Original Article

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Association of sodium intake with adverse left atrial function and left atrioventricular coupling in Chinese

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Objectives: High sodium intake is strongly associated with hypertension and obesity. This study aims to investigate the relationship between 24-h urinary sodium (a surrogate measure of sodium intake), ambulatory blood pressure parameters, left atrial function, and left atrioventricular coupling. Further, we intend to examine whether blood pressure and BMI might be mediators of the relationship between 24-h urinary sodium and subclinical cardiac function.

Methods: Our study had 398 participants, all of whom were subjected to 24-h urine collection, 24-h ambulatory blood pressure measurement, and cardiac magnetic resonance imaging.

Results: The average age of the participants was 55.70 $\pm$ 11.30 years old. The mean urinary sodium of the participants was 172.01 $\pm$ 80.24 mmol/24 h. After adjusting for age, sex, history of diabetes, smoking status, alcohol consumption, and use of diuretics, 24-h urinary sodium was correlated with multiple ambulatory blood pressure parameters, BMI, left atrial function, and the left atrioventricular coupling index (LACI) ($P < 0.05$). Mediation analysis showed that BMI explained 16% of the indirect effect of 24-h urinary sodium and left atrial function and 30% of the indirect effect of LACI. Independent of the mediator, 24-h urinary sodium had a significant direct effect on left atrial function and left atrioventricular coupling.

Conclusions: Higher 24-h urinary sodium was associated with a greater BMI as well as poor left atrial function and left atrioventricular coupling, and the BMI mediated the relationship between 24-h urinary sodium and subclinical left cardiac function. Furthermore, and more importantly, 24-h urinary sodium may have directly affected the left atrial function and left atrioventricular coupling independent of intermediary factors.

Keywords: atrial function, obesity, sodium intake, strain, urinary sodium

Abbreviations: *A*, the peak late transmitral flow velocity; BMI, body mass index; BPV, blood pressure coefficient of variation; CMR, cardiovascular magnetic resonance imaging; CMR-FT, cardiac magnetic resonance feature tracking (CMR-FT); DBP, diastolic blood pressure; *E*, the peak early transmitral flow velocity; *e'*, the lateral mitral annular velocity; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; HR, heart rate; LA, the left atrium/the left atrial; LACI, left atrioventricular coupling index; LAEDV, LV end-diastole volume; LAs-a, LA booster strain; LAs-e, LA conduit strain; LAsr-a, LA booster strain rate; LAsr-e, LA conduit strain rate; LAsr-s, LA reservoir strain rate; LAs-s, LA reservoir strain; LAV, left atrial volume; LAVmin, minimum volume of LA; LV, left ventricular; LVDD, left ventricular diastolic dysfunction; LVMI, LV mass index; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SR, strain rate LAV

INTRODUCTION

Dietary high sodium intake is known to be associated with a range of health outcomes, such as hypertension, cardiovascular disease, and death [1]. A growing body of evidence suggests that night-time blood pressure and a nondipper or riser pattern of night-time blood pressure are independently associated with total cardiovascular event rates, especially in heart failure [2], where the elevation of night-time blood pressure or non-dipper patterns are associated with increased circulating volume, which is largely determined by sodium intake [3].

Observational studies [4,5] have also demonstrated the potential role of sodium intake in obesity, that is, sodium intake is positively correlated with urinary sodium and body mass index (BMI). High sodium intake and obesity, both prevalent worldwide, are shared risk factors for many

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chronic diseases, and they also have adverse health consequences and disease burdens.

The left atrium (LA) is increasingly regarded as a bellwether, with its function providing critical prognostic information as a diagnostic of subclinical disease [6], indicating diastolic dysfunction [7]. The LA is a dynamic structure. LA function has three phases, serving as a reservoir in systole, as a conduit in early diastole, and as a booster in late diastole [8]. Myocardial strain analysis is a relatively new technique for determining the function of the LA.

In addition, the close physiological relationship between LA and left ventricular (LV) suggests a decoupling between the functions of the two cardiac chambers, the left atrium, and left ventricle, which can also lead to heart failure and cardiac dysfunction [9]. A recent mesa study [10] indicates that the left atrioventricular coupling index (LACI), assessed by cardiovascular magnetic resonance imaging (CMR), defined as the ratio between the left atrial and LV end-diastolic volumes, has improved prognostic value in predicting heart failure events compared with traditional heart failure factors.

In recent years, cardiac magnetic resonance feature tracking (CMR-FT) has emerged as a new magnetic resonance technology that enables high spatial resolution and superior contrast. Stability and repeatability are advantageous [11]. More crucially, several CMR-FT investigations [12,13] on LA strain and strain rate (SR) have demonstrated high inter-and intraobserver repeatability.

Urinary sodium is a surrogate indicator for sodium intake [14], with 24-h urinary sodium regarded as the gold standard method [15]. An earlier study reported the effects of sodium intake (represented by 24-h urinary sodium replacement) on LV function [16], but no research has focused on the effects of sodium intake on LA function and left atrioventricular coupling.

Thus, we investigated the relationship between 24-h urinary sodium, a surrogate measure of sodium intake, and cardiac MRI-assessed LA function and left atrioventricular coupling, with the assumption that in individuals without clinical heart failure, higher 24-h urinary sodium is associated with worse LA function (myocardial strain) and left atrioventricular coupling (expressed by the LACI). As previously described, sodium intake is closely related to blood pressure and BMI, so we used mediation analysis to investigate whether blood pressure and BMI are mediators in the relationship between 24-h urinary sodium and LA function and left atrioventricular coupling.

MATERIALS AND METHODS

Study population

In this study, 398 patients of higher economic status volunteered to undergo relevant examinations, including cardiac magnetic resonance imaging, 24-h urine collection, and 24-h ambulatory blood pressure measurement. They were recruited from the ward of the International Medical Department of the Second Affiliated Hospital of Dalian Medical University from December 2020 until December 2021. Obesity was defined according to the standard BMI as defined by the World Health Organization (WHO) (Asian cutoff $\geq$25 kg/m^2) [17], and BMI was calculated as weight in kilograms divided by the square of height in meters. All participants were aged 20–90 years and had eaten regular meals for the past 1 month.

The exclusion criteria were as follows: secondary hypertension; coronary heart disease; HF with reduced ejection fraction (EF); moderate or severe valvular disease; atrial fibrillation; severe arrhythmia; cardiomyopathy; severe hepatic and renal dysfunction; stroke; malignant tumor; use of SGLT2i,Sodium-glucose cotransporter 2 inhibitor; use of glucocorticoids; and, finally, urine samples not able to be collected continuously throughout the day or whose 24-h urine volume is less than 500 ml.

All participants provided informed consent to participate in this study before enrollment. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Dalian Medical University and complied with the principles of the Declaration of Helsinki. A written informed consent form was obtained from each participant.

Biochemical tests

After the participants had fasted for at least 8 h, venous blood was collected and analyzed. For participants on the regular diet, the participant's bladder was emptied and abandoned at 0700 h on the first day. All the urine discharged within 24 h of this time was stored, up until any last urination at 0700 h the next morning. Urinary sodium was determined by the electrode method and expressed as mmol/d. Renal function was represented by the estimated glomerular filtration rate (eGFR).

Blood pressure measurement

All patients were subjected to 24-h ambulatory BP monitoring using an oscillometric device (Spacelabs90207; Spacelabs, Snoqualmie, Washington, USA). The arm cuff was placed around the nondominant upper limb. Automatic BP recordings were obtained regularly every 30 min during the daytime period and every 1 h during the night-time period. The International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes criteria were used to define a complete ambulatory blood pressure (ABPM) measurement, defined as at least 10 daytime (1000–2000 h) and at least five night-time (midnight–0600 h) SBP and DBP measurements [18]. Then, ambulatory BP monitoring was removed, and these recordings for 24 h were used to obtain the mean 24-h, daytime, and night-time SBP, DBP, and HR, Heart rate were downloaded onto a computer and processed with the Medicom software International Database on ABPM. Patients were asked to attend to their daily activities, but to remain still while being measured. The patterns of night-time BP dipper were calculated based on the reduction in SBP while night-time vs. daytime: dippers (10–<20%); nondippers (0–<10%); and risers (night-time-to-daytime systolic BP [SBP] ratio >1.0) [19].

Conventional echocardiography

Each patient underwent an echocardiography examination, which was measured with a Vivid E9 ultrasound system (GE Vingmed Ultrasound, Horten, Norway). Transmitral inflow velocities were assessed during diastole by pulsed-wave Doppler and obtained with the sample volume placed between the tips of the mitral leaflets on the apical four-chamber

view. The early diastolic (*E*) and late atrial (*A*) transmitral flow velocities were measured, and the *E*/*A* ratio was calculated. On the apical four-chamber view, pulsed-wave tissue Doppler was used to evaluating mitral plane movement. The early diastolic velocity of the myocardium (e') was measured by placing the sample volume at the lateral mitral annulus.

MRI protocol

All MR measurements were performed using a 3.0-T whole-body scanner (Trio Tim; Siemens Medical Solutions, Erlangen, Germany) with a dedicated 32-channel body phased-array coil for when patients are in the supine position. Cardiac dimensions and function were assessed with ECG-triggered balanced steady-state free precession (b-SSFP) cine sequences during a brief breath-holding period. Cine images including three long-axis views (two-chamber, three-chamber, four-chamber) and two-chamber short-axis views were acquired (repetition time [TR] 3.4 ms, segments 12, echo time [TE] 1.31 ms, matrix size 208 × 139, the field of view [FOV] 234 mm × 280 mm, slice thickness 8 mm, and flip angle 39°).

Imaging analysis

Left atrium feature-tracking analysis

LA myocardial feature tracking (FT) analysis was performed using CVI42 software (Circle Cardiovascular Imaging, Inc., Calgary, Canada). The images were analyzed blinded to the individuals' basic personal information (including age, sex, etc.). The LA endocardial (pulmonary veins and LA appendages were excluded) and epicardial borders were manually traced using a point-and-click technique in the two- and four-chamber images at the minimum LA volume following atrial contraction. In all two- and four-chamber views, the endocardial LA strain, and SR values were averaged across three tracking studies. The LA strain parameters included reservoir strain (LAs-s, which corresponds to atrial reservoir function at LV end-systole), conduit strain (LAs-e, which corresponds to atrial conduit function during early diastole), and booster strain (LAs-a, which corresponds to atrial booster function during late diastole). Thus, their associated SR characteristics, which include peak positive SR (SRs), peak early negative SR (SRe), and peak late negative SR (SRa), were obtained simultaneously.

Left atrium volumetric analysis

Manual tracings of the LA length and area were performed in the two-chamber and four-chamber long-axis views using CVI software. LA volume parameters were evaluated using the validated biplane area-length method according to a previously described formula [20]. LA appendages and pulmonary veins were excluded from the LA volume. For each of these phases, the maximum volume of LA (LAV) was defined at the left ventricle's end-systole and the minimum volume of LA (LAVmin) at the left ventricle's end-diastole [21].

Left atrioventricular coupling index

LACI was defined for each participant by the ratio between the LA end-diastolic volume and the LV end-diastolic volume assessed by CMR, as previously described. The LV volume was determined from the stack of short-axis cine images, while the LA volume was established from the two-chamber and four-chamber views. Both volumes were measured during the same end-diastolic phase, as determined by the closure of the mitral valve. This index is expressed as a percentage, and a higher LACI indicates a greater disproportion between the LA and LV volumes at the ventricular end-diastole, indicating a greater impairment of left atrioventricular coupling [22].

Left ventricular function and morphology analysis

LV end-diastolic volume was calculated using Simpson's rule (the summation of areas on each separate slice multiplied by the sum of slice thickness and image gap). LV mass (LVM) was determined by the sum of the myocardial area (the difference between the endocardial and epicardial contour) times slice thickness plus the image gap in the end-diastolic phase multiplied by the specific gravity of the myocardium (1.05 g/ml) [23]. The LVM was indexed for BSA to determine the LVM index (LVMI). LVEF was calculated as LV stroke volume divided by LV end-diastolic volume multiplied by 100.

The LV feature tracking analyzes the radial, circumferential, and longitudinal strain on the standard CMR b-SSFP sequence using the same software as above. The LV endocardial and epicardial borders were manually drawn in the two-chamber, four-chamber, and short-axis view of the end-diastolic and the end-systole phase. The longitudinal strain and strain rate were obtained by tracking the long horizontal axis cines, whereas the circumferential, radial strain and strain rate were derived from the short-axis cines [24].

Statistical analysis

Calculation of clinical features, laboratory data, and routine echocardiographic and CMR feature tracking parameters was carried out for all patients. We employed the designation of low, moderate, and high sodium intake which were based on current recommended intake (low), average intake (moderate), and above average intake (high) [25], the selected patients were divided into three groups according to 24-h urinary sodium, namely the low urinary sodium group: urinary sodium less than or equal 100 mmol/24 h (sodium intake $\leq$ 6 g/day), moderate urinary sodium group: 100 mmol/24 h < urinary sodium less than or equal 200 mmol/24 h (6 g/day < sodium intake $\leq$ 12 g/day), high urinary sodium group: urinary sodium at least 200 mmol/24 h (sodium intake >12 g/day).

All data were analyzed using SPSS statistical software (version 26.0; SPSS Inc., Chicago, Illinois, USA). Categorical data are presented as numbers (percentages) and were compared using the chi-square. Normally distributed continuous variables are expressed as the mean ± SD and were compared using a one-way analysis of variance (ANOVA). Pearson's or Spearman's correlation coefficient was used to analyzing the bivariable correlations as appropriate. Two-sided *P* values of <0.05 were considered to be statistically significant. Because night-time blood pressure and BMI are along the putative causal pathway between 24-h urinary sodium (a surrogate marker of estimated sodium intake) sodium and adverse left atrial function and left atrioventricular coupling, we performed mediation analysis to understand

these indirect effects. We calculated the proportion explained by the intermediate factors as follows: 100% × [beta-coefficient$_{model}$ − beta-coefficient$_{model+intermediatefactor}$]/[beta-coefficient$_{mod-el}$] [26]. An application of Process V4.0's plug-in to investigate the mediating effect of BMI and night-time blood pressure on the effect of 24-h urinary sodium on left atrial function and left atrioventricular coupling was carried out.

RESULTS

Characteristics of study participants

Descriptive characteristics of the study sample are displayed in Table 1, dichotomized by 24-h urinary sodium. A total of 398 patients were included in the study. The mean age was 55.70 ± 11.30 years, 58% were male, and obesity was common (mean BMI: 25.46 ± 3.78 kg/m^2, 51.6% obese [BMI ≥ 25 kg/m^2]). The lab results indicate that kidney function remained normal (eGFR: 118.89 ± 38.46 ml/min per 1.73 m^2) and that there was a median 24-h urinary sodium 172.01 ± 80.24 mmol/day. No significant differences were observed between the groups in the application of ACEI/ARBs and diuretics ($P > 0.05$). In general, the study subjects were characterized by higher 24-h urinary sodium and higher rates of hypertension and obesity, as well as a higher BMI ($P < 0.01$).

Table 2 lists the ambulatory blood pressure parameters of the study participants. The 24-h urinary sodium was higher in patients who also had higher ambulatory blood pressure (BP) levels (including the 24-h blood pressure, daytime blood pressure, and night-time blood pressure). In terms of circadian rhythm, the night-time systolic blood pressure drop rate was lowest in the high urinary sodium group as compared with the moderate and low urinary sodium groups. The distribution of the dipper, nondipper, and riser groups was different among the different urinary sodium groups, with the riser type share gradually increasing from the low to the medium urinary sodium group to the high urinary sodium group.

Table 3 lists the conventional echocardiographic parameters, cardiac magnetic resonance structure, and function parameters of the study participants. No difference was observed between different 24-h urinary sodium groups in terms of E/A and E/e'. In terms of LA structure, it was shown that the maximal left atrial volume (LAV) was significantly increased in the high urinary sodium group when compared to the low and moderate urinary sodium groups ($P < 0.001$). This study found that concerning LA function, in addition to LA booster function, LA reservoir function and LA conduit function was significantly reduced with an increase in 24-h urinary sodium among participants in various groups ($P < 0.01$). In addition, the mean LACI was 21 ± 12%, which (LACI) was significantly higher in the high urinary sodium group compared with the low and moderate urinary sodium groups ($P < 0.001$). As a final point, the EF of all participants was within the normal range, with a mean value of 60.64 ± 7.34%, and the LV

TABLE 1. Clinical and laboratory characteristics by 24-h urinary sodium in the study population

	All ($n = 398$)	Low urinary sodium group ($n = 58$)	Moderate urinary sodium group ($n = 224$)	High urinary sodium group ($n = 116$)	*P*
Characteristic					
Age (years)	55.70 ± 11.30	57.29 ± 11.61	55.14 ± 11.35	55.99 ± 11.04	0.411
Height (cm)	169.75 ± 7.86	163.47 ± 6.11	169.39 ± 7.81*	173.62 ± 6.42 *#	<0.001
Weight (kg)	73.81 ± 14.62	60.35 ± 9.30	73.25 ± 12.96*	81.70 ± 14.66 *#	<0.001
Male, *n* (%)	231 (58)	6 (10.3)	118 (52.7)	107 (92.2)	<0.001
BMI (kg/m^2)	25.46 ± 3.78	22.57 ± 3.10	25.40 ± 3.24*	27.04 ± 4.17 *#	<0.001
Medical history, *n* (%)					
Any alcohol use, *n* (%)	31 (7.8)	1 (1.7)	14 (6.3)	16 (13.8)	0.009
Smoker, *n* (%)	105 (26.4)	3 (5.2)	58 (25.9)	44 (37.9)	<0.001
Diabetes, *n* (%)	171 (43.1)	15 (25.9)	99 (44.2)	57 (49.6)	0.011
Hypertension, *n* (%)	189 (47.5)	17 (29.3)	106 (47.3)	66 (56.9)	0.003
Obesity, *n* (%)	205 (51.6)	13 (22.4)	118 (52,7)*	74 (64.3)*#	<0.001
Antihypertensive medication, n (%)					
ACEI /ARB	73 (18.3)	9 (15.5)	40 (17.9)	24 (20.7)	0.68
β-Blocker (%)	27 (6.8)	1 (1.7)	12 (5.4)	14 (12.1)	0.017
CCB (%)	90 (22.6)	13 (22.4)	47 (21)	30 (25.9)	0.594
Diuretics (%)	11 (2.8)	0 (0)	9 (4)	2 (1.7)	0.18
Laboratory data					
Hs-CRP (mg/l)	1.68 ± 3.54	0.90 ± 1.76	1.84 ± 4.19	1.77 ± 2.69	0.204
BNP (pg/ml)	50.69 ± 233.84	38.39 ± 28.18	29.62 ± 27.26	105.46 ± 456.82#	0.106
FBG(mmol/l)	6.01 ± 2.06	5.21 ± 0.74	6.01 ± 1.91*	6.41 ± 2.63*	0.001
LDL-C (mmol/l)	2.99 ± 0.89	2.98 ± 0.85	3.02 ± 0.86	2.93 ± 0.97	0.687
TC (mmol/l)	5.14 ± 1.08	5.28 ± 1.08	5.17 ± 1.05	5.02 ± 1.14	0.305
TG(mmol/l)	1.80 ± 1.40	1.28 ± 0.58	1.81 ± 1.56*	2.04 ± 1.31*	0.003
eGFR (ml/min per 1.73 m^2)	118.89 ± 38.46	112.87 ± 30.91	119.53 ± 41.56	120.68 ± 35.54	0.422
24-h urinary sodium	172.01 ± 80.24	72.76 ± 20.12	146.81 ± 27.52*	270.30 ± 67.90*#	<0.001

Values are mean ± SD, or *n* (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium antagonists; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.
*$P < 0.05$ vs. the low urinary sodium group.
#$P < 0.05$ vs. the moderate urinary sodium group.
*#$P < 0.05$ vs. the low and the moderate urinary sodium group.

TABLE 2. Indices of ambulatory blood pressure (ABPM) by 24-h urinary sodium in the study population

	All ($n=398$)	Low urinary sodium group ($n=58$)	Moderate urinary sodium group ($n=224$)	High urinary sodium group ($n=116$)	*P*
24-h mean SBP (mmHg)	124.20 ± 15.31	116.39 ± 13.91	123.12 ± 14.76*	129.78 ± 15.06 *#	<0.001
24-h mean DBP (mmHg)	73.35 ± 9.16	66.73 ± 6.87	72.61 ± 8.59*	77.78 ± 8.94 *#	<0.001
Daytime mean SBP (mmHg)	125.46 ± 15.11	119.52 ± 14.31	124.63 ± 14.83*	130.09 ± 14.81 *#	<0.001
Daytime mean DBP (mmHg)	74.64 ± 9.58	68.38 ± 7.54	74.38 ± 9.41*	78.42 ± 9.08 *#	<0.001
Night-time mean SBP (mmHg)	120.10 ± 17.38	112.78 ± 16.03	117.84 ± 16.25	127.64 ± 17.54 *#	<0.001
Night-time mean DBP (mmHg)	69.83 ± 10.07	62.71 ± 8.77	68.67 ± 9.04*	75.24 ± 9.76 *#	<0.001
24-h SBP load (%)	29.71 ± 28.22	18.24 ± 22.21	27.86 ± 27.86*	38.39 ± 29.09 *#	<0.001
24-h DBP load (%)	22.36 ± 20.66	10.39 ± 10.89	20.42 ± 19.20*	31.42 ± 22.95 *#	<0.001
Daytime SBP load (%)	22.29 ± 26.28	15.12 ± 20.02	21.25 ± 26.46	27.96 ± 27.89 *#	0.015
Daytime DBP load (%)	12.40 ± 19.48	3.70 ± 6.77	11.25 ± 18.12*	19.08 ± 23.81 *#	<0.001
Night-time SBP load (%)	47.11 ± 36.82	32.41 ± 35.00	41.41 ± 34.63	64.30 ± 35.69 *#	<0.001
Night-time DBP load (%)	49.32 ± 34.11	29.22 ± 31.82	44.42 ± 32.67*	67.57 ± 29.43 *#	<0.001
24-h BPV SBP (%)	10.75 ± 2.64	11.01 ± 2.86	10.78 ± 2.53	10.59 ± 2.74	0.685
24-h BPV DBP (%)	13.35 ± 3.78	13.99 ± 4.16	13.69 ± 3.90	12.44 ± 3.22 *#	0.022
Daytime BPV SBP (%)	10.15 ± 2.91	10.46 ± 3.13	10.04 ± 2.74	10.18 ± 3.10	0.671
Daytime BPV DBP (%)	13.10 ± 5.88	13.39 ± 4.68	13.37 ± 6.50	12.44 ± 5.22	0.427
Night-time BPV SBP (%)	8.86 ± 3.64	8.92 ± 3.82	9.13 ± 3.71	8.32 ± 3.37	0.241
Night-time BPV DBP (%)	6.72 ± 3.14	7.24 ± 3.78	6.84 ± 3.02	6.26 ± 3.00	0.194
Night-time SBP decline (%)	4.15 ± 7.55	4.22 ± 6.82	5.25 ± 7.16	2.10 ± 8.21#	0.006
Night-time DBP decline (%)	6.30 ± 9.08	7.23 ± 9.93	7.28 ± 9.23	4.07 ± 8.05#	0.021
Dipper patterns					0.027
Dipper pattern (%)	65 (22.3)	6 (14.6)	45 (27.6)	14 (15.9)	
Nondipper pattern (%)	142 (48.6)	24 (58.6)	79 (48.5)	39 (44.3)	
Riser pattern (%)	85 (29.1)	11 (26.8)	39 (23.9)	35 (39.8)	

Values are mean ± SD, or *n* (%).
BPV, blood pressure coefficient of variation; DBP, diastolic blood pressure; SBP, systolic blood pressure.
*$P < 0.05$ vs. the low urinary sodium group.
#$P < 0.05$ vs. the moderate urinary sodium group.
*#$P < 0.05$ vs. the low and the moderate urinary sodium group.

function (LV global longitudinal strain, LV global circumferential strain, and LV global radial strain) of participants in the high urinary sodium group was significantly lower than that of participants in the low urinary sodium and moderate urinary sodium groups.

Associations between 24-h urinary sodium, ambulatory blood pressure parameters, BMI, and cardiac structure/function

A tripartite relationship between 24-h urinary sodium and ambulatory blood pressure parameters/BMI, and cardiac

TABLE 3. Indices of left cardiac structure and function by 24-h urinary sodium in the study population

	All ($n=398$)	Low urinary sodium group ($n=58$)	Moderate urinary sodium group ($n=224$)	High urinary sodium group ($n=116$)	*P*
Echocardiographic statistics					
E/A	0.94 ± 0.32	0.94 ± 0.37	0.95 ± 0.32	0.92 ± 0.28	0.767
E/e'	8.52 ± 2.58	8.69 ± 2.58	8.25 ± 2.40	8.90 ± 2.86	0.2
CMR statistics					
LAV (ml)	59.78 ± 25.65	52.82 ± 23.37	55.31 ± 23.47	72.16 ± 26.90 *#	<0.001
LAs-s (%)	38.76 ± 13.67	45.75 ± 12.15	39.47 ± 13.03*	33.61 ± 13.83 *#	<0.001
LAs-a (%)	17.16 ± 6.25	18.14 ± 4.81	17.63 ± 6.37	15.76 ± 6.56#	0.07
LAs-e (%)	21.44 ± 9.70	27.70 ± 9.39	21.52 ± 9.28*	17.89 ± 8.98 *#	<0.001
LAsr-s (s)	1.75 ± 0.65	2.01 ± 0.68	1.78 ± 0.65*	1.56 ± 0.58 *#	0.002
LAsr-a (s)	2.22 ± 0.77	2.32 ± 0.60	2.28 ± 0.78	2.04 ± 0.82#	0.074
LAsr-e (s)	2.17 ± 1.03	2.72 ± 1.07	2.24 ± 1.01*	1.75 ± 0.89 *#	<0.001
LV EDV(ml)	134.95 ± 28.33	119.60 ± 21.27	132.10 ± 25.56*	148.86 ± 30.95 *#	<0.001
LVMI (g/m^2)	75.83 ± 21.54	71.76 ± 20.26	73.27 ± 17.89	82.98 ± 26.59 *#	0.002
EF (%)	60.64 ± 7.34	61.42 ± 7.84	61.45 ± 6.54	58.68 ± 8.17#	0.026
LV GRS (%)	31.65 ± 7.84	34.34 ± 6.92	31.93 ± 7.49	29.60 ± 8.56 *#	0.012
LV GCS (%)	−18.40 ± 3.16	−19.54 ± 2.50	−18.49 ± 3.12	−17.57 ± 3.38 *	0.009
LV GLS (%)	−16.42 ± 3.54	−18.17 ± 1.96	−16.44 ± 3.99*	−15.39 ± 2.83 *#	0.001
LACI (%)	20.86 ± 12.14	18.73 ± 10.10	18.95 ± 9.98	25.92 ± 15.45#	<0.001

Values are mean ± SD, or *n* (%).
A, the peak late transmitral flow velocity; *E*, the peak early transmitral flow velocity; *e'*, the lateral mitral annular velocity; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrial; LACI, left atrioventricular coupling index; LAEDV, LV end-diastole volume; LAs-a, LA booster strain; LAs-e, LA conduit strain; LAsr-a, LA booster strain rate; LAsr-e, LA conduit strain rate; LAsr-s, LA reservoir strain rate; LAs-s, LA reservoir strain; LAV, LA volume; LV, left ventricular; LVMI, left ventricular mass index.
*$P < 0.05$ vs. the low urinary sodium group.
#$P < 0.05$ vs. the moderate urinary sodium group.
*#$P < 0.05$ vs. the low and the moderate urinary sodium group.

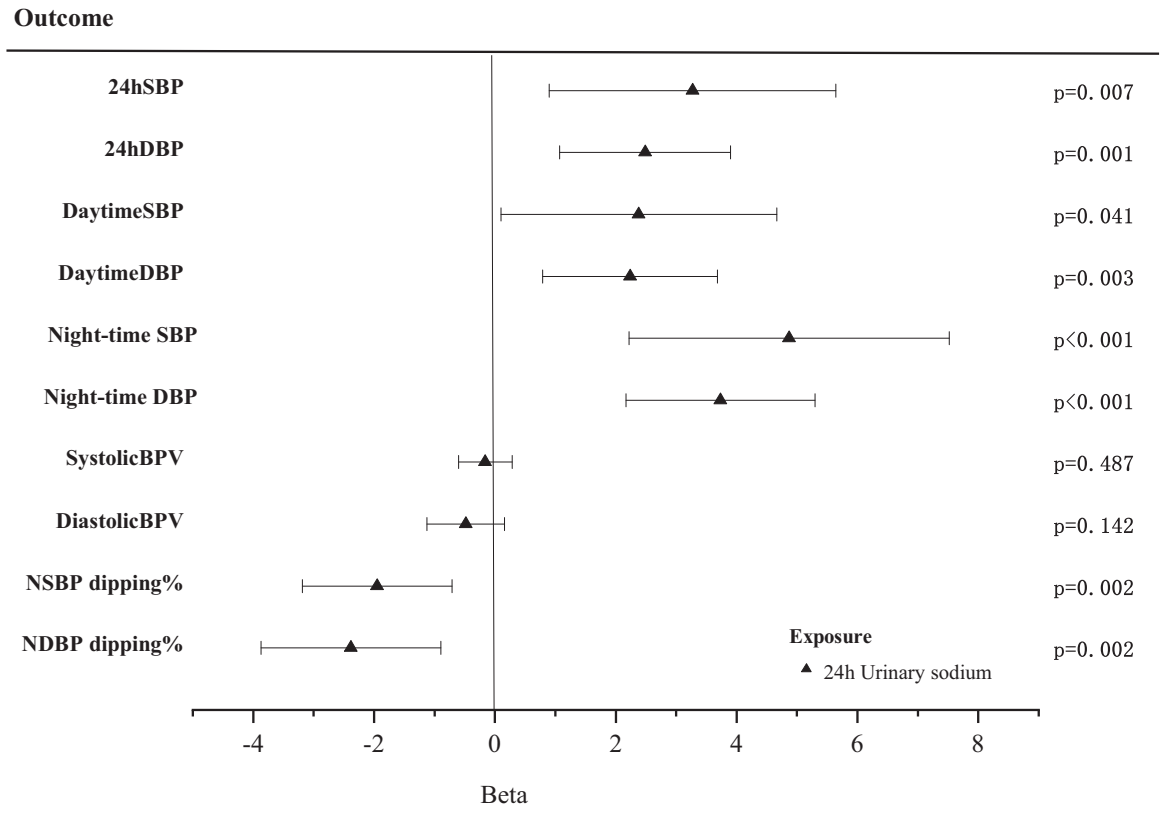


FIGURE 1 Association of urinary sodium with 24-h systolic blood pressure (SBP), 24-h diastolic blood pressure (DBP), daytime SBP, daytime DBP, night-time SBP (NSBP), night-time DBP (NDBP), diastolic blood pressure coefficient of variation (BPV), systolic BPV and percentage dipping. Model adjusted for age, sex, smoking status, alcohol use, diuretic use, and T2DM; beta reflects the change in the dependent variable per 100 mmol increase in urinary sodium.

structure and function was confirmed. After adjusting for variables such as age, sex, smoking history, drinking history, diabetes mellitus, and diuretic use, it is worth noting that 24-h urinary sodium is associated with multiple ambulatory blood pressure parameters, especially night-time diastolic blood pressure (see Fig. 1), as well as the circadian rhythm of blood pressure (night-time blood pressure decline) and riser pattern (see Fig. 2).

Notably, while an association was demonstrated between 24-h urinary sodium and LV function on univariate analysis ($P < 0.01$), the relationship was nonsignificant after multivariable adjustment ($P > 0.05$, see Table 4). Upon multivariate adjustment, 24-h urinary sodium was also significantly associated with BMI, LAV, LA function, and left atrioventricular coupling index in addition to LV function (see Fig. 3).

Lastly, we confirmed that BMI, night-time diastolic blood pressure, and LAV were all correlated with LA function. Furthermore, BMI and the LACI also show a strong positive correlation (see Fig. 4).

BMI, night-time blood pressure, and left the atrial structure as a mediator between 24-h urinary sodium and left cardiac function

A formal mediation analysis included all variables that were consistent with a three-way association between 24-h urinary sodium, night-time blood pressure/BMI, and left cardiac function (LA reservoir function, LA conduit function, LACI). In a mediation analysis, LAV explained a portion of the indirect effects between 24-h urinary sodium and LA function, revealing that high sodium intake may not only adversely affect LA structure and result in deterioration of LA function but may also directly affect LA function independently of LA structure.

In addition to LA booster function, 16% of the association between 24-h urinary sodium and LA reservoir and 16% of the association with LA conduit function may be explained by BMI, respectively. Furthermore, we were also surprised to discover that BMI resulted in a 29.88% mediating effect between 24-h urinary sodium and LACI.

When the confidence interval was set to 90%, night-time diastolic blood pressure mediated 14% of the indirect effect between 24-h urinary sodium and LA conduit function, but when the confidence interval was set to 95%, no statistical significance was observed. In this regard, it can be speculated that night-time diastolic blood pressure may play an important role in 24-h urinary sodium and LA function (see Fig. 5).

DISCUSSION

Our study is the first to investigate the relationship between sodium intake and left atrial function and left atrioventricular coupling. Through our study, BMI is an important mediator. Moreover, the data we have obtained may provide mechanistic insights into the association between high sodium intake and functional deterioration in the early stages of cardiovascular disease.

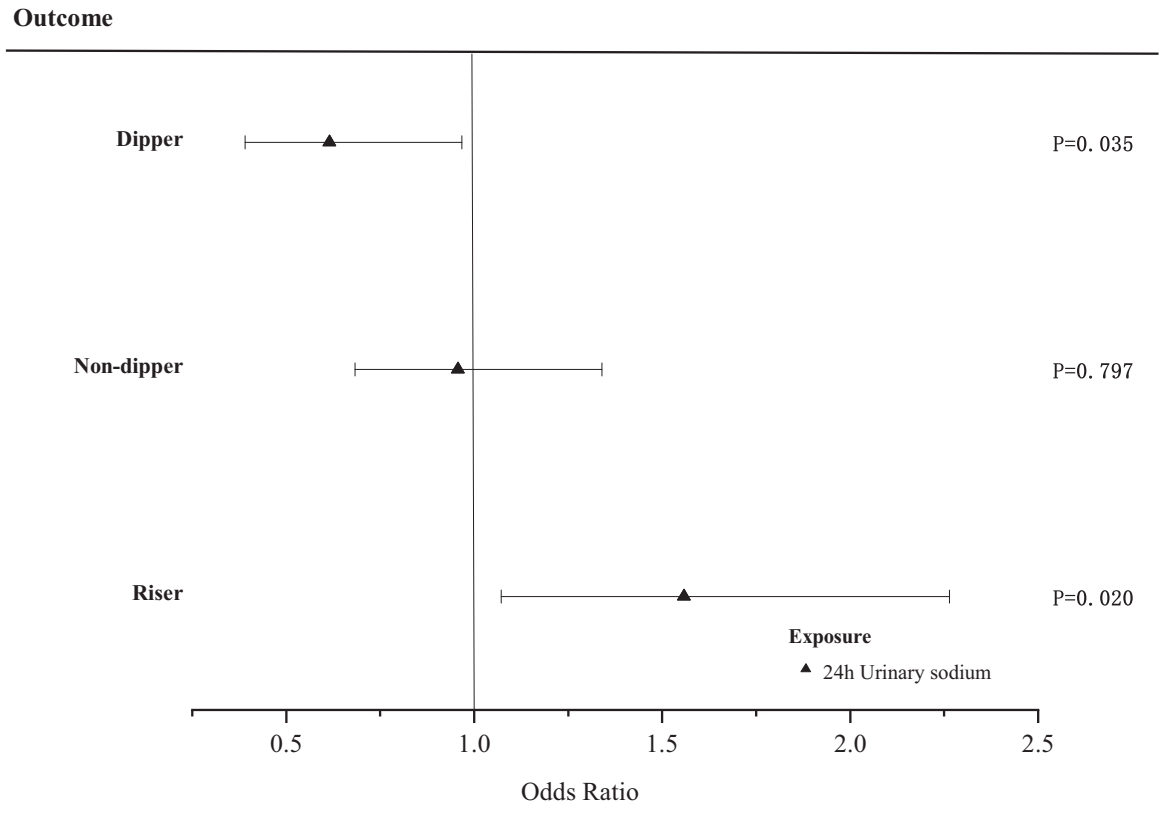


FIGURE 2 Association of urinary sodium with ambulatory blood pressure phenotypes (dipper patterns). Model adjusted for age, sex, smoking status, alcohol use, diuretic use, and T2DM The patterns of night-time BP dipper were calculated based on the reduction in SBP while night-time vs. daytime: dippers (10–<20%); nondippers (0–<10%); and risers and risers (any increase). The odds ratio reflects the change in the dependent variable per 100 mmol increase in urinary sodium.

According to the WHO's guidelines, a sodium intake of more than 2000 mg/day (24-h sodium excretion > 87 mmol/day) was considered excessive [27]. A recent meta-analysis reviewing the published 24-h urinary sodium data in China over the past four decades showed that sodium excretion was 189.07 mmol/24 h [28]. In this study, the 24-h urinary sodium median of the participants was 172.01 ± 80.24 mmol/day. Despite its small sample size, the study also revealed that Chinese sodium intake is higher than the intake recommended by the WHO.

Previously, it was suggested that both a riser pattern of night-time BP and elevated night-time BP appear to be

TABLE 4. Associations of 24-h urinary sodium with left cardiac structure and function in crude and multivariable-adjusted analyses

Dependent variable	Model	24-h urinary sodium (mmol)	
		β-coefficient (95% CI)	*P*
LAV (ml)	Crude	8.096 (4.226 to 11.967)	<0.001
	Multivariable-adjusted[a]	7.538 (2.906 to 12.17)	0.002
LAs-s (%)	Crude	−5.601 (-7.626 to −3.576)	<0.001
	Multivariable-adjusted[a]	−4.595 (−6.948 to −2.243)	<0.001
LAs-a (%)	Crude	−1.735 (−2.691 to −0.78)	<0.001
	Multivariable-adjusted[a]	−1.647 (−2.776 to −0.519)	0.004
LAs-e (%)	Crude	−3.829 (−5.272 to −2.387)	<0.001
	Multivariable-adjusted[a]	−2.752 (−4.345 to −1.16)	0.001
LV GRS (%)	Crude	−1.69 (−2.949 to −0.431)	0.009
	Multivariable-adjusted[a]	−0.337 (−1.783 to 1.11)	0.647
LV GCS (%)	Crude	0.7 (0.193 to 1.207)	0.007
	Multivariable-adjusted[a]	0.21 (−0.377 to 0.797)	0.481
LV GLS (%)	Crude	0.991 (0.429 to 1.553)	0.001
	Multivariable-adjusted[a]	0.248 (−0.4 to 0.897)	0.451
LACI (%)	Crude	3.118 (1.182 to 5.054)	0.002
	Multivariable-adjusted[a]	0.039 (0.009 to 0.07)	0.011

Beta-coefficients reflect the change in the dependent variable per 100 mmol increase in urinary sodium.
CI, confidence interval; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LACI, left atrioventricular coupling index; LAs-a, LA booster strain; LAs-e, LA conduit strain; LAs-s, LA reservoir strain; LAV, LA volume.
[a]Model adjusted for age, sex, smoking status, alcohol use, diuretic use, and T2DM.

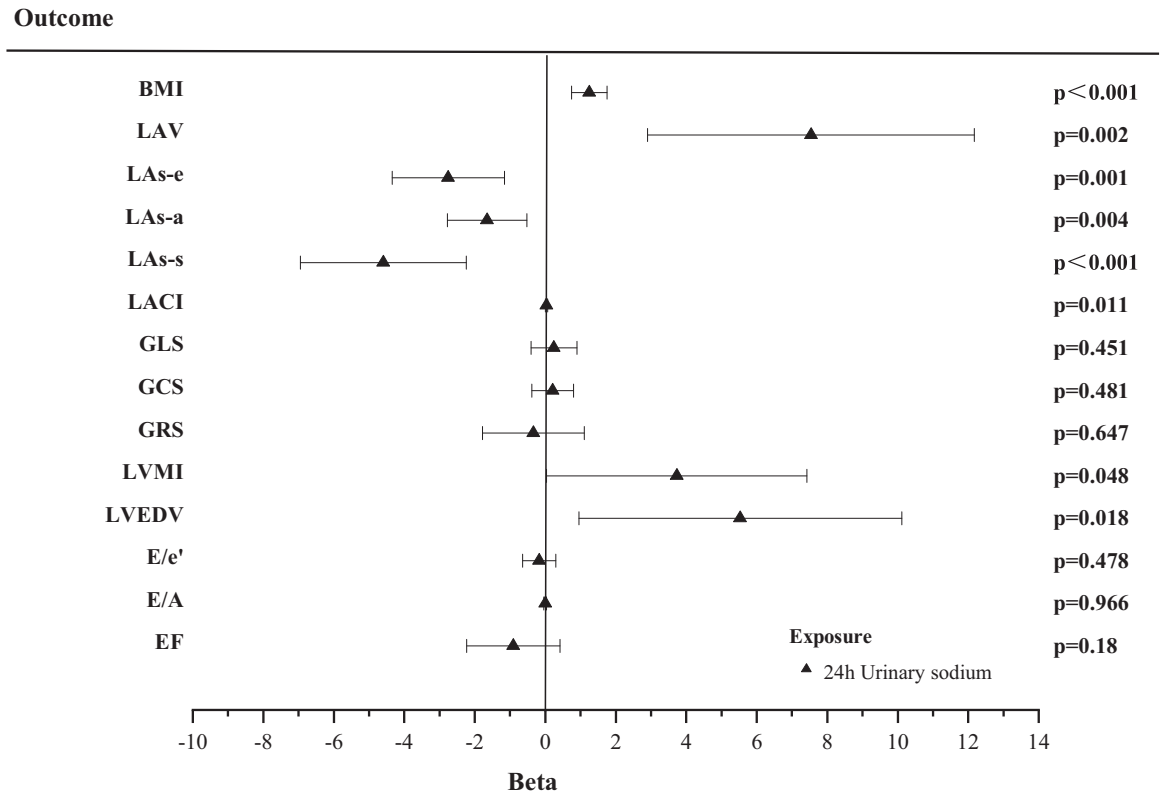


FIGURE 3 Association of urinary sodium with BMI and left cardiac structure and function. Model adjusted for age, sex, smoking status, alcohol use, diuretic use, and T2DM. *A*, the peak late transmitral flow velocity; *E*, the peak early transmitral flow velocity; *e'*, the lateral mitral annular velocity; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LACI, left atrioventricular coupling index; LAEDV, LV end-diastole volume; LAs-a, LA booster strain; LAs-e, LA conduit strain; LAs-s, LA reservoir strain; LAV, LA volume; LVMI, left ventricular mass index; beta coefficients reflect the change in the dependent variable per 100 mmol increase in urinary sodium.

important risk factors for the development of cardiac remodeling, independent of overall ambulatory BP levels [2]. Asians are at high risk of developing night-time hypertension due to having both a high sodium sensitivity and high sodium intake [29]. We confirmed that 24-h urinary sodium correlates well with several ambulatory blood pressure parameters, particularly night-time diastolic blood pressure and the riser pattern of night-time blood pressure. Accordingly, increased sodium intake may be one of the key factors that contribute to high blood pressure and an ABPM phenotype, and thus may be an important area for future research.

According to our findings, 24-h urinary sodium correlates with LA function, with LA function gradually declining (except for LA booster function) as urinary sodium increases. Interestingly, other studies have reported different results regarding the LA booster function, including normal [30], increased [31], or reduced [32]. These discrepancies may be explained by the disease stages of the study population or that the primary function of LA is to modulate LV filling, so the LA booster function is increased with LA volume to maintain a normal cardiac output [33], when the optimal Franke-Starling relationship is exceeded (this mechanism has been proved to apply to LA), in the case of severe LA expansion, the booster function gradually deteriorates as the disease progresses [33]. A larger-scale study might be needed to clarify this issue.

Additionally, a correlation exists between 24-h urinary sodium and LV function, but it is not significant following multivariate analysis, in contrast to previous finding [16], possibly due to the small sample size. Furthermore, the close correlation between urinary sodium and LA function, in comparison to LV function, implies that urinary sodium has a stronger influence on LA. Further research and larger sample sizes are required to verify this issue.

The results of the Multi-Ethnic Study of Atherosclerosis [10] recently showed that the LACI was an independent predictor of heart failure events, resulting in improved identification and reclassification of HF events. Thus, it is necessary to evaluate left atrioventricular coupling. Notably, our results indicate that elevated 24-h urinary sodium is not only related to deteriorating LA function, but may also contribute to poor left atrioventricular coupling, which could be an indicator of individuals with poor dietary habits. If causal, high sodium intake (expressed as 24-h urinary sodium) may be associated with more impaired cardiac function.

A previous study has demonstrated that BMI was independently associated with LA function [34]. Emerging evidence suggests a strong and direct relationship between high sodium intake and obesity [5], consistent with our findings. The bidirectional association between obesity and sodium intake indicates the formation of a vicious cycle, in which people with higher BMI are prone to consume more sodium, which then further increases BMI [35]. Obesity,

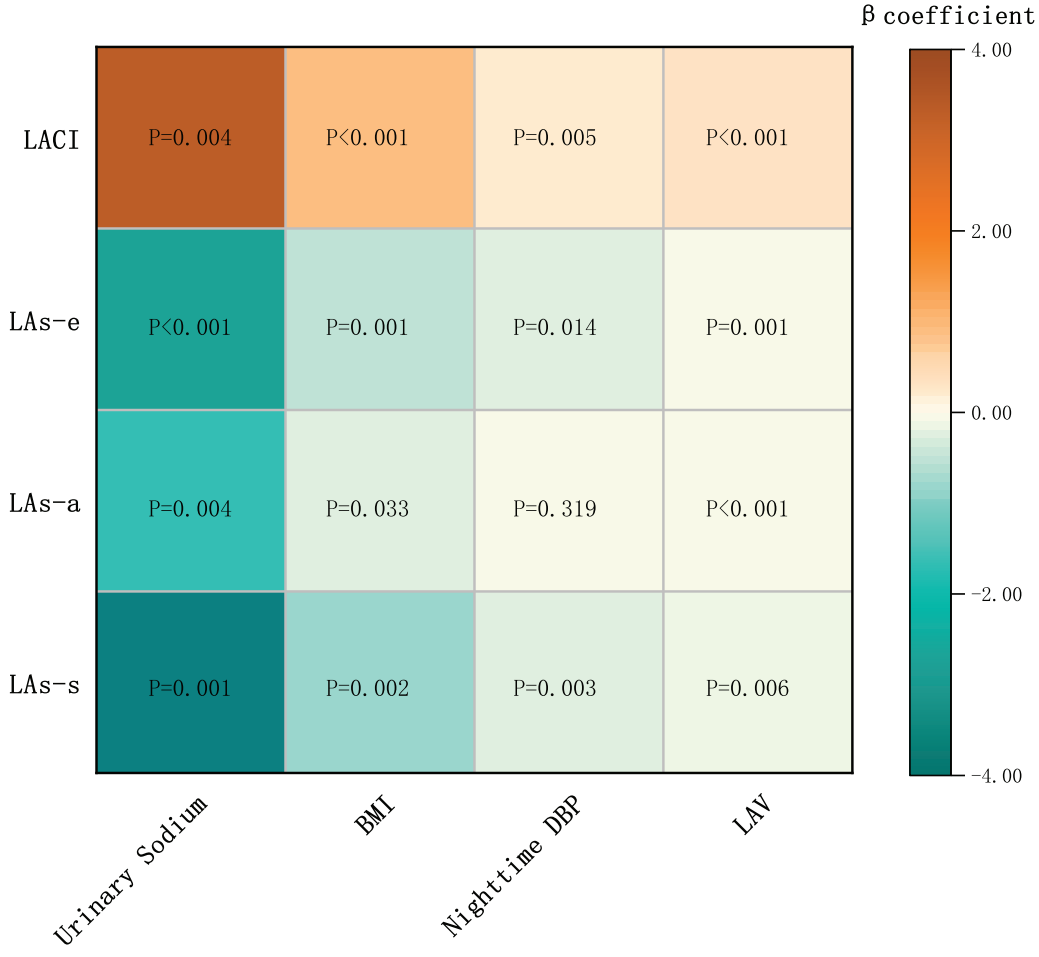


FIGURE 4 Heatmap of associations of 24-h urinary sodium and mediator (BMI, night-time DBP, LAV) with indices of left atrial function and LACI. The LV functions (GRS, GCS, GLS) are not shown because of their lack of association with 24-h urinary sodium. The values in the cells represent the *P* values for the associations. The color and intensity of each cell depict the *β*-coefficients from linear regression models adjusted for age, sex, smoking status, alcohol use, diuretic use, and T2DM. The left atrial function indices and LACI significantly negatively correlate with 24-h urinary sodium, and mediators (thus fulfilling the assumptions for mediation analysis) are highlighted in green, whereas positive correlations are highlighted in brown. DBP, diastolic blood pressure; LA, left atrial; LACI, left atrioventricular coupling index; LAs-a, LA booster strain; LAs-e, LA conduit strain; Las-s, LA reservoir strain; LAV, LA volume; LV, left ventricular.

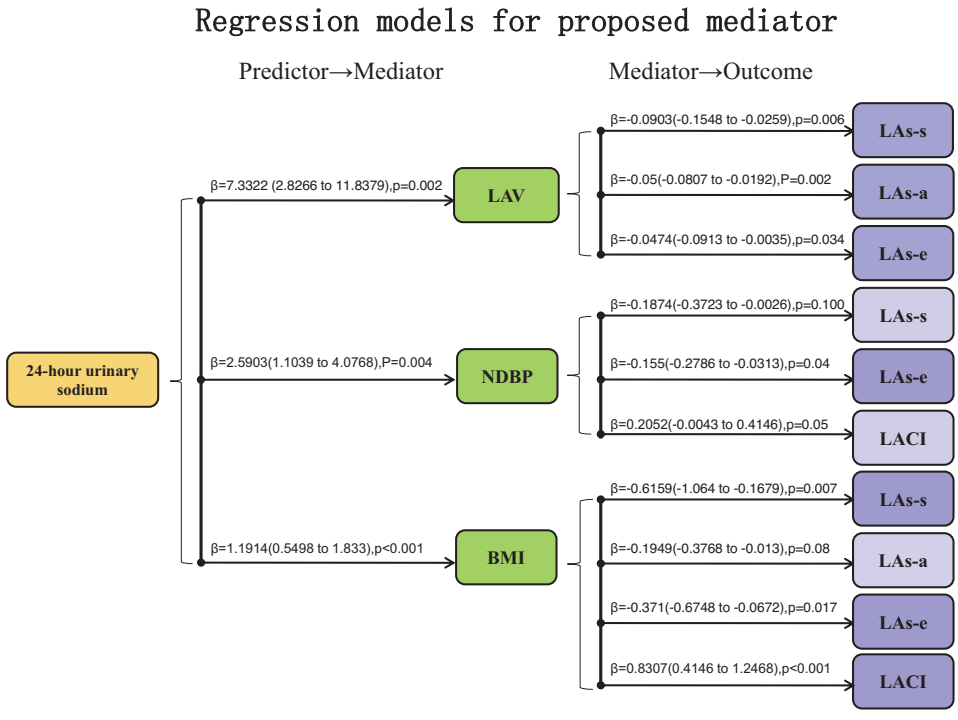
acting synergistically with high sodium intake, may accelerate adverse cardiac remodeling, and obesity may be a potent mediator of the association of sodium intake with poor cardiac function, as our study has demonstrated. Obesity contributes to chronic stretching and a profibrotic milieu in the LA [36], raising the possibility that obesity or overweight may exacerbate the impairment of LA function [34].

According to current knowledge, fibrosis reduces LA elasticity and leads to a decrease in LA compliance, which may be a crucial substrate for LA remodeling [37,38]. Moreover, factors affecting the atrioventricular coupling may be related to left atrial fibrosis [39]. A high sodium intake promotes the hyperplasia and hypertrophy of myocardial cells, and it facilitates the deposition of collagen in myocardial cells, resulting in myocardial fibrosis and cardiac hypertrophy [40]. Furthermore, it is well established that a high sodium diet induces cardiac hypertrophy and fibrosis in part due to the actions of the renin–angiotensin system (RAS) [41], which could lead to a progressive decrement in strain. As part of our study, CMR-LGE was used to evaluate whether high sodium intake leads to myocardial fibrosis, but all LGE were negative. A possible explanation for this result is that no participant in this study had previous organic heart disease, and neither CMR-LGE nor global native T1 (and ECV) could detect early-stage myocardial fibrosis [42,43], not excluding the possibility of false negatives. As imaging is limited, multiple technical tools (e.g., plasma biomarkers combined with imaging) [44] and additional studies may be required in the future to identify patients with early myocardial fibrosis. Perhaps sodium has a direct impact on myocardial damage, the mechanisms of which are currently unclear (there may be many other mechanisms besides possible myocardial fibrosis). Further, high sodium intake can lead to obesity, which further affects the properties or mechanical loading of the LA [45]. To confirm the relevant mechanisms, further studies are needed.

Clinical significances

Our findings highlight the detrimental consequences of high sodium intake on blood pressure, obesity, and left cardiac function. According to our findings, the mean BMI was close to 23 kg/m^2 in the low urinary sodium group,

(a)



(b1)

Outcomes	β	95% CI	Percentage mediated by LAV
LAs-s	-0.6623	-1.4158 to -0.1233	15%
LAs-a	-0.3663	-0.8014 to -0.0692	24%
LAs-e	-0.3474	-0.7846 to -0.0341	13%

(b2)

Outcomes	β	95% CI	90% CI	Percentage mediated by NDBP(90%CI)
LAs-e	-0.4014	-1.0974 to 0.0285	-0.95 to -0.0231	14%

(b3)

Outcomes	β	95% CI	Percentage mediated by BMI
LAs-s	-0.7338	-1.5171 to -0.1763	16%
LAs-e	-0.442	-0.9543 to -0.0638	16%
LACI	0.9802	0.3286 to 1.8652	30%

25 kg/m^2 in the moderate urinary sodium group, and 27 kg/m^2 in the high urinary sodium group. There is a great deal of significance in the three BMIs associated with different sodium intakes. For Asians, a BMI of 23–27.5 kg/m^2 is regarded as the threshold for increased risk, and a BMI over 27.5 kg/m^2 is regarded as the threshold for high risk of CVD [46]. In pooled analyses of 20 prospective cohorts in Asia, an increased risk of death was observed in all BMI values greater than 25 for overall CVD and ischemic stroke, and values greater than 27 for overall stroke and hemorrhagic stroke [47]. Sodium reduction and control of blood pressure and weight loss programs have been widely implemented in a variety of settings, but separately. Our findings provide important support for recommendations for reducing sodium intake and weight loss in Asians, in addition to sodium reduction and blood pressure control, weight management should be prioritized, and controlling these potentially reversible risk factors is clinically important for the early prevention of hypertension, target organ damage, and heart failure, and the improvement of cardiovascular prognosis.

Strengths and limitations

The strengths of our study include the application of cardiac MRI with high spatial resolution and superior contrast capabilities as an examination modality, to understand the association between high sodium intake and adverse cardiovascular event mechanisms. Moreover, mediation analysis is included as a method of causal inference. While mediation is insufficient to establish causality, it goes beyond a simple one-way association analysis. Several limitations should also be taken into account when interpreting our results. First, even when employing the most reliable technique of 24-h urine collection, a single measurement is insufficient to reflect an individual's normal sodium intake. Multiple nonconsecutive 24-h urine collections are required. Next, due to the cross-sectional nature of our study, we were unable to establish causality. Third, as our study included only Chinese participants, results may not generalize to other races and ethnicities with significantly different sodium handling, prevalence, and susceptibility to cardiometabolic diseases, with potential speculation only about broader pan-ethnic group conclusions.

In conclusion, to our knowledge, this is the first study to investigate the relationship between estimated sodium intake (derived from measured 24-h urinary sodium) and cardiac magnetic resonance-measured LA strain and left atrioventricular coupling. Higher 24-h urinary sodium is related not only to multiple ambulatory blood pressure parameters in Chinese but also to higher BMI, poor left atrial function, and adverse left atrioventricular coupling. BMI appeared to explain the significant indirect effect between 24-h urinary sodium and poor cardiac function. It is evident from these data that high sodium intake has early detrimental effects on the cardiovascular system, including, in particular, myocardial effects.

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Conflicts of interest

There are no conflicts of interest.

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FIGURE 5 Mediation modeling includes testing underlying assumptions. Values adjacent to the arrows in A depict β-coefficients (95% CIs) and *P* values from linear regression models adjusted for age, sex, smoking status, alcohol use, diuretic use, and T2DM. The total effect of the association of 24-h urinary sodium with outcomes on linear regression analysis is a prerequisite for mediation analysis. A investigates the assumptions that 24-h urinary sodium is associated with increased mediators (LAV, NDBP, BMI) and that mediators are associated with increased outcomes (left atrial function, LACI). Outcomes in light purple do not fulfill the assumptions for mediation analysis because there is no statistically significant effect between mediator and outcome. Tables B1, B2, and B3 indicate, respectively, the proportion of mediators that relate to the correlation of 24-h urinary sodium with outcomes. For example, in B3 it can be seen that the mediated effect in mediation analysis of parameters fulfills the underlying assumptions, indicating that 30% of the association of 24-h urinary sodium with increased LACI is mediated by BMI. Percentage mediated = mediated effect/total effect × 100. Beta coefficients reflect the change in the dependent variable per 100 mmol increase in urinary sodium. Abbreviations as in Figures 1–4.

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