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Association between Serum Gamma-Glutamyl Transferase Level and Prehypertension among Community-Dwelling Men

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Serum gamma-glutamyl transferase (GGT) activity is a general clinical marker of excessive alcohol consumption, and GGT reflects changes in oxidative stress and implicated in the progression of hypertension. Recent guidelines classify persons with above-optimal blood pressure (BP) but not clinical hypertension as having prehypertension for a systolic BP (SBP) of 120 to 139 mmHg and/or a diastolic BP (DBP) of 80 to 89 mmHg; however, only limited data are available on the association between serum GGT and this entity among community-dwelling men in Japan. We performed a cross-sectional study to examine whether serum GGT was associated with prehypertension. Study participants (754 men, age 56 ± 15 years) without a clinical history of stroke, transient ischemic attack, myocardial infarction, angina, or renal failure were recruited from a single community. Thirty-seven percent of participants had prehypertension and 39.3% had hypertension. Multiple regression analysis using SBP and DBP as objective variables, adjusted for risk factors as explanatory variables, showed that log GGT was significantly and independently associated with elevated SBP (β = 0.109, P = 0.006) and DBP (β = 0.238, P < 0.001). Compared with participants in the lowest tertile of serum GGT (< 29 IU/L), the multivariate-adjusted odds ratio (OR) (95% CI) for prehypertension was 1.73 (1.06-2.81) for the middle tertile (29-53 IU/L) and 2.37 (1.31-4.31) for the highest tertile (> 53 IU/L). Moreover, the respective ORs for hypertension were 1.82 (1.04-3.18) and 3.11 (1.61-6.03). These results suggest that higher serum GGT levels are associated with prehypertension or hypertension in the general male population. ———— gamma-glutamyl transferase; hypertension; prehypertension; risk factor; Japanese men.
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Serum gamma-glutamyl transferase (GGT) is a general clinical marker of alcohol consumption, although it is documented that other factors are also associated with serum levels of GGT. Serum GGT activity reflects changes in oxidative stress, perhaps via a direct role for GGT in generating reactive oxygen species (Lee et al. 2004; Lim et al. 2004) and an indirect role in increasing the transport of glutathione precursors into cells. Thus, several large epidemiological studies have

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shown that elevated GGT levels are associated with cardiovascular disease (CVD). (Lee et al. 2006; Meisinger et al. 2006; Shankar et al. 2007), whereas other have demonstrated that GGT reflects other concomitant risk factors, such as obesity, insulin resistance, diabetes (Lee et al. 2003), hypertension (Shanklar and Li 2007), dyslipidemia, and metabolic syndrome (Lee et al. 2007).

Hypertension is one of the most common diseases in Japan and is strongly associated with an increased risk of CVD. Increased CVD mortality risk occurs when blood pressure (BP) is as low as 115 mmHg systolic BP (SBP) and 70 mmHg diastolic BP (DBP), and the risk increases steadily with elevating BP (Lewington et al. 2002). The most recent references for BP classification in adults are the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) in 2003. In this guideline, people with SBP of 120 to 139 mmHg and/or DBP of 80 to 89 mmHg are categorized as having prehypertension (Chobanian et al. 2003). Prehypertension and even normal BP frequently progress to clinical hypertension over several years, especially in older adults (Vasan et al. 2001). The incremental relationship between BP and CVD risk is continuous and consistent (Miura et al. 1994; Lee et al. 2002). Although prehypertension is associated with an increased risk of major CVD events (Chobanian et al. 2003), only limited data are available on the association between GGT and the prevalence of prehypertension among community-dwelling men in Japan.

Here, we evaluated the distribution of BP and GGT, as well as associated risk factors such as age, using cross-sectional data from community-dwelling men.

Materials and Methods

Subjects

Participants were recruited at the time of their annual health examination in a rural town: Nomura-cho, Seiyo-city, which has a total male population of 5,357 (as of April 2002) and located in Ehime prefecture, Japan, in 2002. Among 4,395 male adults aged 19 to 90 years in this population, 1,284 (29.2%) took part in the program and agreed to join the study. Information on medical history, present conditions, and drug usage was obtained by interview. Subjects with a clinical history of stroke, transient ischemic attack, myocardial infarction, or angina were excluded. The final study sample included 754 eligible men. This study was approved by the ethics committee of Ehime University School of Medicine and all participants gave written informed consent.

Evaluation of Risk Factors

Information on demographic characteristics and risk factors was collected using clinical files. Body mass index was calculated by dividing weight (in kilograms) by the square of the height (in meters). We measured BP with an appropriate-sized cuff on the right upper arm of participants in a sedentary position using an automatic oscillometric BP recorder (BP-103i; Colin, Aichi, Japan) while the subjects was seated after having rested for at least 5 min. Normotension was defined as SBP < 120 mmHg and DBP < 80 mmHg. Prehypertension was defined as SBP 120 to 139 mmHg and/or DBP 80 to 89 mmHg. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg (Chobanian et al. 2003). Cigarette smoking was quantified based on daily consumption and duration of smoking. Fasting total cholesterol (T-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), creatinine (enzymatic method), uric acid and GGT were measured during fasting. Serum GGT concentration was assayed with an automatic analyzer (TBA-c16000, TOSHIBA, Tokyo) and this intraassay-coefficients of variation was 0.87 to 2.11% in GGT. Low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula (Friedewald et al. 1972). Participants with TG levels ≥ 400 mg/dL were excluded (24 cases). The presence of diabetes was defined as a history of treatment for diabetes. Estimated glomerular filtration ratio (eGFR) was calculated with the following equation: $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287}$ (The Japanese Society of Nephrology: Japanese version of GFR estimation. http://www.jsn.or.jp: Updated Oct 29, 2007.). Participants with an eGFR of < 30 mL/min/1.73 m^2 were excluded (1 cases).

Statistical Analysis

Statistical analyses were performed using SPSS 10.0J (Statistical Package for Social Science, Inc., Chicago, IL, USA). All values are expressed as mean ±

standard deviation (S.D.), unless otherwise specified. The differences among groups categorized by serum GGT levels were analyzed by Mann-Whitney U test or chi-square (χ^2) test. Correlations between various characteristics and GGT were determined using Spearman's correlation. Multiple linear regression analysis was used to evaluate the contribution of risk factors for SBP or DBP and logistic regression analyses were used to test significant determinants of prehypertension or hypertension status serving as the dichotomous outcome variable. To examine the consistency of the observed association between serum GGT levels and prehypertension, we performed subgroup analyses by age (< 60, ≥ 60 years), BMI (< 25, ≥ 25 kg/m^2), drinking status (absent, present), TG (< 150, ≥ 150 mg/dL), HDL-C (≥ 40, < 40 mg/dL), and uric acid (< 7.0, ≥ 7.0 mg/dL). A p-value < 0.05 was considered significant.

Results

Subject background factors categorized by body mass index

The subjects consisted of 754 men, age 56 ± 15 (mean ± S.D.; range, 20-87) years. Table 1 shows subject characteristics categorized by serum GGT levels. Participants in higher GGT tertiles were younger, had higher BMI, and were more likely to have elevated DBP, TG, and uric acid. Smoking status, T-C, and FBG were significantly higher only in the middle tertile compared with the low tertile of serum GGT. Drinking status, SBP, HDL-C, and eGFR were significantly higher only in the high tertile compared with middle tertile of serum GGT. There were no intergroup differences in LDL-C and serum creatinine.

Table 1. Characteristics of subjects categorized by serum GGT levels.

	Serum GGT tertiles Men (N = 754)				
Characteristics	Tertile 1 < 29 IU/L N = 262	Tertile 2 29-53 IU/L N = 242	*P-value**	Tertile 3 > 53 IU/L N = 250	*P-value***
Age (years)	60 ± 16	58 ± 14	**0.005**	51 ± 12	**< 0.001**
Body mass index† (kg/m^2)	22.2 ± 2.5	23.1 ± 3.0	**< 0.001**	24.2 ± 3.3	**< 0.001**
Smoking status‡ (pack year)	15 ± 20	20 ± 21	**0.005**	22 ± 20	0.109
Drinking status, g/day	18 ± 8	19 ± 8	0.567	21 ± 4	**< 0.001**
Systolic blood pressure (mmHg)	132 ± 21	134 ± 20	0.060	138 ± 18	**0.020**
Diastolic blood pressure (mmHg)	78 ± 11	82 ± 11	**< 0.001**	85 ± 11	**< 0.001**
Total cholesterol (mg/dL)	182 ± 32	189 ± 34	**0.034**	193 ± 35	0.537
Triglycerides (mg/dL)	91 ± 39	121 ± 63	**< 0.001**	138 ± 68	**0.001**
HDL cholesterol (mg/dL)	58 ± 14	56 ± 14	0.132	61 ± 16	**0.004**
LDL cholesterol (mg/dL)	106 ± 29	109 ± 31	0.468	104 ± 36	0.110
Fasting blood glucose (mg/dL)	97 ± 20	99 ± 20	**0.014**	102 ± 23	0.085
Serum creatinine (mg/dL)	0.77 ± 0.12	0.78 ± 0.12	0.482	0.77 ± 0.13	0.207
Serum uric acid (mg/dL)	5.3 ± 1.2	5.8 ±1.4	**< 0.001**	6.4 ±1.3	**< 0.001**
eGFR (mL/min/1.73 m^2)	83.0 ± 16.2	82.9 ± 15.4	0.927	87.0 ± 16.5	**0.002**

Data presented are mean ± S.D. GGT, gamma-glutamyl transferase; HT, hypertension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate. †Body mass index was calculated using weight in kilograms divided by the square of the height in meters. ‡Smoking status: daily consumption (pack) × duration of smoking (year). eGFR = 194 × Cr$^{-1.094}$ × Age$^{-0.287}$. **P*-value for comparison between lowest tertile of and middle tertile of GGT subjects; ***P*-value for comparison between middle and highest tertile of GGT subjects; Mann-Whitney U test.

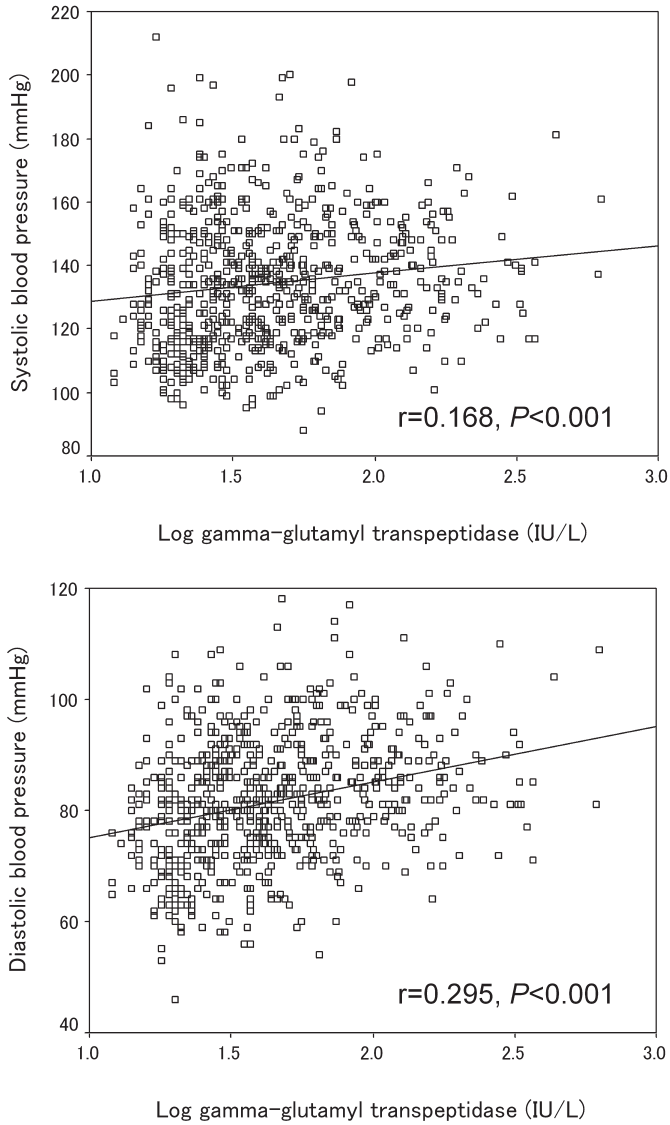

Fig. 1. Relationship between serum gamma-glutamyl transferase (GGT) and blood pressure status. Both Systolic blood pressure (r = 0.168, $P < 0.001$) and diastolic blood pressure (r = 0.295, $P < 0.001$) significantly increased progressively with increasing log GGT. *P*-value: Spearman's correlation.

Association between various characteristics and BP status

Both SBP (r = 0.168, $P < 0.001$) and DBP (r = 0.295, $P < 0.001$) significantly increased progressively with increasing log GGT (Fig. 1). Multiple regression analysis using SBP and DBP as an objective variable, adjusted for risk factors as explanatory variables, showed that SBP independently associated with log GGT ($\beta = 0.109$) with age ($\beta = 0.399$), BMI ($\beta = 0.251$), drinking status ($\beta = 0.079$), HDL-C ($\beta = 0.153$), and FBG ($\beta = 0.116$), and log GGT ($\beta = 0.238$) was also independently associated with DBP.

Association between GGT categories and risk for prehypertension or hypertension

Thirty-seven percent of participants had prehypertension and 39.3% had hypertension. Compared with the lowest tertile of serum GGT, the non-adjusted odds ratio for prehypertension was 1.84 (95% CI, 1.18-2.88) for the middle tertile and 3.05 (95% CI, 1.87-4.97) for the highest ter-

TABLE 2. Relationship between various characteristics and blood pressure status.

Characteristics	Systolic blood pressure β-coefficient (P-value)	Diastolic blood pressure β-coefficient (P-value)
Age (years)	0.399 (**< 0.001**)	0.261 (**< 0.001**)
Body mass index† (kg/m^2)	0.251 (**< 0.001**)	0.219 (**< 0.001**)
Smoking status‡ (pack year)	–0.016 (0.625)	0.010 (0.776)
Drinking status, g/day	0.079 (**0.022**)	0.065 (0.064)
Triglycerides (mg/dL)	0.054 (0.171)	0.094 (**0.019**)
HDL cholesterol (mg/dL)	0.153 (**< 0.001**)	0.146 (**< 0.001**)
LDL cholesterol (mg/dL)	–0.047 (0.171)	0.014 (0.693)
Fasting blood glucose (mg/dL)	0.116 (**0.001**)	0.036 (0.292)
Serum uric acid (mg/dL)	0.009 (0.813)	–0.008 (0.833)
Estimated GFR (mL/min/1.73 m^2)	0.037 (0.327)	–0.029 (0.446)
Log GGT (IU/L)	0.109 (**0.006**)	0.238 (< **0.001**)
R^2	0.222 (**< 0.001**)	0.194 (**< 0.001**)

†Body mass index was calculated using weight in kilograms divided by the square of the height in meters. ‡Smoking status: daily consumption (pack) × duration of smoking (year). HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; GGT, Gamma-glutamyl transferase. Gamma-glutamyl transferase was analyzed after log-transformation because of their skewed distribution. $eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287}$.

tile (Table 4). The age-adjusted odds ratio for prehypertension was 1.95 (95% CI, 1.24-3.07) for the middle tertile and 3.75 (95% CI, 2.25-6.26) for the highest tertile, with multivariate-adjusted odds ratios of 1.73 (95% CI, 1.06-2.81) for the middle tertile and 2.37 (95% CI, 1.31-4.31) for the highest tertile. Moreover, multivariate-adjusted odds ratios for hypertension were 1.82 (1.04-3.18) for the middle tertile and 3.11 (95% CI, 1.61-6.03) for the highest tertile**.**

Association between serum GGT levels and prehypertension

The OR of prehypertension associated with increasing levels of log-transformed serum GGT did not change within subgroups of age, BMI, drinking status, TG, HDL-C or uric acid (Table 4).

DISCUSSION

In this cross-sectional, population-based study, we determined the prevalence of prehypertension and hypertension, as defined by JNC-7 criteria (Chobanian et al. 2003), and their relationship to GGT levels. In our study, participants were only 754 eligible men because of sex differences in GGT (Skurtveit and Tverdal 2002). This study showed that prehypertension is extremely common, affecting 37.1% of male subjects, and both SBP and DBP significantly increased with increasing GGT levels. Furthermore, higher GGT levels were significantly associated with risk for prehypertension or hypertension, even after adjusting for age, BMI, smoking status, drinking status, TG, HDL-C, LDL-C, FBG, uric acid, and eGFR. Our data are in agreement with the results of previous prospective studies (Miura et al. 1994; Lee et al. 2002; Lee et al. 2003) showing that baseline serum GGT was an independent confounding factor for hypertension development, and we further suggest that serum GGT levels are also related to clinical prehypertension, a disease state when primary prevention is possible.

Our study found an overall prehypertension prevalence rate of 34.5% in rural adult male Japanese, similar to levels in Taiwanese adults (Tsai et al. 2005) and American adults (Greenlund

TABLE 3. Association between serum GGT levels and blood pressure status.

	Serum GGT tertiles Men (N = 754)			P -value
	Tertile 1 < 29 IU/L N = 262	Tertile 2 29-53 IU/L N = 242	Tertile 3 > 53 IU/L N = 250	
Normotension (NTN)	90 (34.9)	54 (38.4)	34 (13.6)	
Prehypertension (Pre-HTN)	86 (32.8)	95 (39.3)	99 (39.6)	
Hypertension (HTN)	86 (32.8)	93 (38.4)	117 (46.8)	
Pre-HTN vs. NTN				**< 0.001**
Non-adjusted OR (95% CI)	1.00	1.84 (1.18-2.88)	3.05 (1.87-4.97)	
Age-adjusted OR (95% CI)	1.00	1.95 (1.24-3.07)	3.75 (2.25-6.26)	
Multivariate-adjusted OR (95% CI)	1.00	1.73 (1.06-2.81)	2.37 (1.31-4.31)	
HTN vs. Pre-HTN				**0.583**
Non-adjusted OR (95% CI)	1.00	0.98 (0.65-1.48)	1.18 (0.79-1.77)	
Age-adjusted OR (95% CI)	1.00	1.19 (0.77-1.83)	2.11 (1.33-3.34)	
Multivariate-adjusted OR (95% CI)	1.00	0.99 (0.63-1.58)	1.34 (0.80-2.25)	
HTN vs. NTN				**< 0.001**
Non-adjusted OR (95% CI)	1.00	1.80 (1.15-2.82)	3.60 (2.22-5.84)	
Age-adjusted OR (95% CI)	1.00	2.42 (1.47-4.00)	7.00 (3.96-12.4)	
Multivariate-adjusted OR (95% CI)	1.00	1.82 (1.04-3.18)	3.11 (1.61-6.03)	

Data presented are number (%). GGT, gamma-glutamyl transferase; OR, odds ratio; CI, confidence interval. Multivariate-adjusted for age, body mass index, drinking status, smoking status, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, uric acid and estimated glomerular filtration rate. P-value: χ^2 test.

et al. 2004). We found that higher GGT levels were positively associated with prehypertension or hypertension, independent of other confounders. Similar results were found in a community-based cross-sectional study in US adults (Shankar et al. 2007), with a multivariate-OR (95% CI) of 1.84 (1.37-2.46) comparing quartile 4 of GGT (> 29 U/L) to quartile 1 (< 13 U/L). This association persisted in separate analyses in men and women. Moreover, the results were consistent in subgroup analyses by race-ethnicity, age, smoking status, drinking status, BMI, waist circumference, and diabetes. Also in our study, the OR of GGT for prehypertension did not change within subgroups of age, BMI, drinking status, TG, HDL-C and uric acid. Furthermore, serum GGT levels correlated with relative changes in BP in individuals with normal GGT concentrations, a finding consistent with previous reports looking at hypertension (Miura et al. 1994; Lee et al. 2003). Miura et al. (1994) suggest that the serum GGT levels may predict the future development of hypertension among drinkers after adjustment for baseline BP level and the amount of alcohol consumption, and Yamada et al. (1995) suggest that the association between serum GGT and hypertension appears to be quiet similar in both drinker and nondrinker.

Serum GGT is a marker of drinking alcohol and/or liver dysfunction such as fatty liver (Teschke et al. 1977). Although the association between serum GGT and prehypertension was only present in alcohol drinkers, it strongly persisted after adjusting for grams of alcohol drinking. This suggests that subjects with alcohol-induced serum GGT increases may have increased susceptibility to high BP (Lee et al. 2006). There were no significant differences in the incidence of prehypertension or serum GGT between drinkers and nondrinkers. Yamada et al. (1995) showed

Table 4. Association between serum GGT levels and Prehypertension, within selected subgroups.

Stratified subgroups	N	PHT Cases (%)	Multivariate OR (95% CI)*	*P* -interaction
ALL	458	280 (61.1)	2.96 (1.28-6.85)	------
Age (years)				
< 60 years	287	169 (58.9)	3.08 (1.09-8.66)	0.295
≥ 60 years	171	111 (64.9)	2.89 (0.54-15.4)	
Body mass index†				
< 25 kg/m^2	359	205 (57.1)	3.29 (1.26-8.59)	0.749
≥ 25 kg/m^2	99	75 (75.8)	1.20 (0.15-9.44)	
Drinking status				
Absent	66	37 (56.1)	2.51 (0.94-66.9)	0.913
Present	392	243 (62.0)	2.72 (1.12-6.60)	
Triglycerides				
< 150 mg/dL	362	209 (57.7)	3.32 (1.21-9.11)	0.350
≥ 150 mg/dL	96	71 (74)	1.27 (0.24-6.61)	
HDL cholesterol				
≥ 40 mg/dL	407	249 (61.2)	2.63 (1.08-6.44)	0.543
< 40 mg/dL	51	31 (60.8)	2.91 (0.14-61.8)	
Uric acid				0.315
< 7.0 mg/dL	367	215 (58.6)	3.14 (1.20-8.27)	
≥ 7.0 mg/dL	91	65 (71.4)	3.38 (0.48-23.6)	

Data presented are number (%). GGT, gamma-glutamyl transpeptidase; OR, odds ratio; CI, confidence interval. †Body mass index was calculated using weight in kilograms divided by the square of the height in meters. Multivariate-adjusted for age, body mass index, drinking status, smoking status, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, uric acid and estimated glomerular filtration rate. *Multivariate OR (95% CI) of prehypertension associated with log-transformed GGT, IU/L.

that the association between serum GGT and BP status was present in both drinkers and nondrinkers, suggesting drinking status does not dramatically affect the usefulness of GGT as a biomarker for hypertension risk.

The mechanisms that lead to increased BP in individuals with increased GGT are not completely understood. Serum GGT is associated with hypertension, dyslipidemia, and abnormal glucose tolerance, suggesting that it is related to hepatic insulin resistance rather than non-alcoholic fatty liver disease (Ikai et al. 1994; Nilssen and Førde 1994; Kang et al. 2007). GGT plays a direct role in the generation of reactive oxygen species in the presence of iron or other transition metals (Brown et al. 1998), inducing lipid peroxidation in human biological membranes (Paolicchi et al. 1997), and is an indirect marker of antioxidant systems, with the primary function of maintaining the intracellular concentration of glutathione in response to oxidative stress (Karp et al. 2001). Higher c-reactive protein or other inflammatory parameters, indicating sub-clinical inflammation, correlate with GGT levels, as do levels of nitrotyrosine, an oxidative stress maker (Bo et al. 2005). These findings suggest that GGT could be an early marker of oxidative stress and sub-clinical inflammation, perhaps related to the pathology of in-

creased BP as an oxidative stressor.

Some limitations of this study must be considered. First, our cross-sectional study design does not eliminate potential causal relationships between GGT and increased BP. There still remain important problems on the cumulative effects of these CVD risk factors over several decades and the interactions with other risk factors. The prevalence of various BP categories is based on a single assessment of BP, which may introduce a misclassification bias. Moreover, a single measurement of GGT levels represents a limitation of the present study because 12% of adults with initially elevated GGT levels had normal levels at the second examination in the American general population (Lazo et al. 2008). Therefore the demographics and referral source may limit generalizability.

In conclusion, the present study showed that GGT levels correlate with prehypertension or hypertension in the general male population. The underlying mechanism seems to be independent from traditional cardiovascular risk factors such as age, BMI, dyslipidemia, and diabetes. For community-dwelling healthy persons, prospective population-based studies are needed to investigate the mechanisms underlying this association to determine whether intervention, such as effective lifestyle modifications that decrease GGT in adult male populations, will decrease risks.

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