Salt intake causes B-type natriuretic peptide elevation independently of blood pressure elevation in the general population without hypertension and heart disease

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Abstract

Excessive salt intake causes hypertension and cardiovascular diseases (CVDs). B-type natriuretic peptide (BNP) is synthesized and released from the ventricle, and is a surrogate marker reflecting various CVDs. Moreover, when a slight BNP elevation is shown, it leads to a poor prognosis in the general population. However, the relationship between salt intake and BNP levels in the general population remains unclear, especially in those without hypertension and heart diseases.

In this study, we recruited 1404 participants without hypertension and electrocardiogram abnormalities, who received regular annual health check-ups in Japan. Plasma BNP levels were measured, and daily salt intake levels were evaluated using urinary samples. In addition, some clinical parameters were obtained, and the data were cross-sectionally analyzed.

The median of plasma BNP levels was 10.50 pg/mL, and daily salt intake was 8.50 ± 1.85 g. When dividing participants into quartiles according to daily salt intake, those with the highest daily salt intake revealed the highest plasma BNP levels. Plasma BNP levels were significantly and positively associated with daily salt intake. Moreover, multiple linear regression analyses revealed that plasma BNP levels showed a significant positive association with daily salt intake levels after adjustments.

Plasma BNP levels were significantly and positively associated with daily salt intake after adjustment in the general population. Plasma BNP levels may be a surrogate marker reflecting salt-induced heart diseases.

Abbreviations: BMI = body mass index, BNP = B-type natriuretic peptide, BP = blood pressure, CVDs = cardiovascular diseases, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, LDL = low-density lipoprotein, LVH = left ventricular hypertrophy, ROS = reactive oxygen species, SV1 + RV5 = an S-wave in V1 plus an R-wave in V5 wave, TG = triglyceride.

Keywords: blood pressure, B-type natriuretic peptide, general population, heart disease, hypertension, left ventricular hypertrophy, salt intake

1. Introduction

It is well known that salt intake is associated with blood pressure (BP) levels. We clarified that both relatively high levels of dietary sodium intake and gradual increases in dietary sodium are associated with future increases in BP and hypertension incidence in the general Japanese population.[1] Moreover, Graudal et al meta-analyzed 185 studies that included the association between salt intake and BP, and they concluded that salt reduction resulted in a decrease in BP in participants with hypertension.[2]

Some studies evaluating the relationship between salt intake and cardiovascular diseases (CVDs) have been performed to date. We have indicated that excessive body weight-adjusted salt intake is related to hypertensive organ damage.[3] In addition, Aburto et al meta-analyzed and concluded that increased salt intake was associated with an increased risk of CVDs such as stroke, stroke mortality, and coronary heart disease mortality.[4]

Death due to heart diseases is the secondary cause of death in Japan, with heart failure being the most frequent cause of death among heart diseases. Because left ventricular function deteriorates progressively in patients with heart disease,[5] it is important to identify latent patients with asymptomatic left ventricular dysfunction. Although Doppler echocardiography

and tolerance tests are useful tools to diagnose left ventricular dysfunction, it is difficult and expensive in the primary care setting to screen the general population using these tools.

B-type natriuretic peptide (BNP) is synthesized and released from the ventricle in response to an increase in ventricular filling pressure.[6] Some researchers, including us, have indicated that BNP levels are associated with the independent predictors of cardiovascular mortality in various patients with heart failure and the general population.[7–12]

However, it is unclear whether salt intake is associated with plasma BNP levels in the general population. In addition, few reports have indicated the relationship between salt intake and plasma BNP levels in the general population without hypertension and electrocardiogram (ECG) abnormality having few risk factors for heart diseases. Therefore, this study was performed to verify this relationship.

2. Methods

2.1. Study design

This study was approved by the ethics committee of Hamamatsu University School of Medicine (No. 18–194) and Enshu Hospital, respectively and adhered to the principles of the Declaration of Helsinki. It was performed on participants attending their regular annual health check-ups in Enshu Hospital. Written informed consent was obtained from all patients.

2.2. Study participants and procedures

We recruited 2790 consecutive participants aged ≥20 years who received regular annual health check-ups in Enshu Hospital between February 2019 and June 2019. As part of the annual health check-up, attendees were interviewed regarding their health status and underwent routine physical examination, ECG, and laboratory assessment of some clinical parameters. Blood samples were drawn in the morning while fasted. Serum creatinine concentrations were measured in blood, and the estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine concentrations in the Japanese eGFR equation.[13] Salt intake was assessed using a spot urine sample collected in the morning by estimating 24 hours urinary sodium excretion, calculated using the Tanaka formula as previously described.[14] Voltage in the 12-lead ECG was defined by the following: an S-wave in V1 plus an R-wave in V5 wave (SV1 + RV5). Left ventricular hypertrophy (LVH) on ECG was determined by Sokolow-Lyon voltage criteria (SV1 + RV5 ≥ 3.5 mV) and was assessed as one of the cardiovascular risk factors, as described previously.[3,15] Hypertension and ECG abnormalities, including LVH and arrhythmia such as atrial fibrillation, may influence BNP levels and lead to a poor prognosis of heart diseases.[9] Therefore, we excluded the participants with hypertension and or abnormality of ECG and performed the statistical analysis using 1404 participants. Hypertension was diagnosed when the participants received antihypertensive drugs and/or their systolic and diastolic BPs were more than 140 mm Hg and/or 90 mm Hg, respectively, according to The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019).[16]

2.3. Statistical analyses

The results are expressed as mean ± standard deviation. BNP levels were not normally distributed; thus, logarithmic transfor-

mation was applied for analysis, and the levels were expressed as median (interquartile range).[17] According to daily salt intake levels, we divided all the participants into quartiles. Thereafter, a comparison among the 4 groups was performed by the analysis of variance with the Tukey-Kramer HSD test. The correlations between logarithmic BNP and some clinical parameters were evaluated using the Pearson product-moment correlation test. Multiple linear regression analyses were conducted to evaluate the relationships between logarithmic BNP levels and salt intake levels. Age, sex, body mass index (BMI), and systolic BP were selected as independent variables because these parameters were common in performing multiple linear regression analyses. In addition, eGFR, hemoglobin A1c (HbA1c), uric acid, low-density lipoprotein (LDL)-cholesterol, triglyceride (TG), and hemoglobin were conducted to evaluate the relationships between logarithmic BNP levels and salt intake levels, because these parameters were associated with logarithmic BNP using Pearson product-moment correlation test. We considered values with $P < .05$ as statistically significant. Statistical analyses were performed using the IBMSPSS software version 26 (IBM Corporation, Armonk, NY).

3. Results

3.1. Participants' clinical characteristics

A total of 1404 individuals (male; 830 and female; 574) received regular health check-ups and participated in this study. Their baseline characteristics are presented in Table 1. The average age was 52.3 ± 12.5 years. The averages of the vital signs such as height, body weight, BMI, BPs, and pulse rate and laboratory data such as renal function, serum uric acid, blood glucose, lipid profile, red blood cells as well as SV1 + RV5 were within the

Table 1

Clinical characteristics of participants.

	Total (n = 1404)
Age (yr)	52.3 ± 12.5
Male/Female	830/574
Height (cm)	164.2 ± 9.1
Body weight (kg)	61.4 ± 11.7
Body mass index (kg/m^2)	22.6 ± 3.2
Abdominal circumference (cm)	82.5 ± 9.0
Systolic BP (mm Hg)	117.3 ± 10.7
Diastolic BP (mm Hg)	71.6 ± 8.6
Pulse rate (/min)	64.4 ± 8.5
BNP (pg/mL)	10.50 (5.60–18.30)
Logarithmic BNP (pg/mL)	1.01 ± 0.37
Serum creatinine (mg/dL)	0.78 ± 0.15
eGFR (mL/min/1.73m^2)	75.4 ± 12.9
Uric acid (mg/dL)	5.32 ± 1.31
Fasting blood glucose (mg/dL)	93.9 ± 13.9
Hemoglobin A1c (%)	5.66 ± 0.53
Total cholesterol (mg/dL)	204.6 ± 32.5
LDL cholesterol (mg/dL)	125.0 ± 27.8
HDL cholesterol (mg/dL)	64.8 ± 17.1
Triglyceride (mg/dL)	101.4 ± 74.5
Hemoglobin (g/dL)	14.1 ± 1.4
Hematocrit (%)	42.1 ± 3.8
SV1 + RV5 (mV)	2.30 ± 0.59
Salt intake (g/day)	8.50 ± 1.85

BNP = B-type natriuretic peptide, BP = blood pressure, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SV1 + RV5 = an S-wave in V1 plus an R-wave in V5 wave.

Table 2

Comparison of some clinical parameters among the quartiles according to the salt intake levels in the participants.

	Group 1 (n = 351) <7.23 g/d	Group 2 (n = 351) 7.23–8.33 g/d	Group 3 (n = 351) 8.34–9.62 g/d	Group 4 (n = 351) >9.62 g/d
Age (years)	47.7 ± 11.7	51.1 ± 11.8***	53.2 ± 12.4***	57.1 ± 12.2***,###,+++
Sex (Male/Female) (%)	52.4 / 47.6	56.7 / 43.3	63.5 / 36.5	63.8 / 36.2
Height (cm)	162.3 ± 9.0	164.6 ± 9.3**	164.7 ± 8.9**	165.4 ± 8.9***
Body weight (kg)	57.2 ± 10.9	61.0 ± 11.3***	62.1 ± 11.4***	65.4 ± 11.7***,###,+++
Body mass index (kg/m²)	21.6 ± 2.9	22.4 ± 3.1***	22.8 ± 3.0***	23.8 ± 3.2***,###,+++
Abdominal circumference (cm)	78.8 ± 8.3	81.8 ± 9.0***	83.0 ± 8.4***	86.4 ± 8.6***,###,+++
Systolic BP (mm Hg)	114.4 ± 10.5	117.6 ± 10.4**	118.1 ± 10.5**	119.3 ± 10.9***
Diastolic BP (mm Hg)	69.4 ± 8.0	71.9 ± 8.4***	72.3 ± 8.7***	72.7 ± 8.7***
Pulse rate (/min)	64.6 ± 8.9	64.9 ± 8.8	64.0 ± 8.5	64.2 ± 7.7
BNP (pg/mL)	7.40 (3.90–13.55)	9.10 (5.20–15.10)	11.30 (6.00–20.10)	14.70 (8.60–25.43)
Serum creatinine (mg/dL)	0.78 ± 0.16	0.77 ± 0.15	0.79 ± 0.16	0.78 ± 0.15
eGFR (mL/min/1.73m²)	75.8 ± 12.5	76.2 ± 12.8	75.0 ± 12.9	74.6 ± 13.4
Uric acid (mg/dL)	5.24 ± 1.34	5.36 ± 1.29	5.37 ± 1.39	5.28 ± 1.21
Fasting blood glucose (mg/dL)	90.9 ± 11.5	93.3 ± 14.9	94.3 ± 13.2***	97.0 ± 15.0***,##,+
Hemoglobin A1c (%)	5.54 ± 0.43	5.63 ± 0.54	5.68 ± 0.51**	5.80 ± 0.61***,##,+
Total cholesterol (mg/dL)	203.3 ± 33.4	203.7 ± 32.7	204.4 ± 32.1	206.9 ± 31.9
LDL cholesterol (mg/dL)	123.4 ± 28.5	124.3 ± 27.5	125.5 ± 28.0	126.7 ± 27.4
HDL cholesterol (mg/dL)	67.3 ± 17.2	65.1 ± 18.3	63.9 ± 16.1*	63.0 ± 16.7**
Triglyceride (mg/dL)	86.0 ± 47.0	101.4 ± 83.6*	101.6 ± 65.6**	116.7 ± 91.0***
Hemoglobin (g/dL)	14.01 ± 1.41	14.06 ± 1.51	14.18 ± 1.39	14.14 ± 1.41
Hematocrit (%)	41.7 ± 3.7	42.0 ± 40	42.2 ± 3.7	42.3 ± 3.7
Salt intake (g/day)	6.30 ± 0.76	7.79 ± 0.32***	8.97 ± 0.38***,###	10.95 ± 1.12***,###,+++

BNP = B-type natriuretic peptide, BP = blood pressure, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein.
*, #, +: $P < .05$, **, ##, ++: $P < .01$, ***, ###, +++: $P < .001$. * vs Group 1, # vs Group 2, + vs Group 3.

normal limits. The median of plasma BNP levels was 10.50 pg/mL, and daily salt intake was 8.50 ± 1.85 g.

3.2. Comparison of some clinical parameters among the quartiles according to the salt intake levels in the participants

The participants were divided into quartiles according to the salt intake levels (Table 2). The elderly and burly males were included in the highest quartile of salt intake (Group 4). Although the levels of BPs were within the normal range in all groups, they were higher with increasing daily salt intake. Moreover, in Group 4, the levels of blood glucose, HbA1c, and TG were higher, and the levels of high-density lipoprotein cholesterol were lower than

Figure 1. Comparison of logarithmic B-type natriuretic peptide (BNP) among the quartiles according to the salt intake levels in the participants. The participants were divided into the quartiles according to the salt intake levels. The levels of logarithmic BNP increase according to the increase of daily salt intake. ##;P < .01, ***, ###, +++; P < .001. * vs Group 1, # vs Group 2, + vs Group 3.
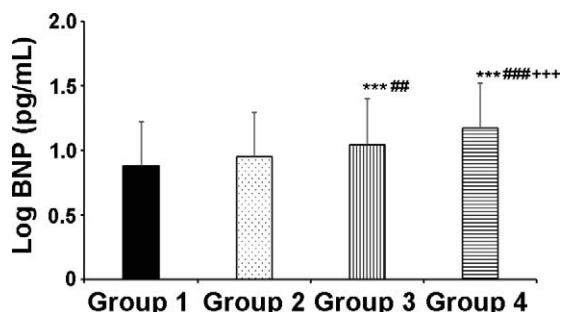
other quartiles. Contrarily, there were no differences in the levels of serum uric acid, total cholesterol, LDL cholesterol, hemoglobin, and hematocrit in the 4 groups. Most participants with renal dysfunction and LVH due to BP elevation were excluded; therefore, significant differences were not found regarding renal function (serum creatinine or eGFR) among the quartiles according to the salt intake levels in the participants. In addition, the levels of logarithmic BNP were higher with increasing daily salt intake (Fig. 1).

3.3. Relationship between logarithmic BNP and some clinical parameters in the participants
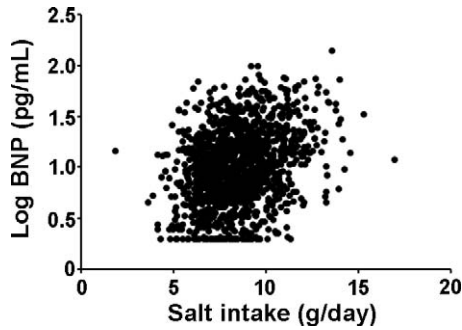
First, we evaluated the relationship between logarithmic BNP and some clinical parameters, including salt intake in the participants. Age was significantly and positively associated with the levels of logarithmic BNP. In addition, significant and positive relationships were found between logarithmic BNP levels and salt intake levels in the participants ($r = 0.31$, $P < .001$) (Fig. 2). Height, body weight, uric acid, hemoglobin, and hematocrit were significantly and negatively associated with logarithmic BNP levels. On the other hand, there were no significant relationships between logarithmic BNP and systolic BP (Table 3).

3.4. Multiple linear regression analyses between logarithmic BNP levels and salt intake levels after adjustment of some clinical parameters in the participants

Subsequently, we performed multiple linear regression analyses between logarithmic BNP levels and salt intake levels after adjusting some clinical parameters. We found significant positive relationships between logarithmic BNP levels and salt intake

Figure 2. Relationship between logarithmic B-type natriuretic peptide (BNP) and the salt intake levels in the participants. Significant and positive relationships were found between logarithmic BNP levels and salt intake levels in the participants ($r = 0.31$, $P < .001$).

levels after adjusting the levels of age, sex, BMI, systolic BP, eGFR, HbA1c, serum uric acid, LDL-cholesterol, TG, and hemoglobin ($\beta = 0.29$, $P < .001$) (Model 4) (Table 4).

4. Discussion

This study clarified that the plasma BNP levels were significantly and positively associated with daily salt intake even after adjusting some parameters in the general population without hypertension and ECG abnormalities who had few risk factors for heart diseases.

It is well known that increased salt intake is associated with BP elevation[2] and increased risk of cardiovascular disease.[4] Excess salt intake causes hypertension due to increased circulating blood volume, leading to LVH.[12,18,19] BNP is synthesized and released from the ventricle in response to an increase in ventricular filling pressure[6]; thus, salt intake is associated with elevated plasma BNP levels by LVH. However, significant and positive relationships were found between plasma BNP levels and salt intake levels after adjustment for systolic BP in the general population without hypertension and LVH in this study. These results

Table 3

Relationship between logarithmic B-type natriuretic peptide (BNP) and some clinical parameters in the participants.

	r	*P*
Age (yr)	0.42	<.001
Height (cm)	−0.34	<.001
Body weight (kg)	−0.33	<.001
Body mass index (kg/m^2)	−0.19	<.001
Abdominal circumference (cm)	−0.15	<.001
Systolic BP (mm Hg)	0.041	.14
Diastolic BP (mm Hg)	−0.064	<.05
Pulse rate (/min)	−0.12	<.001
eGFR (mL/min/1.73m^2)	−0.11	<.001
Uric acid (mg/dL)	−0.31	<.001
Fasting blood glucose (mg/dL)	−0.028	.31
Hemoglobin A1c (%)	0.056	<.05
Total cholesterol (mg/dL)	−0.035	.21
LDL cholesterol (mg/dL)	−0.11	<.001
HDL cholesterol (mg/dL)	0.23	<.001
Triglyceride (mg/dL)	−0.18	<.001
Hemoglobin (g/dL)	−0.44	<.001
Hematocrit (%)	−0.43	<.001

BP = blood pressure, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

suggest that BNP may be induced by salt intake, independent of BP elevation even in the general population without hypertension and heart diseases.

Recently, it was clarified that salt intake causes aggravation of inflammation. Wen et al reported that a high salt diet increased interleukin 17A levels in plasma and peripheral blood mononuclear cells in healthy participants.[20] These data suggest that high salt increases plasma BNP levels by aggravating inflammatory cytokines. In addition to inflammation, reactive oxygen species (ROS) also contribute to elevated plasma BNP levels. Ma et al reported that high salt treatment aggravated ROS production in mitochondria by transient receptor potential channel canonical 3, and as a result, expression of plasma BNP levels was increased.[21] Unfortunately, we could not examine the causal relationships between plasma BNP levels and salt intake levels

Table 4

Multiple linear regression analyses between logarithmic B-type natriuretic peptide (BNP) levels and salt intake levels after adjustment in the participants.

	Model 1		Model 2		Model 3		Model 4	
	R = 0.60	P < .001	R = 0.60	P < .001	R = 0.60	P < .001	R = 0.66	P < .001
	β	P	β	P	β	P	β	P
Age (yr)	0.31	<.001	0.31	<.001	0.32	<.001	0.32	<.001
Sex	0.30	<.001	0.30	<.001	0.30	<.001	0.093	<.01
Body mass index (kg/m^2)	−0.20	<.001	-0.20	<.001	−0.20	<.001	−0.11	<.001
Systolic BP (mm Hg)			0.020	.38	0.020	.86	0.054	<.05
eGFR (mL/min/1.73m^2)					0.029	.24	0.006	.81
Hemoglobin A1c (%)							−0.073	<.01
Uric acid (mg/dL)							−0.037	.18
LDL cholesterol (mg/dL)							−0.088	<.001
Triglyceride (mg/dL)							−0.071	<.01
Hemoglobin (g/dL)							−0.29	<.001
Salt intake (g/d)	0.31	<.001	0.30	<.001	0.30	<.001	0.29	<.001

BP = blood pressure, eGFR = estimated glomerular filtration rate, LDL = low-density lipoprotein.
Logarithmic BNP levels of female were higher than those of male (male; 0.91 ± 0.37 pg/mL and female; 1.15 ± 0.31 pg/mL, $P < .001$).

because this study was performed on participants attending their regular annual health check-ups. However, it is possible that inflammation and ROS causes elevated plasma BNP levels through high salt levels.

Plasma BNP levels are elevated in some patients with coronary heart disease, valvular heart disease, constrictive pericarditis, and pulmonary hypertension. In addition, plasma BNP levels are associated with the independent predictors of cardiovascular mortality in various heart failure patients.[10–12] Santaguida et al reported that higher levels of BNP on admission predicted greater risk for all outcomes and decreased levels on postadmission predicted decreased risk and concluded that BNP levels were associated with the independent predictors of cardiovascular mortality in acutely decompensated heart failure patients by using meta-analyses.[10] Oremus et al analyzed 16 studies that used BNP for chronic heart failure patients as a systematic review and concluded that BNP levels were positively associated with all-cause and heart failure mortality and that BNP levels were useful for estimating prognosis in patients with chronic stable heart failure.[11] Moreover, McDonagh et al reported that the measurement of plasma BNP levels had high sensitivity and specificity for detecting patients with asymptomatic heart failure of left ventricular dysfunction.[12] It is known that most dyspneic patients with heart failure have values above 400 pg/mL of plasma BNP levels and values below 100 pg/mL of plasma BNP levels have a very high negative predictive value for heart failure as a cause of dyspnea.[22] On the other hand, Wang et al reported that BNP values above the 80th percentile (20.0 pg/mL for male and 23.3 pg/mL for female) were associated with multivariable-adjusted hazard ratio for death and various CVDs such as a first major cardiovascular event, atrial fibrillation, stroke or transient ischemic attack, and heart failure during a mean follow-up of 5.2 years by using 3346 persons without heart failure.[23] These values are similar to those of the 75th percentile in this study, especially for women (14.25 pg/mL and 22.80 pg/mL for males and females, respectively; data not shown). In addition, such BNP levels showed a positive association with salt intake levels after adjustment for BP in this study. These results suggest that suppression of BNP due to salt intake restriction may prevent cardiac diseases and lead to improved prognosis even in the general population without hypertension and remarkable complications of cardiac diseases. However, this cross-sectional study could not prove this hypothesis. Future investigations should determine whether suppression of BNP levels within the normal range due to salt intake restriction improves the prognosis in an interventional study.

BNP is cleared by passive excretion; therefore, GFR is inversely related to BNP concentrations.[24,25] As a result, the cut-off values for plasma BNP levels in patients with renal insufficiency are different from those in patients with normal renal function. Thus, renal function is very important in interpreting BNP levels. However, the renal function of the participants was within almost normal limits (eGFR 75.4 ± 12.9 mL/min/1.73 m^2), and no significant differences were found regarding renal function among the quartiles according to the salt intake levels in this study. A significant positive relationship between BNP and salt intake was found after adjustment for eGFR. Therefore, the results between plasma BNP levels and salt intake were not significantly influenced by renal function in this study.

This study had some limitations. First, this was a cross-sectional, single centered study. Therefore, selection bias could not be excluded, and it was impossible to determine the longitudinal relationship between salt intake and plasma BNP levels. Based on the availability of data of regular annual health check-ups over time, we will perform a longitudinal study with close attention to plasma BNP levels and salt intake levels. Second, we used a spot urine sample collected in the morning and calculated 24 hours urinary sodium excretion levels by Tanaka formula to assess salt intake levels.[14] This formula calculates estimated daily urinary sodium excretion using urinary sodium concentration (mEq/L), urinary creatinine concentration (mg/dL) and daily urinary creatinine excretion (mg/d) calculated by body weight, height, and age. Namely, muscle mass is estimated by body weight, height, and age, while daily urinary creatinine excretion is estimated by muscle mass. Therefore, using this formula to estimate daily urinary sodium excretion can lead to errors depending on whether the participants were muscular or obese.[14] As a result, this method is inferior to the 24 hours urinary sodium collection for accuracy. However, not all the participants can collect 24 hours urinary sodium excretion. Moreover, this method is recommended by Guidelines for the Management of Hypertension 2019, recently published by The Japanese Society of Hypertension.[16] Finally, we used ECG to exclude participants with LVH. ECG voltage lacks sensitivity in diagnosing LVH, even though it is relatively specific. False positives are more common in young or thin individuals, whose voltage may exceed conventional thresholds and false negatives may occur with right bundle branch block, obesity, or chronic obstructive pulmonary disease. Although echocardiography is the procedure of choice for identifying LVH, given its widespread availability, ease of use, and lack of associated radiation or nephrotoxic contrast administration, it is difficult for all participants to assess LVH in annual health check-ups. In addition, it has not been completely determined whether the levels of SV1 + RV5 in normal ranges can be used as the marker of left ventricular thickness. However, ECG voltage criteria (SV1 + RV5 $\geq$ 3.5 mV) is confirmed to determine LVH.[3,15] Therefore, we used the levels of SV1 + RV5 to exclude the participants with LVH in this study.

In conclusion, we have clarified that the plasma BNP levels were significantly and positively associated with the daily salt intake even after adjusting some parameters in the general population without hypertension and risk factors for heart diseases. Plasma BNP levels may be a surrogate marker reflecting salt-induced cardiac diseases even in the general population without hypertension and heart diseases. Further research is warranted to investigate the relationships between plasma BNP, salt intake, cardiac diseases, and the prognosis in the general population.

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