

Association Study of Fasting Blood Glucose and Salt Sensitivity of Blood Pressure in Community Population: The EpiSS Study

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Abstract

Background: Some populations showed heterogeneous elevated blood pressure (BP) responses to relatively high salt intake, which is the phenomenon generally referred as salt sensitivity of blood pressure (SSBP). We aimed to evaluate whether the fasting blood glucose (FBG) could be an independent risk factor, and dose-dependent associated with the SSBP in community population.

Methods: This study is based on the baseline survey of systemic epidemiology of salt sensitivity study. Subjects were classified into salt sensitive (SS) and salt resistant (SR) groups according to BP changes during the modified Sullivan's acute oral saline load (ΔBP_1) and diuresis shrinkage (ΔBP_2) test. Multivariate logistic regression and multivariate linear regression were used to evaluate associations between FBG with SS or BP changes.

Results: A total of 2051 participants were included in the analyses with 581 (28.33%) for SS. The median level of FBG and frequency of diabetes were significantly higher in SS group than those in SR group (5.55 vs. 5.39 mmol/L, $P=0.003$; 19.62% vs. 14.49%, $P=0.005$). Multiple logistic analyses showed a positive association between FBG and SS prevalence, for every interquartile range increase in FBG, the *OR* (95%*CI*) for SS was 1.140 (1.069, 1.215). Consistently, multivariate linear regression analyses showed that FBG was independently and positively associated with mean arterial pressure change (ΔMAP_1) ($\beta=0.421$; 95%*CI*, 0.221, 0.622), systolic BP change ($\beta=0.589$; 95%*CI*, 0.263, 0.914) and diastolic BP change ($\beta=0.340$; 95%*CI*, 0.149, 0.531) during saline load, respectively. Compared to the lowest FBG quartile (Q_1), the *OR* (95%*CI*) for SS in Q_3 and Q_4 were 1.342 (1.014, 1.776) and 1.577 (1.194, 2.084), respectively (P for trend ≤ 0.001). Compared to subjects with normal fasting glucose, the β (95%*CI*) for ΔMAP_1 was 0.973 (0.055, 1.891) in subjects with impaired fasting glucose, and was 1.449 (0.602, 2.296) in patients with diabetes (P for trend ≤ 0.001). Stratified analyses showed significant and stronger associations between FBG with SSBP in youngers, females, hypertensives, non-diabetics, non-current smokers and non-current drinkers.

Conclusions: Our findings suggest FBG is an independent, dose-dependent risk factor for SSBP, and prevention of SS focusing on controlling FBG elevation in the early stage is important.

Background

Some populations showed heterogeneous elevated blood pressure (BP) responses to relatively high salt intake, which is the phenomenon generally referred as salt sensitivity of blood pressure (SSBP) [1, 2]. Population can be classified into salt sensitive (SS) and salt resistant (SR) individuals according to the response of BP to salt loading or diuretic shrinkage [2]. SS individuals account for more than 50% of hypertensive patients [3], and the prevalence in Chinese patients reach up to 58.6% [4]. A 18-year follow-up study found that the BP and morbidity of hypertension in the SS subjects were significantly higher than those of the SR group, suggesting that SS is one of risk factors of hypertension [5]. In addition, two prospective cohort studies confirmed that SS is associated with risk of cardiovascular morbidity and

mortality independent of BP, and the correlation between cardiovascular diseases with SS is as strong as that with BP [6, 7]. Therefore, a better understanding of the risk factors associated with SS may possibly reduce the huge burden of cardiovascular diseases.

SS was reported to be influenced by both genetic and environmental factors [2, 8], including race [9], age [10], gender [11], diet [12] and some co-morbidities e.g., diabetes [13, 14] and chronic kidney disease [15]. The association between fasting blood glucose (FBG) and SS has also been proposed for many years. Several studies have showed that the FBG level was higher in SS individuals than that in SR groups in different populations, including healthy male (n = 18) [16], obese subjects with mild hypertension (n = 18) [17], hypertensive patients (n = 99) [18] and young normotensive subjects (n = 23) [19]. Chen *et al.* perform a low and high-sodium diet test in adults and found that the changes of BP were significantly greater in participants with metabolic syndrome [20]. According to the statement from the American Heart Association in 2005, the abdominal obesity, raised BP, high triglycerides (TG) concentration, low high-density lipoprotein cholesterol (HDL-C), or elevated plasma glucose were the main risk factors of metabolic syndrome [21]. This research showed that the risk of salt sensitivity rose with increasing numbers of risk factors for metabolic syndrome [20]. These evidences indicated that FBG might played a more important role in the development of SS. Takashi *et al.* suggested that hyperglycemia may enhance the reabsorption of sodium through sodium glucose cotransporter 2 in proximal tubule especially in diabetes patients [22], thus might stimulate the occurrence of SS. However, whether the level of FBG could be a risk factor for SS has been largely overlooked in these previous studies due to the small sample size and focusing on the insulin or insulin resistance.

Up to now, few population-based epidemiological studies have focused on the association between blood glucose levels and SS. We hypothesized that FBG might be an independent risk factors, and dose-dependent associated with the SSBP. Therefore, based on the study of systemic epidemiology of salt sensitivity (EpiSS), we aimed to analyze the relationship between FBG and BP changes both in acute salt load period and in diuresis shrinkage period, and to compare the differences in SS prevalence and BP changes among subjects with different blood glucose levels.

Methods

Participants

Data analyzed in this study was the baseline of the EpiSS study. This study was registered in the Chinese Clinical Trial Registry (No: ChiCTR1900024725, <http://www.chictr.org.cn/index.aspx>). The protocol for selection of the subjects, sample collection and measurement methods have been described in detail previously [23]. Briefly, participants aged 35 to 70 years were recruited from five community health centers in Beijing and six community health centers in Liaoning Province during July 2014 and July 2016. Patients with hypertension and diabetes were required to stop the intake of all antihypertensive and antidiabetic drugs for at least 24 hours. In addition, patients with secondary stage and above hypertension [systolic BP (SBP) > 160 mmHg and (or) diastolic BP (DBP) > 100 mmHg], and individuals

with clinical diagnosis of cardiovascular disease, kidney disease, liver disease or malignant tumors were excluded.

Determination of salt sensitive

In EpiSS study, the modified Sullivan's acute oral saline load and diuresis shrinkage test (MSAOSL-DST) [24–26] was performed to evaluate the SSBP. As described in the previous study [23], MSAOSL-DST contains the following steps: First, the baseline BP (BP_0) was measured twice and mean BP was calculated before test. Then, the subjects were asked to take 1000 mL of 0.9% saline solution orally within 30 minutes, and the second time BP (BP_1) was measured after two hours from the time individual finished drinking saline. Third, immediately after the second time BP measurements, the subjects were given a 40 mg furosemide, and the third time BP (BP_2) was measured two hours after taking furosemide. Mean arterial pressure (MAP) was defined as the one-third of SBP plus two-third of DBP. The ΔBP_1 (ΔMAP_1 , ΔSBP_1 , ΔDBP_1) was calculated as BP_1 (MAP_1 , SBP_1 , DBP_1) minus BP_0 (MAP_0 , SBP_0 , DBP_0), respectively. The ΔBP_2 (ΔMAP_2 , ΔSBP_2 , ΔDBP_2) was defined as BP_2 (MAP_2 , SBP_2 , DBP_2) minus BP_1 (MAP_1 , SBP_1 , DBP_1), respectively. Individuals with $\Delta MAP_1 \geq 5$ mmHg or $\Delta MAP_2 \leq -10$ mmHg were identified as SS, and the other participants were SR [27].

Data collection and variables

A structured questionnaire was administered by trained staff to obtain sociodemographic information and behavior habits, including age, sex, smoking and alcohol consumption status, dietary, sleep and exercise habits; medical history including coronary artery disease, hypertension, diabetes and stroke, and medication history including the use of antihypertensive drugs including calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor inhibitors, diuretic, beta-blockers, the compound preparation and Chinese patent medicine, and antidiabetic drugs including biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glycosidase inhibitors and insulin.

BP were measured after at least 15-min rest with an automatic sphygmomanometer (Omron HEM-7118, Japan) [28]. BP measurement was carried out twice and the mean value was calculated for data analysis. Hypertension was defined as $SBP \geq 140$ mmHg and/or $DBP \geq 90$ mmHg, or a self-reported physician diagnosed with hypertension, or an individual currently using antihypertensive drugs [29, 30]. According to the Working Group on Obesity in China [31, 32], normal fasting glucose (FNG) was defined as $2.80 \leq FBG < 6.11$ mmol/L, impaired fasting glucose (IFG) was defined as $6.11 \leq FBG < 7.00$ mmol/L, diabetes was defined as $FBG \geq 7.00$ mmol/L. Furthermore, diabetes was also defined as a self-reported physician diagnosis of diabetes, or taking oral hypoglycemic medication or insulin [33].

The anthropometric examinations included height, weight, waist and hip circumference. Body mass index (BMI) was calculated as a person's weight in kilograms divided by the square of his/her height in meters (kg/m^2), and waist-to-hip ratio (WHR) as the ratio of waist circumference to hip circumference (cm). BMI was grouped according to the guidelines for prevention and control of overweight and obesity in Chinese

adults [34], normal weight ($\text{BMI} < 24.0 \text{ kg/m}^2$), overweight ($24.0 \leq \text{BMI} < 28.0 \text{ kg/m}^2$) and obesity ($\text{BMI} \geq 28.0 \text{ kg/m}^2$).

Fasting venous blood samples of each participant were extracted by venipuncture. The FBG was measured via the hexokinase/glucose-6-phosphate dehydrogenase method. The total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C) and HDL-C concentrations were determined by enzymatic methods.

Statistical analysis

All data analyzed were using the statistical package R (<http://www.r-project.org>) and SPSS 24.0 for Windows (SPSS, Inc., Chicago, IL, USA). A two-tailed $P < 0.05$ was statistically significant. Baseline characteristics of the participants were displayed as medians (interquartile range, IQR) for continuous variables (the continuous variables were non-normally distributed) and numbers (percentages) for categorical variables, and were further compared between SS and SR groups using Mann-Whitney U-test or Chi-square test.

The dose-response relationships between FBG with SSBP were conducted by restricted cubic spline (RCS), with knots of 10th, 50th and 90th percentiles of the FBG distribution and the 50th percentile of FBG set as the reference. The FBG was divided into quartiles (Q_1 , Q_2 , Q_3 and Q_4), and the associations between FBG with SS prevalence or with $\Delta\text{BP}_{1,2}$ ($\Delta\text{SBP}_{1,2}$, $\Delta\text{DBP}_{1,2}$ and $\Delta\text{MAP}_{1,2}$) were evaluated using multivariate logistic regression models (odds ratio [OR] and 95% confidence interval [95%CI]) or multivariate linear regression models (beta coefficient [β] and 95%CI), adjusted for major covariables including age, sex, sleep (as a categorical variable), current smoking, current drinking, TG, LDL-C and MAP_0 . Stratified analysis was performed by age, sex, BMI, hypertension status, diabetes status, smoking and drinking. In addition, sensitive analysis was performed to examine whether the antihypertensive or antidiabetic medications could influence the associations between FBG with SSBP.

Result

Characteristics of the Study Population

The characteristics of the study population and the comparison between SS and SR groups are presented in Table 1. A total of 2051 participants were included in the current study, with a median (IQR) age of 59 (54 ~ 63) years old, and 554 (27.01%) of male. There were 28.33% SS and 15.94% diabetes patients in participants. The median level of FBG and frequency of diabetes were significantly higher in SS group than those in SR group (5.55 vs. 5.39 mmol/L, $P = 0.003$; 19.62% vs. 14.49%, $P = 0.005$). Significant differences were also observed in variables including SBP_0 , DBP_0 , MAP_0 , TG, LDL-C, WHR, sleep, current smoking and drinking status ($P < 0.05$), and most of these variables were used as covariates for adjustment in multivariate analyses. The distribution of the ΔMAP_1 and ΔMAP_2 were left and right skewed ($P_{\text{for normality}} < 0.001$, Fig. 1), respectively.

Table 1
Characteristics of the participants classified by salt sensitivity of blood pressure.

Variables	Total	Salt sensitive	Salt resistant	<i>P</i> value
Number (%)	2051	581 (28.33)	1470 (71.67)	-
Age (years) [†]	59 (54 ~ 63)	59 (54 ~ 63)	59 (54 ~ 63)	0.820
Sex (male, n, %) ^{&}	554 (27.01)	174 (29.95)	380 (25.85)	0.068
SBP ₀ (mmHg) [†]	122.32 (108.32 ~ 135.00)	116.82 (103.32 ~ 130.82)	123.82 (110.82 ~ 136.82)	< 0.001
DBP ₀ (mmHg) [†]	76.60 (70.00 ~ 84.60)	74.10 (67.10 ~ 81.60)	77.60 (70.60 ~ 85.60)	< 0.001
MAP ₀ (mmHg) [†]	92.17 (83.51 ~ 101.01)	88.51 (80.34 ~ 97.34)	93.67 (85.01 ~ 102.17)	< 0.001
FBG (mmol/L) [†]	5.43 (4.99 ~ 6.18)	5.55 (5.02 ~ 6.45)	5.39 (4.98 ~ 6.08)	0.003
TC (mmol/L) [†]	5.04 (4.35 ~ 5.73)	4.99 (4.35 ~ 5.67)	5.06 (4.35 ~ 5.75)	0.355
TG (mmol/L) [†]	1.63 (1.13 ~ 2.48)	1.53 (1.09 ~ 2.42)	1.65 (1.16 ~ 2.49)	0.036
HDL-C (mmol/L) [†]	1.44 (1.13 ~ 2.40)	1.46 (1.14 ~ 2.60)	1.44 (1.13 ~ 2.31)	0.519
LDL-C (mmol/L) [†]	2.27 (1.55 ~ 2.97)	2.16 (1.50 ~ 2.94)	2.31 (1.57 ~ 2.99)	0.027
BMI (kg/m ²) [†]	25.92 (23.84 ~ 28.15)	25.92 (24.05 ~ 28.04)	25.92 (23.77 ~ 28.20)	0.877
WHR [†]	0.888 (0.851 ~ 0.927)	0.889 (0.859 ~ 0.930)	0.888 (0.848 ~ 0.926)	0.016
Education (n, %) ^{&}				0.114
Primary school or less	244 (11.90)	69 (11.88)	175 (11.90)	
Junior high school	784 (38.23)	199 (34.25)	585 (39.80)	

SBP₀, the baseline systolic blood pressure; DBP₀, the baseline diastolic blood pressure; MAP₀, the baseline mean arterial pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR, waist-to-hip ratio; Antihypertensive drugs, includes calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor inhibitors, diuretic, beta-blockers, the compound preparation and Chinese patent medicine; Antidiabetic drugs, includes biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glycosidase inhibitors and insulin.

[&], Statistical testing by χ^2 test.

[†], Statistical testing by Mann-Whitney U test.

Variables	Total	Salt sensitive	Salt resistant	<i>P</i> value
Senior high school	648 (31.59)	198 (34.08)	450 (30.61)	
University or above	375 (18.28)	115 (19.79)	260 (17.69)	
Marital status (n, %) ^{&}				0.363
Married	1924 (93.81)	550 (94.66)	1374 (93.47)	
Single/divorced/widowed	127 (6.19)	31 (5.34)	96 (6.53)	
Exercise ^{&}				0.913
<1 hour per week	673 (32.81)	207 (35.63)	466 (31.70)	
1 ~ 2 hours per week	150 (7.31)	48 (8.26)	102 (6.94)	
3 ~ 4 hours per week	168 (8.19)	49 (8.43)	119 (8.10)	
≥5 hours per week	719 (35.06)	213 (36.66)	506 (34.42)	
Missing	341 (16.63)	64 (11.02)	277 (18.84)	
Sleep ^{&}				0.001
<8 hours	1416 (69.04)	370 (63.68)	1046 (71.16)	
≥8 hours	635 (30.96)	211 (36.32)	424 (28.84)	
Current smoking (yes, n, %) ^{&}	311 (15.16)	107 (18.42)	204 (13.88)	0.012
Current drinking (yes, n, %) ^{&}	965 (47.05)	294 (50.60)	671 (45.65)	0.048
Hypertension (n, %) ^{&}	1059 (51.63)	302 (51.98)	757 (51.50)	0.882
Diabetes (n, %) ^{&}	327 (15.94)	114 (19.62)	213 (14.49)	0.005

SBP₀, the baseline systolic blood pressure; DBP₀, the baseline diastolic blood pressure; MAP₀, the baseline mean arterial pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR, waist-to-hip ratio; Antihypertensive drugs, includes calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor inhibitors, diuretic, beta-blockers, the compound preparation and Chinese patent medicine; Antidiabetic drugs, includes biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glycosidase inhibitors and insulin.

[&], Statistical testing by χ^2 test.

[†], Statistical testing by Mann-Whitney U test.

Variables	Total	Salt sensitive	Salt resistant	<i>P</i> value
Antihypertensive drugs (yes, n, %) ^{&}	660 (32.18)	177 (30.46)	483 (32.86)	0.321
Antidiabetic drugs (yes, n, %) ^{&}	104 (5.07)	29 (4.99)	75 (5.10)	0.957
SBP ₀ , the baseline systolic blood pressure; DBP ₀ , the baseline diastolic blood pressure; MAP ₀ , the baseline mean arterial pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR, waist-to-hip ratio; Antihypertensive drugs, includes calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor inhibitors, diuretic, beta-blockers, the compound preparation and Chinese patent medicine; Antidiabetic drugs, includes biguanides, sulfonylureas, thiazolidinediones, glinides, alpha-glycosidase inhibitors and insulin.				
^{&} , Statistical testing by χ^2 test.				
[†] , Statistical testing by Mann-Whitney U test.				

Blood pressure changes of the participants during the MSAOSL-DST

Table 2 presented the BP changes of subjects during the MSAOSL-DST. The median (IQR) of Δ SBP₁ in total participants during saline load period were larger than zero, but the Δ DBP₁ was not. There were significantly different for all Δ BP between subjects with SS and SR ($P < 0.001$).

Table 2
Blood pressure changes of the participants during the MSAOSL-DST.

Variables	Total	Salt sensitive	Salt resistant	P value
Saline load period				
ΔSBP_1	9.18 (1.18 ~ 15.83)	19.18 (14.18 ~ 23.68)	5.18 (-1.82 ~ 11.18)	< 0.001
ΔDBP_1	-3.60 (-7.60 ~ 0.40)	2.40 (-0.10 ~ 5.90)	-5.55 (-9.10 ~ -2.60)	< 0.001
ΔMAP_1	0.49 (-4.01 ~ 4.99)	7.66 (5.99 ~ 10.83)	-1.84 (-5.84 ~ 1.49)	< 0.001
Diuresis shrinkage period				
ΔSBP_2	-3.50 (-10.50 ~ 3.00)	-9.00 (-16.50 ~ -1.50)	-2.00 (-7.50 ~ 4.13)	< 0.001
ΔDBP_2	2.50 (-1.50 ~ 6.50)	-1.50 (-6.50 ~ 2.50)	3.50 (0.01 ~ 7.50)	< 0.001
ΔMAP_2	0.33 (-3.83 ~ 4.67)	-3.83 (-10.00 ~ 0.92)	1.67 (-2.17 ~ 5.83)	< 0.001
Data was represented as median (IQR), MSAOSL-DST, modified Sullivan's acute oral saline load and diuresis shrinkage test; ΔSBP_1 , the change of systolic blood pressure during saline load period; ΔDBP_1 , the change of diastolic blood pressure during saline load period; ΔMAP_1 , the change of mean arterial pressure during saline load period; ΔSBP_2 , the change of systolic blood pressure during diuresis shrinkage period; ΔDBP_2 , the change of diastolic blood pressure during diuresis shrinkage period; ΔMAP_2 , the change of mean arterial pressure during diuresis shrinkage period.				
Statistical testing by Mann-Whitney U test.				

Linear relationship between glucose and salt sensitivity of blood pressure

Multivariable-adjusted RCS analyses suggested that there were significant associations of FBG with SS prevalence, ΔMAP_1 , ΔSBP_1 and ΔDBP_1 in total population (all $P_{\text{for overall}} < 0.05$, Fig. 2). However, no significant relationships between FBG with ΔMAP_2 , ΔSBP_2 and ΔDBP_2 were observed (all $P_{\text{for overall}} > 0.05$, **Supplementary Fig. 1**). We found evidence of linear associations of FBG with the prevalence of SS ($P_{\text{for nonlinear}} = 0.1044$), ΔMAP_1 ($P_{\text{for nonlinear}} = 0.0762$) and ΔSBP_1 ($P_{\text{for nonlinear}} = 0.5013$), but nonlinear relationship between FBG with ΔDBP_1 ($P_{\text{for nonlinear}} = 0.0271$).

Association of fasting blood glucose and salt sensitivity of blood pressure

Table 3 presented the results of associations between FBG with SS or ΔBP_1 . Overall, there were significant positive associations between FBG with frequency of SS or ΔBP_1 . Multiple logistic regression analysis showed that for every IQR (1.19 mmol/L) increase in FBG, the prevalence of SS significantly

increased by 14.0% ($OR = 1.140$, 95% CI : 1.069, 1.215). Compared to the lowest quartile of blood glucose (Q_1), the prevalence of SS in the third quartile (Q_3) and the fourth quartile (Q_4) were increased by 34.2% ($OR = 1.342$, 95% CI : 1.014, 1.776) and 57.7% ($OR = 1.577$, 95% CI : 1.194, 2.084), respectively (P for trend ≤ 0.001). Compared with the NFG group, the prevalence of SS was 30.6% higher in the IFG group ($OR = 1.306$, 95% CI : 0.963, 1.770) and 78.7% higher in diabetes patients ($OR = 1.787$, 95% CI : 1.362, 2.345), respectively (P for trend ≤ 0.001).

Table 3

Associations between glucose with salt sensitive and blood pressure changes during saline loading period.

FBG (mmol/L)	<i>N</i>	OR (95% CI) for SS ^a	β (95% CI) for Δ MAP ₁ ^b	β (95% CI) for Δ SBP ₁ ^b	β (95% CI) for Δ DBP ₁ ^b
Per IQR increase	2051	1.140 (1.069, 1.215) ^{**}	0.421 (0.221, 0.622) ^{**}	0.589 (0.263, 0.914) ^{**}	0.340 (0.149, 0.531) [*]
Quartiles					
Q ₁ (~ 5.00)	519	1.000	0	0	0
Q ₂ (5.00 ~ 5.44)	514	0.845 (0.633, 1.129)	-0.258 (-1.087, 0.571)	-0.827 (-2.169, 0.516)	0.027 (-0.763, 0.817)
Q ₃ (5.44 ~ 6.19)	508	1.342 (1.014, 1.776) [*]	1.052 (0.218, 1.886) [*]	1.124 (-0.227, 2.475)	0.999 (0.205, 1.794) [*]
Q ₄ (6.19 ~)	510	1.577 (1.194, 2.084) [*]	1.476 (0.643, 2.310) [*]	1.794 (0.444, 3.144) [*]	1.319 (0.524, 2.113) [*]
<i>P</i> for trend		< 0.001	< 0.001	0.001	< 0.001
Clinical classifications					
NFG (~ 6.11)	1507	1.000	0	0	0
IFG (6.11 ~ 7.00)	245	1.306 (0.963, 1.770)	0.973 (0.055, 1.891) [*]	0.876 (-0.609, 2.362)	1.028 (0.154, 1.903) [*]
Diabetes (7.00 ~)	299	1.787 (1.362, 2.345) ^{**}	1.449 (0.602, 2.296) [*]	2.395 (1.025, 3.766) [*]	0.983 (0.176, 1.789) [*]
<i>P</i> for trend		< 0.001	< 0.001	0.001	0.004
IQR, interquartile range; FBG, fasting blood glucose; NFG, normal fasting glucose; IFG, impaired fasting glucose; SS, salt sensitive; Δ MAP ₁ , change of mean arterial pressure due to saline loading; Δ SBP ₁ , change of systolic blood pressure due to saline loading; Δ DBP ₁ , change of diastolic blood pressure due to saline loading.					
^a , Statistical testing by multiple logistic regression analyses.					
^b , Statistical testing by multiple linear regression analyses.					
Adjusted for age, sex, sleep, current smoking, drinking, triglycerides, low density lipoprotein cholesterol and baseline mean arterial pressure.					
*, <i>P</i> < 0.05; **, <i>P</i> < 0.001.					

Multiple linear regression analysis showed that for every IQR increase in FBG, the Δ MAP₁, Δ SBP₁ and Δ DBP₁ significantly increased by 0.421 mmHg (95%CI: 0.221, 0.622), 0.589 mmHg (95%CI: 0.263, 0.914)

and 0.340 mmHg (95%CI: 0.149, 0.531), respectively. When FBG was assessed as quartiles, compared to Q_1 the ΔMAP_1 in Q_3 and Q_4 were increased by 1.052 mmHg (95%CI: 0.218, 1.886) and 1.476 mmHg (95%CI: 0.643, 2.310), respectively (P for trend ≤ 0.001). When compared to NFG individuals, the adjusted β for ΔMAP_1 in IFG and diabetic patients were 0.973 (95%CI: 0.055, 1.891) and 1.449 (95%CI: 0.602, 2.296), respectively (P for trend ≤ 0.001). However, we failed to observe significant associations between FBG and BP changes during diuretic shrinkage ($P > 0.05$, **Supplementary Table 1**).

Association of glucose and salt sensitivity of blood pressure in subgroups

Figure 3 presented the associations of FBG with SS and ΔBP_1 in participants with different characteristics. With every IQR increase in FBG, the adjusted OR for SS prevalence and adjusted β for ΔBP_1 (ΔMAP_1 , ΔSBP_1 and ΔDBP_1) in the subgroups of youngers (OR = 1.161, β = 0.519, 0.710 and 0.422), females (OR = 1.155, β = 0.516, 0.823 and 0.364), hypertensives (OR = 1.121, β = 0.382, 0.587 and 0.281), non-diabetics (OR = 1.194, β = 0.610, 0.597 and 0.618), non-current smokers (OR = 1.150, β = 0.443, 0.650 and 0.342) and non-current drinkers (OR = 1.165, β = 0.493, 0.746 and 0.368) were all significant and stronger than the corresponding subgroups. However, no significant relationship between FBG and BP changes during diuretic shrinkage was observed in most subgroups (**Supplementary Fig. 2**).

Sensitive analysis

The associations between FBG with SS, ΔBP_1 , and ΔBP_2 were also analyzed after excluding patients (721 patients) who received antidiabetic drugs or antihypertensive medicines (Table 4 and **Supplementary Table 2**). The positive dose-response associations between FBG with SS prevalence, or with ΔBP_1 were all slightly changed, while the results still significant. In Table 4, when compared to participants in the first FBG quartile (Q_1), the adjusted ORs for SS prevalence in Q_2 , Q_3 and Q_4 were all elevated slightly (P for trend < 0.001). Meanwhile, when compared to NFG individuals, the adjusted ORs for SS prevalence in patients with IFG and diabetes increased slightly (P for trend < 0.001).

Table 4

Associations between FBG with SS and ΔBP_1 after excluding patients who received antidiabetic drugs or antihypertensive medicines.

FBG (mmol/L)	<i>N</i>	OR (95% CI) for SS ^a	β (95% CI) for ΔMAP_1^b	β (95% CI) for ΔSBP_1^b	β (95% CI) for ΔDBP_1^b
Per IQR increase	1330	1.141 (1.052, 1.238) [*]	0.391 (0.143, 0.640) [*]	0.413 (0.023, 0.803) [*]	0.381 (0.138, 0.622) [*]
Quartiles					
Q ₁ (~ 5.00)	357	1.000	0	0	0
Q ₂ (5.00 ~ 5.44)	364	0.856 (0.607, 1.208)	-0.162 (-1.126, 0.803)	-0.667 (-2.184, 0.849)	0.091 (-0.850, 1.032)
Q ₃ (5.44 ~ 6.19)	332	1.380 (0.983, 1.937)	0.886 (-0.103, 1.874)	0.682 (-0.872, 2.236)	0.988 (0.023, 1.952) [*]
Q ₄ (6.19 ~)	277	1.698 (1.191, 2.421) [*]	1.385 (0.341, 2.428) [*]	1.345 (-0.296, 2.985)	1.405 (0.386, 2.423) [*]
<i>P</i> for trend		< 0.001	0.002	0.048	0.002
Clinical classifications					
NFG (~ 6.11)	1030	1.000	0	0	0
IFG (6.11 ~ 7.00)	135	1.325 (0.887, 1.980)	0.375 (-0.811, 1.560)	-0.407 (-2.268, 1.453)	0.766 (-0.392, 1.923)
Diabetes (7.00 ~)	165	1.924 (1.347, 2.748) ^{**}	1.722 (0.633, 2.811) [*]	2.584 (0.876, 4.293) [*]	1.291 (0.227, 2.354) [*]
<i>P</i> for trend		< 0.001	0.003	0.011	0.010
IQR, interquartile range; FBG, fasting blood glucose; NFG, normal fasting glucose; IFG, impaired fasting glucose; SS, salt sensitive; ΔBP_1 , change of blood pressure due to saline loading; ΔMAP_1 , change of mean arterial pressure due to saline loading; ΔSBP_1 , change of systolic blood pressure due to saline loading; ΔDBP_1 , change of diastolic blood pressure due to saline loading.					
^a , Statistical testing by multiple logistic regression analyses.					
^b , Statistical testing by multiple linear regression analyses.					
Adjusted for age, sex, sleep, current smoking, drinking, triglycerides, low density lipoprotein cholesterol and baseline mean arterial pressure.					
*, <i>P</i> < 0.05; **, <i>P</i> < 0.001.					

Discussion

Our study found that a significant positive linear dose-response association between FBG and SSBP in 2051 Chinese adults from the EpiSS study. The associations of FBG with SS prevalence or all BP changes were significantly in saline loading period but non-significantly in diuretic shrinkage period. For every IQR increase in FBG, the SS prevalence was increased by 14%, and ΔMAP_1 , ΔSBP_1 and ΔDBP_1 increased by 0.421 mmHg, 0.589 mmHg and 0.340 mmHg, respectively. Meanwhile, we detected that the ΔMAP_1 increased by 0.973 mmHg and 1.449 mmHg in IFG and diabetic patients compare to NFG individuals. Furthermore, in stratified analyses, we found that the above associations were stronger in youngsters (age < 60 years old), females, hypertensives, non-diabetics, non-current smokers and non-current drinkers than those in the corresponding subgroups. Our results supported that blood glucose could be an independent risk factor of SSBP.

Although the exact mechanisms underlying the relationship of the blood glucose with SSBP is unclear, several researches suggested it may be linked to insulin resistance. Insulin resistance is associated with hyperinsulinemia and hyperglycemia, under insulin resistance, the target cells fail to respond to ordinary levels of circulating insulin thus higher concentrations of insulin are required for a normal response [35]. Meanwhile, the impairment of blood glucose uptake in muscle and an increased gluconeogenesis by the liver resulting in hyperglycemia [36]. Hyperglycemia stimulates the reabsorption of sodium. In general, kidneys reabsorb the same amount of blood glucose as they filter each day as to prevent valuable energy from being lost in the urine. Most of the capacity for renal glucose reabsorption is provided by sodium glucose cotransporter (SGLT) 2 in proximal tubule. However, hyperglycemia could enhance the glucose filtration and increase capacity of glucose/sodium reabsorption [22]. SGLT2 inhibitors, a kind of hypoglycemic drugs, could suppress the cotransport of glucose coupled with sodium and significantly attenuated the high salt-induced elevation of BP [37]. Therefore, many studies performed a series of analyses to uncover the relationships between blood glucose and/or insulin resistance with SSBP.

Studies of the associations between salt sensitivity and insulin resistance have yielded contradictory results. Maaten *et al.* [38] and Dengel *et al.* [39] supported that insulin resistance was negatively correlated with salt sensitivity, but Bigazzi *et al.* [40] and Giner *et al.* [41] observed contrary results. The reasons for these apparent discrepancies are not exactly known but may be related to differences in study populations and study methods. Previous studies focusing on the association between FBG and SSBP obtained consistent results. In animal study, high sucrose diets could increase BP of SS rats [42], and the moderate fructose-enriched diet also stimulates salt-sensitive hypertension in rats [43]. Somova *et al.* observed Dahl salt-sensitive rats significantly decreased blood glucose utilization and clearance [44]. Ilhami *et al.* clarified that basal blood glucose level was significantly higher in SS than in SR rats [45]. In human, Sharma *et al.* [16, 19], Egan *et al.* [17] and Galletti *et al.* [18] uncovered that the FBG was higher in SS individuals than in SR group. This study included adequate samples (n = 2051) and found that the FBG level in SS patients was significantly higher than that in SR individuals. Our analysis supported the previous findings and provided clues to the positive correlation between blood glucose and SSBP.

SSBP is also reported to be elevated in patients with diabetes [13]. The current study observed the prevalence of diabetes in SS patients significantly higher than that in SR individuals. However, we considered that using blood glucose as a risk factor of SSBP and as the basis of preventive strategies for SS is of greater clinical significance than diabetes, since hyperglycemia plays a key role in the genesis of SS in patients with type 2 diabetes [22]. And, we found evidence of significant positive associations between FBG with prevalence of SS ($OR = 1.140$) or with ΔBP_1 (β for ΔMAP_1 , ΔSBP_1 and $\Delta DBP_1 = 0.421$, 0.589 and 0.340). Our results are consistent with previous reports [40, 46] and clarified that blood glucose level could be an independent risk factor for SS.

The present study further demonstrated that there were positive dose-response associations between blood glucose with SS prevalence or with ΔBP_1 in 2051 participants. For every IQR increase in FBG, the SS prevalence and ΔBP_1 significantly increased for a trend. It was worth noting that compared to participants with $FBG < 5.00$ mmol/L (Q_1), both the SS prevalence and the ΔBP_1 showed significantly elevated in the subjects with $5.44 \leq FBG < 6.19$ mmol/L (Q_3) and $FBG > 6.19$ mmol/L (Q_4). And the value of 5.44 mmol/L is even slightly below the diagnostic criteria for IFG of 6.11 mmol/L. Consistently, the ΔBP_1 of IFG participants also significantly increased when compared with NFG individuals. These results suggested that relatively higher glucose, though not diagnosed as diabetic, could also increase the SSBP. We highlighted that controlling the elevation of blood glucose in the early stage might be much more important for preventing SS. Our results need to be validated in more larger population association studies.

We further analyzed the associations between FBG with SSBP after stratified participants according to variables including sex, age, obesity, hypertension, diabetes, smoking and drinking to determine the sensitive population. Our results suggested that the effects of blood glucose on SSBP were a little different in population with different characters. The associations of FBG with SSBP in youngsters (age < 60 years old), females, hypertensives, non-diabetics, non-current smokers and non-current drinkers were more significant than the corresponding subgroups, which suggested that these sensitive population should pay more attention to the effect of blood glucose on SS.

Some strengths and limitations of the current study should be acknowledged. This is the first epidemiologic study based on general population to focus on the associations between blood glucose with the SS or with the BP changes during acute salt load period and diuresis shrinkage period. This study included a large sample size and meticulously controlled conditions, which made the result of statistical analysis more persuasive. Our results uncovered the positive dose-response association between blood glucose and SSBP in population and highlighted that controlling the elevation of blood glucose in the early stage might be much more important for preventing SS. Furthermore, we performed stratified analysis and found the role of blood glucose as an independent risk factor for SS, especially in youngsters, females, hypertensives, non-diabetics, non-current smokers and non-current drinkers. Some scholars claimed that acute salt loading has adverse cardiovascular effects [47], therefore we developed a set of strict inclusion criteria for study subjects, and there was no side effect occurred during saline

loading. The limitations are as follows, although the methods for determining SSBP are not uniform at present, the dietary intervention methods are more accurate than the acute saline load test methods; this is a cross-sectional study and lack of the ability for causal inference analyses like prospective cohort studies, so the causal association between blood glucose and salt sensitivity is not yet available; blood glucose could affect by renal function and insulin resistance, but we didn't take them into concern due to lack of data; participants were all from two cities in northern China, which may affect the extrapolation of results.

Conclusions

In conclusion, our findings suggest that elevated blood glucose is an independent, dose-dependent risk factor for salt sensitivity of blood pressure, especially in younger (age < 60 years old), females, hypertensives, non-diabetics, non-current smokers and non-current drinkers. In addition, relatively higher blood glucose, though not diagnosed as diabetic, might contribute to the salt sensitivity of blood pressure, which highlighted that controlling the elevation of blood glucose in the early stage might be much more important for preventing salt sensitive.

Abbreviations

SSBP, salt sensitivity of blood pressure; SS, salt sensitive; SR, salt resistant; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FBG, fasting blood glucose; NFG, normal fasting glucose; IFG, impaired fasting glucose; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; WHR, waist-to-hip ratio; EpiSS, study of systemic epidemiology of salt sensitivity; MSAOSL-DST, modified Sullivan's acute oral saline load and diuresis shrinkage test; SGLT2, sodium glucose cotransporter 2; IQR, interquartile range; RCS, restricted cubic spline; OR, odds ratio; β , beta coefficient; 95%CI, 95% confidence interval.

Declarations

Ethics approval and consent to participate. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Capital Medical University, Beijing, China. Written informed consent was obtained from all subjects before their enrollment in this study.

Consent for publication. Not applicable.

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 Interest. The authors have no conflicts of interest to declare.

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Authors' contributions. All authors completed the sample collection together. Wenjuan Peng analyzed the data and wrote the manuscript. Ling Zhang designed the study and revised the manuscript.

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Figures

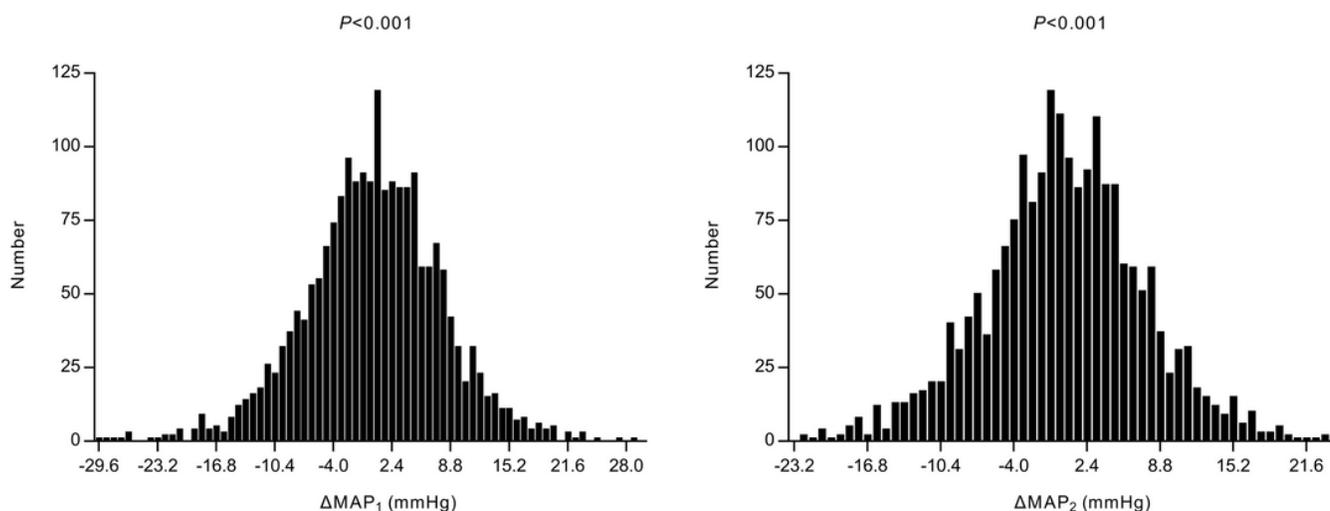


Figure 1

The distribution of the change of mean arterial pressure during MSAOSL-DST. MSAOSL-DST, modified Sullivan’s acute oral saline load and diuresis shrinkage test; ΔMAP_1 , change of mean arterial pressure due to saline loading; ΔMAP_2 , change of mean arterial pressure due to diuretic shrinkage.

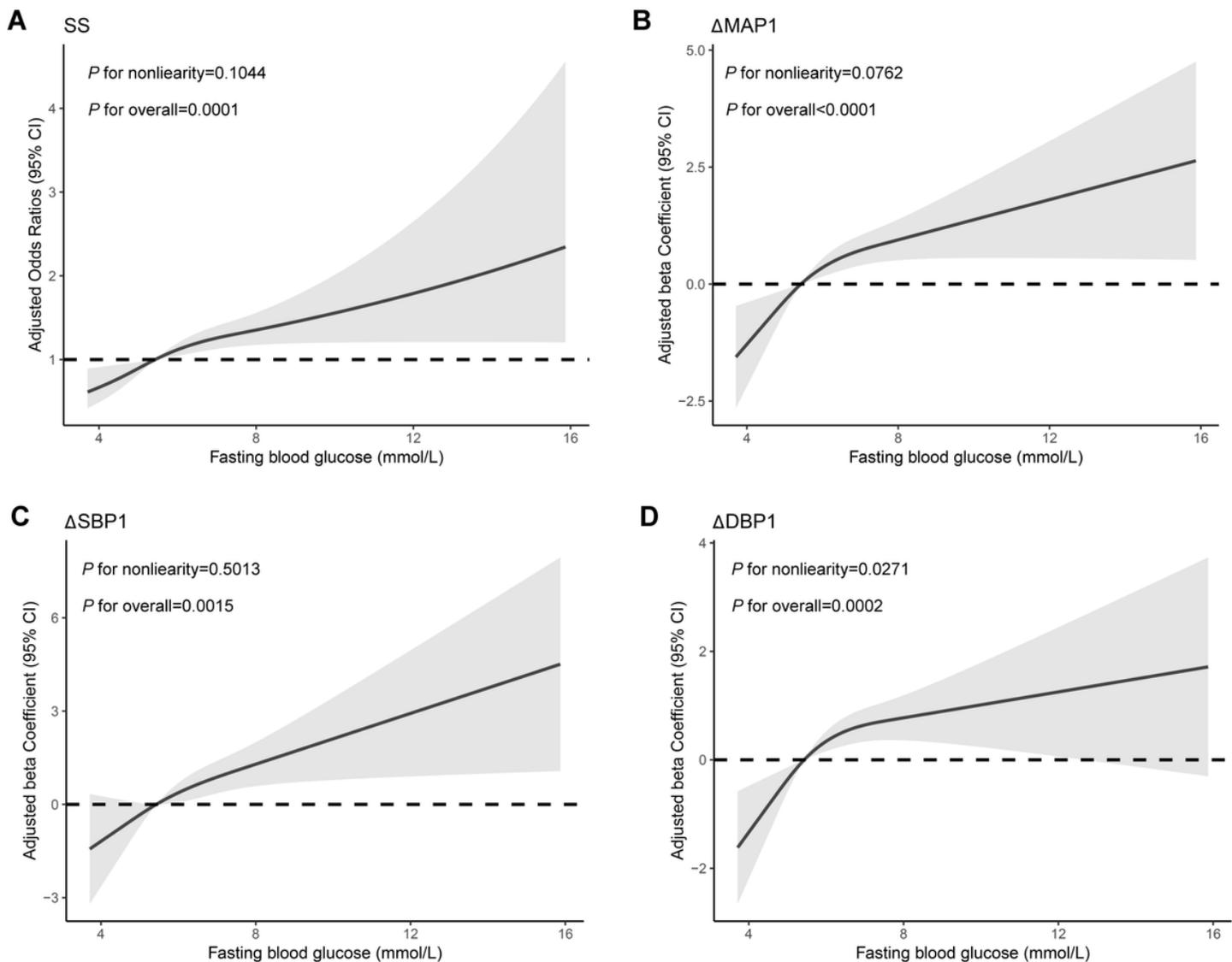


Figure 2

The dose-response associations between fasting blood glucose and salt sensitivity of blood pressure. (A), fasting blood glucose and SS; (B), fasting blood glucose and Δ MAP1; (C), fasting blood glucose and Δ SBP1; (D), fasting blood glucose and Δ DBP1. The spline regression model was adjusted by age, sex, sleep, smoking, drinking, triglycerides, low density lipoprotein cholesterol and baseline mean arterial pressure. SS, salt sensitive; Δ MAP1, change of mean arterial pressure during saline loading; Δ SBP1, the change of systolic blood pressure during saline loading; Δ DBP1, the change of diastolic blood pressure during saline loading.

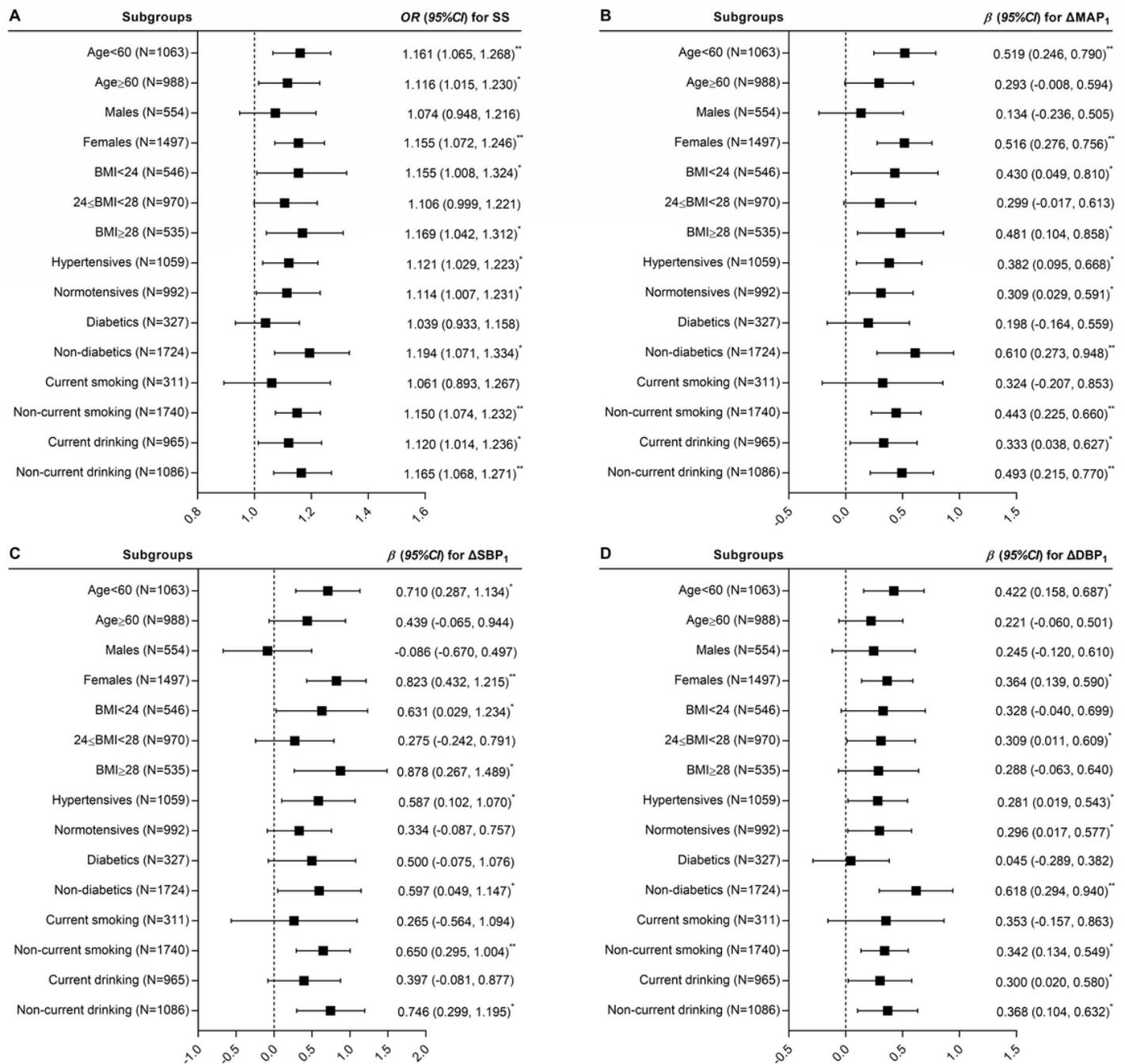


Figure 3

The association between FBG (per IQR increase) with SS or ΔBP₁ in different subgroups. (A), fasting blood glucose and SS; (B), fasting blood glucose and ΔMAP₁; (C), fasting blood glucose and ΔSBP₁; (D), fasting blood glucose and ΔDBP₁. FBG, fasting blood glucose; SS, salt sensitive; ΔBP₁, change of blood pressure due to saline loading; ΔMAP₁, change of mean arterial pressure due to saline loading; ΔSBP₁, change of systolic blood pressure due to saline loading; ΔDBP₁, change of diastolic blood pressure due to saline loading. Statistical analysis by multiple logistic regression analyses (A) and multivariable linear regression analyses (B, C and D). The model was adjusted by age, sex, sleep, smoking, drinking,

triglycerides, low density lipoprotein cholesterol and baseline mean arterial pressure. $P < 0.05$ was considered statistically significant. *, $P < 0.05$; **, $P < 0.001$.

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