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# Relationship Between Renin, Aldosterone, Aldosterone-to-Renin Ratio and Arterial Stiffness and Left Ventricular Mass Index in Young Adults

Roshan A. Ananda, MD; StellaMay Gwini, PhD; Lawrence J. Beilin, MD; Markus P. Schlaich, MD; Michael Stowasser, PhD; Morag J. Young, PhD; Brendan Adler, MBBS; Peter J. Fuller, PhD; Trevor A. Mori, PhD*; Jun Yang, PhD*

**BACKGROUND:** Primary aldosteronism, characterized by renin-independent aldosterone production, is associated with adverse cardiovascular remodeling and outcomes. Elevated cardiovascular risk is observed even in subclinical forms of primary aldosteronism according to studies conducted primarily in middle-aged and elderly populations. This study aimed to assess whether early changes in primary aldosteronism biomarkers during young adulthood are associated with arterial stiffness and left ventricular mass index (LVMI) before the onset of overt disease.

**METHODS:** The Raine Study is a longitudinal, population-based cohort study in Western Australia that enrolled women during pregnancy. We analyzed the data from the offspring of these women at 17 (2006–2009) and 27 (2016–2018) years of age. Participants with elevated high-sensitivity C-reactive protein (>10 mg/L) and female participants who were on oral contraception were excluded. Pulse wave velocity and aortic augmentation index were measured by SphygmoCor Pulse Wave System at both ages, and aortic distensibility and LVMI were measured by cardiac magnetic resonance imaging at 27 years. Multivariable linear regression was used to examine the relationship between plasma renin, aldosterone, or aldosterone-to-renin ratio and arterial stiffness and LVMI. Mediation analysis was used to test the role of systolic blood pressure.

**RESULTS:** This study included 859 participants at 17 (38.0% female) and 758 participants at 27 (33.2% female) years of age. Females had lower renin concentration at both 17 (20.7 mU/L versus 25.7 mU/L; $P<0.001$) and 27 (12.0 mU/L versus 15.4 mU/L; $P<0.001$) years of age; hence, the aldosterone-to-renin ratio was significantly higher at both 17 (18.2 versus 13.5; $P<0.001$) and 27 (21.0 versus 15.6; $P<0.001$) years of age in females compared with males. At 27 years of age, a significant association was detected between aldosterone and LVMI in males ($\beta=0.009$ [95% CI, 0.001–0.017]; $P=0.027$) and between aldosterone-to-renin ratio and LVMI in females ($\beta=0.098$ [95% CI, 0.001–0.196]; $P=0.050$) independently of systolic blood pressure and other confounders. No association was found between primary aldosteronism biomarkers and measures of arterial stiffness (pulse wave velocity, aortic augmentation index, and aortic distensibility) at either age.

**CONCLUSIONS:** Aldosterone concentration and aldosterone-to-renin ratio were positively associated with the LVMI in young males and females, respectively, independently of systolic blood pressure. Long-term follow-up is required to determine whether the relationship persists over time, and clinical trials are needed to assess the cardiovascular benefits of early interventions to block aldosterone.

**Key Words:** aldosterone ■ heart disease risk factors ■ hyperaldosteronism ■ left ventricle ■ renin ■ vascular stiffness



Aldosterone is the predominant mineralocorticoid hormone that contributes to the homeostatic regulation of blood pressure (BP), and its production is stimulated primarily by circulating angiotensin II and potassium.[1] Excess aldosterone production, relatively independently of renin and angiotensin II, leads to

Correspondence to: Jun Yang, PhD, Endocrine Hypertension Group, Centre for Endocrinology and Metabolism, Hudson Institute of Medical Research, 27-31 Wright St, Clayton, Victoria 3168, Australia. Email jun.yang@hudson.org.au
*T.A. Mori and J. Yang contributed equally.
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## Clinical Perspective

### What Is New?

- This study has shown a positive blood pressure–independent association between aldosterone concentration or the aldosterone-to-renin ratio and left ventricular mass index in both males and females from a large population-based cohort of young adults.

### What Are the Clinical Implications?

- Our results suggest that earlier screening for primary aldosteronism may be needed to detect abnormalities in aldosterone concentration or the aldosterone-to-renin ratio in young adults with hypertension.
- In people with raised aldosterone concentration or aldosterone-to-renin ratio without concurrent hypertension, randomized clinical trials will be needed to evaluate whether early intervention with aldosterone blockade can prevent adverse cardiovascular outcomes.

## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ARR** | aldosterone-to-renin ratio |
| **AIx@75** | aortic augmentation index |
| **BMI** | body mass index |
| **BP** | blood pressure |
| **HDL** | high-density lipoprotein |
| **LVMI** | left ventricular mass index |
| **MR** | mineralocorticoid receptor |
| **PA** | primary aldosteronism |
| **PWV** | pulse wave velocity |
| **SBP** | systolic blood pressure |

activation of the mineralocorticoid receptors (MRs) and subsequent sodium and fluid retention, vascular remodeling, and myocardial fibrosis.[2–5] Primary aldosteronism (PA) is a state of autonomous renin-independent aldosterone excess that causes hypertension and increased potassium excretion.[6,7] PA also confers a higher risk of renal, metabolic, and cardiovascular diseases.[8,9] In the cardiovascular system, inappropriate MR activation in cardiac myocytes, vascular endothelium, and smooth muscle cells leads to increased inflammation and fibrosis.[3,8] Targeted treatment with MR antagonists or resection of an aldosterone-producing adrenal tumor can optimize BP and mitigate the excess cardiovascular risk.[8–12]

PA is generally considered an uncommon disease that manifests with resistant hypertension and hypokalemia.[6,7] However, emerging research has revealed a spectrum of renin-independent aldosteronism, ranging from normal BP in subclinical disease to resistant hypertension with cardiovascular complications in more florid disease.[13–19] People ≥40 years of age with a subclinical PA phenotype as defined by low renin concentration or an elevated aldosterone-to-renin ratio (ARR) without meeting the diagnostic criteria for PA were at higher risk of developing incident hypertension and adverse cardiac remodeling.[13–20] In a population-based cohort study of 1284 middle-aged adults (40–69 years of age) from Canada,[19] subclinical PA phenotype was associated with increased arterial stiffness and left ventricular mass index (LVMI), which are important predictors of cardiovascular disease and mortality independently of BP.[21–23]

Although these data provide insight into the association between PA and cardiovascular diseases, there are limited data on the association between biochemical markers of PA and early signs of cardiovascular damage in young adults.[24] Since timely targeted treatment of aldosterone excess can mitigate long-term cardiovascular risk, it is crucial to understand the effects of subclinical PA in young adults to inform early interventions.[6,7,25] Here, we present data examining the association between aldosterone, renin, and the ARR with arterial stiffness and LVMI in males and females at 17 and 27 years of age from the Raine Study. We have previously shown in this population that the ARR at 17 years was positively associated with systolic and diastolic BP at 27 years of age among females but not males.[26] We then hypothesized that a subclinical PA phenotype, characterized by higher aldosterone or higher ARR, is associated with higher arterial stiffness and LVMI in young adulthood.

## METHODS

### Study Setting and Population

Data were derived from the Raine Study, a community population-based, multigenerational life-course study that originated from a pregnancy-birth cohort study.[27] Between 1988 and 1991, 2900 pregnant women were recruited into a randomized controlled trial of ultrasound frequency and pregnancy outcomes in a tertiary health service in Perth, Western Australia.[28] The offspring (generation 2; n=2868 live births) of these pregnant women were invited to attended assessment centers in Perth every 2 to 3 years from birth to 27 years of age. They completed computer-based questionnaires for the assessment of socioeconomic, growth, lifestyle factors, and cardiometabolic health and attended clinic visits for measures of anthropometry (height, weight, and body mass index [BMI]), BP, and fasting blood and urine biochemistry. A more detailed description of the cohort has been reported elsewhere.[27,28] The Raine Study received ethics approval from the human research ethics committee of King Edward Memorial Hospital and Princess Margaret Hospital for Children and the University of Western Australia for the 17- and 27-year cohort recalls, respectively. Written informed consent was obtained from the mother or primary caregiver and the adolescent at 17 years of age and the generation 2 participants at 27 years. The Raine Study is registered in the Australian New Zealand Clinical

Trials Registry (ACTRN12617001599369). Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers may be sent to the Raine Study at rainestudy@uwa.edu.au. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[29]

Data on the relationships between aldosterone, renin, ARR, and BP in the generation 2 participants have been previously published.[26] The current study population differs because of differences in the eligibility criteria, with analyses restricted to participants who also had measures of arterial stiffness and LVMI at either 17 or 27 years of age. Pulse wave velocity (PWV) and aortic augmentation index (AIx@75) were available at 17 and 27 years of age, whereas aortic distensibility and LVMI were available only at 27 years of age. Participants with elevated high-sensitivity C-reactive protein (>10 mg/L; n=29 for 17 years of age; n=51 for 27 years of age; Figures S1 and S2) were excluded because of the confounding effect of inflammation and infection on BP and surrogate markers of cardiovascular health; female participants on hormonal contraception (n=156 for 17 years of age; n=247 for 27 years of age) were excluded because of the confounding effect of exogenous sex steroids on renin and aldosterone levels.[30]

## Renin, Aldosterone, and ARR

The method of aldosterone and renin measurement has been reported previously.[26] In brief, fasting blood specimens collected in supine position were centrifuged, and both EDTA plasma and serum were stored at −80 °C until analysis. Serum aldosterone was measured with a chemiluminescent immunoassay (LIAISON Aldosterone DiaSiasorin Inc, Stillwater, MN). Direct renin concentration was measured with a chemiluminescent assay (LIAISON Direct Renin, DiaSiasorin Inc). Although plasma is preferred for determining renin concentration, the availability of plasma was limited; hence, renin concentration was measured in serum samples. To calibrate the serum samples, renin concentration was measured in 90 paired serum and EDTA plasma samples and used to produce the conversion equation based on Peters-Belson regression: calculated plasma renin=(serum renin+0.97)/0.229 (Spearman rank correlation, $r$=0.813). The calculated plasma renin was used for all statistical analysis reported herein. ARR was calculated by dividing aldosterone concentration by plasma renin concentration.

## Arterial Stiffness and LVMI

Two measures, PWV and AIx@75 at 17 years of age, were used to assess arterial stiffness; PWV, AIx@75, and aortic distensibility were used at 27 years of age. At 17 years of age, PWV and AIx@75 were measured with a SphygmoCor Pulse Wave System (SCOR-Vx) and Pulse Wave Analysis System (SCOR-Px), as previously described.[31] At 27 years of age, PWV and AIx@75 were measured with SphygmoCor XCEL and SphygmoCor XCEL software version 1.2 (AtCor Medical Pty Ltd, Sydney, Australia). Tonometer placements differed for the 2 age groups: carotid and distal dorsalis pedis artery at 17 years of age and carotid and femoral artery at 27 years of age. Distance measurements were taken between the manubrium sternum and the sampling sites. Pulse wave measures were collected from the supported radial artery with wrist facing upward. PWV equaled the distance between tonometers divided by the transit time of the arterial pulse wave, expressed as meters per second. AIx@75 was calculated by dividing the difference between second and first systolic pressures by the pulse pressure, normalized to a heart rate of 75 bpm.[32]

At 27 years of age, aortic distensibility and LVMI were measured with cardiac magnetic resonance imaging on a Siemens Magnetom Aera 1.5T (Siemens AG, Erlangen, Germany) using XQ gradients (Max slew rate of 200 $T{\cdot}m^{-1}{\cdot}s^{-1}$; 45–mT/m rise time; 204×48 channel system) at Envision Medical Imaging, Perth. Participants entered the scanner supine and headfirst with 32-Channel spine array posteriorly and 2 × 18-Channel body array coils anteriorly. Cardiac function was assessed by acquiring cine images in the short axis (mitral valve plane to apex) and long axis (2-, 3-, and 4-chamber views). Cine images were breath-hold True FISP gradient echo 6 mm with 4-mm gap and 256×205 resolution and an acceleration factor of 2. The image data were then analyzed with Siemens Syngo Cardiac Analysis software version VB30. Average LVMI was calculated as the average of end-diastolic and end-systolic myocardial mass measurements. Distensibility data of the descending aorta were acquired at the level of the diaphragm with a through-plane breath-hold FLASH gradient echo sequence (6-mm cross-section). This was run 4 times, enabling an average of maximal (systolic) and minimal (diastolic) areas. Four BP readings (2 right arm and 2 left arm) of the brachial artery were acquired by means of sphygmomanometer cuff, with the average used to calculate aortic distensibility only with the following formula: $(A_{max}-A_{min})/A_{min}\times(P_{max}-P_{min})$, where A is the cross-sectional area of the aorta and $P_{max}$ and $P_{min}$ represents systolic and diastolic BP, respectively. BP used for statistical analysis was measured during clinic visits as described later.

## Covariates

In assessments of the association between ARR, aldosterone, and renin with arterial stiffness and LVMI, age, BMI, smoking status, alcohol consumption, physical activity, insulin resistance (homeostatic model assessment for insulin resistance), non–high-density lipoprotein (HDL) cholesterol, and high-sensitivity C-reactive protein were considered potential confounders. Body weight was measured with a Wedderburn Chair Scale (nearest 100 g), and height was measured with a Holtain stadiometer (nearest 0.1 cm). Information on smoking and alcohol consumption was obtained with the following questions: “Have you smoked in the last four weeks?” and “Have you had an alcoholic drink in the past 7 days?” (with options “yes” or “no”). Physical activity was quantified by self-reported average time spent on exercise daily expressed as minutes per day. Homeostatic model assessment for insulin resistance was calculated as fasting insulin multiplied by fasting glucose and then divided by 22.5.[33] Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol.

During clinic visits, after 5 minutes of rest, 6 BP readings were taken every 2 minutes with an oscillometric sphygmomanometer (Dinamap ProCare 100, GE HealthcareA) and appropriate cuff size. The average of the last 5 readings of BP was calculated and used for analysis. Unlike other covariates, systolic BP (SBP) was examined as a potential mediator but not as a confounder because of the likelihood that SBP is in the causal pathway between cardiovascular markers and ARR/aldosterone/renin.

## Statistical Analysis

All analyses were stratified by sex (male or female). Descriptive characteristics were presented as frequencies with percentages for categorical data, means with SDs for normally distributed data, and median with 25th and 75th percentiles for skewed data. Descriptive characteristics were compared between sexes with the $\chi^2$ test for categorical data, 2-sample *t* test for normally distributed data, and Mood median test for skewed data. Univariable and multivariable linear regression models were used to examine the relationship between cardiovascular markers (PWV, AIx@75, aortic distensibility, and LVMI) and renin, aldosterone, and the ARR, with adjustment for the possible confounders. Further sensitivity analyses were performed by adjusting the linear regression for serum creatinine as a measure of renal function. Variance inflation factor was used to check for multicollinearity of linear regression models, and a variance inflation factor of <4 was used to define absence of multicollinearity. Complete case analysis was performed, and no missing data imputation was conducted. Missingness was assumed to be random, and the detailed information is presented in Tables 1 and 2.

Mediation analysis was performed with the method described by the Baron and Kenny method to determine whether SBP was a mediator in the relationship between cardiovascular surrogate markers and renin, aldosterone, and ARR.[34,35] Significance was determined by a bootstrapping approach, with data resampled 500 times during the process. The mediation analyses were performed only if a statistically significant association was observed for the PA biomarkers and cardiovascular surrogate markers.

All analyses were performed with R version 4.0.2, and a 95% CI was calculated and reported for all regression outcomes. Level of statistical significance was set at 0.05.

# RESULTS

The current analyses included 859 participants at 17 years of age (533 males, 62.0%; 326 females, 38.0%) and 758 participants at 27 years of age (506 males, 66.8%; 252 females, 33.2%; Table 1). Approximately 91% of participants were White. BMI was similar between males and females at both ages, but BMI was higher at 27 years of age ($P<0.001$ for both sexes). More males than females consumed alcohol at 27 years of age, and men spent more time doing physical activities at both 17 and 27 years of age. SBP was significantly higher in males than females at both 17 (mean, 118±9 mm Hg versus 108±9 mm Hg; $P<0.001$) and 27 (mean, 122±11 mm Hg versus 111±9 mm Hg; $P<0.001$) years of age. At 17 years of age, 56 male (10.5%) and 5 female (1.5%) participants had hypertension, as defined by SBP ≥130 mm Hg or diastolic BP ≥80 mm Hg, whereas at 27 years of age, 134 male (26.4%) and 14 female (5.6%) participants had hypertension.[36] Three female participants with hypertension were on antihypertensive medications at 27 years of age, whereas none of the male participants with hypertension were on antihypertensive medications.

## Clinical and Biochemical Characteristics

Homeostatic model assessment for insulin resistance and high-sensitivity C-reactive protein were similar between males and females at both ages. Non-HDL cholesterol was higher in males than females at 27 years of age (mean, 3.5±0.9 mmol/L versus 3.2±0.7 mmol/L; $P<0.001$). Other significant differences between the sexes at 17 and 27 years of age included HDL and low-density cholesterol (Table 1).

Aldosterone concentration was similar between males and females at 17 (median, 346 pmol/L versus 349 pmol/L; $P=0.867$) and 27 (median, 237 pmol/L versus 257 pmol/L; $P=0.143$; Table 1) years of age. However, renin concentration was lower in females than males at both 17 (median, 20.7 mU/L versus 25.7 mU/L; $P<0.001$) and 27 (median, 12.0 mU/L versus 15.4 mU/L; $P<0.001$) years of age; thus, ARR was significantly higher in females than males at both 17 (median, 18.2 pmol/L:mU/L versus 13.5 pmol/L:mU/L; $P<0.001$) and 27 (median, 21.0 pmol/L:mU/L versus 15.6 pmol/L:mU/L; $P<0.001$) years of age.

When males were compared with females, the PWV was higher in males at both 17 (mean, 6.65±0.75 m/s versus 6.22±0.64 m/s; $P<0.001$) and 27 (mean, 6.28±0.77 m/s versus 5.60±0.73 m/s; $P<0.001$) years of age, whereas AIx@75 was lower at both 17 (median, −10.00 versus −6.50; $P<0.001$) and 27 (median, −6.26 versus 0.90; $P<0.001$) years of age. At 27 years of age, aortic distensibility was lower in males (mean, $9.5\pm2.8\times10^{-3}$ mm Hg$^{-1}$ versus $12.6\pm3.2\times10^{-3}$ mm Hg$^{-1}$; $P<0.001$), whereas LVMI was higher in males (mean, 70.2±9.9 g/m$^2$ versus 52.2±7.0 g/m$^2$; $P<0.001$).

## Renin, Aldosterone, ARR, and LVMI at 27 Years of Age

Aldosterone was positively associated with LVMI in males after adjustment for confounding factors (β=0.009 [95% CI, 0.001–0.017]; $P=0.027$; Table 2; Figure). In females, the ARR was positively associated with LVMI (β=0.0983 [95% CI, 0.001–0.196]; $P=0.050$). Further sensitivity analyses showed that these associations remained unchanged after adjustment for serum creatinine (Table S1). There was no association between LVMI and renin or ARR in males or aldosterone in females. In mediation analysis, we did not find evidence that SBP mediated the relationship between aldosterone and LVMI among males or the relationship between ARR and LVMI among females (Table 3).

## Renin, Aldosterone, ARR, and Arterial Stiffness at 17 and 27 Years of Age

At 17 years of age, neither PWV nor AIx@75 was associated with renin, aldosterone, or ARR in males or females

**Table 1. Characteristics of the Participants at 17 and 27 Years of Age**

| | 17-y-old cohort | | | 27-y-old cohort | | |
|---|---|---|---|---|---|---|
| | Males (n=533) | Females (off HC; n=326) | Comparisons (*P* value) | Males (n=506 | Females (off HC; n=252) | Comparisons (*P* value) |
| Age, mean±SD, y | 17.0±0.2 | 17.0±0.2 | 0.357 | 26.7±0.4 | 26.7±0.4 | 0.808 |
| BMI, mean±SD, kg/m²* | 22.8±4.3 | 23.3±4.6 | 0.115 | 25.9±5.0 | 25.5±6.1 | 0.319 |
| Weight, mean±SD, kg* | 72.7±14.8 | 64.5±13.4 | <0.001 | 84.8±17.7 | 71.3±17.3 | <0.001 |
| BP*† | | | | | | |
| SBP, mean±SD, mm Hg | 118±9 | 108±9 | <0.001 | 122±11 | 111±9 | <0.001 |
| DBP, mean±SD, mm Hg | 58±7 | 59±6 | 0.263 | 71±8 | 67±7 | <0.001 |
| SBP ≥130 mm Hg or DBP ≥80 mm Hg, n (%) | 56 (10.5) | 5 (1.5) | <0.001 | 134 (26.4) | 14 (5.6) | <0.001 |
| SBP ≥140 mm Hg or DBP ≥90 mm Hg, n (%) | 11 (2.1) | 1 (0.3) | 0.067 | 27 (5.3) | 1 (0.4) | 0.001 |
| Heart rate, mean±SD, bpm | 64±10 | 66±9 | <0.001 | 67±10 | 72±10 | <0.001 |
| Aldosterone, median (25th, 75th percentile), pmol/L | 346 (237, 473) | 349 (247, 589) | 0.867 | 237 (171, 318) | 257 (177, 390) | 0.143 |
| Renin, median (25th, 75th percentile), mU/L | 25.7 (17.0, 46.0) | 20.7 (14.2, 33.7) | <0.001 | 15.4 (9.3, 24.9) | 12.0 (7.7, 20.6) | <0.001 |
| Renin categories, n (%) | | | | | | |
| <10 mU/L | 51 (9.6) | 44 (13.5) | 0.095 | 145 (28.6) | 102 (40.5) | 0.001 |
| ≥10 mU/L | 482 (90.4) | 282 (86.5) | | 362 (71.4) | 150 (59.5) | |
| ARR, median (25th, 75th percentile), pmol/L:mU/L | 13.5 (8.0, 20.6) | 18.2 (11.0, 26.3) | <0.001 | 15.6 (10.5, 22.9) | 21.0 (13.5, 28.8) | <0.001 |
| ARR categories, n (%) | | | | | | |
| <50 pmol/L:mU/L | 530 (99.4) | 307 (94.2) | <0.001 | 500 (98.6) | 243 (96.4) | 0.091 |
| 50–70 pmol/L:mU/L | 3 (0.6) | 13 (4.0) | | 5 (1.0) | 8 (3.2) | |
| >70 pmol/L:mU/L | 0 | 6 (1.8) | | 2 (0.4) | 1 (0.4) | |
| Blood biochemistry*† | | | | | | |
| Serum creatinine, mean±SD, µmol/L | 80±10 | 67±9 | <0.001 | 79±10 | 64±6 | <0.001 |
| Plasma glucose, mean±SD, mmol/L | 4.9±0.7 | 4.6±0.4 | <0.001 | 4.9±0.6 | 4.6±0.5 | <0.001 |
| HOMA-IR, median (25th, 75th percentile) | 1.5 (1.0, 2.3) | 1.6 (1.1, 2.3) | 0.206 | 1.1 (0.8, 1.6) | 1.1 (0.8, 1.6) | 0.173 |
| hsCRP, median (25th, 75th percentile), mg/L | 0.42 (0.18, 0.97) | 0.49 (0.21, 1.18) | 0.141 | 0.70 (0.33, 1.70) | 0.85 (0.40, 2.10) | 0.076 |
| HDL cholesterol, mean±SD, mmol/L | 1.2±0. | 1.4±0.3 | <0.001 | 1.3±0.3 | 1.6±0.4 | <0.001 |
| Non-HDL cholesterol, mean±SD, mmol/L | 2.7±0.7 | 2.8±0.6 | 0.538 | 3.5±0.9 | 3.2±0.7 | <0.001 |
| LDL cholesterol, mean±SD, mmol/L | 2.2±0.7 | 2.3±0.6 | 0.043 | 3.0±0.8 | 2.8±0.6 | 0.007 |
| Smoking status, n (%)*† | | | | | | |
| Have you smoked in the last 4 wk, n (%) | | | | | | |
| No | 423 (81.7) | 254 (78.4) | 0.284 | 327 (77.3) | 187 (82.0) | 0.191 |
| Yes | 95 (18.3) | 70 (21.6) | | 96 (22.7) | 41 (18.0) | |
| Alcohol consumption, n (%)*† | | | | | | |
| Have you had an alcoholic drink in past 7 d? | | | | | | |
| No | 256 (48.6) | 169 (52.0) | 0.368 | 79 (16.7) | 50 (23.8) | 0.036 |
| Yes | 271 (51.4) | 156 (48.0) | | 395 (83.3) | 160 (76.2) | |
| Time spent in physical activity*† | | | | | | |
| All exercise, median (25th, 75th percentile), min/d | 126 (63, 237) | 87 (45, 184) | <0.001 | 74 (30, 155) | 56 (21, 129) | 0.026 |

(*Continued*)

**Table 1. Continued**

| | 17-y-old cohort | | | 27-y-old cohort | | |
|---|---|---|---|---|---|---|
| | Males (n=533) | Females (off HC; n=326) | Comparisons (*P* value) | Males (n=506 | Females (off HC; n=252) | Comparisons (*P* value) |
| Arterial stiffness and LVMI*† | | | | | | |
| Pulse wave velocity, mean±SD, m/s | 6.65±0.75 | 6.22±0.64 | <0.001 | 6.28±0.77 | 5.60±0.73 | <0.001 |
| Aortic augmentation index @75 y, median (25th, 75th percentile) | −10.00 (−17.50, −2.50) | −6.50 (−14.00, 1.00) | <0.001 | −6.26 (−13.61, 0.80) | 0.90 (−7.54, 10.69) | <0.001 |
| Aortic distensibility, mean±SD, $10^{-3}$ mm $Hg^{-1}$ | … | … | … | 9.5±2.8 | 12.6±3.2 | <0.001 |
| LVMI, mean±SD, g/$m^2$ | … | … | … | 70.2±9.9 | 52.2±7.0 | <0.001 |

ARR indicates aldosterone-to-renin ratio; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HC, hormonal contraception; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVMI, left ventricular mass index; and SBP, systolic blood pressure.

*Missing data at 17 years of age: BMI and weight (3 males and 1 female); blood pressure and heart rate (2 males); plasma glucose and HOMA-IR (1 male); smoking status (15 males and 2 females); alcohol consumption (6 males and 1 female); physical activity (93 males and 33 females); pulse wave velocity (11 males and 6 females); and augmentation index (26 males and 23 females).

†Missing data at 27 years of age: blood pressure and heart rate (1 female); plasma glucose and HOMA-IR (2 males); cholesterol (2 males); smoking status (83 males and 24 females); alcohol consumption (33 males and 42 females); physical activity (76 males and 22 females); pulse wave velocity (3 males and 6 females); augmentation index (2 males and 8 females); aortic distensibility (53 males and 32 females); and LVMI (84 males and 46 females).

(Table 4). At 27 years of age, neither aldosterone nor ARR was associated with measures of arterial stiffness in females or males (Table 2). Among males, aldosterone was inversely associated with aortic distensibility in unadjusted analysis (β=−0.002 [95% CI, −0.004 to −0.001]; *P*=0.039), but the association was no longer significant after accounting for age and BMI. Renin was inversely associated with PWV among females (β=−0.010 [95% CI, −0.018 to −0.002]; *P*=0.010) in the unadjusted analysis, but it was no longer significant after adjustment for confounding factors. Renin was positively associated with aortic distensibility among females (β=0.038 [95% CI, 0.002–0.073]; *P*=0.040) after adjustment for age and BMI but not after adjustment for other cardiovascular risk factors.

## DISCUSSION

This is the largest population-based cohort demonstrating a BP-independent relationship between a subclinical PA phenotype and adverse left ventricular remodeling in young adults of both sexes. At 27 years of age, we found positive associations between aldosterone and LVMI in males and ARR and LVMI in females that were independent of brachial SBP and a number of important demographic, lifestyle, and clinical cardiovascular risk factors. Although the strength of the correlations was not strong, they were clinically and statistically significant, especially for this young age group.

In line with previous studies of middle-aged adults, this study has shown a positive association between markers of PA and LVMI, but at a substantially younger age of 27 years.[14,19] These findings suggest that a subclinical PA phenotype in young adulthood was associated with abnormal left ventricular remodeling, although the mean LVMI (males, 70.2±9.9 g/$m^2$; females, 52.2±7.0 g/$m^2$) was not in the range that would define left ventricular hypertrophy in males (>87 g/$m^2$) or females (>72 g/$m^2$).[37] Although the changes were subtle compared with the higher odds of left ventricular hypertrophy in a middle-aged cohort, a higher LVMI has been shown to increase the risk of cardiovascular disease.[19] According to the Framingham Heart Study offspring cohort study of middle-aged participants without prevalent cardiovascular disease, every 10 g/$m^2$ increase in LVMI was associated with a 33% increase in cardiovascular risk over 8.4 years of follow-up.[38] Our findings that LVMI increased by 0.90 g/$m^2$ with every 100 pmol/L increase in aldosterone concentration among males and that LVMI increased by 0.98 g/$m^2$ with every 10 pmol/L:mU/L increase in ARR among females at 27 years correspond to a 3.0% and 3.2% increase in cardiovascular risk, respectively.[38] Although resting BP did not appear to be mediating the effect in our participants, over multiple years, it is likely that the compounding effect of even a small BP increase will exacerbate the detrimental effect of a subclinical PA phenotype on left ventricular mass and its associated cardiovascular risk.[39] The excess risk may be mitigated by MR antagonists, but the exact role and efficacy of these medications in the absence of hypertension or biochemically confirmed PA are unknown.[11] Follow-up of aldosterone and renin, in addition to measures of arterial stiffness and LVMI, is warranted in these young adults to determine whether the associations persist. Investigation may also be warranted to determine the role of MR antagonists in people with a subclinical PA phenotype to mitigate the increased cardiovascular risk.

Our finding of a sex difference in the association between LVMI and PA biomarkers may be explained in part by differences in estrogen levels between males and

**Table 2. Relationship Between Aldosterone, Renin, ARR and Pulse Wave Velocity, AIx@75, Aortic Distensibility, and LVMI at 27 Years of Age**

| | Unadjusted | | Adjusted | | | |
|---|---|---|---|---|---|---|
| | β (95% CI) | *P* value | β† (95% CI) | *P* value | β‡ (95% CI) | *P* value |
| Outcome: LVMI | | | | | | |
| Aldosterone | | | | | | |
| Males | 0.005 (−0.002 to 0.012) | 0.154 | 0.005* (−0.003 to 0.012) | 0.209 | 0.009* (0.001 to 0.017) | 0.027 |
| Females | 0.001 (−0.004 to 0.006) | 0.713 | 0.001* (−0.004 to 0.006) | 0.714 | 0.002* (−0.004 to 0.007) | 0.593 |
| Renin | | | | | | |
| Males | −0.009 (−0.074 to 0.056) | 0.785 | −0.005* (−0.070 to 0.059) | 0.869 | 0.066* (−0.017 to 0.148) | 0.119 |
| Females | −0.12 (−0.20 to −0.04) | 0.003 | −0.13* (−0.21 to −0.05) | 0.002 | −0.05* (−0.15 to 0.05) | 0.310 |
| ARR | | | | | | |
| Males | 0.068 (−0.016 to 0.152) | 0.111 | 0.054* (−0.031 to 0.139) | 0.216 | 0.019* (−0.078 to 0.117) | 0.699 |
| Females | 0.12 (0.04 to 0.20) | 0.002 | 0.13* (0.05 to 0.21) | 0.002 | 0.0983* (0.0001 to 0.1964) | 0.050 |
| Outcome: PWV | | | | | | |
| Aldosterone | | | | | | |
| Males | −0.0001 (−0.0007 to 0.0004) | 0.599 | −0.0002* (−0.0007 to 0.0003) | 0.358 | −0.0003* (−0.0008 to 0.0003) | 0.329 |
| Females | −0.0001 (−0.0006 to 0.0003) | 0.567 | −0.0001* (−0.0006 to 0.0003) | 0.593 | −0.0003* (−0.0008 to 0.0003) | 0.347 |
| Renin | | | | | | |
| Males | −0.0006 (−0.0054 to 0.0041) | 0.791 | 0.0002* (−0.0044 to 0.0049) | 0.920 | −0.0021* (−0.0075 to 0.0032) | 0.437 |
| Females | −0.010 (−0.018 to −0.002) | 0.010 | −0.006* (−0.014 to 0.010) | 0.089 | −0.007* (−0.015 to 0.001) | 0.100 |
| ARR | | | | | | |
| Males | 0.001 (−0.005 to 0.007) | 0.641 | −0.001* (−0.007 to 0.005) | 0.702 | 0.0001* (−0.0063 to 0.0065) | 0.977 |
| Females | 0.006 (−0.002 to 0.014) | 0.118 | 0.003* (−0.004 to 0.010) | 0.416 | 0.003* (−0.006 to 0.011) | 0.575 |
| Outcome: AIx@75 | | | | | | |
| Aldosterone | | | | | | |
| Males | 0.007 (−0.002 to 0.016) | 0.121 | 0.005* (−0.003 to 0.014) | 0.213 | −0.002* (−0.011 to 0.008) | 0.741 |
| Females | 0.0006 (−0.0118 to 0.0130) | 0.928 | 0.0008* (−0.0112 to 0.0129) | 0.889 | −0.0002* (−0.0143 to 0.0140) | 0.980 |
| Renin | | | | | | |
| Males | 0.03 (−0.06 to 0.11) | 0.540 | 0.04* (−0.04 to 0.12) | 0.283 | 0.02* (−0.08 to 0.11) | 0.739 |
| Females | −0.05 (−0.25 to 0.14) | 0.587 | 0.02* (−0.17 to 0.21) | 0.845 | 0.02* (−0.20 to 0.24) | 0.858 |
| ARR | | | | | | |
| Males | 0.06 (−0.05 to 0.16) | 0.282 | 0.01* (−0.09 to 0.11) | 0.874 | 0.01* (−0.11 to 0.12) | 0.894 |
| Females | 0.06 (−0.13 to 0.24) | 0.538 | 0.01* (−0.17 to 0.19) | 0.906 | −0.02* (−0.25 to 0.20) | 0.853 |

(*Continued*)

**Table 2. Continued**

| | Unadjusted | | Adjusted | | | |
|---|---|---|---|---|---|---|
| | β (95% CI) | *P* value | β† (95% CI) | *P* value | β‡ (95% CI) | *P* value |
| Outcome: aortic distensibility | | | | | | |
| Aldosterone | | | | | | |
| Males | −0.0022 (−0.0042 to −0.0001) | 0.039 | −0.0018* (−0.0039 to 0.0002) | 0.076 | −0.0018* (−0.0041 to 0.0006) | 0.141 |
| Females | −0.00004 (−0.00235 to 0.00227) | 0.974 | −0.00016 (−0.00248 to 0.00216) | 0.891 | −0.00021* (−0.00276 to 0.00234) | 0.869 |
| Renin | | | | | | |
| Males | −0.005 (−0.023 to 0.013) | 0.581 | −0.007* (−0.025 to 0.010) | 0.419 | −0.007 (−0.029 to 0.016) | 0.554 |
| Females | 0.040 (0.004 to 0.075) | 0.028 | 0.038* (0.002 to 0.073) | 0.040 | 0.015* (−0.027 to 0.056) | 0.493 |
| ARR | | | | | | |
| Males | −0.019 (−0.042 to 0.004) | 0.099 | −0.011* (−0.035 to 0.012) | 0.337 | −0.007* (−0.035 to 0.020) | 0.606 |
| Females | −0.023 (−0.057 to 0.011) | 0.184 | −0.024* (−0.058 to 0.011) | 0.181 | −0.016* (−0.058 to 0.026) | 0.445 |

AIx@75 indicates aortic augmentation index; ARR, aldosterone-to-renin ratio; LVMI, left ventricular mass index; and PWV, pulse wave velocity.
*Indicates no evidence of multicollinearity (variance inflation factor <4).
†Adjusted for age and BMI only.
‡Adjusted for age, body mass index, smoking, alcohol, physical activity, homeostatic model assessment for insulin resistance, non–high-density lipoprotein, and high-sensitivity C-reactive protein.

females. Among females, the higher levels of estrogen can antagonize the MR through the estrogen receptor.[40] Thus, comparable levels of aldosterone are likely to have relatively more detrimental effects in males and may explain why aldosterone concentration per se is associated with increased LVMI in males but not in females.[40] Another potential explanation for this phenomenon is that cortisol and aldosterone have similar binding affinities for the MR, so their relative occupancy of MR will be driven by their relative concentrations, noting that cortisol levels are generally 1 to 2 orders of magnitude higher.[1] Hence, cardiac MRs are largely occupied and activated by cortisol under normal circumstances, but this may be substituted and controlled by aldosterone in the pathological state of aldosterone excess.[1] Therefore, corculating aldosterone concentration may not correlate with cardiac injury until later disease stages, especially in the presence of high estrogen concentration in females.[40] The impact of salt intake on aldosterone concentration and cardiac injury is also important to consider; animal models of mineralocorticoid-induced cardiac disease have shown that aldosterone excess has an adverse impact on the heart and vasculature when inappropriate for salt status.[41] Although we do not have data on salt intake in the present study, females generally consume less salt than males and may therefore be less susceptible to cardiac injury associated with circulating aldosterone concentration per se.[42,43] In contrast, the ARR takes

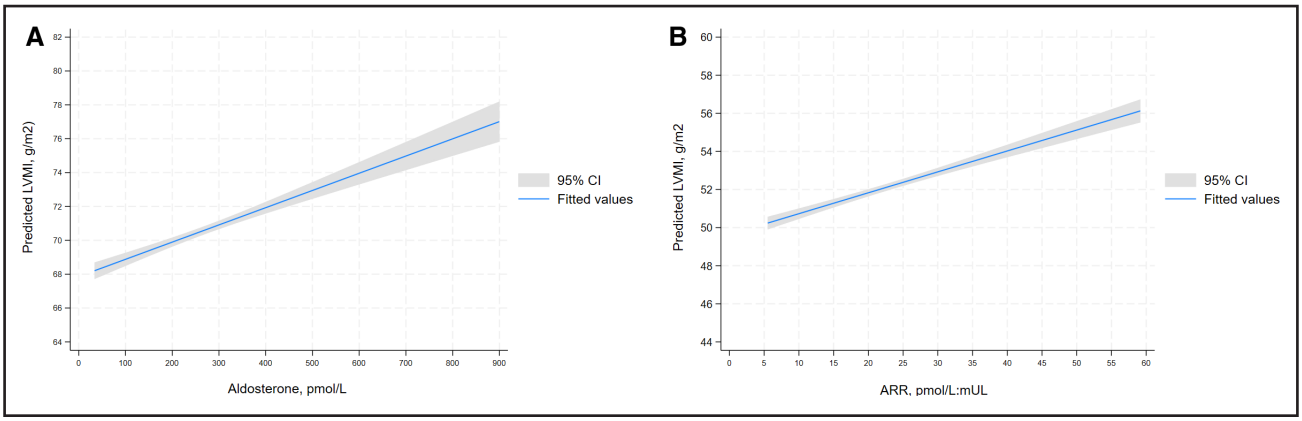


**Figure. Regression plot.**
**A**, Association between aldosterone concentrations and left ventricular mass index (LVMI) among males at 27 years of age. **B**, Association between aldosterone-to-renin ratio (ARR) and LVMI among females at 27 years of age. Adjusted for age, body mass index, smoking, alcohol, physical activity, homeostatic model assessment for insulin resistance, non–high-density lipoprotein, and high-sensitivity C-reactive protein.

**Table 3. Mediation Analysis of 27-Year Cohort**

| Variables | Aldosterone/ARR vs SBP* | |
|---|---|---|
| | β (95% CI) | *P* value |
| Aldosterone in males | −0.005 (−0.012 to 0.002) | 0.159 |
| ARR in females | 0.01 (−0.09 to 0.10) | 0.856 |

ARR indicates aldosterone-to-renin ratio; and SBP, systolic blood pressure.

*Subsequent analyses to assess the mediation effect of SBP were not warranted, given that there were no associations between aldosterone and SBP in males and between ARR and SBP in females. Because these analyses were not warranted, the table was simplified and does not include detailed information of the analysis.

into account aldosterone concentration and factors that regulate renin concentration, including salt intake, which tends to decrease renin.[44] This may explain the association between ARR and LVMI in females in our study.

In this young adult cohort, despite the relationship with LVMI, there was no association between subclinical PA phenotype and arterial stiffness, as measured by PWV, AIx@75, and aortic distensibility. A recent Canadian population-based study of 1284 middle-aged adults demonstrated that a subclinical PA phenotype was associated with increased arterial stiffness in a BP-independent manner.[19] Arterial stiffness is likely attributable to MR-mediated increased oxidative stress in the blood vessel wall, which may promote vascular inflammation and fibrosis of the vessel wall.[3] We postulate that a subtle increase in MR-mediated vascular fibrosis in predominantly healthy and elastic blood vessels of our young participants may not yet be reflected by the surrogate markers of arterial stiffness (eg, PWV and AIx@75) compared with LVMI, which is a more direct measure of left ventricular hypertrophy.[45–48] It will be interesting to determine whether an association between biomarkers of PA and arterial stiffness becomes more prominent as the Raine Study generation 2 participants approach middle age.

The finding that the positive association between subclinical PA phenotype and LVMI was independent of SBP underscores the significance of direct cardiovascular effects associated with increased MR activation. This is consistent with previous studies showing that patients with PA have a higher risk of cardiovascular disease than those with BP-matched essential hypertension and literature describing a subclinical PA phenotype.[8,9,13–16] The effects of inappropriate MR activation on cardiac surrogate markers are underpinned by preclinical and clinical studies that demonstrated MR-mediated vascular and myocardial fibrosis, impaired relaxation, and cardiac hypertrophy.[3,49–51]

## Strength and Limitations

A key strength of our study is the large sample size and relatively young age of the participants compared with previous studies. The finding that a subclinical PA phenotype was associated with increased LVMI in both males and females at 27 years of age was likely clinically relevant given the association between increased LVMI and cardiovascular risk.[38] Our study used cardiac magnetic resonance imaging, which is an accurate measure of LVMI, because it allows more precise left ventricular mass measurement across the entire ventricle than echocardiography and is highly correlated with myocardial fibrosis.[48,52,53] BP is known to directly modify LVMI, but it is also a direct mediator of the effect of aldosterone excess; hence, we performed a separate mediation analysis rather than adjusting it as a covariate in the regression models.[23]

Although our study adjusted for a number of confounders associated with measures of arterial stiffness and LVMI, residual confounding cannot be eliminated in this observational study; therefore, a causal interpretation should be viewed with caution. Another limitation is the lack of adjustment for dietary salt intake, which is known to affect renin and aldosterone, although the ARR is less likely to be affected.[54,55] Our study may be subject to some degree of misclassification bias because only a single measurement of renin and aldosterone was performed on our participants, and significant intraindividual variability has been reported in previous studies.[56] A comparison of PWV over the 2 time points was not possible because of differences in the methodology at the 2 ages. At 17 years of age, PWV was measured with tonometers applied at the carotid–dorsalis pedis arteries rather than the carotid-femoral arteries at 27 years of age because of modesty after a focus group discussion with the younger participants. Another limitation is that clinic BP measurements were used in our study and may not be a precise measure of long-term BP burden compared with ambulatory BP measurements.[57,58]

## Perspective and Conclusions

This study has shown a positive association between a subclinical PA phenotype and LVMI in a large cohort of young adults that was independent of resting brachial SBP and other conventional cardiovascular risk factors. These findings highlight the potential for MR-mediated left ventricular remodeling to contribute to future cardiovascular risk from a young age. Long-term follow-up of these young adults is required to determine whether the relationship between aldosterone or ARR and LVMI persists over time and whether new associations with other cardiovascular markers develop at later time points. Given the availability of highly effective treatments for PA, including emerging nonsteroidal MR antagonists, clinical trials may be warranted to test the impact of early intervention in patients with new-onset hypertension or an elevated ARR on their long-term cardiovascular health outcomes.[59]

**Table 4. Relationship Between Aldosterone, Renin, ARR and Pulse Wave Velocity, and Aortic Augmentation Index at 17 Years of Age**

| | Unadjusted | | Adjusted | | | |
|---|---|---|---|---|---|---|
| | β (95% CI) | *P* value | β† (95% CI) | *P* value | β‡ (95% CI) | *P* value |
| Outcome: PWV | | | | | | |
| Aldosterone | | | | | | |
| Males | 0.0002 (−0.0001 to 0.0006) | 0.148 | 0.0002* (−0.0001 to 0.0006) | 0.153 | 0.0002* (−0.0002 to 0.0006) | 0.349 |
| Females | 0.0001 (−0.0002 to 0.0003) | 0.472 | 0.0001* (−0.0002 to 0.0003) | 0.470 | 0.0001* (−0.0002 to 0.0003) | 0.604 |
| Renin | | | | | | |
| Males | −0.0003 (−0.0020 to 0.0015) | 0.775 | −0.0003* (−0.0020 to 0.0015) | 0.738 | −0.0007* (−0.0027 to 0.0013) | 0.514 |
| Females | −0.0015 (−0.0048 to 0.0017) | 0.345 | −0.0016* (−0.0048 to 0.0017) | 0.348 | −0.0007* (−0.0043 to 0.0030) | 0.724 |
| ARR | | | | | | |
| Males | 0.006 (−0.001 to 0.012) | 0.074 | 0.006* (−0.001 to 0.012) | 0.070 | 0.0070* (−0.0001 to 0.0140) | 0.052 |
| Females | 0.002 (−0.003 to 0.006) | 0.510 | 0.002* (−0.003 to 0.006) | 0.520 | 0.0001* (−0.0052 to 0.0053) | 0.979 |
| Outcome: AIx@75 | | | | | | |
| Aldosterone | | | | | | |
| Males | −0.0005 (−0.0054 to 0.0044) | 0.853 | 0.0003* (−0.0045 to 0.0051) | 0.897 | −0.0032* (−0.0085 to 0.0021) | 0.241 |
| Females | −0.0013 (−0.0050 to 0.0023) | 0.474 | −0.0011* (−0.0047 to 0.0026) | 0.562 | −0.0003* (−0.0042 to 0.0036) | 0.877 |
| Renin | | | | | | |
| Males | 0.006 (−0.019 to 0.032) | 0.629 | 0.012* (−0.013 to 0.037) | 0.340 | 0.011* (−0.017 to 0.038) | 0.437 |
| Females | −0.009 (−0.057 to 0.038) | 0.700 | −0.013* (−0.061 to 0.035) | 0.590 | 0.004* (−0.047 to 0.054) | 0.890 |
| ARR | | | | | | |
| Males | −0.0004 (−0.0939 to 0.0931) | 0.993 | −0.0185* (−0.1094 to 0.0723) | 0.689 | −0.0469* (−0.1481 to 0.0543) | 0.363 |
| Females | 0.007 (−0.066 to 0.079) | 0.859 | 0.007* (−0.065 to 0.080) | 0.845 | 0.008* (−0.069 to 0.084) | 0.844 |

AIx@75 indicates aortic augmentation index; ARR, aldosterone-to-renin ratio; and PWV, pulse wave velocity.

*Indicates no evidence of multicollinearity (variance inflation factor <4).

†Adjusted for age and body mass index only.

‡Adjusted for age, body mass index, smoking, alcohol, physical activity, homeostatic model assessment for insulin resistance, non–high-density lipoprotein, and high-sensitivity C-reactive protein.



## ARTICLE INFORMATION

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### Affiliations

Endocrine Hypertension Group, Centre of Endocrinology and Metabolism, Hudson Institute of Medical Research, Clayton, Victoria, Australia (R.A.A., P.J.F., J.Y.). School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia (S.G.). Medical School (L.J.B., T.A.M.) and Dobney Hypertension Centre, Medical School (M.P.S.), Royal Perth Hospital Unit, University of Western Australia, Australia. Endocrine Hypertension Research Centre, UQ Frazer Institute, Brisbane, Queensland, Australia (M.S.). Cardiovascular Endocrinology Laboratory, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia (M.J.Y.). Department of Cardiovascular Health and Disease, Baker and University of Melbourne, Victoria, Australia (M.J.Y.). Envision Medical Imaging, Perth, Western Australia, Australia (B.A.). Department of Molecular and Translational Science (J.Y.) and Department of Medicine (J.Y.), Monash University, Clayton, Victoria, Australia.

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## Disclosures

None.

## Supplemental Material

Figures S1 and S2
Table S1

## REFERENCES


1. Funder JW. Aldosterone and mineralocorticoid receptors: physiology and pathophysiology. *Int J Mol Sci*. 2017;18:1032. doi: 10.3390/ijms18051032
2. Brilla CG. Renin-angiotensin-aldosterone system and myocardial fibrosis. *Cardiovasc Res*. 2000;47:1–3. doi: 10.1016/s0008-6363(00)00092-4
3. Lijnen P, Petrov V. Induction of cardiac fibrosis by aldosterone. *J Mol Cell Cardiol*. 2000;32:865–879. doi: 10.1006/jmcc.2000.1129
4. Robert V, Silvestre JS, Charlemagne D, Sabri A, Trouvé P, Wassef M, Swynghedauw B, Delcayre C. Biological determinants of aldosterone-induced cardiac fibrosis in rats. *Hypertension*. 1995;26:971–978. doi: 10.1161/01.hyp.26.6.971
5. Lieb W, Larson MG, Benjamin EJ, Yin X, Tofler GH, Selhub J, Jacques PF, Wang TJ, Vita JA, Levy D, et al. Multimarker approach to evaluate correlates of vascular stiffness: the Framingham Heart Study. *Circulation*. 2009;119:37–43. doi: 10.1161/CIRCULATIONAHA.108.816108
6. Rossi GP, Bernini G, Caliumi C, Desideri G, Fabris B, Ferri C, Ganzaroli C, Giacchetti G, Letizia C, Maccario M, et al; PAPY Study Investigators. A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol*. 2006;48:2293–2300. doi: 10.1016/j.jacc.2006.07.059
7. Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF, Montori VM. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101:1889–1916. doi: 10.1210/jc.2015-4061
8. Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, Sechi LA. Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med*. 2008;168:80–85. doi: 10.1001/archinternmed.2007.33
9. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, Mulatero P. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6:41–50. doi: 10.1016/S2213-8587(17)30319-4
10. Young MJ, Kanki M, Fuller PJ, Yang J. Identifying new cellular mechanisms of mineralocorticoid receptor activation in the heart. *J Hum Hypertens*. 2021;35:124–130. doi: 10.1038/s41371-020-0386-5
11. Gaddam K, Corros C, Pimenta E, Ahmed M, Denney T, Aban I, Inusah S, Gupta H, Lloyd SG, Oparil S, et al. Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism: a prospective clinical study. *Hypertension*. 2010;55:1137–1142. doi: 10.1161/HYPERTENSIONAHA.109.141531
12. Chang YY, Liao CW, Tsai CH, Chen CW, Pan CT, Chen ZW, Chen YL, Lin LC, Chang YR, Wu VC, et al; TAIPAI Study Group. Left ventricular dysfunction in patients with primary aldosteronism: a propensity score-matching follow-up study with tissue Doppler imaging. *J Am Heart Assoc*. 2019;8:e013263. doi: 10.1161/JAHA.119.013263
13. Baudrand R, Guarda FJ, Fardella C, Hundemer G, Brown J, Williams G, Vaidya A. Continuum of renin-independent aldosteronism in normotension. *Hypertension*. 2017;69:950–956. doi: 10.1161/HYPERTENSIONAHA.116.08952
14. Brown JM, Wijkman MO, Claggett BL, Shah AM, Ballantyne CM, Coresh J, Grams ME, Wang Z, Yu B, Boerwinkle E, et al. Cardiac structure and function across the spectrum of aldosteronism: the Atherosclerosis Risk in Communities study. *Hypertension*. 2022;79:1984–1993. doi: 10.1161/HYPERTENSIONAHA.122.19134
15. Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, Vaidya A. The unrecognized prevalence of primary aldosteronism: a cross-sectional study. *Ann Intern Med*. 2020;173:10–20. doi: 10.7326/M20-0065
16. Joseph JJ, Pohlman NK, Zhao S, Kline D, Brock G, Echouffo-Tcheugui JB, Sims M, Effoe VS, Wu WC, Kalyani RR, et al. Association of serum aldosterone and plasma renin activity with ambulatory blood pressure in African Americans: the Jackson Heart Study. *Circulation*. 2021;143:2355–2366. doi: 10.1161/CIRCULATIONAHA.120.050896
17. Vasan RS, Evans JC, Larson MG, Wilson PW, Meigs JB, Rifai N, Benjamin EJ, Levy D. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med*. 2004;351:33–41. doi: 10.1056/NEJMoa033263
18. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum aldosterone concentration, blood pressure, and coronary artery calcium: the Multi-Ethnic Study of Atherosclerosis. *Hypertension*. 2020;76:113–120. doi: 10.1161/HYPERTENSIONAHA.120.15006
19. Hundemer GL, Agharazii M, Madore F, Vaidya A, Brown JM, Leung AA, Kline GA, Larose E, Piché ME, Crean AM, et al. Subclinical primary aldosteronism and cardiovascular health: a population-based cohort study. *Circulation*. 2024;149:124–134. doi: 10.1161/CIRCULATIONAHA.123.066389
20. Brown JM, Robinson-Cohen C, Luque-Fernandez MA, Allison MA, Baudrand R, Ix JH, Kestenbaum B, de Boer IH, Vaidya A. The spectrum of subclinical primary aldosteronism and incident hypertension: a cohort study. *Ann Intern Med*. 2017;167:630–641. doi: 10.7326/M17-0882
21. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;55:1318–1327. doi: 10.1016/j.jacc.2009.10.061
22. Manyari DE. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;323:1706–1707. doi: 10.1056/NEJM199012133232413
23. Devereux RB, Wachtell K, Gerdts E, Boman K, Nieminen MS, Papademetriou V, Rokkedal J, Harris K, Aurup P, Dahlöf B. Prognostic significance of left ventricular mass change during treatment of hypertension. *JAMA*. 2004;292:2350–2356. doi: 10.1001/jama.292.19.2350
24. Schlaich MP, Klingbeil AU, Jacobi J, Delles C, Schneider MP, Schmidt BM, Schmieder RE. Altered aldosterone response to salt intake and angiotensin II infusion in young normotensive men with parental history of arterial hypertension. *J Hypertens*. 2002;20:117–124. doi: 10.1097/00004872-200201000-00017
25. Young WF Jr. Diagnosis and treatment of primary aldosteronism: practical clinical perspectives. *J Intern Med*. 2019;285:126–148. doi: 10.1111/joim.12831
26. Yang J, Gwini SM, Beilin LJ, Schlaich M, Stowasser M, Young MJ, Fuller PJ, Mori TA. Relationship between the aldosterone-to-renin ratio and blood pressure in young adults: a longitudinal study. *Hypertension*. 2021;78:387–396. doi: 10.1161/HYPERTENSIONAHA.121.17336
27. McKnight CM, Newnham JP, Stanley FJ, Mountain JA, Landau LI, Beilin LJ, Puddey IB, Pennell CE, Mackey DA. Birth of a cohort: the first 20 years of the Raine study. *Med J Aust*. 2012;197:608–610. doi: 10.5694/mja12.10698
28. Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet*. 1993;342:887–891. doi: 10.1016/0140-6736(93)91944-h
29. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453–1457. doi: 10.1016/S0140-6736(07)61602-X
30. Yang J, Gwini SM, Beilin LJ, Schlaich M, Stowasser M, Young MJ, Fuller PJ, Mori TA. Effect of oral contraception on screening tests for primary aldosteronism: a 10-year longitudinal study. *J Clin Endocrinol Metab*. 2023;108:1686–1695. doi: 10.1210/clinem/dgad010
31. Huang RC, Beilin LJ, Ayonrinde O, Mori TA, Olynyk JK, Burrows S, Hands B, Adams LA. Importance of cardiometabolic risk factors in the association between nonalcoholic fatty liver disease and arterial stiffness in adolescents. *Hepatology*. 2013;58:1306–1314. doi: 10.1002/hep.26495
32. Lee D, Byun K, Hwang M-H, Lee S. Augmentation index is inversely associated with skeletal muscle mass, muscle strength, and anaerobic power in young male adults: a preliminary study. *Appl Sci*. 2021;11:3146. doi: 10.3390/app11073146
33. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419. doi: 10.1007/BF00280883

34. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51:1173–1182. doi: 10.1037//0022-3514.51.6.1173
35. Judd CM, Kenny DA. Process analysis: estimating mediation in treatment evaluations. *Eval Rev*. 1981;5:602–619. doi: 10.1177/0193841x8100500502
36. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269–1324. doi: 10.1161/HYP.0000000000000066
37. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M, Salerno M, Teague SD, Valsangiacomo-Buechel E, van der Geest RJ, et al. Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. *J Cardiovasc Magn Reson*. 2020;22:87. doi: 10.1186/s12968-020-00683-3
38. Tsao CW, Gona PN, Salton CJ, Chuang ML, Levy D, Manning WJ, O'Donnell CJ. Left ventricular structure and risk of cardiovascular events: a Framingham Heart Study Cardiac magnetic resonance study. *J Am Heart Assoc*. 2015;4:e002188. doi: 10.1161/JAHA.115.002188
39. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation*. 1997;96:308–315. doi: 10.1161/01.cir.96.1.308
40. Barrett Mueller K, Lu Q, Mohammad NN, Luu V, McCurley A, Williams GH, Adler GK, Karas RH, Jaffe IZ. Estrogen receptor inhibits mineralocorticoid receptor transcriptional regulatory function. *Endocrinology*. 2014;155:4461–4472. doi: 10.1210/en.2014-1270
41. Sato A, Saruta T. Aldosterone-induced organ damage: plasma aldosterone level and inappropriate salt status. *Hypertens Res*. 2004;27:303–310. doi: 10.1291/hypres.27.303
42. Mill JG, Baldo MP, Molina M, Schmidt MI, Barreto SM, Chor D, Griep RH, Matos SM, Ribeiro ALP, Duncan BB, et al. Sex-specific patterns in the association between salt intake and blood pressure: the ELSA-Brasil study. *J Clin Hypertens (Greenwich)*. 2019;21:502–509.
43. Heller B, Reiter FP, Leicht HB, Fiessler C, Bergheim I, Heuschmann PU, Geier A, Rau M. Salt-intake-related behavior varies between sexes and is strongly associated with daily salt consumption in obese patients at high risk for MASLD. *Nutrients*. 2023;15:3942. doi: 10.3390/nu15183942
44. Brown JJ, Davies DL, Lever AF, Robertson JI. Influence of sodium loading and sodium depletion on plasma-renin in man. *Lancet*. 1963;2:278–279. doi: 10.1016/s0140-6736(63)90176-4
45. Lu Y, Kiechl SJ, Wang J, Xu Q, Kiechl S, Pechlaner R; Global Pulse Wave Velocity Study Group. Global distributions of age- and sex-related arterial stiffness: systematic review and meta-analysis of 167 studies with 509,743 participants. *EBioMedicine*. 2023;92:104619. doi: 10.1016/j.ebiom.2023.104619
46. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, Havlik R, Lakatta EG, Spurgeon H, Kritchevsky S, et al; Health ABC Study. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*. 2005;111:3384–3390. doi: 10.1161/CIRCULATIONAHA.104.483628
47. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: "establishing normal and reference values." *Eur Heart J*. 2010;31:2338–2350. doi: 10.1093/eurheartj/ehq165
48. Rudolph A, Abdel-Aty H, Bohl S, Boyé P, Zagrosek A, Dietz R, Schulz-Menger J. Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. *J Am Coll Cardiol*. 2009;53:284–291. doi: 10.1016/j.jacc.2008.08.064
49. Bienvenu LA, Morgan J, Rickard AJ, Tesch GH, Cranston GA, Fletcher EK, Delbridge LM, Young MJ. Macrophage mineralocorticoid receptor signaling plays a key role in aldosterone-independent cardiac fibrosis. *Endocrinology*. 2012;153:3416–3425. doi: 10.1210/en.2011-2098
50. Yang J, Young MJ, Cole TJ, Fuller PJ. Mineralocorticoid receptor signalling in primary aldosteronism. *J Endocrinol*. 2023;259:e220249. doi: 10.1530/JOE-22-0249
51. Freel EM, Mark PB, Weir RA, McQuarrie EP, Allan K, Dargie HJ, McClure JD, Jardine AG, Davies E, Connell JM. Demonstration of blood pressure-independent noninfarct myocardial fibrosis in primary aldosteronism: a cardiac magnetic resonance imaging study. *Circ Cardiovasc Imaging*. 2012;5:740–747. doi: 10.1161/CIRCIMAGING.112.974576
52. Massera D, McClelland RL, Ambale-Venkatesh B, Gomes AS, Hundley WG, Kawel-Boehm N, Yoneyama K, Owens DS, Garcia MJ, Sherrid MV, et al. Prevalence of unexplained left ventricular hypertrophy by cardiac magnetic resonance imaging in MESA. *J Am Heart Assoc*. 2019;8:e012250. doi: 10.1161/JAHA.119.012250
53. Hindieh W, Weissler-Snir A, Hammer H, Adler A, Rakowski H, Chan RH. Discrepant measurements of maximal left ventricular wall thickness between cardiac magnetic resonance imaging and echocardiography in patients with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging*. 2017;10:e006309. doi: 10.1161/CIRCIMAGING.117.006309
54. Baudrand R, Guarda FJ, Torrey J, Williams G, Vaidya A. Dietary sodium restriction increases the risk of misinterpreting mild cases of primary aldosteronism. *J Clin Endocrinol Metab*. 2016;101:3989–3996. doi: 10.1210/jc.2016-1963
55. Takeda Y, Yoneda T, Demura M, Furukawa K, Miyamori I, Mabuchi H. Effects of high sodium intake on cardiovascular aldosterone synthesis in stroke-prone spontaneously hypertensive rats. *J Hypertens*. 2001;19:635–639. doi: 10.1097/00004872-200103001-00017
56. Ng E, Gwini SM, Libianto R, Choy KW, Lu ZX, Shen J, Doery JCG, Fuller PJ, Yang J. Aldosterone, renin, and aldosterone-to-renin ratio variability in screening for primary aldosteronism. *J Clin Endocrinol Metab*. 2022;108:33–41. doi: 10.1210/clinem/dgac568
57. Staplin N, de la Sierra A, Ruilope LM, Emberson JR, Vinyoles E, Gorostidi M, Ruiz-Hurtado G, Segura J, Baigent C, Williams B. Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients. *Lancet*. 2023;401:2041–2050. doi: 10.1016/S0140-6736(23)00733-X
58. Schwartz JE, Muntner P, Kronish IM, Burg MM, Pickering TG, Bigger JT, Shimbo D. Reliability of office, home, and ambulatory blood pressure measurements and correlation with left ventricular mass. *J Am Coll Cardiol*. 2020;76:2911–2922. doi: 10.1016/j.jacc.2020.10.039
59. Cohen JB, Bancos I, Brown JM, Sarathy H, Turcu AF, Cohen DL. Primary aldosteronism and the role of mineralocorticoid receptor antagonists for the heart and kidneys. *Annu Rev Med*. 2023;74:217–230. doi: 10.1146/annurev-med-042921-100438