Supplemental Material

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Data S1. Physical Examination and Blood Pressure Measurement.

Evaluations of physical examination, anthropometry and other laboratory assessments were described in previous publications. In FOS, blood pressure measurement was performed according to a standardized protocol: using a mercury-column sphygmomanometer and a cuff of the appropriate size, a physician measured the systolic blood pressure (SBP) and diastolic blood pressure (DBP) twice in the left arm while the participant kept seated. The average of two readings was considered the blood pressure at each examination. A diagnosis of hypertension was established on the basis of SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or a history of hypertension, or taking antihypertensive medication at previous visits. In CONPASS, blood pressure was measured in both of the patient's arms by an electronic sphygmomanometer, and the average of two readings was documented as the measured blood pressure. A diagnosis of hypertension was established by SBP ≥140 mmHg and/or DBP ≥90 mmHg on at least 3 occasions on different days (including at least 1 out-of-office BP measurement).

Subjects were categorized into different groups according to their blood pressure: normotension (SBP < 120 mmHg and DBP < 80 mmHg, and no history of hypertension, and not taking antihypertensive medication), prehypertension (SBP 120-139 mmHg and DBP 80-89 mmHg, and no history of hypertension, and not taking antihypertensive medication), stage 1 hypertension (SBP 140–159 mmHg and DBP 90–99 mmHg), stage 2 hypertension (SBP 160–179 mmHg and DBP 100–109 mmHg), stage 3 hypertension (SBP >180 mmHg or DBP >110 mmHg). Non-hypertension was defined as normotension or prehypertension, or subjects who did not meet the diagnostic criteria of hypertension.

Data S2. Laboratory assessment.

For FOS, the procedures of venous blood collection, serum/plasma separation and specimen storage have been previously described. Plasma renin concentration (PRC) was measured with an immunechemiluminometric assay (Nichols Advantage ® Direct Renin assay), and serum aldosterone concentration (SAC) was measured by radioimmunoassay (Quest Diagnostics). In CONPASS, before the evaluation of renin and aldosterone concentration, all antihypertensive medications that can interfere with RAAS activity (including diuretics, β-blockers, angiotensin-converting enzyme inhibitors [ACEi], and angiotensin-1 receptor blockers[ARBs]) were withdrawn, or changed to verapamilor α-adrenergic blockers. Hypokalemia was also corrected. Blood samples were collected in the morning. Plasma aldosterone concentration (PAC) and PRC were measured with automated chemiluminescence immunoassays (LIAISON; DiaSorin, Italy).

Data S3. Renin-independent and renin-dependent aldosteronism.

In the FOS population, in addition to SAC and PRC, as intravascular volume depletion is thought to be a main promotor of renin-dependent aldosteronism, we used pro-atrial natriuretic peptide (proANP) and B-type natriuretic peptide (BNP), well recognized markers of intravascular fluid volume, to validate the classification of aldosteronism. A lower level of circulating proANP or BNP indicates a relative intravascular volume depletion that would increase renin-dependent aldosterone production.

In CONPASS population, the procedure of CCT has previously been described in detail. In brief, patients received 50 mg captopril orally at 8-9 a.m. after sitting or standing for at least 1 h; blood samples were drawn at time zero and 2 h after the challenge; PAC-post CCT (cutoff 10 $ng \cdot dl^{-1}$) was used for differentiating renin-dependent aldosteronism and renin-independent aldosteronism.

Data S4. Mineralocorticoid Receptor (MR) Activity in CONPASS.

The 24-hour urine samples were routinely collected to measure urinary potassium and sodium excretion. The degree of MR activation was indirectly assessed via 24-hour urinary potassium-to-sodium excretion based on a previous report.

Data S5. Assessment of Outcomes.

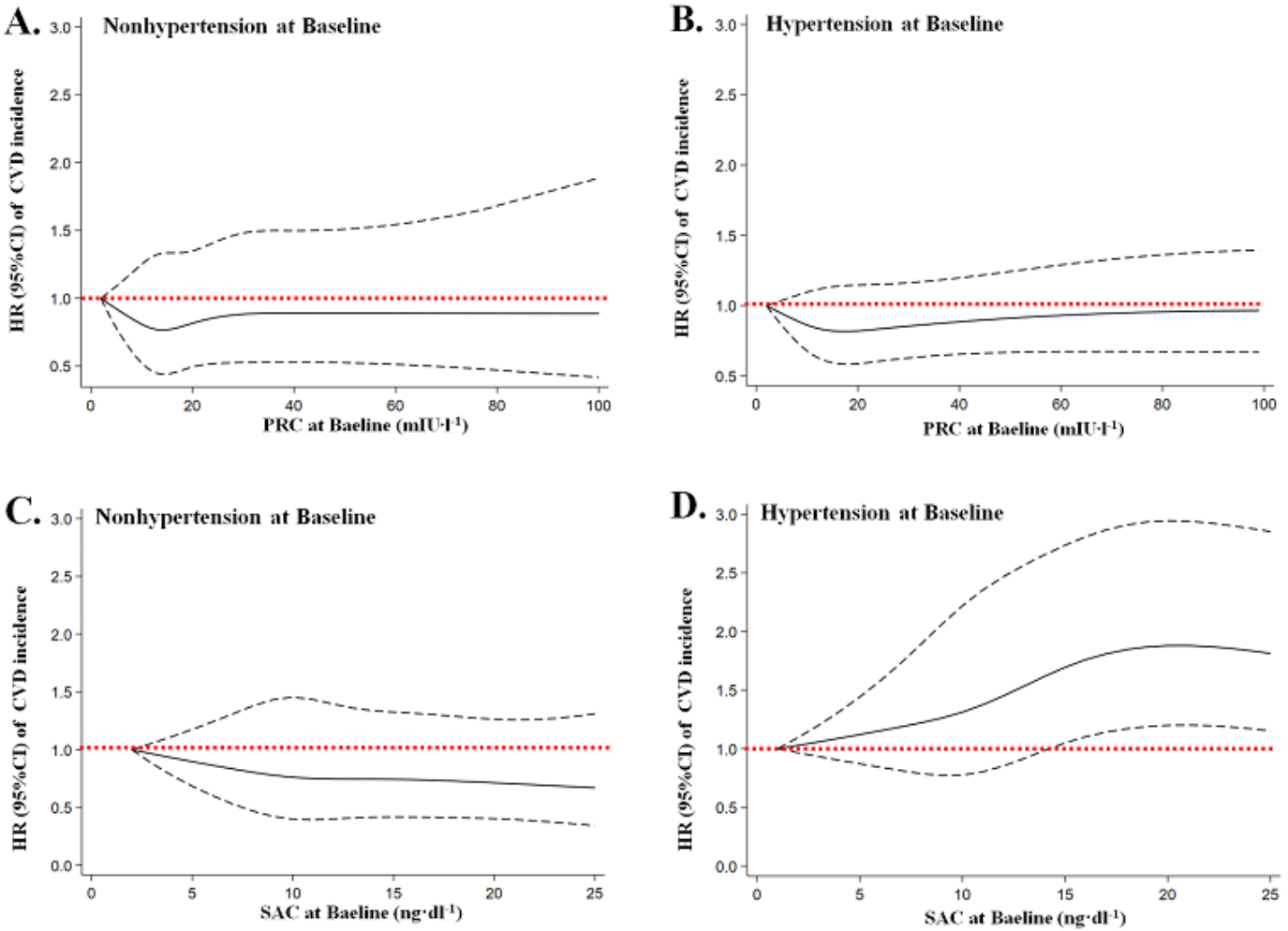
In FOS, the primary outcome in this analysis is the incidence of CVD, which included coronary heart disease (CHD), congestive heart failure (CHF), stroke or transient ischemic attack (TIA). A person having more than one cardiovascular manifestation within the follow-up period was counted as an incident case only at the time of the first event. All cardiovascular events were assessed based on the FOS sequence of events protocols. Subjects were diagnosed as having developed CHD if upon review of the case a panel of three investigators (the Framingham Endpoint Review Committee) agreed on one of the following definite manifestations of CHD: myocardial infarction, coronary insufficiency, angina pectoris, sudden death from CHD, non-sudden death from CHD. The diagnosis of cerebrovascular disease (stroke and TIA) was based on the occurrence of a clinically evident stroke documented by clinical records reviewed by at least two neurologists. Stroke was defined as the sudden or rapid onset of a focal neurologic deficit persisting for greater than 24 hours. TIA was defined as a focal neurologic deficit of sudden or rapid onset that fully resolved in less than 24 hours. A diagnosis of CHF depended on symptoms, physical signs and x-ray. In CONPASS, CVD was confirmed if there was a definite manifestation of CHD, stroke (including TIA) or CHF. The diagnosis of CVD was based on evaluations by at least two senior physicians from the First Affiliated Hospital of Chongqing Medical University.

Table S1. Demographic, Clinical and Biochemical Characteristics among hypertensive subgroup of FOS.

	Normal Aldosterone	Renin-Dependent Aldosteronism	Renin-Independent Aldosteronism	P Value
Women/Men	281/363	179/178	252/180	<0.001
Median age (yr)	60.96(60.27,61.66)	59.77(58.79,60.75)	62.11(61.29,62.93)	0.001
Body-mass index (kg/m^2)	29.08(28.64,29.52)	29.38(28.84,29.91)	29.36(28.85,29.88)	0.604
Average SBP (mmHg)	139(138,141)	134 (132,136)	142 (140,143)	<0.001
Average DBP (mmHg)	79(78,80)	78 (77,79)	80 (79,81)	0.002
Current smoker (%)	13.2	14.3	10.2	0.180
History of diabetes (%)	14.9	16.5	12.3	0.223
Fasting Plasma Glucose (mg/dl)	108.51(106,111.02)	111.73(107.93,115.53)	106.28(103.76,108.81)	0.059
HDL-c(mg/dl)	49.25(48.06,50.45)	50.66(48.95,52.38)	50.17(48.63,51.71)	0.370
Triglyceride (mg/dl)	151.44(142.14,160.74)	144.85(135.70,154)	161.30(152.79,169.82)	0.080
LDL-c(mg/dl)	127.03(124.63,129.44)	128.24(124.9,131.57)	130.49(127.43,133.55)	0.214
Serum aldosterone concentration (ng/dl)	6.48(6.33,6.62)	18.96(17.87,20.06)	14.67(14.17,15.16)	<0.001
Plasma renin concentration (mIU/l)	41.95(29.11,54.79)	73.08(49.51,96.65)	8.04(7.66,8.41)	<0.001
Urine sodium (mmol/day)	110.62(106.67,114.56)	87.93(82.55,93.32)	92.96(88.52,97.39)	<0.001
BNP (pg/ml)	17.01(15.35,18.66)	13.54(11.54,15.54)	17.90(16.02,19.78)	0.007
proANP (pmol/l)	426.07(404.38,447.76)	340.81(315.85,365.77)	405.01(381.84,428.18)	<0.001

Data were expressed as mean (95% CI) and the number (%).Normal Aldosterone: serum aldosterone concentration (SAC)<10 ng·dl^{-1}; Renin-Dependent Aldosteronism: SAC≥10 ng·dl^{-1} and plasma renin concentration (PRC) >15 mU/l ; Renin-Independent Aldosteronism:SAC≥10 ng·dl^{-1} and PRC ≤15 mU/l; SBP: systolic blood pressure, DBP:diastolic blood pressure, LDL-c: Low Density Lipoprotein cholesterol, HDL-c: High Density Lipoprotein cholesterol. BNP:B-type natriuretic peptide; NT_ANP: N-Terminal pro-atrial natriuretic peptide. For SAC, 1 ng/dl=27 pmol/l.

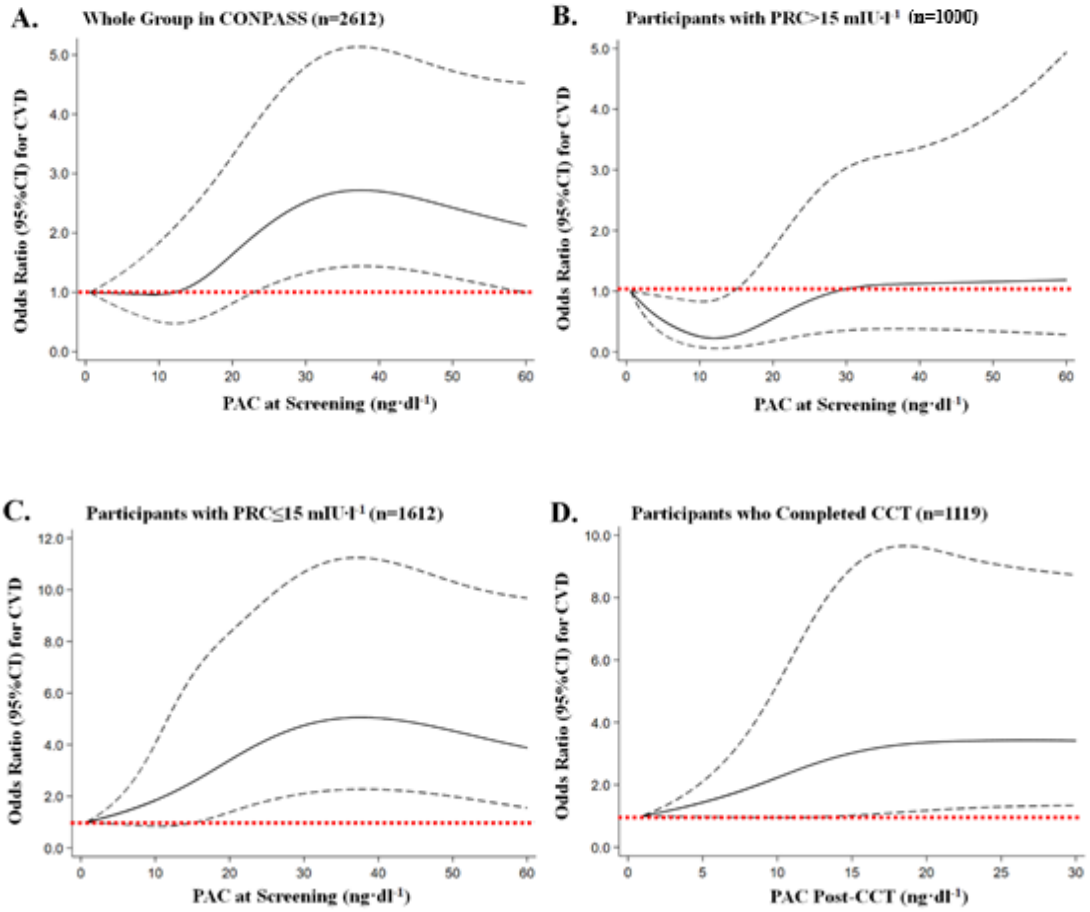
Figure S1. Relationships between circulating concentrations of aldosterone and renin at baseline and long-term risk of cardiovascular diseases, among nonhypertensive and hypertensive participants from FOS.



The hazard ratios (HR) and 95% CIs were delineated on the basis of restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles. Red dot line of vertical axis (HR=1.0) was used as reference for risk of CVD incidence. Panel A and panel B showed the HR (95% CIs) of plasma renin concentration (PRC) and CVD incidence among nonhypertensive (A) and hypertensive (B) participants, respectively. Panel C and panel D showed the HR (95% CIs) of serum aldosterone concentration (SAC) and CVD incidence among nonhypertensive (C) and hypertensive (D) participants, respectively. For SAC, 1 ng/dl=27 pmol/l.

All of these effects were calculated based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, antihypertensive medication use, sodium status.

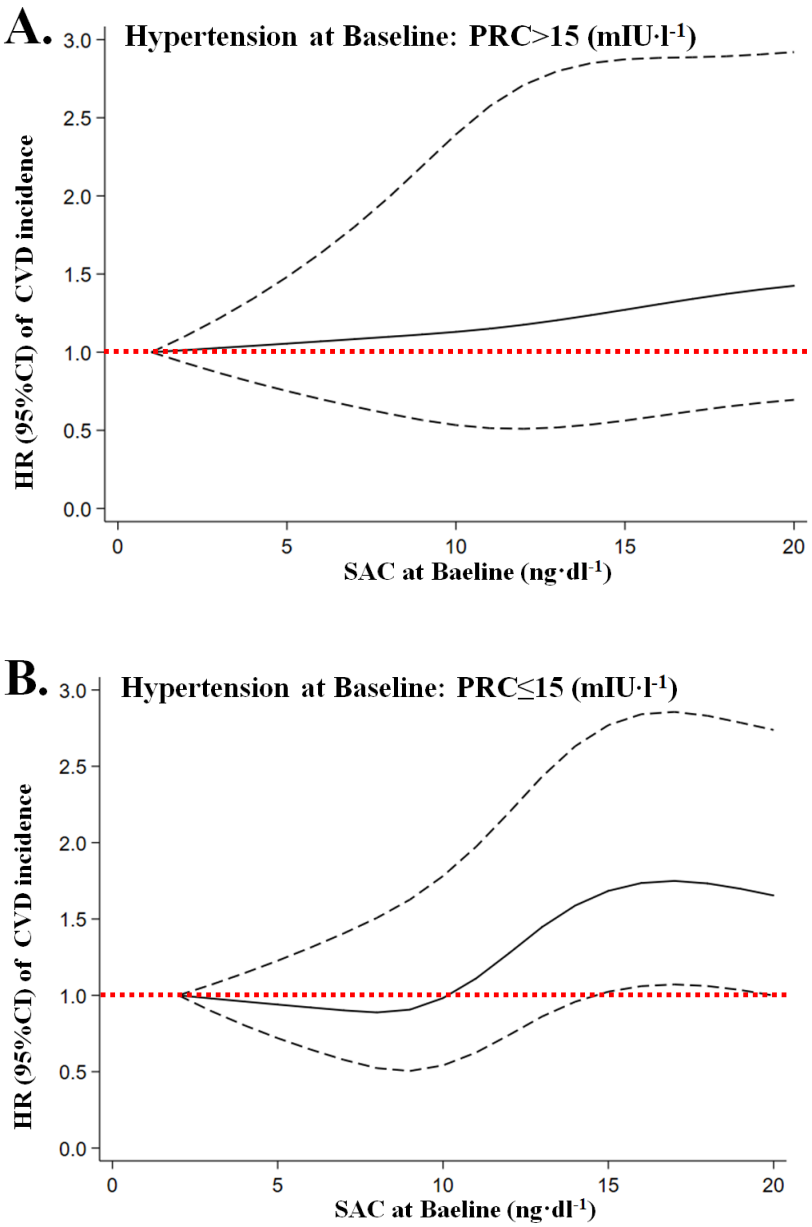
Figure S2. Cardiovascular diseases risk for aldosterone and renin among validation hypertensive population of CONPASS.



The restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles was used for delineation. Panel A showed the odd ratios (OR) and 95% CIs of CVD for plasma aldosterone concentration (PAC). Panel B showed the OR and 95% CIs of CVD for PAC in the setting of plasma renin concentration (PRC) >15 $mIU \cdot l^{-1}$. Panel C showed the odd ratios and 95% CIs of PAC in the condition of PRC≤15 $mIU \cdot l^{-1}$. Panel D showed the odd ratios and 95% CIs of PAC-post captopril challenge test (CCT). For PAC, 1 ng/dl=27 pmol/l.

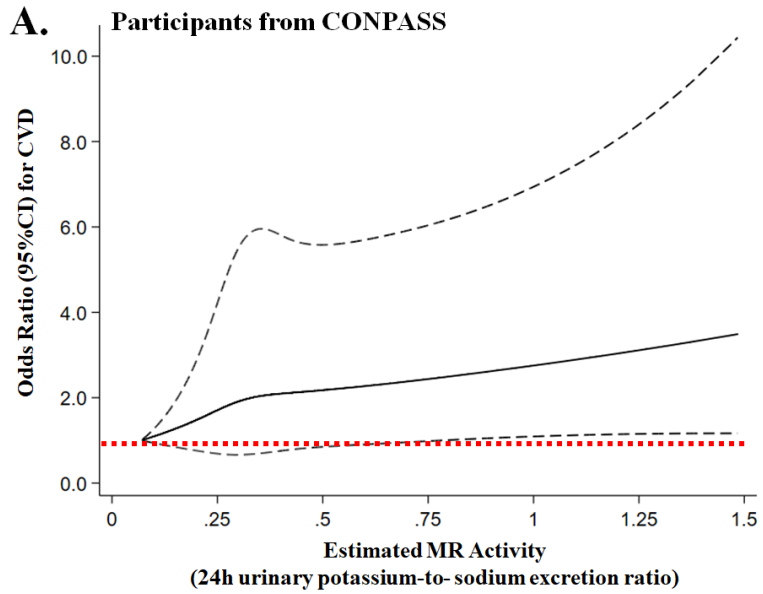
All of these effects were based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, sodium status.

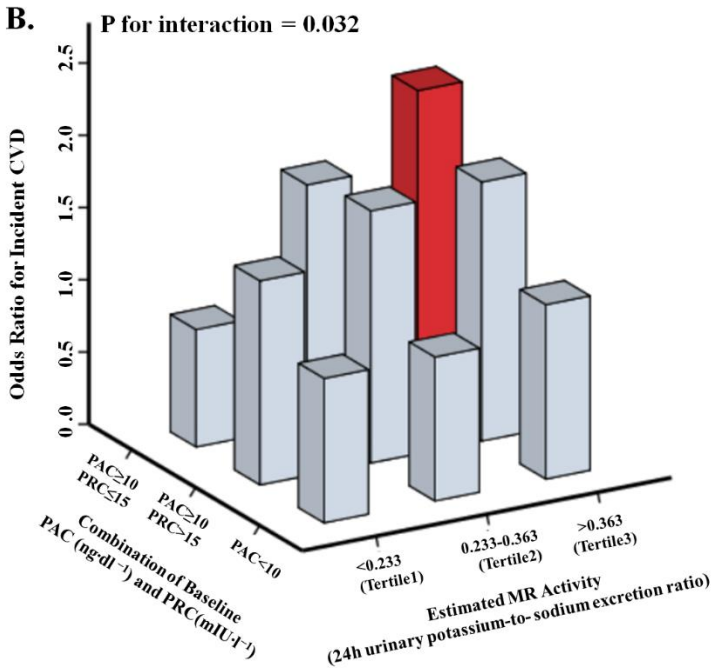
Figure S3. Relationship between aldosterone and cardiovascular diseases in settings of different renin phenotypes, among hypertensive population from FOS.



The hazard ratios and 95% Cis were calculated on the basis of restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles. Red dot line of vertical axis (HR=1.0) was used as reference for risk of cardiovascular diseases (CVD) incidence. Panel A showed the hazard ratios of CVD with increasing serum aldosterone concentration (SAC) in the condition of plasma renin concentration (PRC) >15 mU/l screening at baseline. Panel B showed the hazard ratios of CVD with an increasing SAC in the condition of PRC ≤15 mU/l screening at baseline. For SAC, 1 ng/dl=27 pmol/l. All of these effects based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes, antihypertensive medication use, sodium status.

Figure S4. Mineralocorticoid receptor activity, different subtypes of aldosteronism, and risk of cardiovascular diseases among validation hypertensive population from CONPASS.





The restricted cubic spline regression with four equally spaced knots at 25th, 50th, 75th, and 95th percentiles were used for delineation. Panel A showed the odd ratios and 95% CIs of estimated MR Activity (calculated by the 24h urinary potassium-to- sodium excretion ratio). In Panel B, subjects with PRC ≤15 mU/l and SAC≥10 ng·dl^{-1} were suspected as renin-independent aldosteronism, and subjects with PRC >15 mU/l and SAC≥10 ng·dl^{-1} were suspected as renin-dependent aldosteronism.

All of these effects were based on the multivariate model, which adjusted for age, sex, body mass index, systolic blood pressure, current smoking status, alcohol consumption, total cholesterol, presence or absence of diabetes. Columns colored as red indicated the false discovery rate is less than 0.05.