Positive relationships between annual changes in salt intake and plasma B-type natriuretic peptide levels in the general population without hypertension and heart diseases

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Title Page

Positive relationships between annual changes in salt intake and plasma B-type natriuretic peptide levels in the general population without hypertension and heart diseases

Naro Ohashi [1]; Hiroyuki Takase [2]; Taro Aoki [1]; Sayaka Ishigaki [3]; Takamasa Iwakura [1]; Shinsuke Isobe [1]; Tomoyuki Fujikura [1]; Akihiko Kato [3]; Hideo Yasuda [1]

1. Internal Medicine 1, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu 431-3192, Japan

2. Department of Internal Medicine, Enshu Hospital, 1-1-1 Chuo, Naka-ku Hamamatsu 430-0929, Japan

3. Blood Purification Unit, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu 431-3192, Japan

Correspondence to:

Naro Ohashi, MD, PhD

Internal Medicine 1, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu 431-3192, Japan

Telephone number: +81-53-435-2261; Fax number: +81-53-434-9447

Email address: ohashi-n@hama-med.ac.jp

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Abstract

Excessive salt intake causes hypertension and heart diseases. B-type natriuretic peptide (BNP) is a surrogate marker of heart disease, and a slightly elevated BNP level is associated with a poor prognosis. Our previous cross-sectional study demonstrated that plasma BNP has a significant positive association with daily salt intake in the general population. However, the relationship between changes in salt intake and changes in plasma BNP remains unknown.

We recruited 3051 participants without hypertension or electrocardiogram abnormalities who underwent annual health check-ups for two consecutive years. Clinical parameters, including plasma BNP, were obtained, and daily salt intake was evaluated using urinary samples. Annual changes in these parameters were calculated.

The median plasma BNP level was 12.9 pg/mL, and the daily salt intake was 8.73±1.89 g. The annual changes in plasma BNP and daily salt intake were 4.79±36.38% and 2.01±21.80%, respectively. Participants in the highest quartile of annual changes in daily salt intake showed the largest annual changes in plasma BNP. Annual changes in plasma BNP indicated a significant positive association with daily salt intake. Moreover, multiple linear regression analyses revealed that annual changes in plasma BNP showed a significant positive association with daily salt intake after adjustments.

Our study showed a significant positive relationship between annual changes in plasma BNP and annual changes in daily salt intake. The suppression of plasma BNP is therefore induced by salt intake restriction. The monitoring of plasma BNP while reducing salt intake may therefore prevent heart diseases and lead to improved prognoses in the general population without heart diseases.

Keywords: Annual change, B-type natriuretic peptide, General population, Salt intake

Introduction

It is well known that salt intake is associated with blood pressure (BP) levels. Indeed, a meta-analysis of 185 studies by Graudal *et al*. found that a reduction in salt intake caused a decrease in BP in participants with hypertension.[1] In addition, some studies of the association between salt intake levels and heart diseases have been performed vigorously. In a meta-analysis of 19 studies in non-acutely ill adults and children, Aburto *et al*. found that increased salt intake was associated with an increased risk of stroke, stroke mortality, and coronary heart disease mortality.[2]

B-type natriuretic peptide (BNP) is synthesized and released from the ventricle in response to an increase in ventricular filling pressure.[3] Salt intake is associated with elevated plasma BNP levels due to left ventricular hypertrophy. Excess salt intake increases BNP levels by increasing ventricular filling pressure in individuals without ventricular hypertrophy. Therefore, plasma BNP levels are associated with independent predictors of cardiovascular mortality and have a high sensitivity and specificity for detecting patients with heart failure.[4-8] However, because it was unclear whether salt intake is associated with plasma BNP levels in the general population, our previous study recruited 1553 participants who were not taking antihypertensive medication and exhibited normal electrocardiogram readings. These participants received regular annual

health check-ups in Japan. We found that plasma BNP levels were significantly and positively associated with daily salt intake after adjusting for some parameters in the general population with few risk factors for heart diseases.[9]

However, the relationship between changes in salt intake and changes in plasma BNP levels in the general population without heart disease and hypertension has yet to be determined. Therefore, we conducted the current study to investigate the relationship between them.

Methods

Study design

This study was approved by the Ethics Committee of Hamamatsu University School of Medicine (No. 21-176) and Enshu Hospital and adhered to the principles of the Declaration of Helsinki. This study involved human participants attending regular annual health check-ups at Enshu Hospital. Informed consent was obtained from all participants using an information disclosure document.

Study participants and procedures

We recruited 5244 consecutive participants aged ≥20 years who received regular annual health check-ups in both 2017 and 2018. As part of the check-up, attendees were

interviewed regarding their health status and underwent a routine physical examination, an electrocardiogram (ECG), and laboratory assessments for some clinical parameters. Blood samples were collected in the morning after overnight fasting. Serum creatinine concentrations were measured in blood, and the estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine concentrations and applying the Japanese eGFR equation.[10] Salt intake was assessed using the first morning urine sample by estimating 24-hour urinary sodium excretion, calculated using Tanaka's formula as previously described.[11] The voltage in the 12-lead ECG was defined as follows: an S-wave in the V1 wave plus an R-wave in the V5 wave (SV1 + RV5). Left ventricular hypertrophy (LVH) on ECG was determined using the Sokolow-Lyon voltage criteria (SV1 + RV5 ≥ 3.5 mV) and was assessed as one of the cardiovascular risk factors, as described previously.[12, 13] The annual percentage changes in some clinical parameters were calculated as follows: (data in 2018 – data in 2017)/data in 2017 × 100.

Hypertension, the administration of antihypertensive medication, LVH, and ECG abnormalities such as arrhythmia influence BNP levels and lead to a poor prognosis of heart diseases.[5] Therefore, we excluded participants who had hypertension (BP ≥ 140/90 mmHg) or were taking antihypertensive medication (1857 participants) in 2017 or 2018 and participants with LVH (506 participants) and ECG abnormalities without LVH (338

participants). The final statistical analyses were performed with 3051 participants.

Statistical analyses

The results are expressed as the mean ± standard deviation. BNP levels were not normally distributed; thus, logarithmic transformation was applied for analysis, and the levels are expressed as the median (interquartile range).[9, 14] According to the annual changes in daily salt intake, we divided all the participants into quartiles. Thereafter, the baseline characteristics and annual changes in some clinical parameters, including the logarithmic BNP levels, among the four groups were compared using an analysis of variance test with a Tukey–Kramer HSD post hoc test. Correlations between logarithmic BNP levels and some clinical parameters in 2017 and correlations between annual changes in logarithmic BNP levels and annual changes in some clinical parameters were evaluated using Pearson's product-moment correlation test. Multiple linear regression analyses were performed to evaluate the relationships between annual changes in logarithmic BNP levels and annual changes in salt intake levels. Age, sex, and annual changes in body mass index (BMI) were selected as independent variables because these parameters are common when performing multiple linear regression analyses. Baseline BMI, systolic BP, hemoglobin A1c (HbA1c), low-density lipoprotein (LDL) cholesterol, triglyceride, and hemoglobin levels were selected as the independent variables because

each of these was used in our previous study,[9] while baseline eGFR, logarithmic BNP, and salt intake levels were used because each of these decreased with increasing annual percentage changes in salt intake. In addition, annual changes in systolic BP, eGFR, SV1 + RV5, HbA1c, uric acid, LDL cholesterol, triglyceride, and hemoglobin levels were calculated to evaluate the relationships between annual changes in logarithmic BNP levels and annual changes in salt intake. These parameters were associated with annual changes in logarithmic BNP levels as determined by a Pearson's product-moment correlation test and were needed to adjust the influence of BP and ventricular filling pressure; these parameters were also used in our previous study.[9, 14] We considered values of $p < 0.05$ to be statistically significant. β in a multiple linear regression analysis indicates a standardized regression coefficient. Statistical analyses were performed using IBM® SPSS® software version 26 (IBM Corporation, Armonk, NY, USA).

Results

Participant clinical characteristics

A total of 3051 participants (1804 men, 1247 women) underwent regular health check-ups in both 2017 and 2018 and participated in this study. The baseline characteristics are presented in Table 1. The average age was 54.7 ± 11.4 years. The vital

sign averages, such as height, body weight, BMI, BPs, and heart rate, were within normal limits. Additionally, laboratory data such as renal function, serum uric acid, blood glucose, the lipid profile, red blood cell count, and SV1 + RV5 were also within normal limits. The median plasma BNP levels were 12.9 pg/mL, and the daily salt intake was 8.73 ± 1.89 g.

Annual percentage changes in clinical parameters

The annual percentage changes in some clinical parameters between 2017 and 2018 are shown in Table 2. The annual percentage changes in logarithmic BNP levels and daily salt intake were 4.79% and 2.01%, respectively.

Comparison of the baseline clinical parameters, including logarithmic BNP levels, among the quartiles according to the annual percentage changes in salt intake levels

The participants were divided into quartiles according to their annual percentage changes in salt intake (Group 1: < -12.58%; Group 2: -12.57% to 0.14%; Group 3: 0.15% to 14.12%; and Group 4: > 14.13%).

The baseline serum creatinine levels were higher, while the baseline logarithmic BNP, eGFR, and salt intake levels decreased as the annual percentage changes in salt intake increased (Table 1).

Comparison of the annual percentage changes in the clinical parameters, including logarithmic BNP levels, among the quartiles according to the annual percentage changes

in salt intake levels

When we divided the data into the four groups as described above, the annual percentage changes in body weight, BMI, systolic and diastolic BP, eGFR levels, triglyceride levels, and logarithmic BNP levels increased, while those of the changes in serum creatinine, uric acid, hemoglobin, and hematocrit levels decreased with increasing annual percentage changes in salt intake (Figure 1, Table 2).

Relationship between logarithmic BNP levels and some clinical parameters in 2017

Next, we evaluated the relationship between logarithmic BNP levels and the clinical parameters, including salt intake, in 2017. Age and salt intake were significantly and positively associated with logarithmic BNP levels. In contrast, height, body weight, BMI, uric acid levels, hemoglobin levels, and hematocrit levels were significantly and negatively associated with logarithmic BNP levels (Supplementary Table 1). These results are consistent with those of our previous study.[9]

Relationship between annual percentage changes in logarithmic BNP levels and some clinical parameters, including salt intake levels

We evaluated the relationship between annual percentage changes in logarithmic BNP levels and some clinical parameters, including salt intake, in the participants. Annual percentage changes in eGFR levels were significantly and positively associated with

those of logarithmic BNP levels. Conversely, annual percentage changes in serum creatinine, uric acid, total cholesterol, hemoglobin, and hematocrit levels were significantly and negatively associated with those of logarithmic BNP levels (Table 3). In addition, significant and positive relationships were found between annual percentage changes in logarithmic BNP levels and those of salt intake in the participants ($r = 0.33$, $p < 0.001$) (Figure 2). Because the daily salt intake levels differed between the sexes (males: 8.89 ± 1.89 g/day vs. females: 8.51 ± 1.86 g/day, $p < 0.001$), we analyzed the relationship between annual changes in plasma BNP levels and daily salt intake by sex. Similar significant results were obtained for each sex (males: $r = 0.35$, $p < 0.001$; females: $r = 0.29$, $p < 0.001$) (data not shown).

Multiple linear regression analyses between annual percentage changes in logarithmic BNP levels and salt intake levels after adjustment for some clinical parameters.

We subsequently performed multiple linear regression analyses between annual percentage changes in logarithmic BNP levels and salt intake after adjusting for some clinical parameters. We found significant positive relationships between annual percentage changes in logarithmic BNP levels and those of salt intake after adjusting for age, sex, and annual percentage changes in BMI, systolic BP, eGFR, SV1 + RV5, HbA1c, serum uric acid, LDL cholesterol, triglyceride, and hemoglobin levels ($\beta = 0.26$, $p < 0.001$)

(Model 5) (Table 4). Moreover, when the baseline BMI, systolic BP, eGFR, HbA1c, LDL cholesterol, triglyceride, hemoglobin and logarithmic BNP levels and salt intake as well as markers of annual percentage changes were added, significant positive relationships were noted between annual percentage changes in logarithmic BNP levels and those of salt intake ($\beta = 0.24$, $p < 0.001$) (Model 6) (Table 4).

Sensitivity analysis

Moreover, we performed a sensitivity analysis that was limited to participants with BNP levels within the normal range (<18.4 pg/mL). A total of 1737 participants (1193 men, 544 women) with a mean age of 51.5 ± 10.6 years were investigated. The median plasma BNP level was 7.80 pg/mL, while the mean daily salt intake was 8.43 ± 1.81 g. The annual changes in the plasma BNP levels and daily salt intake were 5.88 ± 38.84% and 2.30 ± 21.66%, respectively. The participants in the highest quartile of annual changes in daily salt intake showed the largest annual changes in plasma BNP levels. Annual changes in plasma BNP levels were significantly positively associated with daily salt intake ($r = 0.32$, $p < 0.001$). Moreover, multiple linear regression analyses revealed that annual changes in plasma BNP levels showed a significant positive association with daily salt intake after adjustments for the same independent variables used in Table 4, Model 5 ($\beta = 0.26$, $p < 0.001$) (data not shown).

Discussion

This study showed that annual percentage changes in plasma BNP levels were significantly and positively associated with salt intake in the general population without hypertension and heart diseases.

A previous study by our group found that plasma BNP levels were significantly and positively associated with salt intake in the general population. However, because this was a cross-sectional study, it was not possible to determine the causal relationships between plasma BNP levels and daily salt intake. In our current retrospective cohort study, we showed the following: (1) When allocating the participants into quartiles according to annual changes in salt intake, the participants within the highest quartile of annual changes in salt intake showed the highest levels of annual changes in plasma BNP levels; (2) Annual changes in plasma BNP levels were significantly and positively associated with annual changes in salt intake; and (3) Annual changes in plasma BNP levels showed a significant positive association with salt intake after adjustments in the multiple linear regression analyses. Based on these results, we believe that this study clarified that annual percentage changes in plasma BNP levels were significantly and positively associated with salt intake in the general population without hypertension and heart diseases.

The management of normal to slightly high BNP levels may not be clear. Wang *et al*. reported that BNP levels above the 80th percentile (20.0 pg/mL for males and 23.3 pg/mL for females) in 3346 participants without heart failure were associated with a multivariable-adjusted hazard ratio for death and various cardiovascular diseases, 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.[15] Our previous and current studies have indicated positive relationships between salt intake and plasma BNP levels in the general population, even though the participants' plasma BNP levels were normal to slightly high.[9] Moreover, when we performed the sensitivity analysis limited to the participants in this study whose BNP levels were within the normal range (<18.4 pg/mL), similar significant results were obtained. In addition, Damgaard *et al*. also indicated that a change in sodium intake from a low to high dose increased the plasma BNP concentration in 12 healthy individuals.[16] However, Wambach *et al.* demonstrated that BNP secretion was modulated by physical exercise but not volume loading and high salt intake in 21 healthy men.[17] Because the current study was observational, we cannot prove a causal relationship between salt intake and BNP levels. Thus, in the future, it will be necessary to investigate whether BNP levels are reduced and, as a result, whether individuals' prognoses of heart diseases and lifespans are improved by an intervention

study that provides nutritional guidance for salt reduction in the general population without risk factors for heart disease.

Annual changes in plasma BNP levels were not associated with those in BP and SV1 + RV5 in this study. When a person's salt intake increases, fluid volume and left ventricular filling pressure increase, resulting in an increase in their BNP levels. Elevated BNP levels contribute to the correct fluid volume by initiating natriuresis. However, when salt intake levels are remarkably high, the compensatory mechanism is exceeded, and the BP is elevated. Moreover, when the condition continues for many years, left ventricular hypertrophy can occur, which can be perceived as a change in the ECG. However, the average salt intake of the study participants was 8.73 g/day, which was not very high, and the average annual percentage change in salt intake was only 2.01%. In addition, the study evaluation period was only one year. Therefore, it is highly possible that the changes in the participants' salt intake levels were not reflected in their BPs and ECGs. Additionally, recent reports have shown that salt intake aggravates inflammation.[18, 19] Indeed, Wen *et al*. reported that a high-salt diet increased interleukin (IL) 17A levels in healthy participants' plasma and peripheral blood mononuclear cells.[18] In addition, Yi *et al*. showed that healthy subjects on a high-salt diet of 12 g/day displayed a significantly higher number of immune cell monocytes than the same subjects on a low-salt diet. This

decrease in salt intake was accompanied by a reduced production of proinflammatory cytokines, such as IL-6 and IL-23, along with an increased production of the anti-inflammatory cytokine IL-10.[19] Moreover, Koshikawa *et al*. showed that heart failure patients had significantly higher levels of IL-6, C-reactive protein (CRP), and BNP, and the inflammatory cytokine levels significantly and positively correlated with BNP levels.[20] These data suggest that high salt intake increases plasma BNP levels by aggravating inflammatory cytokines. However, annual percentage changes in logarithmic CRP levels measured in both 2017 and 2018 (n = 1229) were not associated with those in logarithmic BNP levels ($r = 0.019$, $p = 0.52$, data not shown). Therefore, it was not possible to explain whether the inflammatory reaction due to salt intake increased plasma BNP levels in this study.

Annual percentage changes in logarithmic BNP levels were positively associated with those in body weight and eGFR and negatively associated with those in serum creatinine, uric acid, and hemoglobin levels in this study (Table 3). We showed a positive relationship between annual percentage changes in salt intake and logarithmic BNP levels ($r = 0.33$ and $p < 0.001$) (Figure 2). We also observed positive relationships between annual percentage changes in salt intake and those in body weight ($r = 0.096$ and $p < 0.001$) and eGFR levels ($r = 0.29$ and $p < 0.001$) and negative relationships between

annual percentage changes in salt intake and those in serum creatinine ($r = -0.29$ and $p < 0.001$), uric acid ($r = -0.22$ and $p < 0.001$), and hemoglobin ($r = -0.043$ and $p = 0.017$) levels (data not shown). Based on these results, we believe that when salt intake increases, fluid volume, including intravascular volume and body weight, and left ventricular filling pressure increase, resulting in an increase in BNP levels. An increase in intravascular volume decreases the levels of serum creatinine, uric acid, and hemoglobin.

Here, we showed that annual changes in plasma BNP levels were significantly and positively associated with annual changes in salt intake. However, it is possible that the participants' baseline characteristics influenced the results. In fact, increasing annual percentage changes in salt intake indicated a significant negative association with baseline salt intake and logarithmic BNP levels. Therefore, we performed a multiple linear regression analysis between annual percentage changes in logarithmic BNP and salt intake levels after adjustment for annual changes in the clinical parameters as well as baseline levels of the clinical parameters, and we observed a significant positive relationship between annual percentage changes in logarithmic BNP and salt intake levels (Table 4, Model 6). These data suggest that the baseline characteristics did not significantly influence the relationships between logarithmic BNP and salt intake levels.

This study is not without limitations. First, the comparison period of only two years

in this study may be seen as a relatively short period. However, the purpose of this study was not to assess organ damage but rather to assess the changes in plasma BNP levels due to changes in salt intake. Therefore, we considered the current study design to be adequate. Second, we used the first morning urine sample and calculated the 24-hour urinary sodium excretion levels by Tanaka's formula to assess salt intake levels.[11] This method is recommended by the Guidelines for the Management of Hypertension 2019 that were recently published by the Japanese Society of Hypertension and can be used to manage hypertensive patients in general clinical practice. However, this method features inferior accuracy for 24-hour urinary sodium collection and is not ideal for research. However, because 24-hour urinary sodium excretion levels were not available for any of the participants, we used this method as a substitute.

Perspectives in Asia

Asians are known to have higher salt intake than individuals in other regions [(21)]. Our present study showed a significant positive association between annual changes in plasma BNP levels and daily salt intake, and it is reported that only a slight elevation of plasma BNP levels is associated with a multivariable-adjusted hazard ratio for death and various cardiovascular diseases in participants without heart failure [(15)]. Therefore, it is

possible that a decrease in plasma BNP levels by salt intake restriction contributes to the prevention of the onset of heart disease and improves prognoses, especially in Asia, where salt intake is high.

Conclusion

This study showed that annual percentage changes in plasma BNP levels were significantly and positively associated with those of salt intake in the general population without hypertension and heart diseases.

Acknowledgments

None.

Source of funding

None.

Conflicts of Interest

The authors declare no conflicts of interest.

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Figure legend

Figure 1: Comparison of annual percentage changes in logarithmic B-type natriuretic peptide (BNP) levels among the quartiles according to the annual percentage changes in salt intake levels

The participants were allocated into quartiles according to their annual percentage changes in salt intake (Group 1: < -12.58%; Group 2: -12.57% to 0.14%; Group 3: 0.15%

to 14.12%; and Group 4: >14.13%). The levels of annual percentage changes in logarithmic BNP levels were higher with increasing annual percentage changes in salt intake.

*, #, +; $p<0.001$, * vs. Group 1, # vs. Group 2, + vs. Group 3.

Figure 2: Relationship between annual percentage changes in logarithmic B-type natriuretic peptide (BNP) levels and those in daily salt intake.

Significant and positive relationships were found between annual percentage changes in logarithmic BNP levels and those in salt intake levels among the participants ($r = 0.33$, $p < 0.001$).

Point of view

Clinical relevance: Plasma BNP levels showed a significant positive association with daily salt intake after adjustments in the general population without hypertension and heart diseases.

Future directions: In the future, we will perform a study to investigate whether BNP levels are reduced by an intervention for salt reduction in the general population without risk factors for heart disease.

Considerations for the Asian population: Because daily salt intake and plasma BNP levels have significant positive relationships in the general population without risk factors for heart disease, Asians who have higher salt intake need to pay attention to excessive salt intake, even if they have no risk factors.

Graphical Abstract Text

We recruited 3051 participants without hypertension and heart diseases for two consecutive years. Participants in the highest quartile of annual changes in daily salt intake showed the largest annual changes in plasma BNP. We concluded that annual changes in plasma BNP indicated a significant positive association with daily salt intake.

Relationships between annual changes in salt intake and plasma BNP levels in the general population

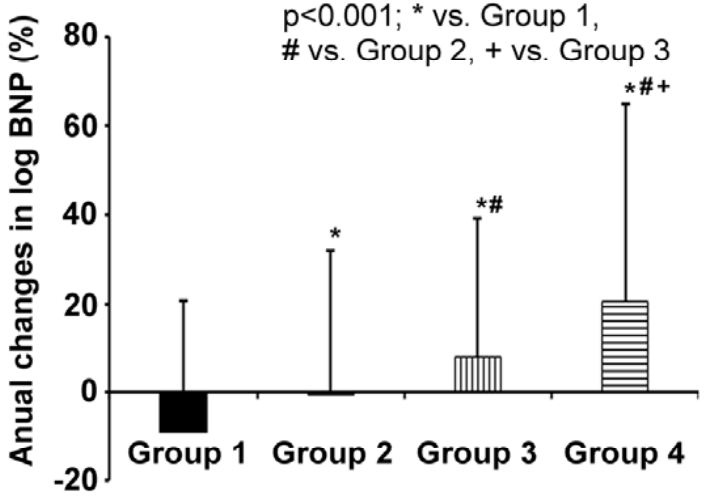
<Design>

5244 participants who received regular annual health check-ups in both 2017 and 2018

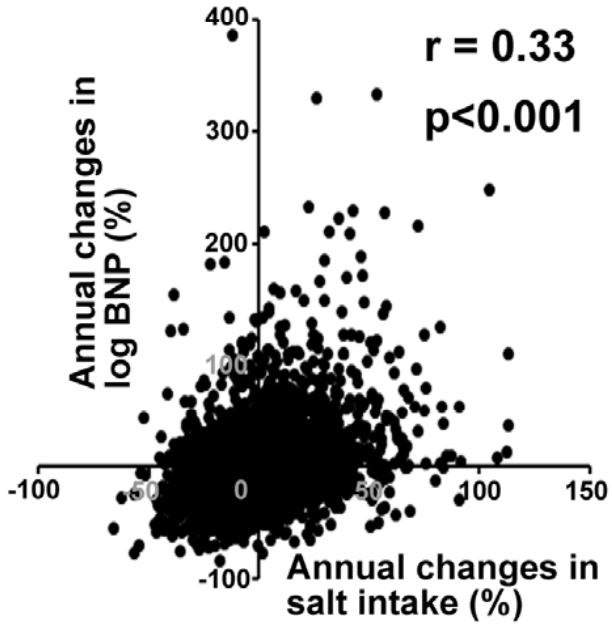
- 1857 participants with HT (≥ 140/90 mmHg) or antihypertensives in either 2017 or 2018
- 506 participants with LVH
- 338 participants with ECG abnormality except for LVH

3051 participants who were finally evaluated in this study

<Main results>



Division into quartiles according to the annual changes in salt intake



<Purpose>

To investigate the relationships between annual changes in salt intake and plasma BNP levels

<Conclusion>

We have shown a significant positive relationships between annual changes in plasma BNP and annual changes in salt intake.

Figure 1

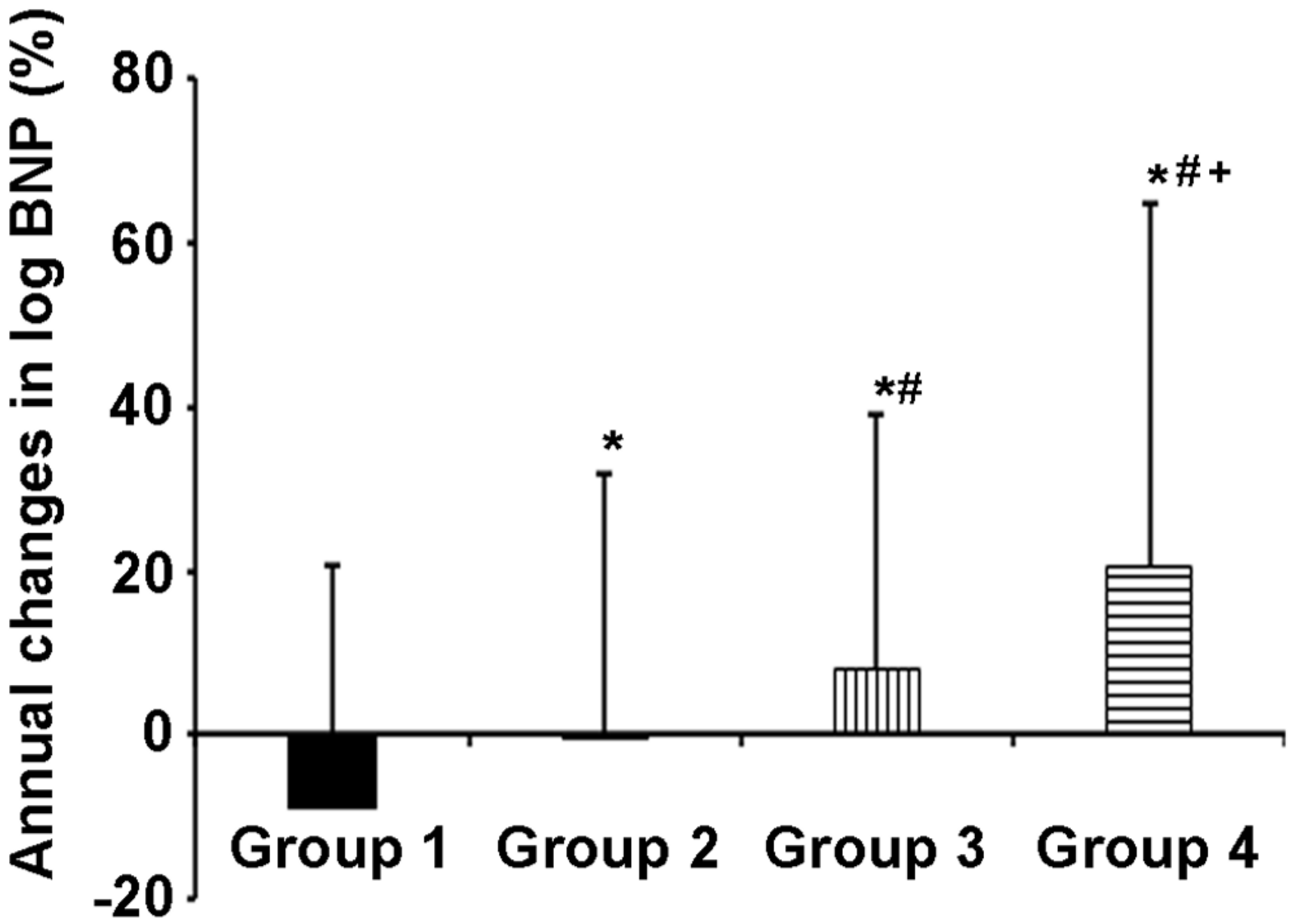

Annual changes in log BNP (%)
80
60
40
20
0
-20
*
*#
*#+
Group 1
Group 2
Group 3
Group 4

Figure 2

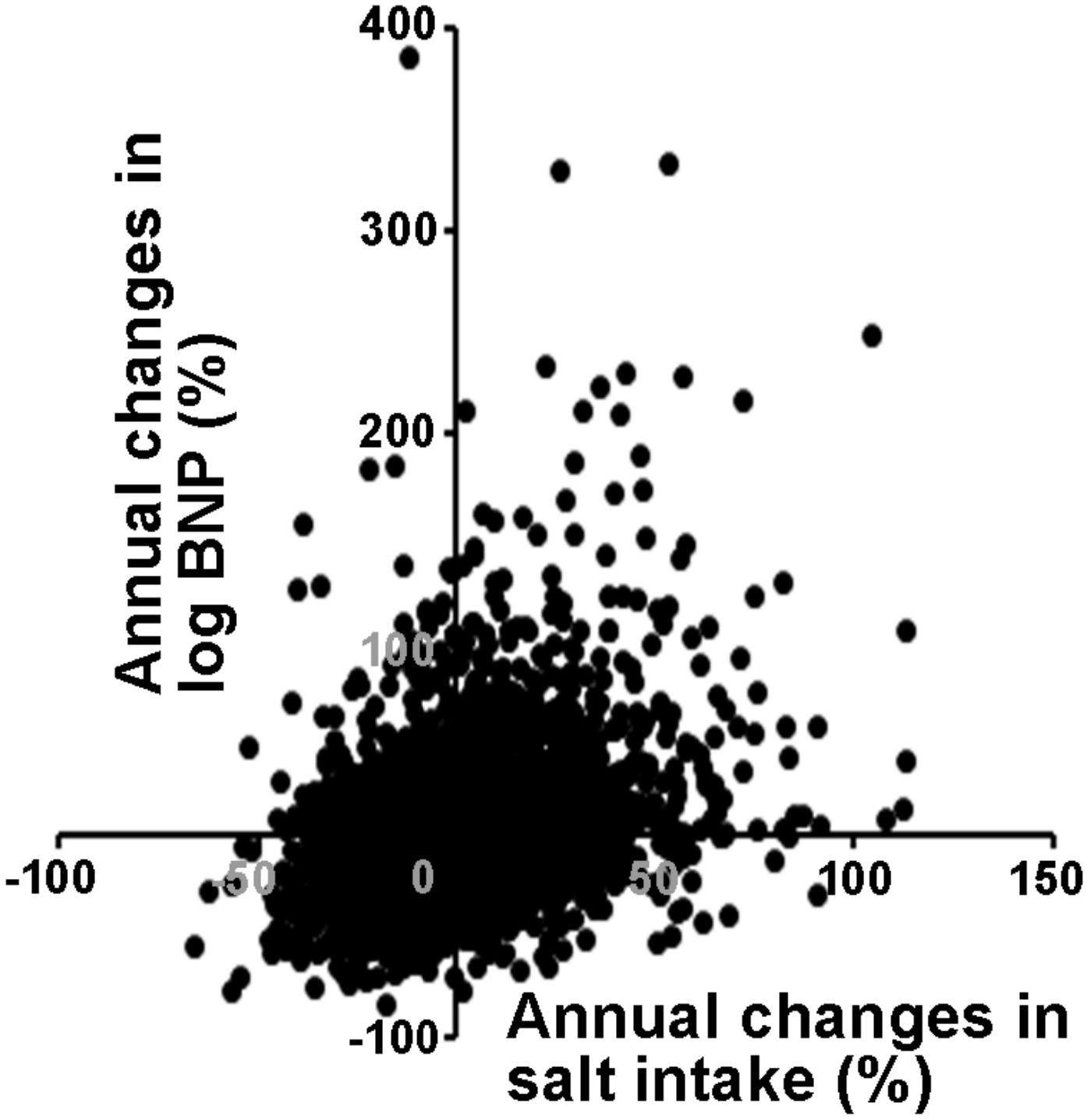

400
300
200
100
-100
-50
0
50
100
150
-100
Annual changes in log BNP (%)
Annual changes in salt intake (%)

Table 1. Comparison of baseline characteristics in some clinical parameters among quartiles according to the annual percentage changes in salt intake levels

	Total (n=3051)	Group 1 (n = 763) < -12.58 (%)	Group 2 (n = 763) -12.57～0.14 (%)	Group 3 (n = 763) 0.15～14.12 (%)	Group 4 (n = 762) >14.13 (%)
Age (years)	54.7 ± 11.4	53.8 ± 11.6	54.7 ± 11.5	55.7 ± 11.3**	54.6 ± 11.3
Male / Female	1804 / 1247	315 / 448	311 / 452	307 / 456	314 / 448
Height (cm)	164.0 ± 9.0	164.0 ± 8.8	163.8 ± 8.8	163.8 ± 9.2	164.3 ± 9.1
Body weight (kg)	60.5 ± 11.8	60.7 ± 11.8	60.2 ± 11.5	60.3 ± 11.8	60.5 ± 11.8
Body mass index (kg/m^2)	22.4 ± 3.3	22.4 ± 3.33	22.4 ± 3.30	22.4 ± 3.29	22.4 ± 3.27
Abdominal circumference (cm)	82.2 ± 9.0	82.3 ± 8.94	81.8 ± 8.78	82.4 ± 8.95	82.5 ± 9.33
Systolic BP (mmHg)	116.9 ± 11.4	116.9 ± 11.4	117.3 ± 11.3	117.2 ± 11.4	116.8 ± 11.2
Diastolic BP (mmHg)	71.9 ± 8.2	71.7 ± 8.08	72.2 ± 8.19	72.1 ± 8.37	71.8 ± 8.18
BNP (pg/mL)	12.9 (6.9–22.6)	15.1 (8.0-27.3)	13.7 (7.6-24.1)	12.3 (6.7-20.8)	10.9 (5.6-19.9)
Logarithmic BNP (pg/mL)	1.09 ± 0.37	1.16 ± 0.37	1.12 ± 0.36	1.07 ± 0.36$^{***, \#}$	1.03 ± 0.38$^{***, \#\#\#}$
Serum creatinine (mg/dL)	0.76 ± 0.15	0.76 ± 0.15	0.77 ± 0.15	0.78 ± 0.16*	0.78 ± 0.15*
eGFR (mL/min/1.73m^2)	75.3 ± 12.6	77.0 ± 12.8	75.4 ± 12.7	74.3 ± 12.4***	74.5 ± 12.4***
Uric acid (mg/dL)	5.23 ± 1.31	5.12 ± 1.28	5.24 ± 1.30	5.27 ± 1.29	5.30 ± 1.34*
Fasting blood glucose (mg/dL)	93.8 ± 14.7	93.0 ± 12.2	94.0 ± 15.5	94.4 ± 17.2	93.7 ± 13.3
Hemoglobin A1c (%)	5.71 ± 0.54	5.69 ± 0.49	5.73 ± 0.59	5.73 ± 0.56	5.70 ± 0.50
Total cholesterol (mg/dL)	202.9 ± 32.0	203.4 ± 32.9	203.8 ± 32.7	202.8 ± 31.4	201.5 ± 30.8

LDL cholesterol (mg/dL)	122.7 ± 27.9	122.4 ± 28.9	123.5 ± 28.4	122.9 ± 26.9	122.1 ± 27.5
HDL cholesterol (mg/dL)	65.5 ± 17.4	65.8 ± 17.1	65.5 ± 17.7	65.6 ± 17.3	65.2 ± 17.7
Triglyceride (mg/dL)	101.9 ± 64.3	105.2 ± 71.0	104.0 ± 62.6	100.9 ± 59.6	97.4 ± 63.4
Hemoglobin (g/dL)	14.1 ± 1.4	14.0 ± 1.4	14.1 ± 1.4	14.1 ± 1.4	14.1 ± 1.3
Hematocrit (%)	42.6 ± 3.7	42.4 ± 3.7	42.7 ± 3.7	42.7 ± 3.7	42.6 ± 3.5
Heart rate (/min)	62.3 ± 8.5	62.1 ± 8.6	62.2 ± 8.7	62.6 ± 8.4	62.4 ± 8.4
SV1 + RV5 (mV)	2.29 ± 0.57	2.31 ± 0.57	2.27 ± 0.55	2.32 ± 0.57	2.27 ± 0.58
Salt intake (g/day)	8.73 ± 1.89	9.83 ± 1.92	8.99 ± 1.75***	8.45 ± 1.58***, ###	7.65 ± 1.58***, ###, +++

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

*, #, +: $p<0.05$, **, ##, ++: $p<0.01$, ***, ###, +++: $p<0.001$. * vs. Group 1, # vs. Group 2, + vs. Group 3

Table 2. Annual percentage changes in clinical parameters

	Total (n=3051)	Group 1 (n = 763) < -12.58 (%)	Group 2 (n = 763) -12.57～0.14 (%)	Group 3 (n = 763) 0.15～14.12 (%)	Group 4 (n = 762) >14.13 (%)
Body weight	0.43 ± 3.25	-0.049 ± 3.23	0.43 ± 3.31*	0.62 ± 2.94***	0.73 ± 3.44***
Body mass index	0.58 ± 3.22	0.11 ± 3.22	0.56 ± 3.28*	0.75 ± 2.91***	0.89 ± 3.39***
Abdominal circumference	0.20 ± 4.26	-0.014 ± 4.23	0.27 ± 4.39	0.40 ± 4.11	0.15 ± 4.31
Systolic BP	1.04 ± 9.26	0.012 ± 9.01	1.25 ± 9.35*	1.10 ± 9.37	1.81 ± 9.25***
Diastolic BP	0.58 ± 11.38	-0.73 ± 10.79	0.11 ± 12.18	0.98 ± 11.44*	1.96 ± 10.89$^{***, \#\#\#}$
Logarithmic BNP	4.79 ± 36.38	-8.79 ± 29.37	-0.47 ± 31.64***	8.00 ± 31.20$^{***, \#\#\#}$	20.45 ± 44.68$^{***, \#\#\#, +++}$
Serum creatinine	1.65 ± 6.90	4.20 ± 6.80	2.49 ± 6.74***	0.59 ± 6.43$^{***, \#\#\#}$	-0.68 ± 6.63$^{***, \#\#\#, ++}$
eGFR	-2.32 ± 7.50	-5.09 ± 7.37	-3.23 ± 7.32**	-1.16 ± 6.99$^{***, \#\#\#}$	0.22 ± 7.22$^{***, \#\#\#, ++}$
Uric acid	1.94 ± 12.24	5.40 ± 12.75	3.12 ± 12.98***	0.61 ± 10.65$^{***, \#\#\#}$	-1.36 ± 11.37$^{***, \#\#\#, ++}$
Fasting blood glucose	1.29 ± 8.97	0.92 ± 7.66	1.51 ± 9.75	1.64 ± 8.47	1.09 ± 9.83
Hemoglobin A1c	0.18 ± 4.27	0.0057 ± 3.93	0.34 ± 4.73	0.30 ± 4.48	0.061 ± 3.86
Total cholesterol	1.38 ± 10.07	1.23 ± 10.37	1.34 ± 9.64	1.11 ± 9.72	1.85 ± 10.52
LDL cholesterol	3.24 ± 15.46	3.66 ± 15.81	3.09 ± 14.91	2.91 ± 14.50	3.30 ± 16.55
HDL cholesterol	0.46 ± 11.70	0.19 ± 12.38	0.53 ± 11.77	0.25 ± 11.24	0.87 ± 11.37
Triglyceride	5.97 ± 44.36	0.030 ± 36.11	4.34 ± 39.01	5.47 ± 40.53	14.06 ± 57.52$^{***, \#\#\#, +++}$
Hemoglobin	-0.36 ± 5.07	0.095 ± 5.52	-0.39 ± 4.79	-0.78 ± 4.79**	-0.39 ± 5.12
Hematocrit	-2.03 ± 4.64	-1.67 ± 5.03	-2.08 ± 4.21	-2.33 ± 4.52*	-2.04 ± 4.74

Heart rate	0.17 ± 9.08	0.57 ± 9.83	-0.23 ± 9.06	0.66 ± 8.69	-0.31 ± 8.66
SV1 + RV5	-1.45 ± 13.25	-1.88 ± 13.50	-1.53 ± 13.43	-1.55 ± 13.12	-0.83 ± 12.97
Salt intake	2.01 ± 21.80	-23.22 ± 8.65	-5.86 ± 3.64***	6.56 ± 4.07$^{***, \#\#\#}$	30.57 ± 16.20$^{***, \#\#\#, +++}$

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

*, #, +: $p<0.05$, **, ##, ++: $p<0.01$, ***, ###, +++: $p<0.001$. * vs. Group 1, # vs. Group 2, + vs. Group 3

Table 3 Relationship between annual percentage changes in logarithmic B-type natriuretic peptide (BNP) and some clinical parameters

	r	p
Body weight	0.061	<0.001
Body mass index	0.055	<0.01
Abdominal circumference	-0.009	0.61
Systolic BP	0.024	0.18
Diastolic BP	-0.018	0.33
Serum creatinine	-0.29	<0.001
eGFR	0.29	<0.001
Uric acid	-0.26	<0.001
Fasting blood glucose	-0.038	<0.05
Hemoglobin A1c	-0.014	0.44
Total cholesterol	-0.21	<0.001
LDL cholesterol	-0.19	<0.001
HDL cholesterol	-0.088	<0.001
Triglyceride	0.039	<0.05
Hemoglobin	-0.30	<0.001
Hematocrit	-0.29	<0.001
SV1 + RV5	-0.007	0.68

Abbreviations: BP; blood pressure, eGFR; estimated glomerular filtration rate, LDL; low-density lipoprotein, HDL; high-density lipoprotein, SV1 + RV5; an S-wave in V1 plus an R-wave in V5 wave

Table 4 Multiple linear regression analyses between annual percentage changes in logarithmic B-type natriuretic peptide (BNP) levels and salt intake levels after adjustment for some clinical parameters

	Model 1		Model 2		Model 3		Model4		Model 5		Model 6	
	R=0.33	p<0.001	R=0.33	p<0.001	R=0.39	p<0.001	R=0.39	p<0.001	R=0.48	p<0.001	R=0.60	p<0.001
	β	p	β	p	β	p	β	p	β	p	β	p
Age (years)	-0.027	0.11	-0.028	0.11	-0.032	0.056	-0.032	0.053	-0.038	0.018	0.099	<0.001
Sex	0.044	0.010	0.044	0.010	0.040	0.017	0.040	0.017	0.026	0.10	-0.029	0.15
Body mass index (% change)	0.022	0.21	0.021	0.22	0.012	0.48	0.012	0.48	0.050	0.003	0.028	0.076
Systolic BP (% change)			0.002	0.90	<0.001	1.00	0.001	0.97	0.008	0.62	0.039	0.020
eGFR (% change)					0.21	<0.001	0.21	<0.001	0.13	<0.001	0.098	<0.001
SV1 + RV5 (% change)							-0.017	0.30	-0.002	0.89	-0.007	0.63
Hemoglobin A1c (% change)									-0.022	0.17	-0.027	0.074
Uric acid (% change)									-0.088	<0.001	-0.072	<0.001
LDL cholesterol (% change)									-0.10	<0.001	-0.084	<0.001
Triglyceride (% change)									0.004	0.81	-0.015	0.35
Hemoglobin (% change)									-0.22	<0.001	-0.20	<0.001
Body mass index (kg/m^2)											-0.036	0.038
Systolic BP (mmHg)											0.050	0.006
eGFR (ml/min/1.73m^2)											-0.012	0.47
Hemoglobin A1c (%)											-0.039	0.016
LDL cholesterol (mg/dL)											-0.044	0.008
Triglyceride (mg/dL)											-0.032	0.055
Hemoglobin (g/dL)											-0.090	<0.001
Logarithmic BNP (pg/mL)											-0.44	<0.001
Salt intake (g/day)											0.086	<0.001
Salt intake (% change)	0.33	<0.001	0.33	<0.001	0.27	<0.001	0.27	<0.001	0.26	<0.001	0.24	<0.001

Abbreviations: BP; blood pressure, eGFR; estimated glomerular filtration rate, SV1 + RV5; an S-wave in V1 plus an R-wave in V5 wave, LDL; low-density lipoprotein