

Observational Study

## How far cardio metabolic and psychological factors affect salt sensitivity in normotensive adult population?

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### Abstract

#### AIM

To evaluate the prevalence of salt sensitivity and the impact of cardiometabolic and psychological characteristics on salt sensitivity in normotensive population.

#### METHODS

Of all participants, anthropometric measurements and fasting venous blood samples were collected, and study questionnaires were completed. Salt Sensitivity was defined based on the difference in mean arterial pressure with infusion of 2 L of normal saline followed by a low sodium diet and administration of three doses

of oral furosemide the day after.

## RESULTS

Of 131 participants, 56 (42.7%) were diagnosed with salt sensitivity. Crude and age and sex adjusted regression analysis showed that low-density lipoprotein cholesterol and depression were positively associated with salt sensitivity (OR = 1.02, 95%CI: 1.01-1.04 and OR = 1.15, 95%CI: 1.00-1.34, respectively).

## CONCLUSION

The high prevalence of salt sensitivity and its significant relation with prevalent risk factors necessitates considering its reduction actions at the population level and the need for further research.

**Key words:** Salt sensitivity; Cardiovascular disease risk factors

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**Core tip:** Mean blood pressure can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals. Normotensive individuals with salt sensitivity trait are more likely to develop hypertension and other health problems. A relatively high prevalence of salt sensitivity has been indicated among Iranian adults. Low-density lipoprotein cholesterol was found to have strong positive association with salt sensitivity. Depressive individuals were more salt sensitive.

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## INTRODUCTION

Hypertension is a prevalent well-documented risk factor for cardiovascular disease and premature mortality and therefore is an important public health issue<sup>[1]</sup>. Essential hypertension is a common disorder in areas with average daily sodium intake of over 100 meq/d (2.3 g sodium), however, is rarely seen with average daily sodium intake of less than 50 meq/d (1.2 g sodium)<sup>[2,3]</sup>.

It has been demonstrated in multiple studies that mean blood pressure (BP) can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals<sup>[4,5]</sup>. Based on these reports, a minimum level of dietary sodium independent of other risk factors is required for development of hypertension<sup>[6,7]</sup>.

There is an important clinical benefit to identify

and target individuals who are more sensitive to alterations in dietary sodium intake by implementing dietary sodium reduction interventions. BP variations in response to changes in dietary sodium intake are known as Salt Sensitivity. This responsiveness of BP, however, may vary significantly from individual to individual<sup>[8,9]</sup>. Normotensive individuals with this trait of salt sensitivity are said to be more likely to develop hypertension and other health problems including Cardiovascular, Respiratory, and renal disorders independent of hypertension later in life<sup>[10,11]</sup>.

Although incompletely understood, multiple mechanisms for sodium sensitivity have been demonstrated, from impaired renal sodium excretion, abnormalities in signaling and vascular tone, to the role of genetics in sodium regulation<sup>[12,13]</sup>.

In spite of the fact that the protocols and methods of salt sensitivity definition vary in different studies, there is a general accordance in the main observations. Salt sensitivity appears to be a reproducible phenomenon with different measurement techniques<sup>[14]</sup>.

Salt sensitivity is a practical clinical concept in spite of all the difficulties in measurement and identifying the sensitive individuals. This fact that is evident by positive outcomes of the recommended dietary approaches for the prevention and treatment of hypertension (HTN) (DASH diet)<sup>[15]</sup> There are certain traits and disorders that are markedly associated with salt sensitivity including African American ethnicity, obesity, chronic kidney disease, and cardiovascular risk factors<sup>[9,16]</sup>.

Previous studies conducted in the Eastern Mediterranean region (EMR) demonstrate a substantially high incidence rate of almost all cardiovascular diseases particularly HTN and increased rate of mortality even in treated subjects<sup>[17-20]</sup>. These findings along with the increasing trend of salt intake at the population level<sup>[21]</sup>, beside the lack of evidence of salt sensitivity of BP in Iran and in the region, highlight the importance of conducting this study. Therefore, we aimed to evaluate the prevalence of salt sensitivity in a normotensive Iranian adult population and to investigate the impact of cardiometabolic risk factors and psychological characteristics, on salt sensitivity.

## MATERIALS AND METHODS

### Participants and studied variables

The study was conducted by the hypertension research center affiliated to Cardiovascular Research Institute (a WHO collaborating center in the EMR) from July to October 2014. In order to find potential volunteers from community, we used a wide range of materials from flyers and brochures to posters. A total of 140 healthy participants volunteered to take part in this cross-sectional study. Eligibility requirements included willingness to participate in the study, age 18 years and older, normal BP defined as systolic BP below 140 mmHg and diastolic BP below 90 mmHg based on 3 screening visits of 1 wk apart. The exclusion criteria was

history of hypertension; history of special diet including low salt diets; history of taking antihypertensive medications and diuretics for any reason, oral contraceptives and nonsteroidal anti-inflammatory drugs; any history of myocardial infarction, heart failure, cerebrovascular accidents and renal failure. Written informed consents were obtained from each participant and the study protocol was approved by the ethical committee of Cardiovascular Research Institute.

A questionnaire was used at the baseline observation by trained staff to collect information on demographic characteristics as well as family history of hypertension, coronary artery disease, and lifestyle habits including regular physical activity, dietary pattern and smoking status. The Hospital Anxiety and Depression Scale questionnaire was also used to determine the score of anxiety and depression. This scale consists of seven items for anxiety and seven items for depression, with scores ranging from 0 to 21. The higher scores demonstrate more intensity in anxiety or depression level. Scores higher than 7, in both domains indicate that participants are likely to be depressed or suffer from anxiety<sup>[22,23]</sup>.

Anthropometric measurements of weight, height, waist and hip circumferences were obtained during baseline examination with the individual in minimal clothing. The WHO STEPS Surveillance Manual (The WHO STEP wise Approach to Chronic Disease Risk Factor Surveillance) was used for measuring waist and hip circumference<sup>[24]</sup>. Body mass index (BMI) was calculated as weight (in kilograms) over height squared (in meters).

Venous blood samples after fasting for at least 8 h were taken for measurement of fasting blood sugar (FBS), serum blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), sodium (Na), potassium (K) levels, and lipid profile including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), and total cholesterol (TC). Plasma measurements were assessed using commercially available kits (Parsazmoun). BP was measured by trained staff for each participant using an automated mercury sphygmomanometer with the individual in sitting position and 5 min of rest. All the participants were asked to avoid consumption of alcohol, tea, or coffee, physical exercise or smoking for at least one hour prior to admission. Mean arterial pressure (MAP) was calculated as  $[(2 \times \text{diastolic}) + \text{systolic}]/3$  and reported for each measurement.

We considered the following definitions for cardiovascular risk factors: Current smoking of at least one cigarette per day; lack of regular physical activity (less than 30 min a day, five days a week); raised blood glucose (FBS > 126 mg/dL); elevated blood cholesterol [TC > 200 mg/dL, TG > 150 mg/dL, LDL > 130 mg/dL, HDL below 40 mg/dL (male) and less than 50 mg/dL (female)]; and being overweight or obese (BMI > 25 kg/m<sup>2</sup>, waist circumference > 92 cm in males and > 88 cm in females)<sup>[25]</sup>.

### Study design

The study was conducted in two days. On the first day of the study, individuals were admitted at 8 AM and were put on a low calorie and low sodium diet (10 mmol/d). At this time, venous blood samples were obtained, anthropometric measurements were calculated, and the questionnaires were filled out from participants by trained staff. Two hours after the admission, three measurements of BP were obtained with five minutes intervals and the mean of them was recorded as the baseline BP.

After obtaining the baseline BP, 2 L of normal saline was administered intravenously over 4 h (500 mL/h). Two hours after normal saline infusion, BP was obtained and post-saline MAP was calculated. Then participants were discharged and were asked to return back to the clinic the next morning.

To ensure compliance to the study protocol, individuals were required to eat pre-packaged foods that were prepared according to the protocol including low-carbohydrate, low-fat, and low-sodium diet (10 mmol/d) and were instructed to avoid any foods that were not provided by the study staff. Participants were also followed up over the night by telephone to evaluate any potential side effects and to ensure their adherence to the study dietary protocol.

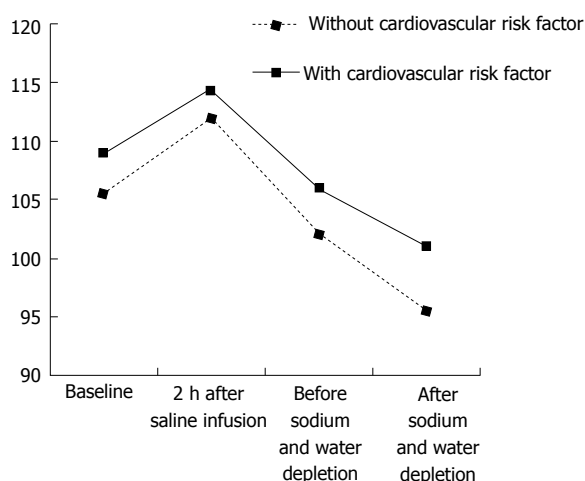
On the following day, participants were admitted again at 8 AM and BPs were obtained. Sodium and volume depletion was then induced by a low sodium diet (10 mmol/d) and administration of three doses of oral furosemide (40 mg each dose, at 10 AM, 2 PM and 6 PM). Two hours after completion of the last dose of furosemide, BP was measured according to the study protocol. The MAP after sodium and volume depletion was compared with the post-saline MAP.

Individuals who demonstrated a decrease in MAP  $\geq$  10 mmHg were defined as "salt sensitive". Those with MAP decrease < 10 mmHg were categorized as "salt insensitive" including both the salt resistant ( $\Delta$ MAP < 6 mmHg) and intermediate ( $\Delta$ MAP 6-10 mmHg) with respect to sodium sensitivity.

### Statistical analysis

All data were analyzed by SPSS, version 15 (SPSS Inc, Chicago, IL, United States). Respectively, a *P* value  $\leq$  0.05 and *P* value  $\leq$  0.1 were considered as statistically and marginally significant for all analyses. Student's *t* test for continuous variables and  $\chi^2$  test for discrete variables were used. Man-Whitney test was applied where appropriate. Multiple Logistic Regression model was carried out to examine the association between demographic, anthropometric, psychological characteristics and laboratory studies of those with the salt sensitivity. Odds ratios (ORs) were reported with the corresponding 95%CI. Repeated measure ANOVA was used for comparing the means of systolic BP in different times.

The dependent variable was salt sensitivity. Inde-



**Figure 1** Means of systolic blood pressure mmHg (vertical axes), measurements at: (1) baseline; (2) 2 h after saline infusion; (3) before sodium and water depletion; and (4) after sodium and water depletion (horizontal axes), among individuals without or with at least one cardiovascular risk factor.

pendent variables included demographic, anthropometric, psychosocial characteristics, laboratory studies, and cardiovascular risk factors of those adjusted based on age and sex. The statistical methods of the study were reviewed by biomedical statistician.

## RESULTS

Of the total of 140 participants, 9 who failed to adhere to dietary protocol or did not complete the intervention were excluded from the study. Among the 131 individuals included in the study, 56 participants (42.7%) were diagnosed with salt sensitivity while 75 (57.3%) participants including 52 (39.7%) salt resistant and 23 (17.6%) intermediate were determined as salt insensitive group. Of participants, hundred were male and 31 were female, with a mean age of  $25.70 \pm 5.71$ . Significant differences were not statistically detected in the age or sex distribution between both groups.

Table 1 shows the baseline demographic, psychological and anthropometric characteristics of participants as well as laboratory evaluations. Lipid profile tests revealed that LDL cholesterol level was significantly higher in Salt Sensitive group compared with Salt Insensitive one ( $P = 0.038$ ). In the Salt Sensitive group, BMI, FBS, BUN, and Cr levels were higher than those in the Salt Insensitive group with a marginally significant difference ( $P = 0.057, 0.072, 0.077, 0.067$ , respectively). There wasn't any significant difference in the Depression or Anxiety Score between two groups.

Table 2 shows the Crude, and age and sex-adjusted logistic regression analysis with salt sensitivity as an outcome. As shown in Table 2, with adjusted logistic regression analysis, LDL along with Depression were found to be the only two variables of significance (OR = 1.02, 95%CI: 1.01-1.04 and OR = 1.15,

95%CI: 1.00-1.34, respectively). At last, multiple logistic regression model with variables including, WC, Depression, FBS, LDL, Cr, age and sex was performed. Finding showed that there were not statistically difference between the result of multiple logistic regression model and age and sex adjusted logistic regression analysis and depression and LDL was still significant.

Means of systolic and diastolic BP measurements in participants without any cardiovascular risk factor compared with those with at least one risk factor at the baseline observation, 2 h after saline infusion, and before and after sodium and water depletion is shown in Figure 1. It has been founded that there is significant difference between baseline, 2 h after saline infusion and before and after sodium and water depletion ( $F = 102.02, P \leq 0.001$ ). No significant interaction was observed between groups and times. ( $F = 0.99, P = 0.39$ ).

## DISCUSSION

As a whole, 131 normotensive individuals properly completed the study protocol and were included in the study analysis. This study showed a relatively high prevalence of salt sensitivity among Iranian adults as well as significant and positive association between the level of LDL cholesterol and salt sensitivity. Based on age and sex adjusted logistic regression analysis, LDL cholesterol and depression were found to have strong positive association with salt sensitivity.

Multiple studies conducted in the EMR have shown high incidence rate of hypertension and its low control level in the region<sup>[18-20]</sup>. This factor along with high average intake of sodium in the Iranian diet<sup>[21]</sup> highlight the importance of integrating salt sensitivity in risk assessment and management of hypertension in the region.

The heterogeneity and susceptibility of individual BP response to Sodium intake is the basis for development of salt sensitivity and appears to be a common, normally distributed biological concept in populations<sup>[10,26]</sup>. The salt sensitivity definition and categorizing individuals to salt sensitive or insensitive is arbitrary and several methods exist to measure salt sensitivity. It can be defined as BP variations in response to a change in dietary salt or as the difference in MAP with infusion of normal saline followed by a low sodium diet and loop diuretic administration the day after<sup>[15,16]</sup>. Our protocol, with salt loading and depletion, allowed us to maximize the follow-up and adherence to the protocol with a more practical and controllable intervention. Despite the differences in the measurement or definition methods, there has been accordance in several findings<sup>[26,27]</sup>.

Overall, 42.7% of participants in our study were diagnosed with salt sensitivity. Even though relatively high, it is still in line with previous reports. The salt sensitivity has been observed in 25%-50% of normotensives and 40%-75% of hypertensive patients



**Table 1** Baseline demographic, cardiometabolic and psychological characteristics of participants with respect to salt sensitivity

Variable	Salt insensitive <i>n</i> = 75	Salt sensitive <i>n</i> = 56	<i>P</i> value
Sex (male) (%)	55 (73.3)	45 (80.4)	0.349 <sup>1</sup>
Age (yr) (mean ± SD)	25.23 ± 4.68	26.36 ± 6.91	0.272 <sup>2</sup>
Family history of HTN (y/n) (%)	22 (29.3)	16 (28.6)	0.995 <sup>1</sup>
Family history of CAD (y/n) (%)	7 (9.3)	6 (10.7)	0.770 <sup>1</sup>
Regular physical activity (y/n) (%)	30 (40.0)	19 (33.9)	0.522 <sup>1</sup>
Current smoker (y/n) (%)	12 (16.0)	8 (14.3)	0.865 <sup>1</sup>
Weight (kg) (mean ± SD)	68.21 ± 13.05	71.16 ± 12.33	0.193 <sup>2</sup>
Body mass index (kg/m <sup>2</sup> ) (mean ± SD)	22.75 ± 2.71	23.71 ± 2.93	0.057 <sup>2</sup>
Waist circumference (cm) (mean ± SD)	81.54 ± 8.96	82.86 ± 8.41	0.404 <sup>2</sup>
Hip circumference (cm) (mean ± SD)	96.97 ± 5.90	97.38 ± 5.77	0.698 <sup>2</sup>
Waist to hip ratio (mean ± SD)	0.83 ± 0.06	0.84 ± 0.05	0.346 <sup>2</sup>
Waist to height ratio (mean ± SD)	0.47 ± 0.04	0.48 ± 0.49	0.382 <sup>2</sup>
Fasting blood sugar (mg/dL) (mean ± SD)	79.71 ± 6.16	82.64 ± 10.74	0.072 <sup>2</sup>
Total cholesterol (mg/dL) (mean ± SD)	156.54 ± 28.70	164.66 ± 26.64	0.109 <sup>2</sup>
High-density lipoprotein cholesterol (mg/dL) (mean ± SD)	46.23 ± 11.90	44.09 ± 12.23	0.327 <sup>2</sup>
Low-density lipoprotein cholesterol (mg/dL) (mean ± SD)	82.56 ± 21.27	90.05 ± 17.49	0.038 <sup>2</sup>
Triglyceride (mg/dL) (mean ± SD)	136.75 ± 97.26	145.32 ± 75.93	0.594 <sup>2</sup>
Uric acid (mg/dL) (mean ± SD)	6.91 ± 6.57	6.42 ± 1.56	0.597 <sup>2</sup>
Sodium (mg/dL) (mean ± SD)	140.30 ± 2.42	140.46 ± 2.39	0.699 <sup>2</sup>
Potassium (mg/dL) (mean ± SD)	4.38 ± 0.53	4.34 ± 0.34	0.662 <sup>2</sup>
Blood urea nitrogen (mg/dL) (mean ± SD)	12.56 ± 3.72	13.73 ± 3.63	0.077 <sup>2</sup>
Creatinine (mg/dL) (mean ± SD)	0.92 ± 0.12	0.96 ± 0.10	0.067 <sup>2</sup>
Depression score (mean ± SD)	4.00 ± 2.66	3.25 ± 2.15	0.095 <sup>3</sup>
Anxiety score (mean ± SD)	3.73 ± 3.18	3.08 ± 3.25	0.161 <sup>3</sup>

<sup>1</sup>*P* value obtained from  $\chi^2$ ; <sup>2</sup>*P* value obtained from t-test; <sup>3</sup>*P* value obtained from Man-Whitney. HTN: Hypertension; CAD: Coronary artery disease.

**Table 2** Crude, age and sex-adjusted logistic regression analysis with salt sensitivity as an outcome

Variable	Crude OR (95%CI)	<i>P</i> value	Adjusted OR (95%CI)	<i>P</i> value
Total cholesterol (mg/dL)	1.01 (1.00-1.02)	0.11	1.01 (1.00-1.03)	0.12
Triglyceride (mg/dL)	1.01 (1.00-1.01)	0.59	1.00 (1.00-1.01)	0.87
High-density lipoprotein cholesterol (mg/dL)	0.99 (0.96-1.02)	0.33	0.99 (0.96-1.02)	0.45
Low-density lipoprotein cholesterol (mg/dL)	1.02 (1.01-1.04)	0.04	1.02 (1.01-1.04)	0.04
Fasting blood sugar (mg/dL)	1.04 (1.00-1.09)	0.06	1.04 (0.99-1.09)	0.14
Sodium (mg/dL)	1.06 (0.97-1.04)	0.35	1.03 (0.98-1.05)	0.37
Potassium (mg/dL)	1.05 (0.99-1.07)	0.51	1.06 (0.98-1.06)	0.41
Body mass index (kg/m <sup>2</sup> )	1.14 (1.00-1.28)	0.06	1.12 (0.97-1.28)	0.13
Waist circumference (cm)	1.02 (0.98-1.06)	0.40	1.02 (0.97-1.06)	0.49
Waist to hip ratio	1.19 (0.83-1.69)	0.34	1.16 (0.76-1.79)	0.48
Regular physical activity (y/n)	0.79 (0.38-1.64)	0.52	0.85 (0.39-1.82)	0.66
Smoking (y/n)	1.07 (0.95-1.15)	0.40	1.08 (0.97-1.25)	0.47
Depression (y/n)	1.14 (0.98-1.32)	0.06	1.15 (1.00-1.34)	0.04
Family history of HTN (y/n)	1.19 (0.37-3.85)	0.77	1.28 (0.35-4.76)	0.70

HTN: Hypertension.

depending on the measurement techniques and geographic variation of studies in different ethnic populations<sup>[4,5,28]</sup>.

Several mechanisms for sodium sensitivity have been demonstrated<sup>[29]</sup>. Impaired renal sodium excretion with resultant sodium retention that leads to volume expansion has been suggested as one of the underlying mechanism<sup>[30-32]</sup>. Abnormalities in signaling and vascular tone in response to sodium intake are another possible process<sup>[13,14]</sup>. Multiple genes are shown to be associated with sodium regulation and salt sensitivity<sup>[33,34]</sup>. This genetic predisposition is thought to be responsible for several relations seen in the salt sensitive group.

The strong, positive association of LDL cholesterol level with salt sensitivity presented in Table 2 can be interpreted by the role of genetic predisposition. In a study by Hoffmann *et al.*<sup>[35]</sup>, the endothelial nitric oxide synthase (*ENOS*) gene polymorphism was shown to be associated with higher levels of LDL cholesterol and reduced levels of nitric oxide (NO) production that can be responsible for the increased BP sensitivity to salt. Several previous studies have also revealed that the alpha-adducin gene polymorphisms may increase the LDL cholesterol levels and are probably responsible for salt sensitivity of BP<sup>[33,36,37]</sup>.

In the present study, depression was found to

be a potential predictive variable for salt sensitivity. The mechanism by which depression is related to salt sensitivity is not clearly understood and further studies are required. However, this association can be explained by the role of stress as a predisposing factor to depression in susceptibility of BP to salt. Previous studies have demonstrated the contribution of the stress and sympathetic nervous system to salt sensitivity<sup>[10,38,39]</sup>. One mechanism might be the impaired stress-induced renin-angiotensin-aldosterone system regulation<sup>[40]</sup>.

Depression and elevated LDL cholesterol level are reported to be highly prevalent among the Iranian population<sup>[41]</sup>. The fact that makes the importance of these two factors in salt sensitivity was even more significant among Iranian population.

Our findings showed that in the crude model, BMI, FBS, BUN and Cr levels were related to salt sensitivity with a marginally significant difference. The association between BMI and salt sensitivity has been noted in previous studies<sup>[39,42]</sup>. This relation may be explained by the higher sodium renal tubular reabsorption in obese individuals or due to drinking more soft drinks while eating salty products. Multiple previous studies have identified strong association between the plasma glucose level as a metabolic risk factor with salt sensitivity of BP independent of BMI, physical activity and hypertension<sup>[43]</sup>. Reduced renal function, which can be monitored with the level of BUN and Cr, has been also shown in previous observations to be associated with salt sensitivity<sup>[31]</sup>.

The prevalence of salt sensitivity is increased among older individuals with a family history of hypertension<sup>[11,29]</sup>, however, our results failed to show an association between higher age or positive family history of HTN and salt sensitivity. Multiple Factors such as including only normotensive participants, and relatively small sample size of the study can be considered as the reason for these inconclusive observations or differences found in our study compared to others.

The limitations of our study include relatively small sample size, the measurement method used for defining salt sensitivity, and exclusion of hypertensive individuals from the study. Even though all these factors were intentionally incorporated into the study design to enhance the practicality, feasibility and efficacy of the study, they ought to be considered as the limitations of the study.

According to our knowledge, this study is the first to investigate and report the prevalence and characteristics of salt sensitivity in our country and the EMR. The important clinical and public health implications of our study necessitate the need for more studies with larger sample size and to consider hypertensive patients too.

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## COMMENTS

### Background

Blood pressure (BP) can be reduced following a decrease in sodium intake in both hypertensive and normotensive individuals. There is an important clinical benefit to identify and target individuals who are more sensitive to alterations in dietary sodium intake by implementing dietary sodium reduction interventions. Normotensive individuals more likely develop hypertension and other health problems including cardiovascular, respiratory, and renal disorders independent of hypertension later in life.

### Research frontiers

Increasing trend of salt intake at the population level beside the lack of evidence of salt sensitivity of BP in Iran and in the region, highlight the importance of conducting this study.

### Innovations and breakthroughs

This study evaluates the prevalence of salt sensitivity in a normotensive Iranian adult population and to investigate the impact of cardiometabolic risk factors and psychological characteristics, on salt sensitivity. According to our knowledge, this study is the first to investigate and report the prevalence and characteristics of salt sensitivity in our country and the Eastern Mediterranean Region.

### Applications

Salt sensitivity is a practical clinical concept in spite of all the difficulties in measurement and identifying the sensitive individuals.

### Terminology

Salt sensitivity is a measure of how your BP responds to salt intake. People are either salt-sensitive or salt-resistant. Salt sensitive individuals are more likely to have high BP than those who are resistant to salt; Normotensive having or denoting a normal BP.

### Peer-review

This is an interesting manuscript about the relations of salt sensitivity to cardiometabolic risk factors and psychological characteristics.

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