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# Serum γ-glutamyltransferase levels and obesity status changes the risk of prehypertension in Chinese adults

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ABSTRACT

*Objective:* It's well known that γ-Glutamyltransferase (γ-GGT) and obesity plays an important role in the development of preHT. However, the effect of γ-GGT on preHT in populations with different obesity status remains unclear.

*Methods:* From February 2014 to January 2018, a total of 20,368 participants were enrolled in this study after excluding those with hypertension and liver diseases. Fasting blood samples were collected to measure γ-GGT and blood lipid levels and glucose indices. Demographic and clinical parameters such as sex, age, height, weight, neck circumference (NC), waist circumference (WC), hip circumference (HC), and body fat ratio (BFR); and information on smoking and alcohol consumption were collected by trained medical professionals.

*Results:* Participants were divided into three groups based on obesity status. The prevalence of preHT was 83.5 % in the obesity group was higher than that in the overweight group (58.9 %) and the normal group (47.1 %). γ-GGT in different categories of obesity indices were significantly different, and higher obesity indices were found with higher γ-GGT levels. The interaction of γ-GGT and obesity indices such as NC, WC, HC, and BFR on the prevalence of preHT was significant ($P = 0.028$, 0.002, 0.007, and 0.034, respectively). Serum γ-GGT was found to be positively associated with preHT in participants with normal and overweight body mass indices.

*Conclusion:* Our results indicate that γ-GGT is a risk factor for preHT in participants who are nonobese, and that the obesity indices NC, WC, HC, BFR, and γ-GGT were contributing factors in increasing the risk of preHT.

## 1. Introduction

According to the Seventh Report of the Joint National Committee (JNC-7) criteria (Chobanian et al., 2003), prehypertension (preHT) is a clinical condition characterized by systolic blood pressure (SBP) of 120–139 mm Hg and diastolic blood pressure (DBP) of 80–89 mm Hg (Parthaje et al., 2016). PreHT is a common public health concern worldwide and a risk factor for cardiovascular disease, cerebrovascular disease (stroke), and end-stage renal disease (Konlan et al., 2022; Strilchuk et al., 2020). The Strong Heart Study reported that the incidence of clinical hypertension (HT) in patients with preHT reached 38 % (De Marco et al., 2009). Moreover, results of the Framingham Heart Study suggested that the risk of HT among patients in the preHT group was twice that of patients in the normotensive group (Vasan et al., 2001). Studies have also confirmed that the risk of cardiovascular disease is 1.8 times higher in patients with preHT than in those who are normotensive (Zhang et al., 2006). Furthermore, the body mass index (BMI), body fat ratio (BFR), neck circumference (NC), hip circumference (HC), and waist circumference (WC) are significantly higher in subjects with HT, revealing that being overweight or obese are characteristics that mainly accompany this condition (Albanese et al., 2022). Associations of elevated BMI with blood pressure that is above the optimal

*Abbreviations:* BP, Blood pressure; γ-GGT, γ-glutamyltransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic BP; DBP, diastolic BP; preHT, prehypertension; HT, hypertension; WHR, waist-to-hip ratio; WC, waist circumference; ALT, alanine aminotransferase; NC, neck circumference; AST, aspartate aminotransferase; TC, total cholesterol; TG, triglyceride.

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range reinforce obesity as a risk factor for preHT and subsequent HT (Albanese et al., 2022). However, whether preHT alone or related risk factors are more important in determining the optimal preventive strategy remains unknown.

Serum γ-glutamyltransferase (γ-GGT) is a glycoprotein consisting of two proteins and having a molecular weight of 68 kDa (Lee et al., 2004). It is found in the liver, kidneys (Xavier Júnior et al., 2022); lungs (Lee et al., 2021); pancreas (Long et al., 2017), and vascular endothelium (Perticone et al., 2020). γ-GGT has been used as a biological marker to indicate alcohol intake or liver cell damage (AlSaid et al., 2015). Studies suggest that serum γ-GGT levels links with an increased risk of stroke and myocardial infarction (Li et al., 2022). These associations are partially explained by known associations of γ-GGT with factors such as changes in blood lipids, BMI, HT, insulin resistance, or type 2 diabetes and nonalcoholic fatty liver disease, that are recognized in the pathogenesis of cardiovascular diseases. Researchers in China have found that monitoring γ-GGT levels might help in the prevention and monitoring of preHT, and obesity and elevated γ-GGT levels are independent risk factors for preHT (Zhu et al., 2014; Chun et al., 2013).However, the interaction between obesity and γ-GGT in preHT is unclear. In this study, we analyzed serum γ-GGT levels in patients with preHT and different obesity statuses to determine their association and clinical significance in the prevention and control of related diseases.

## 2. Methods

### 2.1. Patient recruitment and exclusion criteria

This study was carried out from February 2014 to January 2018 on 20,368 subjects admitted to the second people's Hospital of Lianyungang. Participants' ages ranged from 20 to 88 years. Ethics approval was obtained from the Ethics Committees of the second people's hospital of Lianyungang, and the study was conducted in accordance with the principles of the Declaration of Helsinki (2001). Written informed consent was obtained from all participants.

The diagnostic criteria for preHT were based on the JNC-7 criteria (Chobanian et al., 2003). Normal blood pressure (BP) was defined as not being on antihypertensive medication, and having SBP $<$ 120 mm Hg and DBP $<$ 80 mm Hg. PreHT was defined as not being on antihypertensive medication and having SBP of 120–139 mm Hg or DBP of 80–89 mm Hg. Participants with liver diseases such as chronic viral hepatitis, autoimmune liver disease, and secondary causes of liver steatosis (e.g., the use of systemic corticosteroids), and those with incomplete data were excluded.

All clinical and laboratory data were obtained from an electronic database and patient medical records. The physical examination form comprised a unified design. Qualified and trained physicians recorded the general characteristics, sex, age, and past history of diseases. We chose five indices to reflect the obesity status, weight, WC, NC, HC, and BFR, and used the measuring methods as detailed subsequently. For equal weight distribution, subjects were made to stand with their feet 25–30 cm apart. During steady breathing, the WC was measured in the middle of the iliac crest and the lower margin of the 12th rib; NC was measured with a flexible tape in a standardized manner horizontally above the cricothyroid cartilage to 1-mm accuracy, and in men, just below the laryngeal prominence (Ben-Noun et al., 2001); the hip circumference was measured at the most prominent part of the pelvis. The BFR was assessed using the electrical impedance method with an Inbody 3.0 body composition analyzer (Biospace, Seoul, Korea). Participants were in a fasted state, calm, and not wearing shoes or socks during the measurements. All indicators were measured three times and the average value was used: BMI = weight (kg)/height ($m^2$). After the subject had rested for 15 min, SBP and DBP were measured by well-trained personnel using a standardized aneroid sphygmomanometer and cuffs of appropriate sizes with the subjects' arms placed at heart level while in a sitting position. Three measurements were taken and the mean was calculated.

Blood from the elbow vein was collected in the morning on an empty stomach, after fasting for more than 10 h after dinner. Serum γ-GGT, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG) levels, and other biochemical indices were measured using enzymatic methods with a Hitachi 7600 automatic biochemical analyzer. The smoking status of "smokers" meant that individuals had consumed more than 100 cigarettes in the past year. Drinking status of "yes" meant that individuals had consumed more than 500 mL alcohol in the past year.

Subjects were categorized into the following 4 groups based on physical examination data and γ-GGT levels: Q1, GGT $\leq$ 12.0 U/L; Q2, 12.0 U/L $<$ GGT $\leq$ 17.0U/L; Q3, 17.0 U/L $<$ GGT $\leq$ 27.0U/L; Q4, GGT $>$ 27.0 U/L. They were also categorized into the following 3 groups based on BMI (Chinese Society of Health Management, 2018; Pan et al., 2021): normal group, 18.0 kg/$m^2$ $<$ BMI $\leq$ 24 kg/$m^2$; overweight group, 25 kg/$m^2$ $<$ BMI $\leq$ 27 kg/$m^2$; obesity group, BMI $\geq$ 28 kg/$m^2$. The prevalence of preHT in each group was assessed.

### 2.2. Statistical analysis

The measurement data are expressed as the median and IQR. One-way analysis of variance was used to compare differences among various metabolic indicators at different BMI levels. Chi-square tests were conducted to examine the differences in preHT prevalence across various γ-GGT categories. The interaction between obesity indices and γ-GGT for the risk of preHT was explored using binary unconditional logistic regression. The association between γ-GGT and the risk of preHT in different BMI categories was analyzed using the restricted cubic spline plot. The statistical software SAS 9.1.3 was used for statistical analysis. Two tailed $P < 0.05$ was considered statistically significant.

## 3. Results

### 3.1. Participants and baseline characteristics

Table 1 shows that indicators such as age and BP, and blood lipid, uric acid, AST, and ALT levels varied at different BMI levels. In addition, these differences showed a linear trend with increasing BMI. In particular, HDL levels decreased with increasing BMI. Among the three groups, the obesity group had the highest prevalence of preHT and the normal group had the lowest prevalence; 83.5 % of subjects had preHT in the obesity group. Smoking status and alcohol consumption were significantly different at different BMI levels.

### 3.2. γ-GGT at different levels of obesity indices and among both sexes

The scatter plots were to show that the associations between serum γ-GGT and obesity indices in both sexes. Males had higher γ-GGT levels than women, and subjects with higher obesity indices also had higher γ-GGT levels (Fig. 1).

### 3.3. Prevalence of preHT at different BMIs and serum γ-GGT levels

The prevalence of preHT increased with an increase in BMI, regardless of γ-GGT levels. Moreover, the prevalence of preHT increased with increasing BMI at all four γ-GGT levels, and this increase was statistically significant (Table 2). In the normal and overweight groups, the prevalence of preHT increased with increasing γ-GGT levels; however, this trend was not observed in the obesity group.

### 3.4. Serum γ-GGT levels and the risk for preHT at different BMIs

Serum γ-GGT levels associated positively with preHT at normal and overweight BMI levels (Table 3). Furthermore, this independent risk

**Table 1**
The distribution of selected socio-demographic, serological indicator and anthropometric characteristics of participants with aged 20–88 years in study urban areas of Lianyungang, China, 2018 (N = 20,368).

| | BMI | | | |
|---|---|---|---|---|
| | Normal | Overweight | Obesity | *P* |
| n | 11,127 | 7336 | 1905 | |
| Sex(male), n(%) | 4759(43.2) | 3282(44.8) | 876(45.9) | <0.001[a] |
| Age(years) | 42.0[38.0 ~ 47.0] | 44.0[39.0 ~ 51.0] | 46.0[39.0 ~ 52.0] | <0.001[b] |
| SBP (mmHg) | 114.0 [105.0 ~ 120.5] | 120.0[114.0 ~ 128.0] | 123.0 [118.0 ~ 130.0] | <0.001[b] |
| DBP (mmHg) | 74.0[68.0 ~ 80.0] | 78.0[72.0 ~ 82.0] | 80.0[75.0 ~ 83.0] | <0.001[b] |
| FPG(mmol/L) | 4.9[4.6 ~ 5.2] | 5.0[4.7 ~ 5.4] | 5.1[4.8 ~ 5.5] | <0.001[b] |
| Fins(μU/ml) | 6.4[4.6 ~ 8.7] | 8.8[6.3 ~ 11.8] | 13.3[9.8 ~ 17.2] | <0.001[b] |
| TC(mmol/L) | 4.9[4.4 ~ 5.5] | 5.0[4.5 ~ 5.7] | 5.1[4.7 ~ 5.7] | <0.001[b] |
| TG (mmol/L) | 0.9[0.6 ~ 1.4] | 1.4[0.9 ~ 2.0] | 1.8[1.3 ~ 2.5] | <0.001[b] |
| HDL cholesterol (mmol/L) | 1.4[1.2 ~ 1.6] | 1.2[1.0 ~ 1.3] | 1.1[0.9 ~ 1.2] | <0.001[b] |
| LDL cholesterol (mmol/L) | 2.8[2.4 ~ 3.4] | 3.0[2.6 ~ 3.5] | 3.1[2.6 ~ 3.5] | <0.001[b] |
| SUA(μmol/L) | 208.7 [189.4 ~ 274.2] | 269.3[214.7 ~ 304.2] | 310.4 [247.0 ~ 481.2] | <0.001[b] |
| ALT(U/L) | 8.9[4.1 ~ 24.3] | 15.8[8.7 ~ 29.4] | 21.3[14.2 ~ 49.7] | <0.001[b] |
| GOT(U/L) | 11.4[7.6 ~ 29.9] | 16.1[9.4 ~ 37.6] | 19.1[11.3 ~ 48.4] | <0.001[b] |
| γ-GGT(U/L) | 15.0[12.0 ~ 22.0] | 24.0[17.0 ~ 39.0] | 33.0[22.0 ~ 50.0] | <0.001[b] |
| Smoking,n(%) | 2331(20.9) | 1395(19.0) | 384(20.2) | 0.006[a] |
| No-smoking, n(%) | 8796(79.1) | 5941(81.0) | 1521(79.8) | |
| Drinking, n(%) | 4345(39.1) | 3015(41.1) | 856(44.9) | <0.001[a] |
| No-drinking, n(%) | 6782(60.9) | 4321(58.9) | 1049(55.1) | |
| Prehypertension, n (%) | 5240(47.1) | 5236(71.4) | 1590(83.5) | <0.001[a] |
| Normotension, n(%) | 5891(52.9) | 2100(28.6) | 315(16.5) | |

Notion: a: The Chi-square test; b: The ANOVA test; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; Fins: fasting insulin; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SUA: serum uric acid; ALT: alanine transaminase; GOT: glutamic oxalacetic transaminase; γ-GGT: γ-gamma glutamyl transpeptidase.

remained after adjusting for risk factors such as age, and blood glucose, blood lipid, and uric acid levels. Nonetheless, serum γ-GGT was not associated with the risk of preHT in subjects who were obese.

### 3.5. Interaction effect on the prevalence of preHT

Fig. 2 shows the interaction between obesity indices and γ-GGT with respect to the prevalence of preHT. Subjects with the highest obesity indices and highest γ-GGT levels were found to have the highest prevalence of preHT. Significant interactions on preHT were found between NC and γ-GGT (P = 0.028, Fig. 2A), WC and γ-GGT (P = 0.002, Fig. 2B), HC and γ-GGT (P = 0.007, Fig. 2C) and BFR and γ-GGT (P = 0.034, Fig. 2D).

### 3.6. Serum γ-GGT level influences the prevalence of preHT at different BMIs

We assessed the association between γ-GGT and the prevalence of preHT using the restricted cubic spline plot in different BMI categories. The risk of preHT was found to increase with increasing γ-GGT levels (Fig. 3). This trend was observed in subjects who were of normal weight or overweight; however, there was no relationship between γ-GGT and the risk of preHT in subjects who were obese (Fig. 3D).

## 4. Discussion

In this study, we analyzed the association of serum γ-GGT levels in participants with preHT and different obesity indices. Our study shows that the prevalence of preHT in normal and overweight categories of BMI increases with increasing γ-GGT levels, but in the obesity category, the relationship between the risk of preHT and γ-GGT was not evident although the enrolled subjects had the highest prevalence of preHT. This finding may be attributed to the interaction between BMI and γ-GGT leading to the risk of preHT. Except for BMI, which reflects the complete obesity status of an individual, we found that obesity indices such as NC, WC, HC, and BFR were associated with γ-GGT levels, and that the interaction of obesity indices and γ-GGT played a role in the prevalence of preHT. To the best of our knowledge, this is the first report to show that the risk of preHT caused by serum γ-GGT levels gradually decreases with increasing BMI and that the interaction of serum γ-GGT and obesity indices has an effect on the prevalence of preHT in Chinese adults.

HT is currently one of the most serious public health problems worldwide (Nugroho et al., 2022; Pattanittum et al., 2021), and subsequent cardiovascular, cerebrovascular, and end-stage renal diseases could impose a significant burden on patients (Ngamjarus et al., 2010). In 2003, the definition of preHT was first proposed in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (Chobanian et al., 2003). Studies have confirmed that preHT is more likely to progress to clinical HT than normal BP (Banga et al., 2019). In China, the prevalence of preHT and HT is increasing with the development of society and the aging of the population (Wang et al., 2019). Additionally, clustering of risk factors for cardiovascular disease was observed in Han and Mongolian adults with preHT (Li et al., 2017). Among the many risk factors that can lead to preHT, the role of obesity factors has gradually surfaced. Previous studies have confirmed that every 10 % increase in BMI can lead to an increase of 2.75 mm Hg of SBP (Yang et al., 2023). Moreover, the risk of HT within 4 years increases by 50 % in men and 40 % in women with every 3 % increase in BMI (Timpson et al., 2009). The indices reflective of obesity in individuals, such as NC, WC, HC, and BFR, have been proven to be positively associated with HT and preHT in previous studies. Our results showed that higher obesity indices were associated with a higher prevalence of preHT. Except for the obesity indices, γ-GGT was also a risk of HT.

Studies have shown that an increase in serum γ-GGT in healthy individuals is a risk factor for all-cause death and cardiovascular disease death (Kengne et al., 2012; Ninomiya et al., 2024:e032276.; Wu et al., 2022). Additionally, an increase in serum γ-GGT levels highly links with metabolic syndrome, and metabolic syndrome itself can further promote the occurrence and development of atherosclerosis and cardiovascular diseases (Olszewska-Słonina, 2021). Serum γ-GGT is an important reference diagnostic index indicative of liver disease and disorders of the biliary tract, especially cholestasis (Arora et al., 2019). As γ-GGT is present in cells of the liver, gallbladder, kidneys, pancreas, intestine, heart, brain, and prostate, among others, it has been studied in various contexts. For instance, this enzyme is associated with pancreatitis, myocardial damage, renal failure, and diabetes, or while taking certain drugs (Lee et al., 2004; Perticone et al., 2020; Li et al., 2022).

Although the mechanism of how serum γ-GGT causes preHT is unclear (Takemura et al., 2021), a few explanations have been provided. First, serum γ-GGT is regarded as a reliable marker of oxidative stress (Bulusu and Sharma, 2016). It plays a vital role in maintaining the intracellular defense mechanism by initiating the catabolism of extracellular glutathione (Koenig and Seneff, 2015). γ-GGT is also the main antioxidant in mammalian cells. Studies have shown that the oxidative stress response in vascular smooth muscles and vascular endothelial cells through vasoconstriction and sodium retention can cause an increase in BP (Bulusu and Sharma, 2016). Second, insulin resistance plays

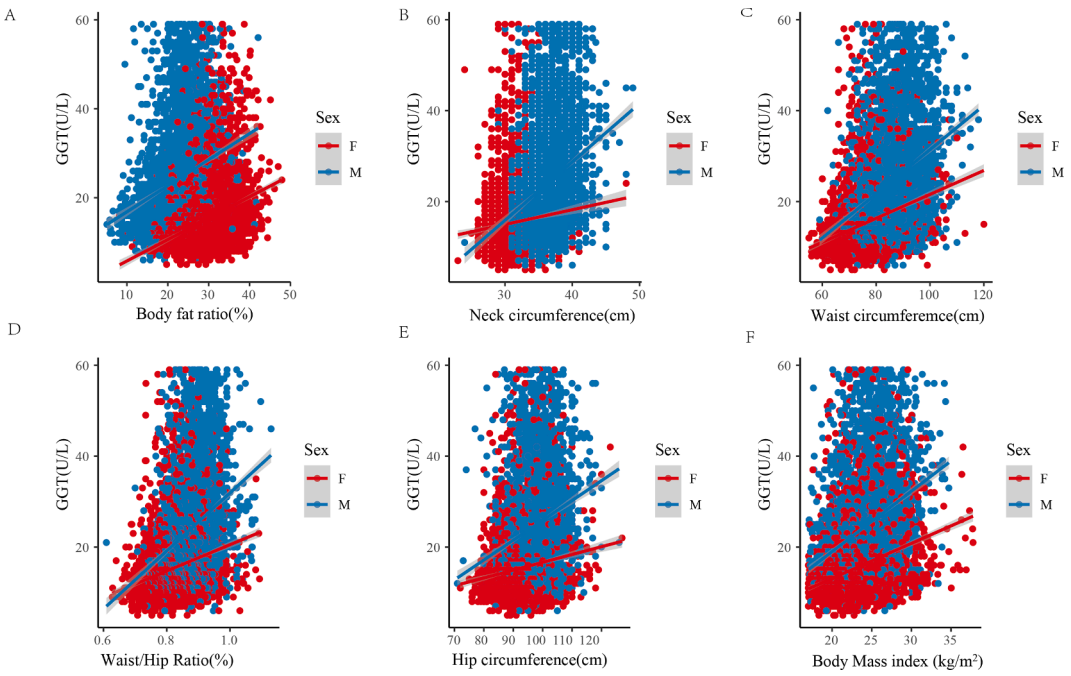


**Fig. 1.** Scatter plot to show that the associations between serum γ-GGT levels and obesity indices among participants aged 20 to 88 in urban areas of Lianyungang, China in 2018, based on both sexes (N = 20,368). **(A)**: The scatter plot of serum γ-GGT levels and BFR in different genders. **(B)**: The scatter plot of serum γ-GGT levels and NC in different genders. **(C)**: The scatter plot of serum γ-GGT levels and WC in different genders. **(D)**: The scatter plot of serum γ-GGT levels and WHR in different genders. **(E)**: The scatter plot of serum γ-GGT levels and HC in different genders. **(F)**: The scatter plot of serum γ-GGT levels and BMI in different genders.

**Table 2**
The chi-square test and linear association test were used to investigate the prevalence of prehypertension among participants aged 20 to 88 in urban areas of Lianyungang, China in 2018, based on different levels of serum γ-GGT and obesity status (N = 20,368).

| | | | BMI | | | |
|---|---|---|---|---|---|---|
| | | | Normal | Overweight | Obesity | *P for trend* |
| γ-GGT | Q1 | Prehypertension, n(%) | 1572(36.8) | 632(60.5) | 95(83.3) | <0.001 |
| | | Normotension, n(%) | 2703(63.2) | 412(39.5) | 19(16.7) | |
| | Q2 | Prehypertension, n(%) | 1483(47.3) | 1060(68.4) | 248(84.1) | <0.001 |
| | | Normotension, n(%) | 1650(52.7) | 489(31.6) | 47(15.9) | |
| | Q3 | Prehypertension, n(%) | 1286(55.7) | 1631(72.2) | 470(81.6) | <0.001 |
| | | Normotension, n(%) | 1021(44.3) | 627(27.8) | 106(18.4) | |
| | Q4 | Prehypertension, n(%) | 899(63.5) | 1913(76.9) | 777(84.5) | <0.001 |
| | | Normotension, n(%) | 517(36.5) | 572(23.1) | 143(15.5) | |
| *P for trend* | | | <0.001 | <0.001 | 0.534 | |

**Table 3**
The multiple Logistic regression analysis was performed to explore the association between serum γ-GGT and the risk of prehypertension among participants aged 20 to 88 in urban areas of Lianyungang, China in 2018, based on different BMI status (N = 20,368).

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| Categories | OR | 95 %C.I | OR | 95 %C.I |
| Normal | 1.450 | 1.397 ~ 1.504 | 1.129 | 1.066 ~ 1.196 |
| Over weight | 1.281 | 1.221 ~ 1.344 | 1.129 | 1.051 ~ 1.212 |
| Obesity | 1.035 | 0.908 ~ 1.180 | 0.948 | 0.794 ~ 1.132 |

Model 1: No adjustment.
Model 2: Adjustment for sex, age, FBG, TG, TC, HDL, LDL, UA, smoking and alcohol consumption.

an important role in the relationship between serum γ-GGT and preHT, because serum γ-GGT is an important indicator of fatty liver and insulin resistance (Bulusu and Sharma, 2016; Koenig and Seneff, 2015). Studies have shown that fat cells secrete leptin to stimulate sympathetic nerves by regulating the secretion of hormones in the hypothalamus, causing rapid heart rhythm and an increase in BP (Machado et al., 2022). In this study, we divided BMI into three levels, namely, normal, overweight, and obesity, and explored the relationship between serum γ-GGT and preHT at these levels. The results showed that at normal BMI, the increase in serum γ-GGT was significant in the prehypertensive phase, suggesting that when the body weight is normal, an increase in serum γ-GGT is one of the causes of preHT. This is because serum γ-GGT reflects the oxidative response in the body. This important indicator of stimulation is more sensitive to the effect of BP when the body weight is normal. Studies have shown that many pathological mechanisms can cause HT, such as increased cardiac output (Khanna et al., 2022); plasma volume expansion (Gyselaers, 2022); sodium retention, sympathetic nerve stimulation and renin-angiotensin-aldosterone system activation (De Bhailis and Hypertension, 2005), insulin resistance, adipokine imbalance, extravascular fat dysfunction, and sleep apnea syndrome in individuals who are considered obese. Inflammation/oxidative stress is one of the pathological mechanisms, but its effect is relatively weakened. This was also reflected in our study. An increase in serum γ-GGT led to a relative lowering of the risk of preHT, although the prevalence in this weight status was the highest (Fig. 3).

Our study had some limitations. First, it was a retrospective survey, and we failed to establish a cause-effect relationship between risk factors

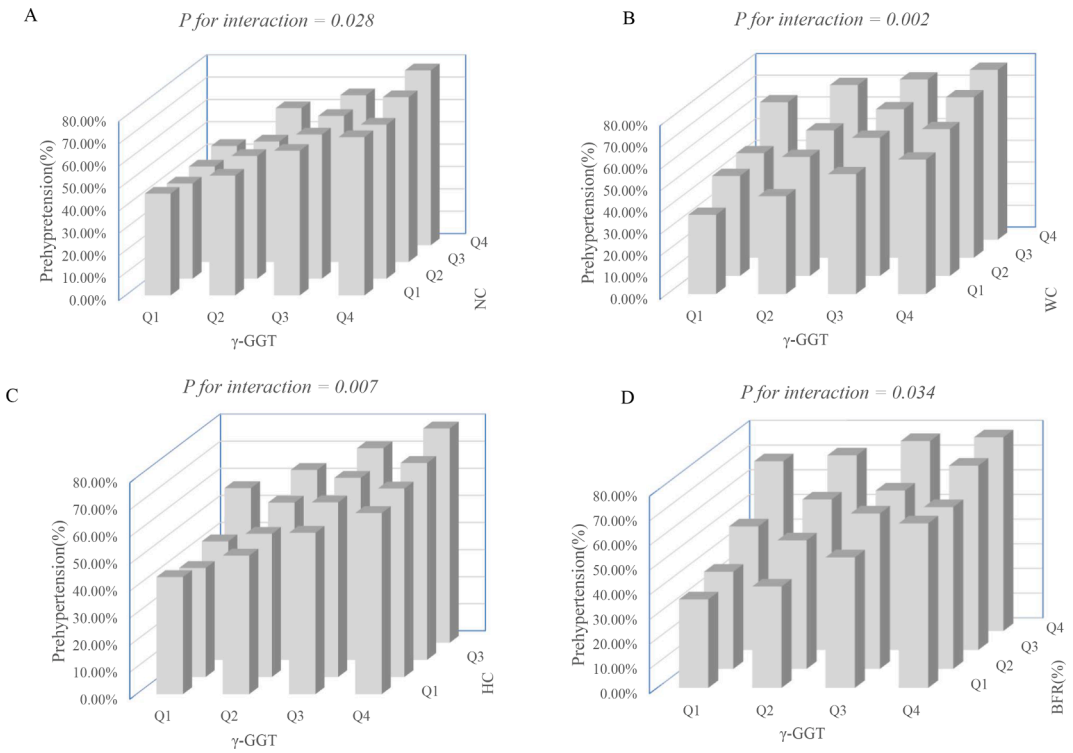


**Fig. 2.** Using the multiple Logistic regression analysis to explore the interaction effect of obesity indices and serum γ-GGT on the prevalence of prehypertension among participants aged 20 to 88 in urban areas of Lianyungang, China in 2018 (N = 20,368). **(A):** Interaction between γ-GGT and NC affects the prevalence of preHT. **(B):** Interaction between γ-GGT and WC affects the prevalence of preHT. **(C):** Interaction between γ-GGT and HC affects the prevalence of preHT. **(D):** Interaction between γ-GGT and BFR affects the prevalence of preHT.

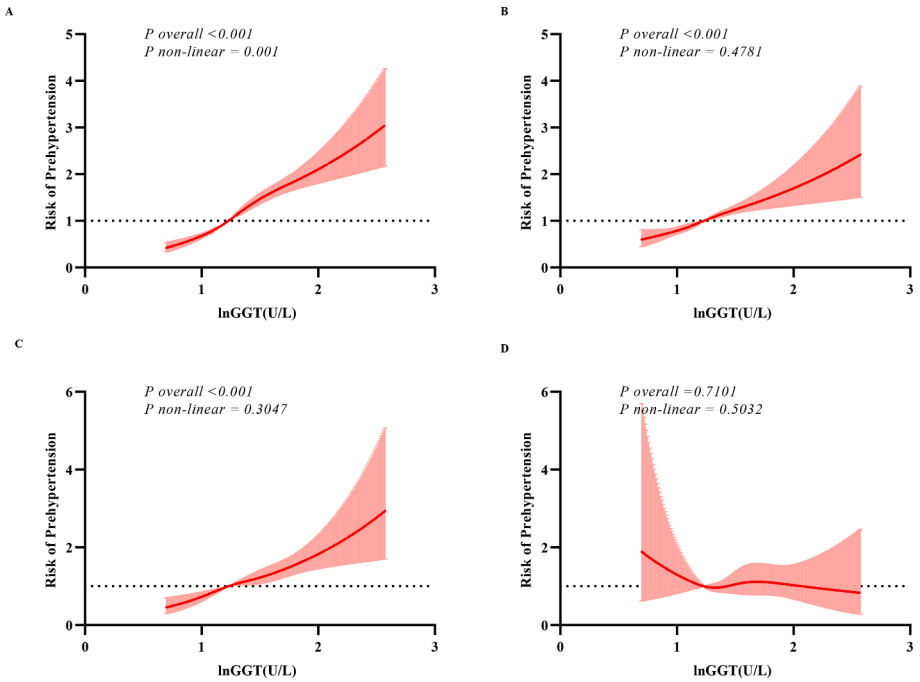


**Fig. 3.** Using the restricted cubic spline plot to explore the relationship between serum γ-GGT and the risk of preHT among participants aged 20 to 88 in urban areas of Lianyungang, China in 2018, based on different BMI categories (N = 20,368). **(A):** Relationship between γ-GGT and the risk of preHT in all participants. **(B):** Relationship between γ-GGT and the risk of preHT in subjects with normal BMI. **(C):** Relationship between γ-GGT and the risk of preHT in subjects with overweight. **(D):** Relationship between γ-GGT and the risk of preHT in subjects with obesity. Note: ln GGT: serum γ-GGT was transferred by ln.

and the development of preHT. Second, there may have been recall bias, resulting in differences in the information provided. Third, this study was performed in the North China and Han nationality population. Although many studies agreed with our result, the causal relationship between γ-GGT and preHT need to verify using experiment or further study.

Our results indicate differences between serum γ-GGT levels and the risk of preHT at different BMI levels, and the positive interaction effect of obesity indices and γ-GGT responsible for the prevalence of preHT. These finds suggest that close attention should be paid to changes in γ-GGT levels and obesity indices in nonobese individuals to prevent the occurrence of preHT.

## 5. Data sharing statement

All data generated or analyzed during this study are included in this manuscript.

## 6. Disclosure

All authors declare that there is no duality of interest associated with this manuscript.

## 7. Ethics approval and consent to participate

The study was reviewed and approved by the ethics committee of the second people's hospital of Lianyungang. The no. of ethics committee approval is 2021103A152.

## CRediT authorship contribution statement

**Zhi Wang:** Writing – original draft, Methodology, Conceptualization. **Dongjun Chen:** Writing – original draft, Formal analysis, Data curation. **Lingling Peng:** Visualization, Investigation, Data curation. **Xian Wang:** Visualization, Software, Data curation. **Qun Ding:** Methodology, Investigation, Data curation. **Liang Li:** Writing – review & editing, Writing – original draft, Software, Data curation, Conceptualization. **Tongdao Xu:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

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## References

Albanese, N.N.Y., Lin, I., Friedberg, J.P., Lipsitz, S.R., Rundle, A., Quinn, J.W., et al., 2022. Association of the built environment and neighborhood resources with obesity-related health behaviors in older veterans with hypertension. Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association. 41 (10), 701–709. https://doi.org/10.1037/hea0001161. PubMed PMID: 35389690, Epub 2022/04/08.

AlSaid, M., Mothana, R., Raish, M., Al-Sohaibani, M., Al-Yahya, M., Ahmad, A., et al., 2015. Evaluation of the effectiveness of Piper cubeba extract in the amelioration of CCl4-induced liver injuries and oxidative damage in the rodent model. Biomed Res Int. 2015, 359358 https://doi.org/10.1155/2015/359358. PubMed PMID: 25654097; PubMed Central PMCID: PMCPMC4310260, Epub 2015/02/06.

Arora, A., Kumar, A., Anand, A.C., Puri, P., Dhiman, R.K., Acharya, S.K., et al., 2019. Indian national association for the study of the liver-federation of obstetric and gynaecological societies of india position statement on management of liver diseases in pregnancy. J. Clin. Exp. Hepatol. 9 (3), 383–406. https://doi.org/10.1016/j.jceh.2019.02.007. PubMed PMID: 31360030; PubMed Central PMCID: PMCPMC6637074, Epub 2019/07/31.

Banga, S., Mungee, S., Patel, A.R., Singh, S., Kizhakekuttu, T.J. Management of resistant hypertension based on recommendations from different guidelines and the systolic blood Pressure Intervention Trial. Cureus. 2019;11(8):e5371. doi: 10.7759/cureus.5371. PubMed PMID: 31612099; PubMed Central PMCID: PMCPMC6784919. Epub 2019/10/16.

Ben-Noun, L., Sohar, E., Laor, A., 2001. Neck circumference as a simple screening measure for identifying overweight and obese patients. Obes. Res. 9 (8), 470–477. https://doi.org/10.1038/oby.2001.61. PubMed PMID: 11500527, Epub 2001/08/14.

Bulusu, S., Sharma, M., 2016. What does serum γ-glutamyltransferase tell us as a cardiometabolic risk marker? Ann. Clin. Biochem. 53 (Pt 3), 312–332. https://doi.org/10.1177/0004563215597010. PubMed PMID: 26139450, Epub 2015/07/04.

Chinese Society of Health Management, 2018. Chinese nutrition society, reproductive medicine branch of china international exchange and promotion association for medicine and healthcare, china health promotion foundation, zhejiang provincial clinical nutrition centerexpert consensus & standard on weight management for overweight or obese people. Chin. J. Health Manage. 12 (1), 200–207. https://doi.org/10.3760/cma.j.issn.1674-0815.2018.03.003.

Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo Jr, J.L., et al., 2003. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 289 (19), 2560–2572. https://doi.org/10.1001/jama.289.19.2560. PubMed PMID: 12748199, Epub 2003/05/16.

Chun, H., Park, S.K., Ryoo, J.H., 2013. Association of serum γ-glutamyltransferase level and incident prehypertension in Korean men. J Korean Med Sci. 28 (11), 1603–1608. https://doi.org/10.3346/jkms.2013.28.11.1603. PubMed PMID: 24265522; PubMed Central PMCID: PMCPMC3835501, Epub 2013/11/23.

De Bhailis, Á.M., Kalra, P.A., 2022. Hypertension and the kidneys. Br. J. Hospital Med. (London, England: 2005) 83, 1–11. https://doi.org/10.12968/hmed.2021.0440. PubMed PMID: 35653320. Epub 2022/06/03.

De Marco, M., de Simone, G., Roman, M.J., Chinali, M., Lee, E.T., Russell, M., et al., 2009. Cardiovascular and metabolic predictors of progression of prehypertension into hypertension: the Strong Heart Study. Hypertension 54 (5), 974–980. https://doi.org/10.1161/hypertensionaha.109.129031. PubMed PMID: 19720957; PubMed Central PMCID: PMCPMC2776057, Epub 2009/09/02.

Gyselaers, W., 2022. Hemodynamic pathways of gestational hypertension and preeclampsia. Am. J. Obstet. Gynecol. 226 (2s), S988–s1005. https://doi.org/10.1016/j.ajog.2021.11.022. PubMed PMID: 35177225, Epub 2022/02/19.

Kengne, A.P., Czernichow, S., Stamatakis, E., Hamer, M., Batty, G.D., 2012. Gamma-glutamyltransferase and risk of cardiovascular disease mortality in people with and without diabetes: pooling of three British Health Surveys. J. Hepatol. 57 (5), 1083–1089. https://doi.org/10.1016/j.jhep.2012.06.034. PubMed PMID: 22796154, Epub 2012/07/17.

Khanna, S., Amarasekera, A.T., Li, C., Bhat, A., Chen, H.H.L., Gan, G.C.H., et al., 2022. The utility of cardiac magnetic resonance imaging in the diagnosis of adult patients with acute myocarditis: a systematic review and meta-analysis. Int. J. Cardiol. 363, 225–239. https://doi.org/10.1016/j.ijcard.2022.06.047. PubMed PMID: 35724801, Epub 2022/06/21.

Koenig, G., Seneff, S., 2015. Gamma-glutamyltransferase: a predictive biomarker of cellular antioxidant inadequacy and disease risk. Dis. Markers 2015, 818570. https://doi.org/10.1155/2015/818570. PubMed PMID: 26543300; PubMed Central PMCID: PMCPMC4620378, Epub 2015/11/07.

Konlan, K.D., Lee, H., Lee, M., Kim, Y., Lee, H., Abdulai, J.A., 2022. Risk factors associated with the incidence and prevalence of hypertension in Ghana: an integrated review (2016–2021). Int. J. Environ. Health Res. 1–16. https://doi.org/10.1080/09603123.2022.2076814. PubMed PMID: 35578383. Epub 2022/05/18.

Lee, D.H., Blomhoff, R., Jacobs Jr., D.R., 2004. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Radic. Res. 38 (6), 535–539. https://doi.org/10.1080/10715760410001694026. PubMed PMID: 15346644, Epub 2004/09/07.

Lee, Y.J., Han, K.D., Kim, D.H., Lee, C.H., 2021. Determining the association between repeatedly elevated serum gamma-glutamyltransferase levels and risk of respiratory cancer: a nationwide population-based cohort study. Cancer Med. 10 (4), 1366–1376. https://doi.org/10.1002/cam4.3735. PubMed PMID: 33638317; PubMed Central PMCID: PMCPMC7925999, Epub 2021/02/28.

Li, G., Guo, G., Wang, W., Wang, K., Wang, H., Dong, F., et al., 2017. Association of prehypertension and cardiovascular risk factor clustering in Inner Mongolia: a cross-sectional study. BMJ Open. 7 (6) https://doi.org/10.1136/bmjopen-2016-015340. PubMed PMID: 28667215; PubMed Central PMCID: PMCPMC5734362. Epub 2017/07/02.

Li, S., Wang, A., Tian, X., Zuo, Y., Meng, X., Zhang, Y., 2022. Elevated gamma-glutamyl transferase levels are associated with stroke recurrence after acute ischemic stroke or transient ischemic attack. CNS Neurosci. Ther. 28 (10), 1637–1647. https://doi.org/10.1111/cns.13909. PubMed PMID: 35789538; PubMed Central PMCID: PMCPMC9437228, Epub 2022/07/06.

Long, Y., Jia, D., Wei, L., Yang, Y., Tian, H., Chen, T., 2017. Liver-specific overexpression of gamma-glutamyltransferase ameliorates insulin sensitivity of male C57BL/6 mice. J. Diabetes Res. 2017, 2654520. https://doi.org/10.1155/2017/2654520. PubMed PMID: 28660214; PubMed Central PMCID: PMCPMC5474247, Epub 2017/07/01.

Machado, S.A., Pasquarelli-do-Nascimento, G., da Silva, D.S., Farias, G.R., de Oliveira, S. I., Baptista, L.B., et al., 2022. Browning of the white adipose tissue regulation: new insights into nutritional and metabolic relevance in health and diseases. Nutrition & Metabolism. 19 (1), 61. https://doi.org/10.1186/s12986-022-00694-0. PubMed PMID: 36068578; PubMed Central PMCID: PMCPMC9446768. Epub 2022/09/07.

Ngamjarus, C., Pattanittum, P., Somboonporn, C., 2010. Roselle for hypertension in adults. The Cochrane Database of Systematic Reviews 2010 (1), Cd007894. https://doi.org/10.1002/14651858.CD007894.pub2. PubMed PMID: 20091658; PubMed Central PMCID: PMCPMC7182310 Somboonporn: none known. Epub 2010/01/22.

Ninomiya, K., Serruys, P.W., Garg, S., Kageyama, S., Kotoku, N., Masuda, S., et al., 2024. γ-glutamyl transferase and long-term survival in the SYNTAXES trial: is it just the liver? J. Am. Heart Assoc., e032276 https://doi.org/10.1161/jaha.123.032276. PubMed PMID: 38563386. Epub 2024/04/02.

Nugroho, P., Andrew, H., Kohar, K., Noor, C.A., Sutranto, A.L., 2022. Comparison between the world health organization (WHO) and international society of hypertension (ISH) guidelines for hypertension. Ann. Med. 54 (1), 837–845. https://doi.org/10.1080/07853890.2022.2044510. PubMed PMID: 35291891; PubMed Central PMCID: PMCPMC8933011, Epub 2022/03/17.

Olszewska-Słonina, D.M., 2021. Serum arylsulfatase and acid phosphatase activity in patients with metabolic syndrome as a result of oxidative damage to lysosomes. Protein Pept. Lett. 28 (11), 1246–1258. https://doi.org/10.2174/0929866528666210712095134. PubMed PMID: 34931962, Epub 2021/12/22.

Pan, X.F., Wang, L., Pan, A., 2021. Epidemiology and determinants of obesity in China. Lancet Diabetes Endocrinol. 9 (6), 373–392. https://doi.org/10.1016/s2213-8587(21)00045-0. PubMed PMID: 34022156, Epub 2021/05/23.

Parthaje, P.M., Unnikrishnan, B., Thankappan, K.R., Thapar, R., Fatt, Q.K., Oldenburg, B., 2016. Prevalence and correlates of prehypertension among adults in urban South India. Asia Pac. J. Public Health 28 (1 Suppl), 93s–101s. https://doi.org/10.1177/1010539515616453. PubMed PMID: 26596285; PubMed Central PMCID: PMCPMC4802005, Epub 2015/11/26.

Pattanittum, P., Ngamjarus, C., Buttramee, F., Somboonporn, C., 2021. Roselle for hypertension in adults. The Cochrane Database of Systematic Reviews 11 (11), Cd007894. https://doi.org/10.1002/14651858.CD007894.pub3. PubMed PMID: 34837382; PubMed Central PMCID: PMCPMC8626866 Somboonporn: none known. Epub 2021/11/28.

Perticone, M., Maio, R., Caroleo, B., Sciacqua, A., Suraci, E., Gigliotti, S., et al., 2020. Serum γ-glutamyltransferase concentration predicts endothelial dysfunction in naïve hypertensive patients. Biomedicines. 8 (7) https://doi.org/10.3390/biomedicines8070207. PubMed PMID: 32664562; PubMed Central PMCID: PMCPMC7400291. Epub 2020/07/16.

Strilchuk, L., Cincione, R.I., Fogacci, F., Cicero, A.F.G., 2020. Dietary interventions in blood pressure lowering: current evidence in 2020. Kardiol Pol. 78 (7–8), 659–666. https://doi.org/10.33963/KP.15468. PubMed PMID: 32631027, Epub 2020/07/08.

Takemura, K., Board, P.G., Koga, F., 2021. A systematic review of serum γ-glutamyltransferase as a prognostic biomarker in patients with genitourinary cancer. Antioxidants (Basel, Switzerland) 10. https://doi.org/10.3390/antiox10040549. PubMed PMID: 33916150; PubMed Central PMCID: PMCPMC8066142. Epub 2021/05/01.

Timpson, N.J., Harbord, R., Davey Smith, G., Zacho, J., Tybjaerg-Hansen, A., Nordestgaard, B.G., 2009. Does greater adiposity increase blood pressure and hypertension risk?: mendelian randomization using the FTO/MC4R genotype. Hypertension 54 (1), 84–90. https://doi.org/10.1161/hypertensionaha.109.130005. PubMed PMID: 19470880, Epub 2009/05/28.

Vasan, R.S., Larson, M.G., Leip, E.P., Kannel, W.B., Levy, D., 2001. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet (London, England). 358 (9294), 1682–1686. https://doi.org/10.1016/s0140-6736(01)06710-1. PubMed PMID: 11728544, Epub 2001/12/01.

Wang, Y.J., Li, Z.X., Gu, H.Q., Zhai, Y., Zhou, Q., Jiang, Y., et al. China Stroke Statistics: an update on the 2019 report from the National Center for Healthcare Quality Management in Neurological Diseases, China National Clinical Research Center for Neurological Diseases, the Chinese Stroke Association, National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention and Institute for Global Neuroscience and Stroke Collaborations. Stroke and vascular neurology. 2022. doi: 10.1136/svn-2021-001374. PubMed PMID: 35443985. Epub 2022/04/22.

Wu, Q., Li, J., Zhu, J., Sun, X., He, D., Li, J., et al., 2022. Gamma-glutamyl-leucine levels are causally associated with elevated cardio-metabolic risks. Front. Nutr. 9, 936220 https://doi.org/10.3389/fnut.2022.936220. PubMed PMID: 36505257; PubMed Central PMCID: PMCPMC9729530, Epub 2022/12/13.

Xavier Júnior, F.A.F., Morais, G.B., Silveira, J.A.M., Sampaio, T.L., Martins, A.M.C., Silva, I.N.G., et al., 2022. Kidney injury molecule-1 and urinary gamma-glutamyl transferase as biomarkers of acute kidney injury in cats. J. Small Anim. Pract. 63 (3), 203–210. https://doi.org/10.1111/jsap.13440. PubMed PMID: 34665457, Epub 2021/10/20.

Yang, S., Zhou, Z., Miao, H., Zhang, Y., 2023. Effect of weight loss on blood pressure changes in overweight patients: a systematic review and meta-analysis. J. Clin. Hypertens. (Greenwich) 25 (5), 404–415. https://doi.org/10.1111/jch.14661. PubMed PMID: 37141231; PubMed Central PMCID: PMCPMC10184479, Epub 2023/05/04.

Zhang, Y., Lee, E.T., Devereux, R.B., Yeh, J., Best, L.G., Fabsitz, R.R., et al., 2006. Prehypertension, diabetes, and cardiovascular disease risk in a population-based sample: the Strong Heart Study. Hypertension 47 (3), 410–414. https://doi.org/10.1161/01.Hyp.0000205119.19804.08. PubMed PMID: 16446387, Epub 2006/02/01.

Zhu, Y., Gong, Y., Zhu, R., Liu, X.K., Sun, Y.T., Wang, Y., et al., 2014. Relationship between serum gamma-glutamyltransferase levels and prehypertension in Chinese adults: the cardiometabolic risk in Chinese study. J. Clin. Hypertens. (Greenwich) 16 (10), 760–765. https://doi.org/10.1111/jch.12381. PubMed PMID: 25113653; PubMed Central PMCID: PMCPMC8031597, Epub 2014/08/13.