Association of Urinary Sodium Excretion and Left Ventricular Hypertrophy in Patients With Type 2 Diabetes: A Cross-Section Study

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Original investigation

Keywords: Urinary sodium excretion, Left ventricular hypertrophy, Cardiovascular disease, Type 2 diabetes

Posted Date: March 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-239931/v1

Abstract

Background: It has been well documented that left ventricular hypertrophy (LVH) is highly associated with incidence of cardiovascular disease (CVD). Evidence indicated that high sodium intake has been observed related with LVH in general population. However, information is not available regarding the association between urinary sodium excretion and LVH in patients with type 2 diabetes (T2DM). This study aimed to explore the association between urinary sodium excretion and LVH in patients with T2DM.

Methods: A total of 1356 patients with T2DM were recruited. Urinary sodium was measured from 24-hour urine samples of inpatients and morning fasting urine samples of outpatients. LVH was assessed by echocardiography. The associations between urinary sodium excretion and the risk factors for cardiovascular events, LVH and left ventricular mass index (LVMI) were examined using linear regression analysis, logistic regression and restricted cubic splines.

Results: Urinary sodium excretion levels was positively associated with cardiometabolic risk factors, including systolic blood pressure (P<0.001), body mass index (P<0.001), waist circumference (P<0.001) and LVMI (P<0.001). In multivariable logistic regression analyses, increased urinary sodium excretion were significantly associated with increased risks of LVH [OR (95% CI), 1.47 (1.02-2.10); P=0.037] and CVD [OR (95% CI), 2.08 (1.20-3.61); P=0.009], after adjusted for demographics, lifestyle risk factors and cardiovascular risk factors. Multivariable-adjusted restricted cubic spline analyses of the association between urinary sodium excretion and LVMI showed a significant association (P=0.002) and provided no evidence of a nonlinear association (P=0.135).

Conclusions: This study indicated that high urinary sodium excretion was independently associated with increased risk of LVH and CVD in patients with T2DM, suggesting that control of sodium intake is valuable in the prevention of diabetic cardiovascular complications.

Background

Cardiovascular disease (CVD) is the leading cause of death in patients with type 2 diabetes (T2DM) [1, 2]. The condition affects 15–41% of middle-aged people with diabetes in western countries [3]. In China, 14.6% patients with T2DM have CVD [4]. It has been well documented that left ventricular (LV) hypertrophy (LVH), an increase in LV mass (LVM), is an important predictor of cardiovascular events such as congestive heart failure and cardiovascular mortality [5–7]. Consequently, investigation of the origins of LVH and CVD in patients with T2DM has implications for developing preventive strategy for cardiovascular complication in diabetes.

It has been proposed that sodium intake is significantly associated with increased risk of LVH [8]. The possible pathogenetic mechanisms linking sodium intake to LVH include elevated activity of the renin angiotensin system [9], increased reactivity of sympathetic nervous system [10, 11] and the increase of cardiac volume load [8, 12]. Longitudinal studies have indicated that urinary sodium excretion was significant associated with incidence of LVH in normotensive [13, 14] and hypertensive subjects [15, 16]. However, the relationship between urinary sodium excretion levels and LVH in patients with T2DM remains largely unclear. In the current study, we aimed to explore the association between urinary sodium excretion levels and LVH in patients with T2DM.

Methods

Study participants

The NanFang Prospective Diabetes Study (NFPDS) is a prospective cohort study of adults over aged 20 years old with T2DM recruited from the Nanfang Hospital of Southern Medical University, Guangzhou, China. This study was designed to explore the associations of urinary sodium excretion and possible risk factors with T2DM complications in Chinese population. In the current analysis, a total of 1356 patients with valid urine collections and LV dimensions measurements were included from January 2018 to July 2020. All patients completed a uniform questionnaire including social-demographic status, lifestyle habits (i.e., smoking status, alcohol consumption) and medical history. Patients with any of the following conditions were excluded: 1) NYHA class III or IV congestive heart failure; 2) patients being treated with dialysis; 3) patients with severe systemic infections; 4) women who were pregnant, or planning to become pregnant; 5) patients who are unwilling or unable to sign the informed consent. Hypertension was defined as mean blood pressure (BP) of 140/90 mmHg or greater or self-reported use of antihypertensive medication. Hyperlipidemia was defined as total cholesterol (TC) ≥ 6.22mmol/L, or low-density lipoprotein cholesterol (LDL-c) ≥ 4.14 mmol/L, or triglycerides (TG) ≥ 2.26 mmol/L.

Written informed consent was obtained from each patient. The study protocol was approved by the Institutional Review Board of Nanfang Hospital of Southern Medical University. The methods were carried out in accordance with the approved guidelines.

Clinical and biochemical measurements

Anthropometric measurements included height, weight, waist circumference and BP. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level of 1cm above the umbilicus. Three measurements were obtained with a non-stretchable tape, and the mean value was used for analysis. BP was assessed in triplicate using an electronic sphygmomanometer (OMRON Company).

Blood samples of all patients were collected after 12-hour fasting and tested in the laboratory of Nanfang hospital. Fasting plasma glucose concentrations were measured using the hexokinase method. Glycated hemoglobin (HbA1c) was measured by high performance liquid chromatography. TG, TC, and LDL-c were measured by enzymatic methods using a fully automated biochemical analyzer.

Inpatients were requested to collect 24-hour urine specimens for the measurement of urinary sodium level, which be considered the most reliable estimate of sodium intake [17]. For outpatients, we collected urine samples in the morning after fasting to determine spot urinary sodium and used the Kawasaki formula

to estimate 24-hour sodium urinary excretion. This formula is valid for estimating of sodium intake in healthy participants and patients taking antihypertensive therapy [18, 19]. 24-hour and spot urinary sodium concentrations were measured by using ion selective electrode method.

Echocardiography

LV dimensions were assessed by 2-dimensional guided M-mode echocardiography with 2.25- and 3.5-MHz transducers according to American Society of Echocardiography recommendations [20]. LVM was calculate by using Penn-cube method, a necropsy-validated formula: LVM = 1.04((interventricular septal thickness + LV internal dimension + posterior wall thickness)^3 - LV internal dimension^3) - 13.6 [21]. To reduce the confounding effects of body size, LVM was indexed for body height ($m^{2.7}$) as LV mass index (LVMI). The presence of left ventricular hypertrophy (LVH) was defined LVMI >44 g/$m^{2.7}$ in women and LVMI >48 g/$m^{2.7}$ in men [22]. Relative wall thickness was calculated as interventricular septal thickness plus posterior wall thickness divided by LV end-diastolic diameter.

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) or median (interquartile range), and categorical variables are presents as frequencies and percentages. Data that were not normally distributed were logarithmically transformed before analysis. Baseline characteristics of study participants were compared across quartiles of urinary sodium excretion using general linear models (GLM) for continuous variables and χ^2 -test for categorical variables. Linear regression analyses were used to investigate the association of the following variables with urinary sodium excretion: BMI, waist circumference, systolic BP (SBP), diastolic BP (DBP), duration of diabetes, HbA1c, fasting glucose, TC, TG, LDL-c and LVMI. Multivariable logistic regression models were used to examine the association of urinary sodium excretion levels with risks of LVH and CVD. Forest plot was used to analyze the relationship between urinary sodium excretion levels and LVH in different subgroups. The relationship between urinary sodium excretion and LVMI was examined with restricted cubic splines [23]. Analyses were multivariable-adjusted and used 5 knots (located at the 5th, 25th, 50th, 75th, and 95th percentiles). The urinary sodium excretion of less than 2 g/day recommended by the World Health Organization (WHO) was chosen to be the reference group for all spline plots [24]. All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc). Two-sided values of $P < 0.05$ were considered statistically significant.

Results

Table 1 summarizes demographic and clinical characteristics of patients categorized by quartiles of urinary sodium excretion levels. A total of 1356 patients (mean age, 55 years; 63.9% males) with T2DM were included in this study. Overall, the average duration of diabetes was 8.6 years and the mean ± SD of the estimated 24-hour urinary sodium excretion was 3.3±1.4 g/day. Male subjects had higher urinary sodium excretion than female subjects. Patients with higher urinary sodium excretion had higher proportion of a history of smoking and longer duration of diabetes. Compared to patients in the lowest quartile of urinary sodium excretion, those in the highest quartile had higher levels of BMI, waist circumference and lower levels of HbA1c, TC, LDL-c. Of note, the level of LVM, LVMI and the proportion of LVH was significantly higher in subjects with highest levels of urinary sodium excretion than those with lowest values after adjusted for age and gender.

Clinical characteristic by gender and quartiles of urinary sodium excretion levels was showed in Table 2. Both male and female patients with the highest quartile had higher levels of BMI, waist circumference, SBP, LVM and lower levels of HbA1c, TC. Compared with the lowest quartiles of urinary sodium excretion, the level of LVMI and the proportion of LVH significantly increased in the higher quartiles in males after adjusted for age.

Results of linear regression analysis of urinary sodium excretion on the cardiovascular risk factors are showed in Table 3. Urinary sodium excretion levels were significantly correlated with BMI, SBP, waist circumference, duration of diabetes, LVMI and HbA1c after adjusting age, gender, smoking, alcohol consumption and use of renin-angiotensin system (RAS) blocking agents, diuretics, statin, antidiabetic medication (all P<0.05). The significant negative associations were found between urinary sodium excretion and TC, LDL-c, but disappeared after adjusted for demographics, lifestyle risk factors and current medication use.

The odds ratios (ORs) with 95% confidence interval (CI) for LVH and CVD according to changes in urinary sodium excretion levels are showed in Table 4. Compared with patients in quartile 1, the risk of LVH was significantly increased in quartile 2 [OR (95% CI), 1.63 (1.15-2.30; *P*=0.006], quartile 3 [OR (95% CI), 1.52 (1.08-2.16); *P*=0.018] and quartile 4 [OR (95% CI), 1.54 (1.08-2.19); *P*=0.028] after adjusted for age, gender, smoking status and alcohol consumption, use of antihypertension or antihyperlipidemic medication. These relationships also remained significant when further adjusting for HbA1c and use of antidiabetic medication. Furthermore, patients in the highest quartiles had significantly higher risks of CVD than those in the lowest quartiles, even after adjusting for demographics, lifestyle risk factors and cardiovascular risk factors (all *P*<0.05).

In addition, the subgroup analysis was performed to explore the association between LVH and urinary sodium excretion levels among different populations, according to the following variables: age (<60 years/≥60 years), gender (male/female), hypertension (yes/no), duration of diabetes (≤5 years/>5 years) (Figure 1). The association of urinary sodium excretion with the LVH was significant in the hypertensive patients but not in normotensive patients (*P* for interaction<0.01). No significant differences were found in the associations between urinary sodium excretion and LVH among the subgroups by age, gender and duration of diabetes (all *P* for interaction>0.05).

Multivariable-adjusted restricted cubic spline analyses suggested that urinary sodium excretion was significantly associated with LVMI in total patients (*P*=0.002), males (*P*=0.047) and females (*P*=0.048). However, the non-linear associations of urinary sodium excretion and LVMI were not significant (all *P*>0.05) (Figure 2).

Discussion

It has been documented that dietary sodium intake plays a role in modulating myocardial mass and cardiac structure [8, 25-27]. In the present study, our data indicated that diabetic patients with high urinary sodium excretion had higher level of LVMI. Additionally, we found possible J-shaped association A between urinary sodium excretion and LVMI, instead of the direct linear relation Urinary sodium excretion was positively associated with cardiometabolic risk factors, including SBP, BMI and waist circumference. Of note, we provided the novel evidence that diabetic patients with higher urinary sodium excretion have a significantly increased risk of LVH and CVD independent of demographic factors, lifestyle risk factors and cardiovascular risk factors. These findings suggest that moderate sodium reduction among patients with T2DM may lower the risks of LVH and CVD.

It has been established that sodium intake influence the cardiovascular system profoundly in general population [8, 13-16, 27]. Several studies reported that increased urinary sodium excretion was significant associated with greater LVM in healthy young adults and patients with hypertension [13, 14]. However, information regarding the association of urinary sodium excretion with increase of LVMI in patients with T2DM is limited. In the present study, we found a positively association between urinary sodium excretion and LVMI in patients with T2DM. Of note, our data demonstrated that higher urinary sodium excretion concentrations were independently associated with increased risk of LVH in patients with T2DM. Our findings were consist with previous study in individuals with essential hypertension [8]. In addition, several epidemiological studies reported that high sodium intake is strongly and independently associated with an increased risk of CVD and all-cause mortality [28, 29]. Consistently, our data also indicated that high urinary sodium excretion was significantly associated with the increased risk of CVD in patients with T2DM. These findings have implication for moderate sodium reduction among patients with T2DM may lower CVD risk.

Additionally, several studies indicated the association between sodium consumption and CVD or mortality is J-shaped in general population [30-32]. Evidence indicated that subjects with estimated sodium intake between 3 g/day and 6 g/day was associated with a lower risk of cardiovascular morbidity and mortality than those either with a higher or lower estimated level of intake [30, 31]. In the present study, it same to be a possible J-shaped association between sodium excretion and LVMI in patients with T2DM. In addition, our data indicated that individuals with 2 g/day of urinary sodium excretion were associated with lower levels of LVMI, supporting that 2 g/day of urinary sodium excretion recommended by WHO and American Diabetes Association may be reasonable for patients with T2DM [24, 33].

Extensive observations have indicated that obesity and hypertension are the most important determinants of LVH in the general population [34-36]. Elevated BP plays a driving role in the development of LVH through chronic hemodynamic overload and increased central pressure[37]. Our data demonstrated that urinary sodium excretion was significantly and positively correlated with SBP after adjusted for demographics and lifestyle risk factors. Furthermore, our data showed that the association of sodium intake with LVH remained significant after adjusted for blood pressure. These data indicated that other mechanisms may play a role in the effect of dietary sodium on LVH in patients with T2DM, which was consistent with previous findings of a positive association between dietary sodium intake and CVD independent of blood pressure [29, 38]. Some possible mechanisms independent of blood pressure include the change of circulating fluid volume [14], insulin resistance [39, 40] and obesity [36]. Evidence from epidemiological studies have indicated that adiposity is one of the major predictors of LVH [36]. Cross-sectional studies demonstrated that high sodium intake is independently associated with elevated risk of obesity and central obesity [41, 42]. In consist, our data also indicated that urinary sodium excretion was positively correlated with BMI and waist circumference. These results suggest that high sodium intake was significant associated with CVD risks, and may be an important risk factor for LVH and CVD risks among patients with T2DM.

To our knowledge, this is the first analysis of the association between urinary sodium excretion levels and LVH in patients with T2DM, which can provide novel evidence for cardiovascular risk management in these patients. However, several limitations of this study must be considered. First, this was a cross-sectional study of baseline measurements. It is not possible to determine a causal relationship between urinary sodium excretion and the development of LVH. Second, we used spot urine samples instead of 24-hour urine collection for the estimation of sodium excretion in outpatients. Although the 24-hour urinary sodium can't be measured directly in outpatients, the Kawasaki formula is the most valid and least biased method of estimating 24-h urinary sodium excretion [43]. Third, it was not possible to compare clinical outcomes among patients with urinary sodium excretion less than 2g/day due to the very small sample sizes among these subgroups. However, the average sodium intake in our study is similar with previous study, which reported the average sodium intake of Chinese people is about 3.5g/day in 2009-2011 [44].

Conclusion

In summary, our study provides the clinical evidence revealing that high urinary sodium excretion level is independently increased associated with LVH and CVD in patients with T2DM. These findings suggests that it is critical to control sodium intake for the prevention of CVD in patients with T2DM. Further prospective studies are required to confirm the associations and explore the underlying mechanism.

Abbreviations

LVH: Left ventricular hypertrophy; CVD: Cardiovascular disease; T2DM: Type 2 diabetes; LV: Left ventricular; LVM: Left ventricular mass; NFPDS: the NanFang Prospective Diabetes Study; BP: Blood pressure; TC: Total cholesterol; LDL-c: Low-density lipoprotein cholesterol; TG: Triglycerides; BMI: Body mass index; HbA1c: Glycated hemoglobin; LVMI: Left ventricular mass index; SD: Standard deviation; GLM: General linear models; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WHO: World Health Organization; ORs: Odds ratios; CI: Confidence interval, RAS: renin-angiotensin system

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Nanfang Hospital of Southern Medical University. The methods were carried out in accordance with the approved guidelines.

Consent for publication

Written informed consent was obtained from each patient.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Key Research and Development Project (No.2018YFA0800404), Natural Science Foundation and Key-Area Research and Development Program of Guangdong Province (Nos.2018B030311031 and 2019B020227004), the National Natural Science Foundation of China (No.81970736) and Key-Area Clinical Research Program of Southern Medical University (LC2019ZD010). Dr. Huijie Zhang was partially supported by Distinguished Young Scholars Training Program of Nanfang Hospital.

Authors' contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

Acknowledgement

The authors are grateful to all participants for their time and effort.

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Tables

Table 1 Characteristics of subjects categorized by quartile of urinary sodium

Variables	Estimated 24-hour urinary sodium excretion level				P-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Sample size	338	338	341	339	-
Urine sodium (g/day)	1.74±0.43	2.72±0.24‡	3.53±0.26‡	5.20±1.23‡	<0.001
Age (years)	55.3±11.3	56.2±10.4	55.7±10.4	54.5±10.4	0.224
Gender (Male n, %)	188 (55.6)	203 (60.1)	228 (66.9)	247 (72.9)	<0.001
Smoking (n, %)	136 (40.2)	142 (42.1)	172 (50.7)	174 (51.6)	0.003
Alcohol use (n, %)	103 (30.5)	114 (34.0)	135 (39.9)	118 (35.3)	0.078
Duration of diabetes (years)	5 (2-11)	8 (3-13) ‡	8 (3-14) ‡	8 (3-13) ‡	<0.001
BMI (kg/m^2)	23.9±3.5	24.3±3.3	24.7±3.3‡	25.5±3.8‡	<0.001
Waist circumference (cm)	86.7±9.5	87.7±9.0	89.3±8.8‡	90.9±10.0‡	<0.001
SBP (mmHg)	127.4±18.5	127.3±18.7	127.8±18.0	129.6±17.6	0.341
DBP (mmHg)	77.2±11.5	76.8±10.4	76.5±11.1	78.1±10.8	0.228
Hypertension (n, %)	134 (39.6)	118 (34.9)	112 (32.9)	110 (32.6)	0.198
Hyperlipidemia (n, %)	193 (57.1)	200 (59.2)	203 (59.7)	182 (54.0)	0.429
CVD (n, %)	31 (9.2)	49 (14.5)	43 (12.6)	51 (15.0)	0.094
Antidiabetic medication (n, %)	221 (65.4)	249 (73.7)	282 (82.7)	276 (81.4)	<0.001
RAS blocking agents (n, %)	54 (16.0)	49 (14.5)	65 (19.1)	50 (14.8)	0.345
Diuretics (n, %)	12 (3.6)	7 (2.1)	7 (2.1)	8 (2.4)	0.555
Statin (n, %)	42 (12.4)	47 (13.9)	57 (16.7)	47 (13.9)	0.441
Aspirin (n, %)	28 (8.3)	22 (6.5)	36 (10.6)	35 (10.3)	0.209
HbA1c (%)	10.1±2.7	9.5±2.5‡	8.8±2.4‡	8.8±2.2‡	<0.001
Fasting glucose (mmol/L)	7.56 (5.51-10.37)	7.42 (5.73-10.61)	7.38 (5.48-9.82)	7.41 (5.74-9.82)	0.248
Triglycerides (mmol/L)	1.34 (0.95-2.29)	1.52 (0.99-2.37)	1.47 (1.04-2.34)	1.55 (1.04-2.55)	0.799
Total cholesterol (mmol/L)	5.06±1.48	5.15±1.29	4.82±1.30†	4.92±1.20	0.006
LDL-c (mmol/L)	3.25±1.02	3.34±0.98	3.10±0.95	3.14±0.84	0.004
LVM (g)	154.6±41.5	163.0±42.8†	169.0±43.5‡	171.1±47.7‡	<0.001*
LVMI ($g/m^{2.7}$)	42.5±11.7	44.8±11.8†	45.7±12.1‡	44.9±12.8‡	<0.001*
RWT	0.50±0.09	0.50±0.09	0.50±0.09	0.50±0.09	0.977
LVH (n, %)	119 (35.2)	147 (43.5) †	135 (39.6) †	128 (37.8) †	0.050*

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; CVD=cardiovascular disease; RAS=renin-angiotensin system; HbA1c=glycated hemoglobin; LDL-c= Low-density lipoprotein cholesterol; LVM=left ventricular mass; LVMI=left ventricular mass index; RWT=relative wall thickness; LVH=left ventricular hypertrophy.

†P< 0.05 compared with Quartile 1 of urinary sodium.

‡P< 0.01 compared with Quartile 1 of urinary sodium.

*adjusted for age and gender.

Table 2 Characteristics of subjects categorized by quartile of urinary sodium and gender

Variables	Males (n=866)				P-value	Females (n=490)				P-valu
	Estimated 24-hour urinary sodium excretion level					Estimated 24-hour urinary sodium excretion level				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Sample size	216	217	216	217	-	122	123	122	123	-
Urine sodium (g/day)	1.8±0.5	2.9±0.3‡	3.7±0.3‡	5.5±1.3‡	<0.001	1.6±0.4	2.5±0.2‡	3.3±0.2‡	4.7±1.0‡	<0.0
Age (years)	51.9±11.3	54.5±10.4†	54.0±10.5†	53.3±11.1	0.064	60.0±10.1	59.0±8.7	59.4±9.9	57.5±8.4†	0.17
Duration of diabetes (years)	3 (1-10)	7 (2-13) ‡	8 (2-12) ‡	8 (3-13) ‡	<0.001	7 (2-14)	9 (4-14)	10 (5-13)	8 (3-15)	0.81
Smoking (n, %)	154 (71.3)	149 (68.7)	158 (73.5)	150 (69.1)	0.674	3 (2.5)	0 (0.0)	7 (5.8)	3 (2.5)	0.01
Alcohol use (n, %)	105 (48.8)	111 (51.4)	114 (53.3)	101 (47.0)	0.577	8 (6.6)	12 (9.8)	11 (9.2)	8 (6.7)	0.71
BMI (kg/m2)	24.0±3.6	24.0±3.0	24.8±3.6‡	25.7±3.6‡	<0.001	23.5±3.4	25.0±3.4‡	24.8±3.1‡	25.0±3.9‡	<0.0
Waist circumference (cm)	87.6±9.9	87.9±8.5	89.9±9.6†	92.1±9.6‡	<0.001	85.1±9.0	87.8±8.8†	88.3±8.3‡	87.7±10.2†	0.03
SBP (mmHg)	124.1±18.2	125.4±19.0	127.4±17.7	129.6±16.1‡	0.010	130.2±17.7	131.6±18.4	129.7±17.4	130.4±20.8	0.87
DBP (mmHg)	77.7±11.9	77.5±10.6	77.7±11.1	79.9±10.2†	0.060	75.5±10.8	77.2±10.2	73.8±10.7	74.8±11.1	0.08
Hypertension, (n, %)	73 (33.8)	63 (29.0)	65 (30.2)	69 (31.8)	0.733	54 (44.3)	56 (45.5)	52 (42.6)	42 (34.7)	0.31
Hyperlipidemia, (n, %)	125 (57.9)	125 (57.6)	127 (59.1)	122 (56.2)	0.948	66 (54.1)	75 (61.0)	76 (62.3)	62 (51.2)	0.23
CVD (n, %)	15 (6.9)	25 (11.5)	29 (13.4)	30 (13.8)	0.095	16 (13.1)	22 (17.9)	21 (17.2)	16 (13.0)	0.58
Antidiabetic medication (n, %)	127 (58.8)	150 (69.1)	175 (81.0)	172 (79.3)	<0.001	92 (75.4)	99 (80.5)	108 (88.5)	105 (85.4)	0.04
RAS blocking agents (n, %)	28 (13.0)	27 (12.4)	39 (18.1)	31 (14.3)	0.338	24 (19.7)	25 (20.3)	26 (21.3)	18 (14.6)	0.54
Diuretics (n, %)	5 (2.3)	4 (1.8)	5 (2.3)	4 (1.8)	0.972	5 (4.1)	5 (4.1)	3 (2.5)	3 (2.4)	0.79
Statin (n, %)	19 (8.8)	20 (9.2)	38 (17.6)	29 (13.4)	0.017	25 (20.5)	20 (16.3)	28 (23.0)	14 (11.4)	0.09
Aspirin (n, %)	13 (6.0)	17 (7.8)	20 (9.3)	22 (10.1)	0.430	15 (12.3)	7 (5.7)	15 (12.3)	12 (9.8)	0.26
HbA1c (%)	10.6±2.7	9.4±2.8‡	8.8±2.3‡	9.0±2.3‡	<0.001	9.7±2.7	9.2±2.4	8.9±2.2‡	8.5±2.1‡	<0.0
Fasting glucose (mmol/L)	8.23 (5.90-11.15)	7.71 (5.57-10.98)	7.33 (5.72-9.45) ‡	7.25 (5.64-9.76) ‡	0.002	6.74 (5.19-8.88)	7.14 (5.54-9.19)	7.30 (5.61-9.94)	7.69 (5.60-10.31)	0.82
Triglycerides (mmol/L)	1.35 (0.90-2.68)	1.41 (1.01-2.42)	1.46 (1.00-2.36)	1.61 (1.09-2.84)	0.583	1.30 (0.96-1.98)	1.66 (1.09-2.42)	1.52 (1.21-2.08)	1.43 (0.97-2.09)	0.27
Total cholesterol (mmol/L)	5.13±1.59	5.08±1.23	4.79±1.45‡	4.82±1.16†	0.014	4.85±1.20	5.30±1.39‡	4.92±1.21	5.14±1.12	0.01
LDL-c (mmol/L)	3.29±1.04	3.32±0.95	3.06±0.99†	3.10±0.80†	0.059	3.12±0.97	3.41±1.03†	3.18±0.91	3.26±0.91	0.09
LVM (g)	159.6±45.3	167.2±46.8	178.8±45.3‡	176.5±46.7‡	<0.001*	147.3±34.8	153.7±34.0	155.7±37.6	157.7±43.6‡	0.04
LVMI ($g/m^{2.7}$)	40.1±11.9	42.3±11.7	45.2±12.0‡	44.1±12.4‡	<0.001*	45.4±11.2	47.6±10.0	48.2±11.7†	47.9±13.3†	0.05
RWT	0.49±0.09	0.49±0.08	0.50±0.09	0.50±0.08	0.332	0.51±0.10	0.51±0.08	0.52±0.11	0.49±0.10	0.12
LVH (n, %)	46 (21.3)	57 (26.3)	71 (32.9) †	67 (30.9) †	0.014*	61 (50.0)	84 (68.3) ‡	74 (60.7)	69 (56.1)	0.28

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; CVD=cardiovascular disease; RAS=renin-angiotensin system; HbA1c=glycated hemoglobin; LDL-c=low-density lipoprotein cholesterol; LVM=left ventricular mass; LVMI=left ventricular mass index; RWT=relative wall thickness; LVH=left ventricular hypertrophy.

†P< 0.05 compared with Quartile 1 of urinary sodium.

‡P< 0.01 compared with Quartile 1 of urinary sodium.

*adjusted for age.

Table 3 Clinical correlation of urinary sodium levels with clinical and biochemical variables

Variables	Regression coefficient β	Standard error	P-value	Multiple adjusted P-value §
BMI (kg/m^2)	0.554	0.094	<0.001	<0.001
Waist circumference (cm)	1.511	0.260	<0.001	<0.001
SBP (mmHg)	1.402	0.497	0.005	<0.001
DBP (mmHg)	0.740	0.300	0.014	0.059
Duration of diabetes (year)	0.628	0.189	<0.001	0.006
HbA1c (%)	-0.434	0.068	<0.001	<0.001
Fasting glucose (mmol/L)	-0.078	0.122	0.520	0.655
Triglycerides (mmol/L)	0.004	0.058	0.994	0.809
Total cholesterol (mmol/L)	-0.084	0.036	0.020	0.226
LDL-c (mmol/L)	-0.055	0.026	0.034	0.302
LVMI (g/m$^{2.7}$)	0.838	0.330	0.011	<0.001

BMI=body mass index; SBP=systolic blood pressure; DBP=diastolic blood pressure; HbA1c=glycated hemoglobin; LDL-c=low-density lipoprotein cholesterol; LVMI=left ventricular mass index; RAS=renin-angiotensin system.

§ : adjusted for age, gender, smoking, alcohol consumption, RAS blocking agents, diuretics, statin and antidiabetic medication.

Table 4 Odds ratios (ORs) of LVH and CVD according to urinary sodium levels

Variables	LVH			CVD		
	OR	95% CI	P-value	OR	95% CI	P-value
Crude model						
urinary sodium (g/day)						
(Quartile 2 vs. Quartile 1)	1.42	1.04-1.93	0.028	1.68	1.04-2.71	0.033
(Quartile 3 vs. Quartile 1)	1.21	0.88-1.65	0.238	1.43	0.88-2.33	0.152
(Quartile 4 vs. Quartile 1)	1.12	0.82-1.53	0.491	1.75	1.09-2.82	0.020
Model 1						
urinary sodium (g/day)						
(Quartile 2 vs. Quartile 1)	1.55	1.11-2.17	0.011	1.72	1.04-2.84	0.036
(Quartile 3 vs. Quartile 1)	1.43	1.02-2.01	0.038	1.43	0.85-2.40	0.177
(Quartile 4 vs. Quartile 1)	1.48	1.05-2.08	0.026	2.13	1.28-3.54	0.004
Model 2						
urinary sodium (g/day)						
(Quartile 2 vs. Quartile 1)	1.63	1.15-2.30	0.006	1.80	1.06-3.08	0.030
(Quartile 3 vs. Quartile 1)	1.52	1.08-2.16	0.018	1.36	0.79-2.37	0.271
(Quartile 4 vs. Quartile 1)	1.54	1.08-2.19	0.016	2.31	1.35-3.97	0.002
Model 3						
urinary sodium (g/day)						
(Quartile 2 vs. Quartile 1)	1.59	1.12-2.25	0.010	1.73	0.94-3.17	0.079
(Quartile 3 vs. Quartile 1)	1.45	1.02-2.07	0.040	1.25	0.70-2.58	0.372
(Quartile 4 vs. Quartile 1)	1.47	1.02-2.10	0.037	2.08	1.20-3.61	0.009

LVH=left ventricular hypertrophy; CVD=cardiovascular disease; OR=odds ratio; CI=confidence interval; RAS=renin-angiotensin system; DBP=diastolic blood pressure; HbA1c=glycated hemoglobin.

Crude model: without adjustment.

Model 1: adjusted for age, gender, smoking and alcohol consumption.

Model 2: adjusted for model 1+ DBP, RAS blocking agents, diuretics, hyperlipidemia and statin.

Model 3: adjusted for model 2+ HbA1c and antidiabetic medication.

Figures

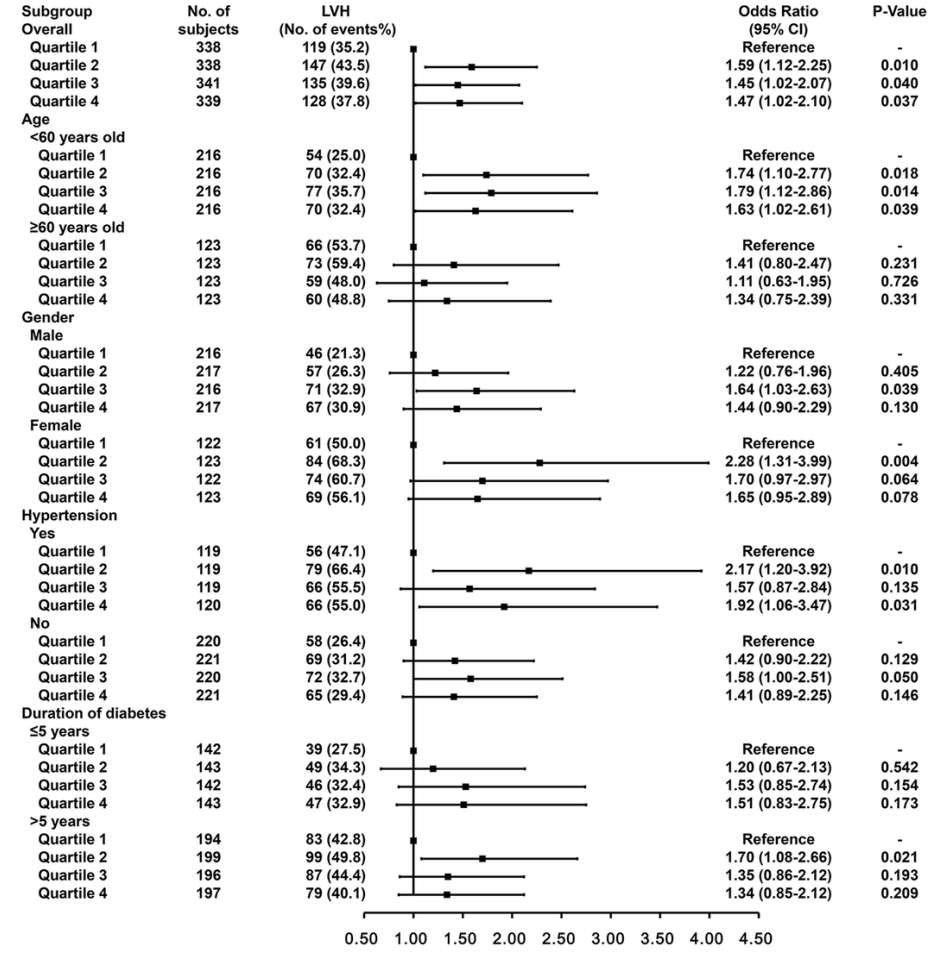

Figure 1

Forest plot of odds ratio of LVH according to urinary sodium levels in different subgroups. Adjusted for age, gender, smoking, alcohol consumption, DBP, use of RAS blocking agents, use of diuretics, history of hyperlipidemia, use of statin, HbA1c and use of antidiabetic medication.

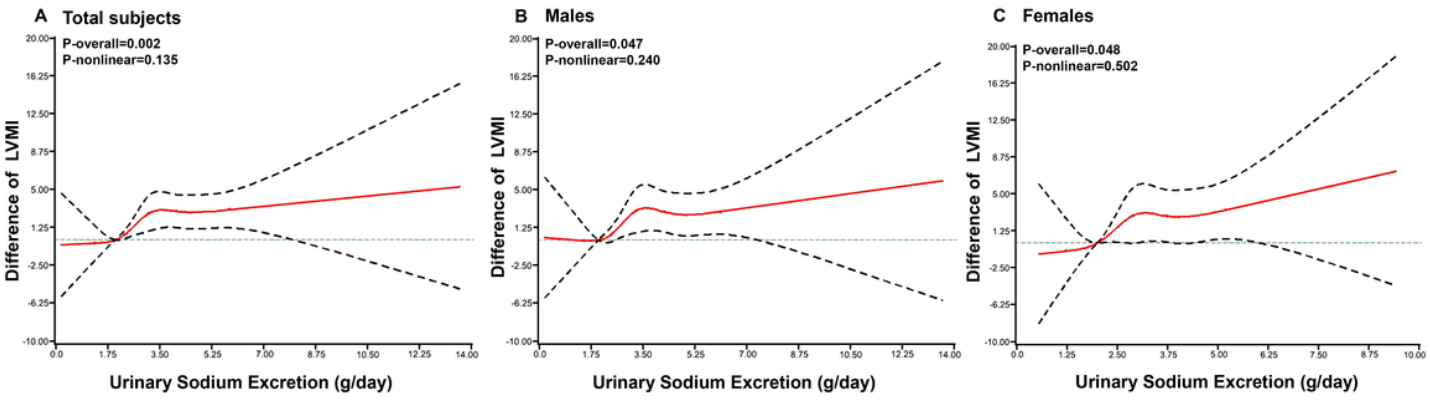

Figure 2

Association of urinary sodium excretion with LVMI. The restricted cubic spline (RCS) regression was used to analyze the relationships of urinary sodium excretion(g/day) with left ventricular mass index (LVMI) after adjusting for age, gender, smoking, alcohol consumption, DBP, use of RAS blocking agents, use of diuretics, history of hyperlipidemia, use of statin, HbA1c and use of antidiabetic medication in total subjects(A), males(B), females(C). Urinary sodium excretion was coded using an RCS function with five knots located at the 5th, 25th, 50th, 75th, 95th percentiles of the distribution of urinary sodium excretion. Y-axis represents the difference in LVMI between individuals with any value of urinary sodium excretion with individuals with 2g/day of urinary sodium excretion. Black dashed lines are 95 percent confidence intervals.