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Adiposity, aldosterone and plasma renin activity among African Americans: The Jackson Heart Study

Grace Lee[a,1], **Bjorn Kluwe**[a,1], **Songzhu Zhao**[b], **David Kline**[b], **Divya Nedungadi**[a], **Guy N. Brock**[b], **James B. Odei**[c], **Veena Kesireddy**[a], **Neal Pohlman**[a], **Mario Sims**[d], **Valery S. Effoe**[e], **Wen-Chih Wu**[f], **Rita R. Kalyani**[g], **Gary S. Wand**[g], **Justin Echouffo-Tcheugui**[g], **Sherita H. Golden**[g], **Joshua J. Joseph**[a,*]

[a]Division of Endocrinology, Diabetes and Metabolism, Department of Internal Medicine, The Ohio State University College of Medicine, Columbus, OH, USA

[b]Department of Biomedical Informatics, Center for Biostatistics, The Ohio State University, Columbus, OH, USA

[c]Division of Biostatistics, The Ohio State University College of Public Health, Columbus, OH, USA

[d]Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

[e]Department of Medicine, Morehouse School of Medicine, Atlanta, GA, USA

[f]Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI, USA

[g]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract

Objective: To analyze associations between adiposity and the renin-angiotensin-aldosterone system (RAAS) in a large African American (AA) cohort.

Methods: Cross-sectional associations of adiposity (body mass index [BMI], waist circumference [WC], waist:height ratio, waist:hip ratio, leptin, adiponectin, leptin:adiponectin ratio [LAR], subcutaneous [SAT] and visceral adipose tissue [VAT], and liver attenuation [LA]) with aldosterone, plasma renin activity (renin), and aldosterone:renin ratio (ARR) were assessed in the Jackson Heart Study using adjusted linear regression models.

Results: A 1-SD higher BMI was associated with a 4.8 % higher aldosterone, 9.4 % higher renin, and 5.0 % lower ARR (all $p < 0.05$). Log-leptin had the largest magnitude of association with renin (30.2 % higher) and ARR (9.6 % lower), while the strongest association of aldosterone existed for log-LAR (15.3 % higher) (all 1-SD, $p < 0.05$). SAT was only associated with renin. VAT was associated with higher aldosterone, renin, and ARR. Liver fat was associated with

*Corresponding author at: Department of Medicine, The Ohio State University Wexner Medical Center, Suite 5000E, 700 Ackerman Road, Columbus, OH 43202, USA. Joshua.Joseph@osumc.edu (J.J. Joseph).

[1]These authors contributed equally to this manuscript.

Declaration of competing interest

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aldosterone and renin, but not ARR. Associations of WC, BMI, and SAT with aldosterone were greater in men while the association with VAT was greater in women (p-interactions < 0.05).

Conclusion: Multiple measures of adiposity are associated with the RAAS in AAs. Further studies should examine the role of RAAS in obesity-driven cardiometabolic diseases.

Keywords

Renin; Aldosterone; Adipose tissue; African Americans

1. Introduction

African Americans (AA) have the highest prevalence of obesity in the United States (Hales et al., 2020). Obesity influences cardiometabolic diseases through numerous, well-established mechanisms including inflammation and sympathetic nervous system activation (Hall et al., 2015; Hotamisligil, 2006; Koch and Sharma, 1999). Another potential pathway is through the renin-angiotensin-aldosterone system (RAAS). Higher levels of plasma renin activity and aldosterone are associated with risk of incident CVD (coronary heart disease, stroke, and/or heart failure) (Joseph et al., 2017a) and incident diabetes (Joseph et al., 2016) among AAs with and without prevalent hypertension. Evidence from basic science research supports a relationship between greater adiposity and heightened RAAS activity. The discovery of adipocyte-specific aldosterone synthase indicates that adipose tissue may directly contribute to elevated circulating aldosterone (Briones et al., 2012). Adipokines including leptin and adiponectin, stimulate the aldosterone synthase gene and modulate levels of aldosterone in adrenal cells (Huby et al., 2015; Li et al., 2009). Increased aldosterone production that is partially independent from classic RAAS activation may lead to higher aldosterone:renin ratios (ARR), a key marker used in the diagnosis of primary aldosteronism (Maiolino et al., 2017).

Evidence from smaller observational studies regarding the relationship between adiposity and RAAS activity is mixed among European and non-Hispanic whites (NHWs) but tend to be positively associated (Licata et al., 1994; Rossi et al., 2008; O'Seaghdha et al., 2012). In AAs, this relationship is inconsistent with three studies finding either positive or no associations between adiposity and the RAAS (Kidambi et al., 2007; Huan et al., 2012; Kidambi et al., 2009). Additionally, the relationship between adiposity and RAAS activity may be modified by sex but findings are again inconsistent. In NHWs, stronger associations have been identified in women compared to men (Goodfriend et al., 1999a, 1999b), but these findings were not replicated among NHWs in the Framingham Heart Study (O'Seaghdha et al., 2012).

There are significant racial/ethnic differences in both adipose tissue distribution and RAAS-linked disease risk factor burdens such as hypertension (Hales et al., 2020; Katzmarzyk et al., 2010; Joseph et al., 2017a). Thus, it is critical to gain a nuanced understanding of how specific measures of adiposity are related to RAAS activity in AAs. However, these associations have not been fully elucidated largely as a result of sample size limitations and an inability to measure depot specific distributions of adipose tissue and adipokine levels.

To our knowledge, there are no large cohort studies of AA participants evaluating multi-detector computed tomography (CT) measures of adiposity and adipokines with aldosterone, renin, or the aldosterone-renin ratio (ARR). Thus, the aim of the study was to examine the association of anthropometric (BMI, WC), adipokine (leptin, adiponectin, leptin adiponectin ratio), and body fat distribution (VAT, SAT) measures of adiposity with aldosterone, and renin among AA adults in the Jackson Heart Study (JHS). We hypothesized that adiposity measures would be positively associated with aldosterone and plasma renin activity (PRA).

2. Materials and methods

2.1. Study participants

The JHS is a large, prospective, community-based cohort study of cardiovascular disease in 5306 AA adults aged 21–94 years within the tricounty area of Jackson, Mississippi. Exams were performed between 2000–2004 (Exam 1), 2005–2008 (Exam 2) and 2009–2013 (Exam 3). The JHS design has been described elsewhere (Taylor et al., 2005). The JHS is IRB-approved at participating institutions (Tougaloo College, Jackson State University, and University of Mississippi Medical Center), and written informed consent was provided by study participants. Participants were excluded if they had missing exposures (body mass index (BMI) [n = 5], waist circumference (WC) [n = 2], adiponectin [n = 85], and leptin [n = 20]), outcomes (aldosterone [n = 113]) or important covariates (systolic blood pressure (SBP) [n = 17], diabetes status [n = 5], education [n = 25], smoking status [n = 40]). Participants with supra-physiologic serum aldosterone >2774 pmol/L (100 ng/dL) (n = 2) were excluded in aldosterone analysis and participants with missing renin (n = 2738) were excluded in renin analyses. After exclusions, 4992 and 2256 participants were included in the aldosterone and renin analyses, respectively. The characteristics of participants included vs. excluded based on missing renin are presented in Supplemental Table 1. Excluded participants were younger, more likely to be female, less educated, and had a lower prevalence of diabetes and hypertension. While statistically significant, the differences were small and unlikely to be biologically significant. Supplemental Fig. 1 illustrates the exclusion cascade.

2.2. Exposures: anthropometric, adipokine and body fat distribution adiposity measures

Anthropometric parameters analyzed included WC, BMI, waist: height ratio from Exam 1, and waist: hip ratio from Exam 2. WC was measured at the level of the umbilicus (cm) (Taylor et al., 2005). The waist: height ratio was calculated by dividing WC (cm) by height (m). Hip circumference was measured at the level of the maximal protrusion of the gluteal muscles and the waist: hip ratio was calculated by dividing WC by hip circumference. BMI was calculated as weight (kg) over height squared (m^2). A subset of participants with aldosterone (n = 2709) and renin (n = 1146) measures assessed at Exam 1 underwent CT assessments at Exam 2. CT measures of body fat distribution analyzed included VAT, SAT, and liver attenuation (inverse relationship with liver fat and fibrosis) (Liu et al., 2012). The CT protocol in the JHS has been previously described (Liu et al., 2010, 2012). Given that CT measures and waist: hip ratio were collected at Exam 2, we tested for the stability of adiposity between Exam 1 and 2 (median 4 years) using intraclass correlation coefficients (ICC). The ICCs for BMI, WC, and waist: height ratio were 0.90, 0.83, and 0.8, respectively,

suggesting consistency between visits (Supplemental Table 2) (Cicchetti, 1994). Thus, CT measures and waist: hip ratio were included in cross-sectional analyses.

Biomarkers analyzed included adiponectin, leptin, and leptin: adiponectin ratio from Exam 1. Fasting venous blood samples were collected after a minimum of 20 min in the supine position and processed using a standardized protocol (Taylor et al., 2005). Samples were stored at −80 °C before serum adiponectin and leptin was measured via an ELISA assay (R&D Systems, Minneapolis, MN; interassay coefficient of variation [CV] 8.8 %) and Human Leptin RIA kit (Millipore, Billerica, MA; interassay-CV 10 %), respectively (Bidulescu et al., 2011; Musani et al., 2013).

2.3. Outcomes: aldosterone, renin and the aldosterone-renin ratio (ARR)

Plasma and serum samples were centrifuged within 2 h of fasted blood collection, stored at −70 °C, and sent to central laboratories (University of Minnesota). Serum aldosterone was measured by radioimmunoassay (Coat-a-count aldosterone, Siemens, Munich, Germany) and the intra-assay-CV were 8.7 % and 6.2 % for low and high concentrations, respectively (Musani et al., 2013). Renin (plasma renin activity) was measured using immunoradiometric assays in ng/mL/h with an intra-assay-CV 8.0 % (Joseph et al., 2017a). The ARR was calculated by dividing aldosterone by renin.

2.4. Covariates

Cross-sectional analyses were adjusted for baseline covariates including age, sex, occupation (management/professional versus not), level of education (≥Bachelor's degree versus < Bachelor's degree), tobacco use (current smoking versus non-smoking), SBP (measured twice at 5-min intervals using an appropriately sized cuff with standard Hawksley random-zero instruments and averaged for analysis, calibrated to the Omron device), physical activity (AHA 2020 guidelines) (Lloyd-Jones et al., 2010), and RAAS modulators (angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARB], and mineralocorticoid receptor antagonists). The covariates were chosen on the basis of confounding associations with the adiposity (exposure) and RAAS (outcome) measures.

2.5. Statistical analysis

Baseline characteristics of participants were presented in three BMI categories defined by the World Health Organization (WHO), <25, 25–29.99 and ≥30 kg/m^2. Differences across categories of BMI were tested using chi-square (χ^2) for categorical variables, one-way-ANOVA or Kruskal-Wallis test for continuous variables. Due to skewed distributions, renin, aldosterone, ARR, adiponectin, leptin, SAT, VAT, and liver attenuation were log-transformed prior to analysis. Tobit models were employed to examine the association of adiposity measures with log-aldosterone and log-renin adjusting for age, sex, education, occupation, SBP, smoking, physical activity, and RAAS modulators accounting for left censoring in aldosterone and renin due to lower limits of detection.

Sensitivity analyses were performed on a sample that excluded individuals taking RAAS modulating medications (Supplemental Tables 3, 4, and 5). We tested for interaction by age, sex, and hypertension status as the associations may be modified by these factors (Table

4). To confirm the robustness of findings and explore potential physiological relationships, secondary analyses examined the associations of adiposity: 1) with log-ARR as the outcome, and 2) across renin phenotype categories of renin (ng/mL/h) of ≤0.50 (suppressed renin phenotype), 0.51–0.99 (indeterminate renin phenotype), and ≥1.0 (unsuppressed renin phenotype) (Brown et al., 2017; Joseph et al., 2021). Interpretations of beta-coefficients in the text were transformed as follows: 1) $[(1{:}01)^{\beta} - 1] * 100$ % (Both dependent and independent variables are log transformed) and 2) $(e^{\beta} - 1) * 100$ % (Dependent variable is log transformed). No adjustments were made for multiple comparisons as doing so was considered too conservative for correlated hypotheses. Statistical significance was defined as two-sided p-value < 0.05 in the main analysis and p <0.10 for interactions (Joseph et al., 2017b). Analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

Baseline characteristics of the 4994 study participants at Exam 1 are presented across BMI categories (Table 1). Those with a BMI ≥30 kg/m^2 were more likely to be female, non-smokers, and less physically active with higher percentages of diabetes and hypertension versus lower BMI categories. Levels of WC, waist: hip ratio, waist: height ratio, leptin, leptin: adiponectin ratio, serum aldosterone, and renin were higher in those with higher BMIs while adiponectin and liver attenuation were lower (all p < 0.05). Higher ARRs were driven by lower renin (Fig. 1).

3.2. Association of standardized adiposity measures with renin, aldosterone, and the aldosterone: renin ratio

Adjusted associations of standardized adiposity measures with log-aldosterone, log-renin, and log-ARR are presented in Table 2, Model 1. A 1-SD higher BMI was associated with a 4.8 % higher aldosterone, 9.4 % higher renin, and 5.0 % lower ARR (all p < 0.05). A 1-SD higher WC was associated with a 6.9 % higher aldosterone and 8.1 % higher renin (both p < 0.05), but was not associated with ARR. A 1-SD higher waist: height ratio was associated with a 6.4 % higher aldosterone, 11.0 % higher renin, and 5.1 % lower ARR (all p < 0.05). The waist: hip ratio was associated with an 11.2 % and 11.8 % higher aldosterone and renin (both p < 0.05), respectively, but was not associated with ARR.

A 1-SD higher log-SAT was associated with a 9.8 % higher renin (p = 0.03), but there was no association with aldosterone or ARR. Liver fat was negatively associated with aldosterone and renin (both p < 0.05) but not log-ARR. VAT was positively associated with aldosterone, renin, and negatively associated with ARR across all models (all p < 0.05) and had the largest effect size of the CT measures. Supplemental Table 3 shows that theses associations were similar following exclusion of taking RAAS modulators. However, the ARR was only significant for VAT in Supplemental Table 3.

A 1-SD higher log-adiponectin was associated with a 9.9 % and 14.2 % lower aldosterone and renin (both p < 0.05), respectively, but was not associated with the ARR. A 1-SD higher

leptin was associated with a 14.6 % higher aldosterone, 30.2 % higher renin, and 9.6 % lower ARR ($p < 0.05$). A 1-SD higher log-leptin: adiponectin ratio was associated with a 15.3 % higher aldosterone, 28.3 % higher renin, and 7.1 % lower aldosterone: renin ratio (all $p < 0.05$).

All prior models were further adjusted for either renin in aldosterone models (Model 2) or aldosterone in renin models (Model 3). Associations with aldosterone were mildly attenuated, but remained significant for adiponectin, leptin, LAR, waist: hip ratio, and VAT. Associations with renin were also slightly smaller in magnitude but remained significant for adiponectin, leptin, LAR, BMI, VAT, and liver attenuation.

These associations were similar after excluding participants taking RAAS modulators. However, WC was associated with aldosterone ($p = 0.03$) but VAT became non-significant ($p = 0.08$). The findings for renin were also consistent, but BMI and liver attenuation became non-significant ($p = 0.09$ and $p = 0.10$, respectively).

Associations of categorical adiposity measures with aldosterone, renin, and ARR are presented graphically in Figs. 2A, 2B, and Supplemental Table 4. Adiponectin, leptin, LAR, WC, BMI, Waist: Height Ratio, and VAT in Quartile-4 were associated with higher aldosterone and renin compared to Quartile-1 (all $p < 0.001$; Figs. 2A, 2B). SAT was only significant for renin (Quartile-4 vs. Quartile-1, $p = 0.026$).

3.3. Association of adiposity measures and aldosterone stratified by renin phenotypes

Associations of adiposity measures and aldosterone stratified by renin phenotypes (suppressed, indeterminate, and unsuppressed) are presented in Table 3. Renin phenotype significantly modified associations between BMI, adiponectin, leptin, and SAT (all $p < 0.10$). BMI ($\beta = 0.01$, 95 % CI: 0.002, 0.018) and SAT ($\beta = 0.27$, 95 % CI: 0.09, 0.45) were only associated with aldosterone among individuals with unsuppressed renin. In contrast, the waist: hip ratio ($\beta = 0.88$, 95 % CI: 0.135, 1.628) and adiponectin ($\beta = -0.137$, 95 % CI: −0.203, −0.072) were associated with aldosterone only among those with suppressed renin. Finally, leptin and leptin:adiponectin ratio were associated with aldosterone only among those with either suppressed or unsuppressed renin. Both leptin and LAR ratio were more strongly associated with aldosterone in the unsuppressed versus the suppressed renin phenotype. The associations of adiposity measures and aldosterone stratified by renin phenotypes among individuals taking medications that interact with the RAAS are presented in Supplemental Table 5. All aforementioned associations in the Table 3 remained significant and their effect sizes generally increased. In addition, WC ($\beta = 0.0084$, 95 % CI: 0.0031, 0.0136) and the waist:height ratio ($\beta = 1.4626$, 95 % CI: 0.5904, 2.3348) were significantly associated with aldosterone only among individuals with unsuppressed renin. In contrast to the primary analysis, the LAR ($\beta = 0.0772$, 95 % CI: 0.0034, 0.1509) was associated with aldosterone among those with the indeterminate renin phenotype, in addition to the suppressed and unsuppressed renin phenotypes.

3.4. Effect modification of the associations by age, sex and hypertension

Effect modification of the association of adiposity measures with aldosterone and renin by age, sex, and hypertension are presented in Table 4. The magnitude of positive associations

of WC, BMI, and waist:height with aldosterone were at a minimum 2–3-fold greater in men compared to women (p-interaction ≤ 0.01). The association between SAT and aldosterone was statistically significant in men only (p-interaction = 0.03). The association between VAT and aldosterone was positive for both men and women; however, the effect size was approximately 2-fold greater among women (p-interaction = 0.03). Age only modified the association of leptin (p-interaction = 0.097) and adiponectin (p-interaction = 0.035) with aldosterone. Hypertension only modified the association of adiponectin and leptin with aldosterone (p-interaction = 0.003 and 0.004, respectively) and renin (p-interaction = 0.088 and 0.028, respectively). There was no evidence for effect modification of the relationship between measures of adiposity and renin by age or sex.

4. Discussion

In this large study of AA adults, adiposity measures including BMI, WC, waist:height ratio, waist:hip ratio, VAT, and leptin were positively associated, while adiponectin and liver attenuation were negatively associated with both aldosterone and renin. The associations were robust after controlling for demographic characteristics, cardiovascular risk factors and, RAAS-altering medications. The greatest magnitude of associations was with the adipokines and RAAS.

4.1. The association of BMI, waist:height and waist:hip ratios, and WC with aldosterone, renin, and ARR

Previous studies in AAs investigating associations of BMI and WC with aldosterone have revealed inconsistent findings. Among 397 normo- and hypertensive AAs, WC and BMI were positively correlated with aldosterone (Kidambi et al., 2007). Among 466 normo- and hypertensive AAs aldosterone was associated with WC ($r = 0.13$, $p < 0.01$), but not BMI (Kidambi et al., 2009). Finally, in another study of 483 young AA men and women, continuous measures of WC or BMI were not significantly associated with categorical aldosterone (Huan et al., 2012).

Smaller studies among Europeans and NHWs have identified positive associations between anthropometric measures of adiposity and components of the RAAS. Italians with central obesity (female waist:hip ratio ≥ 0.81 and male ≥ 0.92 + BMI ≥ 30 kg/m^2) compared to lean individuals (BMI ≤ 25 kg/m^2) had higher renin and aldosterone (Licata et al., 1994). In another group of Italians, BMI was positively associated with plasma aldosterone in those with primary hypertension (Rossi et al., 2008). In a study of US men (n = 23) and women (n = 7), BMI and waist:hip ratio were strongly correlated with plasma aldosterone. Notably, the correlation between waist:hip ratio and aldosterone was greatest when renin was suppressed through a high salt diet (Goodfriend et al., 1999a). However, these findings were not replicated in the Third Generation Framingham Heart Study, where no significant associations of BMI and WC with aldosterone or renin were identified (O'Seaghdha et al., 2012).

Evidence suggests that the association between anthropometric measures of adiposity and RAAS components may be modified by sex due to greater adrenal sensitivity to angiotensin II in women (Fisher Naomi et al., 1997). In the current study, all anthropometric measures

of adiposity were positively associated with aldosterone in both sexes but effect sizes were 2-fold greater in men for aldosterone with no differences in renin by sex. Previously, in a small sample of NHWs aldosterone was higher in women with obesity by BMI but not men ($r = 0.55$, $p < 0.05$) (Goodfriend et al., 1999b). In another small study of US men ($n = 27$) and women ($n = 28$), BMI was positively correlated with aldosterone among women but not men (Goodfriend et al., 1999a). Thus, there may be racial and sex differences in the association of adiposity with RAAS, possibly due to known underlying differences in body fat distribution (Katzmarzyk et al., 2010).

4.2. The association of SAT, VAT, and liver attenuation with aldosterone, renin, and ARR

To our knowledge, the association of VAT and SAT with components of the RAAS in a large cohort of AAs has not been previously investigated. The relationship of SAT and VAT with aldosterone and renin is inconsistent in other racial/ethnic groups. Among obese Japanese men and women, SAT but not VAT was positively correlated with urinary aldosterone excretion (Harada et al., 2013). Among majority NHWs in the Third Generation Framingham Heart Study, no association between VAT and aldosterone or renin was identified (O'Seaghdha et al., 2012). However, in other smaller studies of NHWs, there was a positive association of VAT and aldosterone among women (Goodfriend et al., 1999b; Goodfriend et al., 1999a). In the current study, the association between VAT and aldosterone was 2-fold greater among women.

The relationship between liver attenuation and aldosterone has previously been investigated in the JHS (Kumar et al., 2017). Investigators identified a negative association between aldosterone and liver attenuation which was significant only among women. In the current analysis, liver attenuation was negatively associated with aldosterone and renin but there was no association with the ARR in the main analysis. Consistent with the prior study in the JHS, the association of liver attenuation with both aldosterone and renin was only significant among women when stratified by sex. To our knowledge, mechanisms regarding sex differences in the association between CT measures of adiposity and aldosterone have not been clearly elucidated and remain an area for further investigation.

4.3. The association of adiponectin, leptin and leptin:adiponectin ratio with aldosterone, renin, and ARR

The majority of studies provide evidence for a relationship between adipokines and the RAAS system. Adiponectin is protective of insulin resistance and has anti-inflammatory properties. It is produced by adipocytes, but its production is paradoxically decreased in obesity (Frühbeck et al., 2017). Similarly, leptin is produced primarily by adipocytes. It has anorectic effects and regulates numerous physiological processes. In contrast to adiponectin, leptin levels are profoundly increased in obesity but individuals are resistant to its anorectic effects due to central leptin resistance. Recently, the LAR has been shown to be predictive of metabolic syndrome and is a stronger correlate of insulin resistance than either measure alone (Frühbeck et al., 2017).

Our findings extend those of a Multi-Ethnic Study of Atherosclerosis analysis where Allison et al. (Allison et al., 2015) reported that leptin was positively associated with both

aldosterone and renin. Our findings diverge slightly regarding associations of leptin and adiponectin with renin. While adiponectin was negatively associated with aldosterone, no significant associations were identified with renin (Allison et al., 2015). In a small group of normo- and essential hypertensive Turkish individuals, a positive correlation between leptin and renin was identified in both groups (Üçkaya et al., 1999). Similarly, a study of normo- and hypertensive NHWs identified a correlation between leptin and renin but this was only significant among women with hypertension (Adamczak et al., 2000). In the present analysis, leptin was associated with renin irrespective of hypertension status, but the magnitude was greater in the hypertension group. Sex also did not modify this association indicating that racial/ethnic differences by sex may exist in the interaction between leptin and the RAAS. An inverse association between adiponectin and aldosterone has been clearly identified in both rodents and humans (Flynn and Bakris, 2011). Our data further supports this finding and, interestingly, we show that the negative association between adiponectin and aldosterone was only significant in the suppressed renin phenotype group.

4.4. The association of adiposity with aldosterone and renin: classic vs. non-classic RAAS activation mechanisms

To explore whether classic or non-classic RAAS activation may be driving associations: 1) Regression models were mutually adjusted for aldosterone and renin; and 2) Aldosterone associations were examined across categories of renin phenotypes. All adiposity measures except for SAT were associated with both renin and aldosterone prior to mutual adjustment. Following inclusion of renin, the associations of BMI, WC waist:height ratio, and liver attenuation with aldosterone become non-significant. Thus, elevations in these measures likely lead to higher serum aldosterone through the classic RAAS pathway, which may be explained via several mechanisms. First, sympathetic nervous system activity is greater among individuals with obesity and causes activation of the juxtaglomerular cells and subsequently activates renin production (Hall et al., 2015). Second, excess adipose tissue in the abdominal compartment may compress the kidneys, causing sodium reabsorption in the loop of Henle and decreased salt concentration in the filtrate which activates the macula densa cells of the juxtaglomerular apparatus and increases renin production (Hall et al., 2015).

Mutual adjustment for aldosterone and renin led to the attenuation of associations between the adipokines and RAAS components. However, they remained significant in both models. These findings indicate that the adipokines may modulate RAAS activity and aldosterone production through both classic and non-classic pathways. Leptin upregulates sympathetic nerve outflow to the kidneys, thereby upregulating renin production (Simonds et al., 2012). Alternatively, aldosterone production can occur directly in adipocytes that express aldosterone synthase (Briones et al., 2012). Aldosterone synthase is activated in the adrenal zona glomerulosa via adipokines (leptin, CTRP1) and oxidized VLDL particles (Jeon et al., 2008; Xie and Bollag, 2016). Adiponectin may decrease aldosterone through the classic pathway, as intravenous and intra-cerebroventricular injections of adiponectin in rats dose dependently suppress renal sympathetic activity, thus plausibly reducing renin production (Tanida et al., 2007). Additionally, adiponectin lowers aldosterone in a receptor-dependent pathway at the level of the adrenal glomerulosa (Li et al., 2009) and conversely, blocking

the mineralocorticoid receptor increases adiponectin levels (Guo et al., 2008). In the current study, adiponectin was negatively associated with aldosterone only among individuals with the suppressed renin phenotype suggesting that the negative association was driven through a general reduction in RAAS activity which is consistent with adiponectin acting through the classic pathway. Leptin and the LAR were positively associated with aldosterone in both the suppressed and unsuppressed renin groups which reinforces the hypothesis that these measures may influence RAAS activity through both classic and non-classic mechanisms.

Similar to the findings observed with the adipokines, VAT remained significantly associated with renin and aldosterone following mutual adjustment. VAT is metabolically active and produces adipokines which can activate aldosterone synthase expression and aldosterone secretion from the adrenal cortex (Huby et al., 2015). Furthermore, expression of cathepsin D, an angiotensin cleavage enzyme, is upregulated in VAT in obese rodents and humans (Masson et al., 2011). Thus, increased VAT may increase aldosterone via increased production of RAAS intermediaries that are downstream of renin.

4.5. Strengths and limitations

The strengths of this study include a large contemporary population with comprehensive, well-characterized data on a wide variety of adiposity measures, serum RAAS levels, medications, and covariates. The limitations of this study warrant discussion. First, analyses are based on a single-site cohort of AAs located in the Jackson, MS metropolitan area, thus findings may not be generalizable to other AA populations. Second, CT data (Exam 2, 2005–2008) were not obtained at the same exam as the anthropometric and biological estimates (Exam 1, 2000–2004). However, the high ICC for BMI, WC, and waist:height ratio between Exams 1 and 2 suggests that measures of adiposity were stable over time. Thus, the CT measures likely did not change significantly between exams. Third, the findings for effect modification by age, sex, and hypertension status would benefit from further confirmation, given these were preliminary secondary analyses. Fourth, the primary interest was in estimating the association between adiposity measures and RAAS. We present effect estimates and confidence intervals to quantify these associations. We were not specifically focused on making binary decisions based on a significance test. Thus, p-values were presented to be informative rather than as a strict criterion for decision-making. P-values were presented at the nominal level, allowing the reader to take multiplicity into consideration if they choose to interpret the results in terms of a test with a binary decision rule. Finally, analyses were cross-sectional and therefore could not assess temporality.

5. Conclusions

In conclusion, associations of multiple measures of adiposity with both aldosterone and renin exist in AAs. Generally, adipokines had the strongest associations with the RAAS. In models developed to evaluate potential mechanistic relationships with classical and non-classical RAAS activation, we found greater associations of anthropometric measures of adiposity with renin and potential classical RAAS activation, while adipokines and body fat distribution, including adiponectin, leptin, and VAT, were associated with both renin and aldosterone, indicating potential for classical and non-classical RAAS activation. Given the

high rates of obesity in the US, further studies are warranted to evaluate the role of the RAAS system in the development of obesity driven cardiometabolic diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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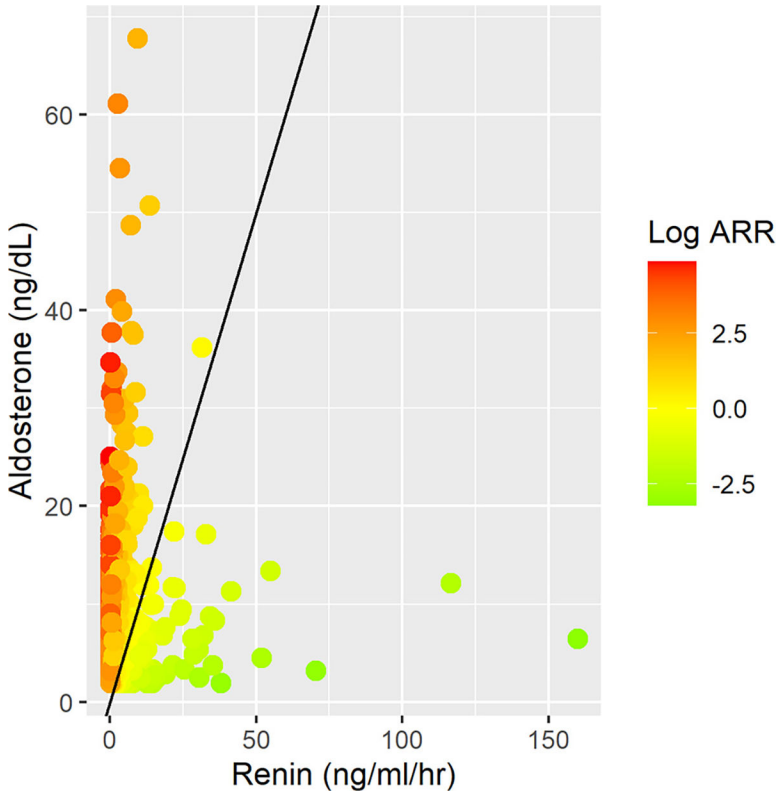

Fig. 1.

Aldosterone and renin contributions to the aldosterone:renin ratio. Abbreviations: ARR = aldosterone:renin ratio, units of aldosterone are ng/dL, units for renin are ng/mL/h. Interpretation: Data points were represented by colors where the highest value of log (ARR) was bright red, the mid-range values were yellow and the lowest value of log (ARR) are green. The clustering of the high log (ARR) values around the zero point for renin indicates that the log (ARR) is driven primarily by low renin values. The black line denotes the slope.

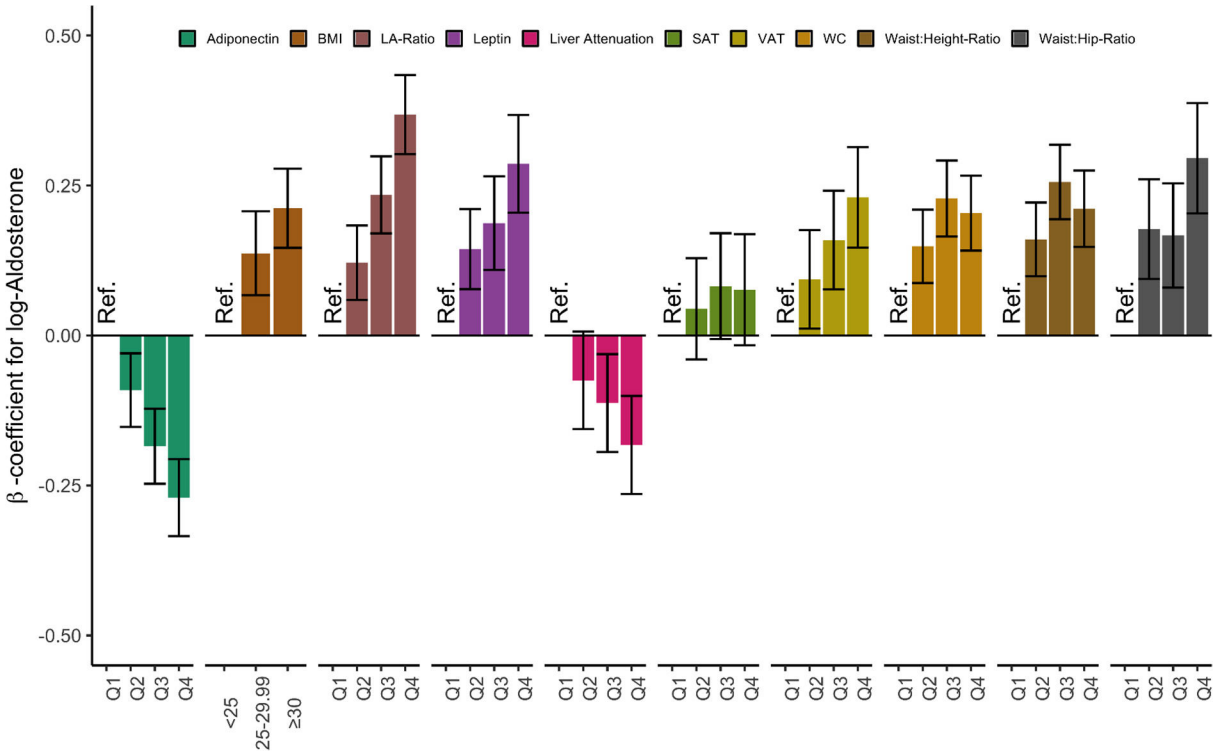

Fig. 2A.

Categorical associations of biomarkers, anthropometric estimates, and CT measures of adiposity with log-aldosterone. Model adjusted for age, sex, education, occupation, systolic blood pressure, smoking, and physical activity (AHA-Life's Simple 7). Aldosterone, biomarkers, and CT images were log-transformed. Abbreviations: SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue, WC = waist circumference, LA-Ratio = leptin:adiponectin ratio.

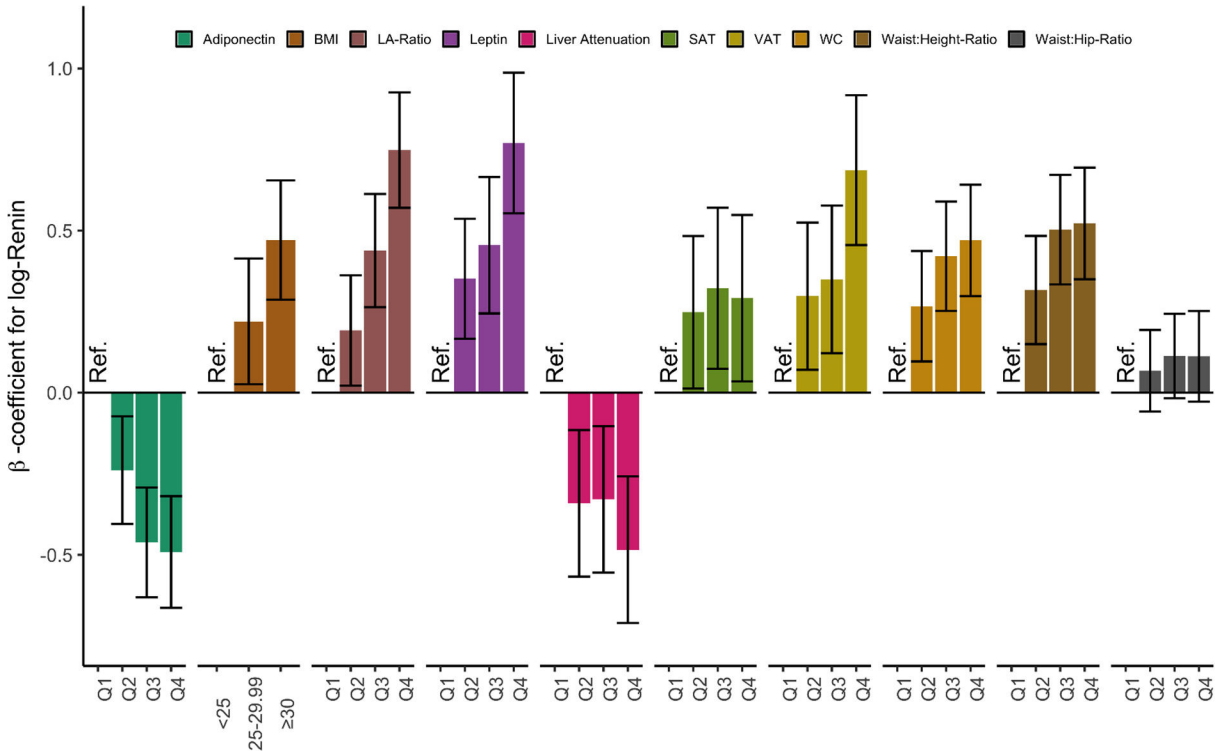

Fig. 2B.

Categorical associations of biomarkers, anthropometric estimates, and CT measures of adiposity with log-renin. Model adjusted for age, sex, education, occupation, systolic blood pressure, smoking, and physical activity (AHA-Life's Simple 7). Aldosterone, biomarkers, and CT images were log-transformed. Abbreviations: SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue, WC = waist circumference, LA-Ratio = leptin:adiponectin ratio.

Table 1

Baseline characteristics of participants in the Jackson Heart Study by BMI categories.

Baseline characteristics	Total (n = 4994)	BMI categories			p-value[a]
		<25 (n = 705)	25–30(n = 1600)	>30 (n = 2689)	
Age[a]	Mean (SD)	54.9 (14.6)	56.4 (12.8)	54.4 (12.3)	<0.0001
Sex (%)	Female	379 (53.8)	860 (53.8)	1921 (71.4)	<0.0001
	Male	326 (46.2)	740 (46.3)	768 (28.6)	
Education (%)	Less than high school education	154 (21.8)	320 (20)	525 (19.5)	0.3909
	High school +	551 (78.2)	1280 (80)	2164 (80.5)	
Occupation (%)	Management/Professional	240 (34)	613 (38.3)	928 (34.5)	0.0266
	Other	465 (66)	987 (61.7)	1761 (65.5)	
Smoking (%)	No	535 (75.9)	1393 (87.1)	2405 (89.4)	<0.0001
	Yes	170 (24.1)	207 (12.9)	284 (10.6)	
Physical activity (%)[b]	Poor health	353 (50.1)	714 (44.6)	1378 (51.2)	<0.0001
	Intermediate health	220 (31.2)	507 (31.7)	850 (31.6)	
	Ideal health	132 (18.7)	379 (23.7)	461 (17.1)	
Diabetes (%)	No	653 (92.6)	1321 (82.6)	1940 (72.1)	<0.0001
	Yes	52 (7.4)	279 (17.4)	749 (27.9)	
Hypertension (%)	No	407 (57.7)	758 (47.4)	1016 (37.8)	<0.0001
	Yes	298 (42.3)	842 (52.6)	1673 (62.2)	
BMI, kg/m^2	31.8 (7.3)	22.6 (1.9)	27.6 (1.4)	36.7 (6.2)	<0.0001
Waist circumference, cm	100.8 (16.2)	81.8 (8.0)	93.0 (8.1)	110.4 (14.4)	<0.0001
Waist:height ratio	0.6 (0.1)	0.48 (0.045)	0.55 (0.046)	0.66 (0.086)	<0.0001
Waist:hip ratio	0.9 (0.078)	0.86 (0.071)	0.89 (0.072)	0.91 (0.081)	<0.0001
Systolic blood pressure, mm Hg	127.5 (16.9)	126.4 (18.5)	126.9 (17.1)	128.1 (16.4)	0.0158
Diastolic blood pressure, mm Hg	75.8 (8.8)	75.5 (9.4)	75.6 (8.6)	76 (8.7)	0.2247
Log-adiponectin, ng/mL	8.4 (0.7)	8.6 (0.7)	8.4 (0.7)	8.3 (0.7)	<0.0001
Log-leptin, ng/mL	2.9 (1.0)	1.9 (0.9)	2.6 (0.8)	3.4 (0.7)	<0.0001
Log- leptin-adiponectin ratio[c]	−5.4 (1.1)	−6.7 (1.1)	− 5.8 (0.9)	− 4.8 (0.8)	<0.0001
Adiponectin, ng/mL	4221 (2682, 6748)	5907 (3606, 9544)	4362 (2712, 6938)	3842 (2530, 5941)	<0.0001

Baseline characteristics	Total (n = 4994)	BMI categories			p-value[a]
		<25 (n = 705)	25–30(n = 1600)	>30 (n = 2689)	
Leptin, ng/mL	22.8 (10.1, 39.2)	7.3 (3.2, 15.1)	14.4 (6.9, 25.2)	34.8 (20.7, 49.5)	<0.0001
Leptin-adiponectin ratio	0.005 (0.002, 0.01)	0.001 (0.0005, 0.003)	0.003 (0.002, 0.006)	0.008 (0.005, 0.014)	<0.0001
Log- subcutaneous adipose tissue, cm^3 (n = 2744)	7.64 (0.51)	7.0 (0.61)	7.41 (0.35)	7.95 (0.32)	<0.0001
Log-visceral adipose tissue, cm^3 (n = 2745)	6.61 (0.51)	6.13 (0.56)	6.51 (0.46)	6.78 (0.43)	<0.0001
Log-liver attenuation, cm^3 (n = 2797)	4.06 (0.20)	4.11 (0.14)	4.08 (0.19)	4.04 (0.20)	<0.0001
Subcutaneous adipose tissue, cm^3 (n = 2744)	2187 (1564, 2991)	1217 (860, 1676)	1702 (1332, 2080)	2893 (2316, 3598)	<0.0001
Visceral adipose tissue, cm^3 (n = 2745)	770 (556, 1043)	494 (335, 682)	689 (514, 927)	906 (681, 1181)	<0.0001
Liver attenuation, Hounsfield Units (n = 2797)	60.5 (55.4, 64.7)	62.2 (58, 66)	61.4 (56.6, 65.2)	59.5 (53.4, 64.2)	<0.0001
Aldosterone, ng/dL	4.4 (2.6, 7.2)	3.8 (2.3, 6.1)	4.4 (2.7, 6.9)	4.6 (2.7, 7.7)	<0.0001
Renin, ng/mL/h (n = 2256)	0.5 (0.2, 1.1)	0.4 (0.2, 0.9)	0.5 (0.2, 1.0)	0.5 (0.2, 1.4)	<0.0001
Aldosterone:renin ratio	9.5 (4.2, 17.3)	10 (4.8, 16.8)	10 (4.8, 18.8)	9 (3.8, 16.7)	0.0085
eGFR CKD-Epi (mL/s/m^2, mL/min/1.73 m^2)	94.5 (21.7)	96.8(22)	92.6 (21.1)	95(21.9)	<0.0001

Abbreviations: AHA, American Heart Association. BMI, Body Mass Index. Renin, Plasma Renin Activity.

Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of antihypertensive therapy.

Diabetes was defined based on 2010 American Diabetes Association guidelines (HbAlc ≥ 6.5 %, fasting glucose ≥ 126 mg/dL, taking diabetes medications or self-reported physician diagnosis).

[a] Mean (SD), median (IQR) or percentages are listed. p values were calculated using χ^2 (categorical variables), ANOVA (parametric continuous variables), Kruskal-Wallis test (nonparametric continuous variables).

[b] Standards of physical activity were determined by AHA 2020 guidelines, and defined as 0 min of moderate to vigorous intensity physical activity.

[c] Log-Leptin-Adiponectin ratio calculated as difference between log-leptin and log-adiponectin.

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Table 2

The association of adiposity measures with log-aldosterone, log-renin, and log-ARR.

Exposure	**Outcome**				
	Log-aldosterone (n = 4992)[a]		**Log-renin (n = 2256)**[a]		**Log-ARR (n = 2255)**[a]
	Model 1	**Model 1 + renin**	**Model 1**	**Model 1 + aldosterone**	**Model 1**
Adiposity measures	**β-Coefficient 95 % CI**	**β-Coefficient 95 % CI**	**β-Coefficient 95 % CI**	**β-Coefficient 95 % CI**	**β-Coefficient 95 % CI**
z-log-adiponectin (ng/mL)	**−0.104 (−0.127, −0.081)**	**− 0.060 (− 0.093, − 0.026)**	**−0.153 (− 0.210, − 0.095)**	**−0.113 (−0.168, −0.058)**	0.042 (− 0.004, 0.088)
z-log-leptin (ng/mL)	**0.136 (0.106, 0.166)**	**0.075 (0.031, 0.119)**	**0.264 (0.189, 0.338)**	**0.200 (0.129, 0.272)**	**−0.100 (−0.160, −0.041)**
z-log-leptin: adiponectin ratio	**0.142 (0.118, 0.166)**	**0.081 (0.046, 0.116)**	**0.249 (0.188, 0.309)**	**0.188 (0.130, 0.247)**	**−0.073 (−0.117, −0.030)**
z-waist circumference	**0.067 (0.045, 0.089)**	0.032 (− 0.002, 0.065)	**0.078 (0.022, 0.134)**	0.050 (−0.003, 0.104)	− 0.021 (− 0.066, 0.023)
z-body mass index (kg/m^2)	**0.047 (0.024, 0.069)**	0.012 (− 0.021, 0.044)	**0.090 (0.033, 0.147)**	**0.070 (0.016, 0.125)**	**− 0.052 (− 0.097, − 0.006)**
z-waist: height ratio	**0.062 (0.039, 0.084)**	0.016 (−0.018, 0.050)	**0.104 (0.046, 0.161)**	**0.081 (0.026, 0.136)**	**−0.052(−0.098, −0.006)**
z-waist: hip ratio	**0.106 (0.073, 0.139)**	**0.052 (0.006, 0.098)**	**0.111 (0.027, 0.196)**	0.074 (−0.007, 0.155)	− 0.021 (− 0.088, 0.046)
z-log-subcutaneous adipose tissue (cm^3)	0.023 (−0.010, 0.056)	0.005 (− 0.045, 0.055)	**0.093 (0.008, 0.179)**	0.077 (−0.005, 0.158)	− 0.054 (−0.121, 0.014)
z-log-visceral adipose tissue	**0.087 (0.057, 0.117)**	**0.049 (0.004, 0.094)**	**0.196 (0.120, 0.273)**	**0.157 (0.084, 0.231)**	**−0.087 (−0.148, −0.027)**
z-log-liver attenuation (Hounsfield Units)	**− 0.062 (− 0.090, − 0.033)**	− 0.033 (−0.075, 0.010)	**−0.102 (−0.176, −0.027)**	**−0.075 (−0.146, −0.004)**	0.045 (− 0.014, 0.105)

Model: Model 1: Adjusted for age, sex, education, occupation, systolic blood pressure, smoking, physical activity (AHA-Life's Simple 7), ACE inhibitors, ARB, and mineral- ocorticoid receptor antagonist.

Superscript:

[a] log transformed

[b] Liver attenuation is the inverse of liver fat

[c] standardized biomarkers using formula $z = \frac{(x - \bar{x})}{S}$ (where $\bar{x}$ is the mean of the biomarker and S is the standard deviation of the biomarker).

Interpretation:

Equation: Dependent variable is log transformed: a 1-unit change in the exposure is associated with a $(e^{\beta} - 1) * 100$ % change in the outcome.

Example: A1-SD higher mean waist circumference is associated with a 6.92 % percent higher aldosterone (Model 1 for outcome log-aldosterone).

A 1-SD higher in mean log-liver attenuation is associated with a 5.96 % percent lower aldosterone (Model 1 for outcome log-aldosterone).

Table 3

The Association of adiposity measures with log-aldosterone by renin phenotype.

	Suppressed renin phenotype (renin ≤ 0.50 ng/mL/h) (n = 1234)	**Indeterminate renin phenotype (renin 0.51–0.99 ng/mL/h) (n = 371)**	**Unsuppressed renin phenotype (renin ≥ 1.0 ng/mL/h) (n = 650)**	**p-value**
Aldosterone (ng/dL), n = 2255[a] [Beta (95 % CI)]				
Waist circumference (cm)	0.001 (−0.002, 0.003)	**0.005 (0.000, 0.010)**	0.003 (− 0.001, 0.007)	0.251
Body mass index (kg/m^2)	− 0.003 (− 0.009, 0.003)	0.005 (−0.005, 0.015)	**0.010 (0.002, 0.018)**	0.026
Waist:height ratio	−0.090 (−0.554, 0.373)	0.661 (−0.141, 1.463)	0.435 (− 0.191, 1.061)	0.183
Waist:hip ratio	**0.881 (0.135, 1.628)**	0.838 (− 0.608, 2.284)	0.118 (− 0.965, 1.202)	0.480
Adiponectin (ng/mL)[a]	**−0.137(−0.203, −0.072)**	−0.079 (− 0.192, 0.034)	−0.017 (− 0.104, 0.069)	0.086
Leptin (ng/mL)[a]	**0.066 (0.011, 0.122)**	0.069 (−0.021, 0.160)	**0.152 (0.084, 0.220)**	0.077
LAR[a]	**0.076 (0.036, 0.116)**	0.057 (−0.012, 0.125)	**0.103 (0.048, 0.158)**	0.547
SAT (cm^3)	−0.060 (−0.178, 0.058)	− 0.008 (− 0.254, 0.238)	**0.267 (0.085, 0.450)**	0.008
VAT (cm^3)	0.103 (− 0.014, 0.220)	0.199 (−0.022, 0.420)	0.092 (− 0.078, 0.263)	0.716
Liver attenuation (Hounsfield Units)[a]	− 0.238 (− 0.534, 0.057)	− 0.200 (− 0.768, 0.367)	− 0.065 (− 0.492, 0.362)	0.806

Abbreviations: LAR = leptin to adiponectin ratio; WC = waist circumference; BMI = body mass index; Renin = plasma renin activity; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.

Model: Model adjusted for age, sex, education, occupation, systolic blood pressure, smoking, and physical activity (AHA-Life's Simple 7).

Superscript:

[a] log transformed

[b] p-value was for interaction term.

Bold = p < 0.05.

Interpretation:

Equation: Both dependent and independent variables are log transformed: a 1 % change in the exposure is associated with a $[(1.01)^{\beta} - 1] * 100$ % change in the outcome.

Example: A1 % higher leptin is associated with a 0.151 % higher aldosterone (Unsuppressed Renin Phenotype).

Equation: Dependent variable is log transformed: a 1-unit change in the exposure is associated with a $(e^{\beta} - 1) * 100$ % change in the outcome.

Example: A1 kg/m^2 higher BMI is associated with 1.005 % higher aldosterone (Unsuppressed Renin Phenotype).

Table 4

Effect modification by hypertension, sex, and age in the association of adiposity markers with log-aldosterone and log-renin.

Log-aldosterone: beta coefficient (95 % CI)										
	WC (cm)	BMI (kg/m^2)	Waist:height ratio (visit 1)	Waist:hip ratio (visit 2)	Adiponectin (ng/mL)[b]	Leptin (ng/mL)[b]	LAR[c]	SAT (cm^3)[b]	VAT (cm^3)[b]	Liver attenuation (HU)[b]
Hypertension										
Yes	0.002 (0.000, 0.004)	0.002 (−0.002, 0.006)	0.332 (0.035, 0.629)	0.96 (0.44, 1.49)	−0.099 (−0.140, −0.058)	0.143 (0.106, 0.180)	0.115 (0.089, 0.142)	0.053 (−0.032, 0.139)	0.163 (0.083, 0.243)	−0.21 (−0.39, −0.028)
No	0.003 (0.001, 0.006)	0.005 (0, 0.009)	0.431 (0.087, 0.775)	1.32 (0.73, 1.91)	−0.193 (−0.242, −0.143)	0.078 (0.039, 0.117)	0.096 (0.067, 0.125)	−0.019 (−0.102, 0.063)	0.098 (0.016, 0.179)	−0.344 (−0.585, −0.102)
p-value[a]	0.247	0.467	0.666	0.342	**0.003**	**0.004**	0.303	0.198	0.261	0.384
Sex										
Female	0.003 (0.001, 0.005)	0.003 (−0.0002, 0.007)	0.441 (0.171, 0.710)	1.51 (1.018, 2.01)	−0.163 (−0.206, −0.121)	0.148 (0.104, 0.192)	0.134 (0.106, 0.162)	−0.017 (−0.108, 0.073)	0.234 (0.159, 0.309)	−0.429 (−0.626, −0.233)
Male	0.008 (0.005, 0.010)	0.018 (0.012, 0.024)	1.43 (0.998, 1.86)	1.22 (0.442, 2.00)	−0.142 (−0.195, −0.090)	0.153 (0.110, 0.197)	0.126 (0.095, 0.156)	0.125 (0.035, 0.216)	0.102 (0.012, 0.192)	−0.213 (−0.44, 0.015)
p-value[a]	**0.001**	**<0.001**	**<0.001**	0.528	0.538	0.860	0.691	**0.028**	**0.026**	0.157
Age										
Lower 50 %	0.005 (0.003, 0.007)	0.008 (0.004, 0.012)	0.773 (0.467, 1.08)	1.88(1.31, 2.45)	−0.193 (−0.240, −0.145)	0.133 (0.096, 0.171)	0.130 (0.102, 0.158)	0.06 (−0.02, 0.14)	0.17 (0.09, 0.25)	−0.36 (−0.55, −0.17)
Upper 50 %	0.004 (0.002, 0.006)	0.007 (0.002, 0.012)	0.644 (0.306, 0.982)	0.963 (0.395, 1.53)	−0.124 (−0.169, −0.079)	0.172 (0.132, 0.211)	0.132 (0.103, 0.160)	0.04 (−0.05, 0.14)	0.19 (0.1, 0.28)	−0.3 (−0.54, −0.06)
p-value[a]	0.736	0.727	0.572	**0.018**	**0.035**	**0.097**	0.937	0.757	0.791	0.705
Log-renin: beta coefficient (95 % CI)										
	WC (cm)	BMI (kg/m^2)	Waist:height ratio (visit 1)	Waist:hip ratio (visit 2)	Adiponectin (ng/mL)[c]	Leptin (ng/mL)[c]	LAR[c]	SAT (cm^3)[c]	VAT (cm^3)[c]	Liver attenuation (HU)[c]
Hypertension										

Yes	0.006 (0.000, 0.011)	0.017 (0.006, 0.027)	1.47 (0.657, 2.277)	1.15 (−0.235, 2.543)	−0.192 (−0.302, −0.082)	0.350 (0.252, 0.448)	0.26 (0.189, 0.331)	0.288 (0.05, 0.526)	0.467 (0.243, 0.69)	−0.583 (−1.08, −0.087)
No	0.008 (0.002, 0.014)	0.012 (−0.001, 0.024)	1.217 (0.264, 2.171)	1.774 (0.121, 3.43)	−0.342 (−0.48, −0.204)	0.212 (0.104, 0.321)	0.2 (0.12,0.28)	0.09 (−0.159, 0.34)	0.363 (0.122, 0.604)	−0.727 (−1.43, −0.022)
p-value[a]	0.561	0.538	0.692	0.550	**0.088**	**0.028**	0.245	0.230	0.537	0.743
Sex										
Female	0.01 (0.005, 0.014)	0.02 (0.011, 0.03)	1.89 (1.158, 2.62)	2.16(0.821, 3.50)	−0.3 (−0.414, −0.187)	0.357 (0.242, 0.472)	0.285 (0.211, 0.36)	0.3 (0.045, 0.554)	0.53 (0.32, 0.74)	−1.02 (−1.53, −0.52)
Male	0.012 (0.005, 0.019)	0.03 (0.013, 0.048)	2.39 (1.11, 3.67)	1.57 (−0.665, 3.81)	−0.277 (−0.427, −0.126)	0.377 (0.254, 0.5)	0.281 (0.194, 0.367)	0.276 (−0.005, 0.56)	0.51 (0.24, 0.79)	−0.4 (−1.13, 0.34)
p-value[a]	0.580	0.305	0.505	0.657	0.804	0.813	0.934	0.904	0.928	0.168
Age										
Lower 50 %	0.01 (0.005, 0.015)	0.021 (0.011, 0.032)	2.04 (1.19, 2.89)	2.34 (0.8, 3.88)	−0.322 (−0.452, −0.193)	0.366 (0.26, 0.472)	0.281 (0.205, 0.357)	0.25 (0.01, 0.49)	0.53 (0.30, 0.76)	−0.86 (−1.42, −0.31)
Upper 50 %	0.011 (0.006, 0.017)	0.023 (0.01, 0.036)	1.99 (1.06, 2.93)	1.55 (−0.035, 3.13)	−0.248 (−0.373, −0.124)	0.364 (0.259, 0.469)	0.277 (0.199, 0.355)	0.34 (0.08, 0.61)	0.49 (0.25, 0.74)	−0.79 (−1.42, −0.16)
p-value[a]	0.735	0.837	0.940	0.455	0.410	0.970	0.942	0.602	0.826	0.864

Models: Models were adjusted for age, sex, education, occupation, systolic blood pressure, smoking, and physical activity (AHA-Life's Simple 7).

Abbreviations: LAR = leptin:adiponectin ratio; WC = waist circumference; BMI = body mass index; HU = Hounsfield Units.

Superscripts:

[a]p-value was for interaction term

[b]Log-transformed.

Interpretation:

Equation: Both dependent and independent variables are log transformed: a 1 % change in the exposure is associated with a $[(1.01)^{\beta} - 1] * 100$ % change in the outcome. Example: A 1 % higher leptin is associated with a 0.142 % higher aldosterone in those with hypertension.

Equation: Dependent variable is log transformed: a 1-unit change in the exposure is associated with a $(e^{\beta} - 1) * 100$ % change in the outcome.

Example: A1 cm greater waist circumference (WC) is associated with 0.803 % higher aldosterone in men.