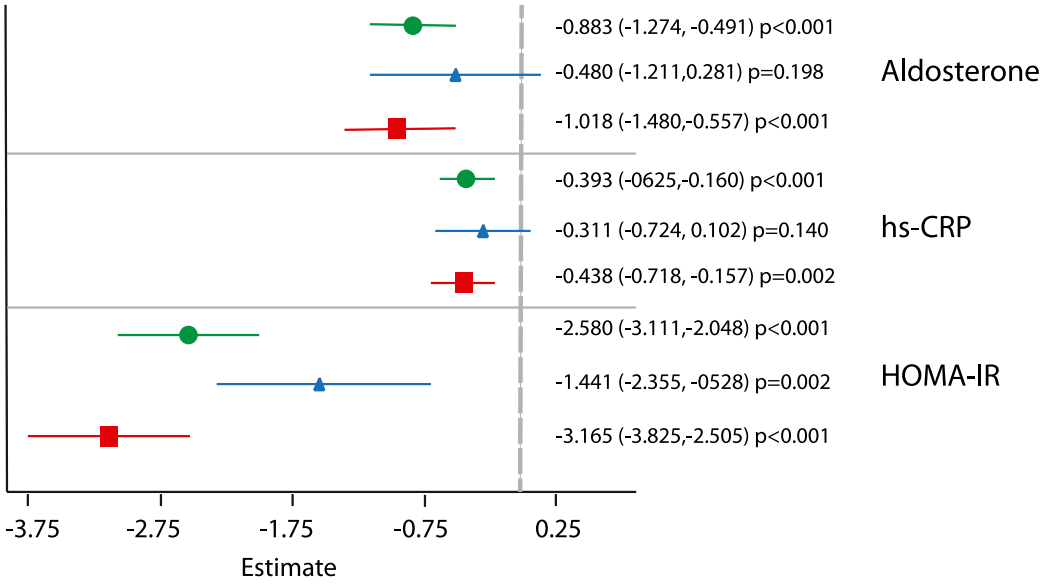
Values represent model estimates (95% CI). *$P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.
[a]Outcome = average LA (HU).
[b]Not calculated for patients with diabetes, including those on diabetes mellitus medications.

was still associated with LA for the pooled analysis ($P = 0.014$) and for women ($P = 0.05$). After including hs-CRP in the multivariable analysis, the pooled analysis was still statistically significant ($P = 0.019$). The significance disappeared for women when analyzed as a subgroup ($P = 0.068$).

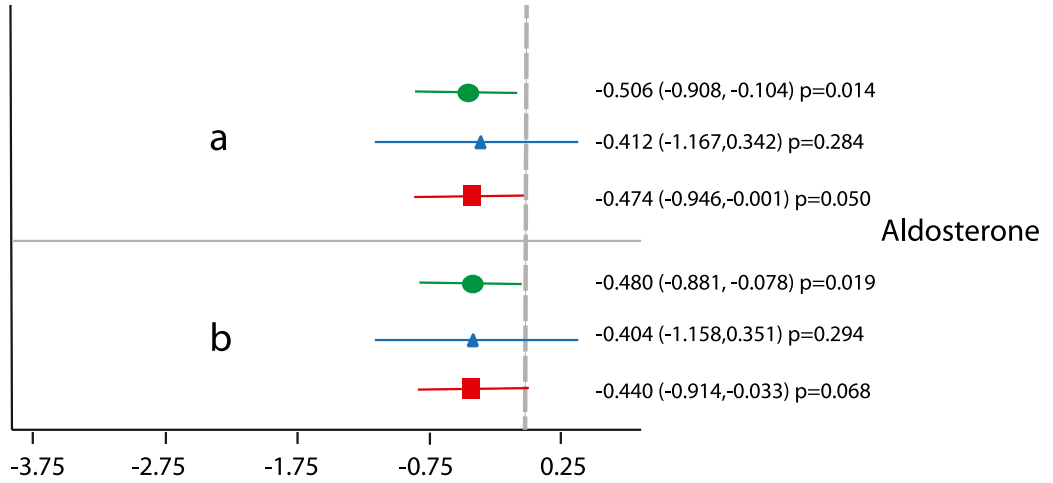
## 3. Discussion

This study demonstrates a positive association between serum aldosterone concentration and fatty liver. So far, there have been limited data regarding the association of aldosterone with fatty liver in populational studies. A small pilot study by Fallo *et al.* (13) suggested that fatty liver is a frequent finding in primary aldosteronism. On univariate analysis, plasma aldosterone, HOMA-IR, and hypokalemia were determinants of fatty liver in primary aldosteronism. However, on multivariate analysis, only hypokalemia was found to be associated with fatty liver. The authors hypothesized that mechanisms regulating insulin sensitivity in primary aldosteronism were mainly dependent on the presence of hypokalemia, whereas the direct effect of aldosterone excess seemed to be of minor relevance. Hypokalemia can worsen insulin resistance and thus potentially lead to fatty liver (14, 15). Although our study did not investigate the effect of hypokalemia, we did determine that the effect of aldosterone is independent of age and BMI.

In our study, HOMA-IR and hs-CRP (inflammation marker) were associated with higher liver fat content on univariate and multivariable analyses. The pathogenesis of fatty liver is still unclear, but it has been explained by a "two-hit" hypothesis. The first hit is the accumulation of triglycerides in the liver, and the next step or "second hit" is described as the result of reactive oxygen species that increase oxidative stress and thus mediate the progression to inflammation and subsequent fibrosis (16). Aldosterone is known to impair insulin sensitivity (increase HOMA-IR) (17). The underlying mechanisms leading to aldosterone-mediated impaired insulin sensitivity remain to be fully elucidated but involve increased production of reactive oxygen species and inflammation (18). This known effect of aldosterone on reactive oxygen species generation and inflammation could implicate aldosterone in leading to steatohepatitis and fibrosis. Interestingly, after including HOMA-IR in the multivariable analysis, aldosterone was still associated with LA for the pooled analysis and for women. When hs-CRP was added to the multivariable analysis, the association persisted for the pooled analysis. This would suggest that the effect of aldosterone on fatty liver is, at least in part, independent of insulin resistance and hs-CRP. The current study is only able to determine the correlation of aldosterone with fatty liver and not directly assess the association with hepatic inflammation or fibrosis. It is important to emphasize that primary




*Pooled models adjusted for age, gender, BMI and alcohol intake
**Stratified models adjusted for age, BMI and alcohol intake




*Pooled models adjusted for age, gender, BMI, alcohol intake, HOMA-IR (a), HOMA-IR and hs-CRP (b)
**Stratified models adjusted for age, BMI , alcohol intake, HOMA-IR (a), HOMA-IR and hs-CRP (b)


**Figure 1.** Multivariable analysis showing the association of LA with aldosterone.

aldosteronism is not physiologically equivalent to upregulation of RAAS. Other components of this system could be playing a role in fatty liver independent of aldosterone.

RAAS has been implicated in the pathogenesis of fatty liver, and studies have demonstrated the benefit of RAAS blockade in fatty liver disease. Randomized controlled trials using angiotensin receptor blockers have shown promising effect. In one study, losartan led to substantial improvement in aminotransferase levels and serum markers of fibrosis in hypertensive patients with nonalcoholic steatohepatitis (19). In another study, telmisartan led

to improvement in fatty liver according to CT attenuation values in hypertensive patients with fatty liver and type 2 diabetes melltius (20). It should be mentioned that some of the positive effects seen with drugs such as telmisartan could be secondary to the pleiotropic effect on peroxisome proliferator activated receptor gamma which is involved in regulation of fatty acid storage and glucose metabolism (21). There is also evidence directly implicating aldosterone in the activation of inflammation and tissue fibrosis. Classically, aldosterone has been described as being produced in the adrenal cortex in response to angiotensin II. More recently, aldosterone was determined to be produced locally during hepatic fibrinogenesis and contribute to organ fibrosis (22). Aldosterone antagonists are thus being investigated in the treatment of fatty liver. So far, the effects of aldosterone antagonists have been shown only in animal studies (22) and small-scale clinical studies (23). Spironolactone and eplerenone attenuated hepatic steatosis and fibrosis in an animal model of fatty liver (24, 25). In addition, spironolactone in combination with vitamin E has been reported to improve insulin resistance in patients with fatty liver (23).

In our study, the association of aldosterone with fatty liver was independent of age, BMI, alcohol intake, and HOMA-IR. On subgroup analyses, the association of serum aldosterone and fatty liver was statistically significant only in women. Previous studies have indeed reported different prevalence rates of fatty liver (26) and different risk factors in men and in women (27), but the reasons for this are unclear, and data concerning the role of sex in fatty liver are complex. Our findings suggest that estrogen could have a deleterious effect on liver in a RAAS-dependent manner. Sex hormones are well known to regulate RAAS. Estrogen increases angiotensinogen levels while decreasing renin levels, angiotensin-converting enzyme activity, AT1 receptor density, and aldosterone production (28). Consistent with the above findings, we demonstrated statistically significant lower levels of aldosterone in women. A recent animal study demonstrated that angiotensinogen is capable of exerting effects independent of angiotensin II, promoting weight gain and hepatic steatosis (29). It is possible that in women with relatively higher RAAS, the estrogen-dependent upregulation of angiotensinogen promotes the development of fatty liver. Future studies are needed to investigate the interaction of sex hormones with RAAS and its role in the pathogenesis of fatty liver.

Our study population consisted of African American individuals only. Multiple studies have shown a lower prevalence of fatty liver in African Americans. In MESA (Muti Ethnic Study of Atherosclerosis), which is a population-based study representing four ethnicities (white, Chinese, African American, and Hispanic) (30), the prevalence of fatty liver was 11% in African Americans, 15% in whites, 20% in Chinese, and 27% in Hispanics (31). Unlike the Dallas Heart Study, we found that African American men had higher liver fat compared with women (32). The discordance in the findings between both studies could be due to the sample size (JHS is a larger study) or to differences in method for liver fat measurement. This difference between men and women could also be due to alcohol intake in men in the JHS. Our findings regarding aldosterone and fatty liver will need to be validated in other ethnic groups.

Limitations of our study are worth mentioning. Although our findings come from a large, well-characterized African American cohort in a longitudinal setting and suggest a positive association of serum aldosterone concentration and fatty liver, causality cannot be established based on our data. We used liver CT HU attenuation to assess liver fat content. Although this is a good method to predict liver fat content (9), LA is affected by other underlying disease of the liver in addition to fat infiltration as iron deposition, which increases liver HU attenuation (33) and liver edema (34). There was a mean difference of 1735 days between the measurement of serum aldosterone and the assessment of LA on CT performed. The JHS cohort has no aldosterone data available for the second visit. We would expect this measurement gap to weaken the association between aldosterone and liver fat content. Previous longitudinal studies have determined that aldosterone levels predict metabolic complications (35). For example, in a four-year follow-up study, Vasan *et al.* (36) demonstrated that aldosterone levels predict the development of hypertension. Patients with relatively higher levels, even if within normal range, are predisposed to long-term metabolic complications. Similarly, in the JHS cohort, aldosterone levels measured on the initial visit are associated

with the development of fatty liver during the follow-up visit. It is possible that alcohol intake could have affected LA in this study beyond what was actually estimated. Alcohol intake was determined by self-report, which has the potential of biasing the data.

## 4. Conclusion

This study is a population-based cohort study demonstrating an association of aldosterone levels with fatty liver, particularly in African American women. These findings are important as they may eventually guide the use of tailored therapies for fatty liver in specific population subgroups. Future studies will need to further delineate the role of RAAS in fatty liver in a broader population.

## Acknowledgments

We appreciate the efforts of the 5306 JHS participants and the JHS study team.

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The current study was supported by the National Institutes of Health (grant numbers R03 DK092542 to A.S. and R01DK088114 to E.O.). The Jackson Heart Study is supported by contracts HHSN268201300046C, HHSN268201300047C, HHSN268201300048C, HHSN268201300049C, and HHSN268201300050C from the National Heart, Lung, and Blood Institute and the National Institute on Minority Health and Health Disparities. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, the National Institutes of Health, or the US Department of Health and Human Services.

Disclosure Summary: A.K., C.B., J.S.S., N.H.E., and A.R.S. have nothing to declare. E.A.O. is a consultant for Astra Zeneca, Aegerion Pharmaceuticals, Ionis Pharmaceuticals, and Akcea Therapeutics; has received grant support from GI Dynamics, Ionis Pharmaceuticals, and Aegerion Pharmaceuticals; and has received nonmaterial support from Aegerion Pharmaceuticals, Aegerion Pharmaceuticals, and Boehringer Ingelheim.

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