Gamma-glutamyl transferase level predicts the development of hypertension in Hong Kong Chinese

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Abstract

Background: Plasma levels of alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase, and γ-glutamyl transferase (GGT) are often elevated in cardiometabolic diseases. We investigated if hypertension is associated with elevated levels of these plasma markers.

Methods: We included 235 hypertensive and 708 normotensive subjects (mean age 47.3±9.6 and 58.0±10.2 years respectively) from the Hong Kong Cardiovascular Risk Factor Prevalence Study-2 (CRISPS-2) in 2000-2004 who had drank less than once per week. In the follow-up study in 2005-2008 (CRISPS-3), 126 out of the 708 subjects had developed hypertension.

Results: Raised plasma ALT (OR=1.22 per SD of log-transformed level, P=0.045) and GGT (OR=1.38 per SD of log-transformed level, P=0.001) levels were associated with hypertension at baseline in CRISPS-2 after adjusting for covariates. Among subjects not on anti-hypertensive medications, plasma ALP, ALT and GGT were related to blood pressure (P<0.01). In subjects normotensive at CRISPS-2, plasma GGT, but not ALP, ALT and AST, was an independent predictor of new-onset hypertension at CRISPS-3 (OR=1.38 per SD of log-transformed level, P=0.020 and OR=2.68 for 3rd tertile vs. 1st tertile, P=0.004) after adjusting for covariates.

Conclusions: Among the four plasma markers, elevated GGT level is the strongest predictor for existing and new-onset hypertension in Hong Kong Chinese.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is caused by the accumulation of fat in the liver in subjects who do not drink alcohol in excess [1]. It has recently been suggested as the hepatic manifestation of obesity and the metabolic syndrome [1]. In NAFLD, plasma markers of liver injury such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (GGT) are often elevated [2].

Apart from liver diseases, these enzymes, especially GGT, have been suggested to be novel markers of cardiovascular diseases [3]. Elevated plasma GGT level has been shown to be associated with hypertension and its development in previous studies in Japanese [4-6], Korean [7], and Caucasians [8,9]. However, all these studies investigated GGT but not the other enzymes, i.e. ALP, ALT, and AST [4-9]. We previously reported that plasma ALP correlates with the inflammatory marker, C-reactive protein (CRP), in Hong Kong Chinese [10] and Americans [11]. As CRP is known to predict the development of hypertension [12], ALP may also be related to the latter. Moreover, elevated plasma ALT is already known to precede the development of the metabolic syndrome [2] and type 2 diabetes [13-17]. Therefore, we hypothesized that plasma markers of liver injury other than GGT may also be elevated in hypertension and predict the future risk of hypertension. If this hypothesis is true, the routine liver function test may help to monitor the risk at minimal extra cost. As there is no prospective study on the relationship of hypertension with all the four plasma markers of liver injury, especially in Chinese, we investigated whether plasma ALP, ALT, AST, and GGT were associated with hypertension in a population-based prospective cohort of Hong Kong Chinese. Since alcohol drinking can increase plasma markers of liver injury and may

have confounding effect, we limited our analysis to subjects who had alcoholic drinks less often than once a week.

2. Methods

2.1. Subjects

The subjects were from the Hong Kong Cardiovascular Risk Factor Prevalence Study-2 (CRISPS-2), details of which have been described previously [18-21]. The study protocol was approved by the Ethics Committee of the University of Hong Kong and all subjects gave written and informed consent. Among the 1944 subjects in the CRISPS-2 study in 2000-2004, plasma levels of all the four markers of liver injury were available in 1371 subjects, and only 1197 of whom had alcoholic drinks less often than once a week. Among these subjects, 943 were followed up in 2005-2008 (CRISPS-3) after a median interval of 5.3 years and were included in this analysis.

2.2. Variables of interest

Plasma ALP, ALT, AST, and GGT were measured on a Hitachi 912 analyzer. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or taking anti-hypertensive medication. Blood pressure was measured three times using a mercury sphygmomanometer by a trained nurse. The readings were taken in a seated position after resting in a quiet temperature-controlled room. The Korotkoff V sound was used to determine DBP. The first measurement was to familiarize the subject with the procedure and the sensation of the inflated cuff. The mean of the second and third readings was used for data analysis. Mean arterial pressure (MAP) was calculated as the sum of DBP and one-third of the difference between SBP and DBP. Data on alcohol

drinking, smoking, and history of hypertension were obtained by interviewing using a questionnaire. Details of the physical examination and measurement methods of clinical parameters, such as triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting glucose, homeostasis model assessment of insulin resistance index (HOMA-IR), fibrinogen, and plasma high-sensitivity CRP had been described previously [18-23].

2.3. Statistical analysis

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL). Variables with skewed distribution were log-transformed before analysis. Multiple linear or logistic regression models were used to estimate the standardized regression coefficient (β) or odds ratio (OR) respectively after adjusting for covariates. Variables were used as covariates in the multiple regression analysis if they are recognized determinants of blood pressure or were significantly different between subjects with and without hypertension. For variables that were highly correlated such as body mass index (BMI) and waist circumference, only one was entered into the regression analysis. In a separate analysis, similar results were obtained when BMI was replaced by waist circumference in the adjustment model. The *P* values for interaction were estimated by including each multiplicative interaction term in the multivariate regression models in full sample after adjusting for the main effects of all covariates. A two-tailed $P<0.05$ was considered statistically significant.

3. Results

Table 1 shows the clinical characteristics of the subjects in CRISPS-2 according to the hypertension status. Among 708 subjects normotensive in CRISPS-2, 126 subjects had

developed hypertension in CRISPS-3. As expected, subjects with prevalent or incident hypertension were older, had higher BMI, waist circumference, SBP, DBP, MAP, triglycerides, fasting blood glucose and HOMA-IR, and had lower HDL cholesterol. Subjects hypertensive at baseline had a higher plasma fibrinogen level but less likely to be smokers.

In CRISPS-2, all the four plasma markers of liver injury were higher in subjects with prevalent hypertension (Table 1). Among 809 subjects not on anti-hypertensive medication in CRISPS-2, the plasma levels of most markers were significantly associated with SBP (ALP: β=0.185, P<0.001; ALT: β=0.137, P=0.001; and GGT: β=0.155, P<0.001), DBP (ALP: β=0.184, P<0.001; ALT: β=0.149, P<0.001; AST: β=0.088, P=0.011; and GGT: β=0.171, P<0.001), and MAP (ALP: β=0.200, P<0.001; ALT: β=0.156, P<0.001; AST: β=0.081, P=0.015; and GGT: β=0.178, P<0.001) after adjusting for age and sex. In a separate analysis, inclusion of the 134 treated subjects using adjusted blood pressure (by adding 10/5 mmHg to blood pressure[24]) produced similar results (data not shown). As women had significantly lower plasma levels of all the four markers than men (P<0.001 after adjusting for age and BMI), sex-specific cut-points were used to define the tertiles of the plasma levels in subsequent analysis. As shown in Table 2, plasma GGT were significantly associated with prevalent hypertension in the full adjustment model (P=0.003 for continuous data and P for trend = 0.008 for tertiles). Plasma ALT was also associated with prevalent hypertension with a borderline significant P value of 0.045 when the plasma level was analyzed as continuous data. There was no significant interaction of plasma GGT and ALT with sex (P >0.05). The clinical characteristics of subjects according to the sex-specific tertiles of plasma GGT levels are shown in Table 3. In CRISPS-2, plasma GGT level increased with increasing age, BMI,

waist circumference, SBP, DBP, MAP, triglycerides, LDL cholesterol, fasting glucose, HOMA-IR, plasma CRP, plasma ALP, plasma ALT and plasma AST, and decreased with increasing HDL cholesterol (all $P<0.05$, Table 3). Plasma fibrinogen and the proportion of smoking did not differ significantly with plasma GGT tertiles.

Among subjects normotensive in CRISPS-2, those who had developed hypertension in CRISPS-3 had significantly higher plasma levels of ALP, ALT, and GGT (Table 1). However, only the association of plasma GGT with incident hypertension remained significant in the full adjustment model (Table 4). There was no significant interaction of plasma GGT with sex ($P=0.207$ for tertiles and 0.072 for continuous level) and other covariates ($P>0.05$ after adjustment for multiple testing). The association of plasma GGT tertiles with incident hypertension was significant in subjects with BMI <25.0 kg/m^2 and BMI ≥25.0 kg/m^2 (P for trend =0.038 and 0.042 respectively). Similar results were obtained when baseline SBP in the adjustment model was replaced by baseline DBP or MAP (data not shown).

4. Discussion

This is the first report of the relationship between all the four plasma markers of liver injury and hypertension in a population-based prospective cohort. We demonstrated that only plasma GGT, but not the other markers, was associated with hypertension at baseline and incident hypertension.

Our results are consistent with previous findings on the association of plasma GGT with hypertension or pre-hypertension in cross-sectional [25-28] and prospective studies [4-9].

The mechanisms underlying the association of GGT with hypertension have not been fully elucidated. Plasma GGT is usually used as a marker of alcohol intake. In this study, the subjects were not regular alcohol drinkers, but elevated GGT level was still associated with both prevalent and incident hypertension. Previous studies also found a similar association in both drinkers and non-drinkers [8,26]. Therefore, the association cannot be explained by alcohol drinking.

Recently, GGT has been suggested as a novel biomarker of cardiovascular risk [3]. Its elevated level has been shown to be associated with the metabolic syndrome in cross-sectional studies [29,30]. In prospective studies, elevated GGT level can predict incident elevation in plasma ALT [31], and the development of cardiovascular diseases, all-cause mortality, and cardiovascular mortality [30,32-34]. In the Framingham Offspring Study, plasma GGT correlated positively with BMI, blood pressure, LDL cholesterol, triglycerides and fasting glucose in cross-sectional analysis, and predicted the development of the metabolic syndrome and cardiovascular diseases over a period of 20 years [35]. It has been suggested that the association of plasma GGT with the metabolic syndrome may be explained by insulin resistance [36]. Indeed, plasma GGT has also been reported to be predictive of incident diabetes [8,37,38] and the close relationship between raised blood pressure and dysglycemia in our population may also contribute to the association of plasma GGT with hypertension [21]. However, in our study, plasma GGT predicted incident hypertension, even after adjusting for covariates including the insulin resistance index, HOMA-IR. Plasma GGT has been suggested as a marker of oxidative stress [3,39], a risk factor of hypertension and cardiovascular diseases. GGT is a key enzyme in the catabolism of glutathione and plays a role in the production of reactive oxygen species through modulating the redox status of

cell surface protein thiols [40]. In a clinical study, serum levels of antioxidants can predict GGT level at 10 year, but not vice versa [39]. A prospective study of American adults revealed significant association of plasma GGT with hypertension only among subjects who were overweight or had increased central body fat [9]. This may suggest fatty liver as an underlying mechanism for the association of plasma GGT with hypertension. Our previous work suggested that plasma GGT correlates with plasma CRP [10,11], so elevated GGT may reflect inflammation that occurs in fatty liver.

Plasma ALP was associated with blood pressure among subjects not on anti-hypertensive medication in CRISPS-2. Although plasma ALP tertiles were not significantly related to hypertension, plasma ALP correlated with SBP and DBP when these were treated as continuous variables. The association of plasma ALP with blood pressure could be explained at least in part by its correlation with plasma GGT levels [10,11,41]. Elevated plasma ALT is associated with the development of the metabolic syndrome [2] and type 2 diabetes [13-17], which are closely related to hypertension in our population [19,21]. In our study, plasma ALT was not an independent predictor of prevalent and incident hypertension in stepwise logistic regression analysis.

There are some limitations in this study. The cohort of this study is community-based and so the number of subjects with prevalent and incident hypertension is relatively small. The degree of variations in plasma ALP, ALT, AST, and GGT among subjects and within an individual may influence the degree of significance of their association with hypertension. Elevation of ALP, ALT, AST, and GGT in plasma can be non-specific and found in other diseases such as hepatitis, biliary diseases, musculoskeletal diseases, and myocardial injury.

However, these non-specific causes of elevation in plasma markers of liver injury are likely to diminish rather than augment the observed association.

In conclusion, among the four plasma markers of liver injury, GGT is the strongest risk factor for hypertension in Hong Kong Chinese. Therefore, further studies to assess the utility of GGT as a biomarker for hypertension and related diseases are warranted.

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Conflict of interest

None.

List of Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRISPS, Hong Kong Cardiovascular Risk Factor Prevalence Study; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, γ-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance index; LDL, low-density lipoprotein; MAP, mean arterial pressure; OGTT, oral glucose tolerance test; OR, odds ratio; SBP, systolic blood pressure.

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Table 1

Clinical characteristics of the subjects in CRISPS-2 (2000-2004).

Characteristics	**All subjects**		**Normotensive subjects in CRISPS-2**	
	Normotension (n=708)	**Hypertension (n=235)**	**Normotension in CRISPS-3 (n=582)**	**Hypertension in CRISPS-3 (n=126)**
Age (years)	47.3±9.7	58.0±10.2‡	46.0±9.0	53.3±10.3‡
Women (%)	60.5	51.1	61.0	57.9
BMI (kg/m^2)	23.3±3.3	25.4±3.4‡	23.1±3.0	24.5±4.0‡
Waist circumference (cm)	77.3±9.5	84.1±9.4‡	76.7±9.2	80.5±10.4‡
SBP (mmHg)§	113.3±10.9	147.9±15.5‡	111.2±10.0	123.1±9.5‡
DBP (mmHg)§	72.0±8.1	89.0±11.5‡	71.0±8.0	76.6±7.1‡
MAP (mmHg)§	85.8±8.2	108.7±9.5‡	84.4±7.8	92.1±6.8‡
Triglycerides (mmol/l)	1.07 (1.03-1.11)	1.45 (1.35-1.55)‡	1.03 (0.99-1.07)	1.26 (1.15-1.38)†
HDL cholesterol (mmol/l)	1.45±0.39	1.33±0.38‡	1.46±0.38	1.39±0.41†
LDL cholesterol (mmol/l)	3.21±0.81	3.36±0.78	3.20±0.80	3.25±0.85
Fasting glucose (mmol/l)	5.13 (5.06-5.19)	5.55 (5.41-5.69)*	5.05(4.99-5.11)	5.52 (5.31-5.75)‡
HOMA-IR	1.57 (1.51-1.64)	2.29 (2.10-2.49)‡	1.50 (1.43-1.57)	1.95 (1.77-2.14)‡
Fibrinogen (g/l)	2.90±0.54	3.11±0.62*	2.89±0.56	2.97±0.47
CRP (mg/l)	0.51 (0.47-0.55)	0.85 (0.75-0.96)‡	0.47 (0.43-0.51)	0.74 (0.64-0.86)‡
ALP (U/l)	66.1 (64.7-67.6)	77.2 (74.5-80.0)†	64.8 (63.2-66.3)	72.7 (68.9-76.6)†
ALT (U/l)	20.0 (19.2-20.9)	24.6 (22.9-26.4)‡	19.5 (18.7-20.4)	22.5 (20.1-25.0)†
AST (U/l)	21.6 (21.0-22.2)	24.2 (23.2-25.4)*	21.5 (20.9-22.1)	23.0 (21.5-24.7)

GGT (U/l)	20.5 (19.7-21.4)	28.2 (26.1-30.6)‡	19.8 (18.9-20.8)	24.1 (21.6-26.9)‡
Current smoking (%)	15.1	10.6*	15.3	14.3

Data are expressed as mean±SD or geometric mean (95% CI) unless otherwise stated.

*P<0.05, †P<0.01, and ‡P<0.001 for normotensive versus hypertensive subjects after adjusting for age and sex. For incident elevated blood pressure, P values were further adjusted for follow-up duration.

§Subjects on anti-hypertensive medication (n=134) were excluded from analysis.

Table 2

Association with prevalent hypertension in CRISPS-2 (n=943).

Liver enzyme	**Unadjusted model**		**Model 1**		**Model 2**	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
ALP tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.46 (0.99-2.16)	0.057	1.33 (0.86-2.04)	0.204	1.13 (0.71-1.82)	0.603
Tertile 3	2.60 (1.79-3.77)	<0.001	1.66 (1.10-2.52)	0.017	1.15 (0.72-1.84)	0.552
P for trend		<0.001		0.058		0.821
ALP, U/l*	1.76 (1.49-2.08)	<0.001	1.37 (1.15-1.64)	0.001	1.23 (0.99-1.52)	0.061
ALT tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.73 (1.18-2.54)	0.005	1.64 (1.06-2.53)	0.025	1.13 (0.71-1.81)	0.605
Tertile 3	2.56 (1.75-3.73)	<0.001	3.11 (2.02-4.77)	<0.001	1.59 (0.98-2.57)	0.060
P for trend		<0.001		<0.001		0.130
ALT, U/l*	1.42 (1.22-1.64)	<0.001	1.56 (1.31-1.87)	<0.001	1.22 (1.01-1.49)	0.045
AST tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.44 (0.99-2.09)	0.058	1.20 (0.79-1.82)	0.394	1.05 (0.67-1.64)	0.842
Tertile 3	2.09 (1.45-3.00)	<0.001	1.74 (1.16-2.61)	0.007	1.43 (0.93-2.21)	0.107
P for trend		<0.001		0.022		0.210
AST, U/l*	1.36 (1.17-1.57)	<0.001	1.25 (1.06-1.47)	0.008	1.16 (0.97-1.38)	0.103
GGT tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.62 (1.08-2.43)	0.020	1.43 (0.91-2.24)	0.120	1.12 (0.69-1.81)	0.656
Tertile 3	3.71 (2.54-5.41)	<0.001	3.77 (2.46-5.77)	<0.001	1.99 (1.21-3.26)	0.007

P for trend		<0.001		<0.001		0.008
GGT, U/l*	1.65 (1.42-1.91)	<0.001	1.73 (1.45-2.06)	<0.001	1.38 (1.12-1.70)	0.003

For ALP, the cut-off values for tertiles 1, 2, and 3 are ≤67, 68-82 and ≥83 U/l in men, and ≤57, 58-74 and ≥75 U/l in women, respectively.

For ALT, the cut-off values for tertiles 1, 2, and 3 are ≤20, 21-31 and ≥32 U/l in men, and ≤14, 15-21 and ≥22 U/l in women, respectively.

For AST, the cut-off values for tertiles 1, 2, and 3 are ≤21, 22-26 and ≥27 U/l in men, and ≤18, 19-23 and ≥24 U/l in women, respectively.

For GGT, the cut-off values for tertiles 1, 2, and 3 are ≤21, 22-33 and ≥34 U/l in men, and ≤14, 15-21 and ≥22 U/l in women, respectively.

Model 1: Adjusted for age and sex.

Model 2: Further adjusted for BMI, triglycerides, HDL cholesterol, HOMA-IR, CRP, fibrinogen, and current smoking.

*ORs are expressed in term of per SD of the log-transformed unit.

Table 3

Clinical characteristics of the subjects in CRISPS-2 according to tertiles of plasma GGT level.

Characteristics	**Tertile 1 (≤21 U/L in men and ≤14 U/L in women)**	**Tertile 2 (22-33 U/L in men and 15-21 U/L in women)**	**Tertile 3 (≥34 U/L in men and ≥22 U/L in women)**	***P* for trend**
n	338	301	304	
Age (years)	48.3±10.6	50.6±10.6	51.1±11.1	0.004
BMI (kg/m^2)	22.8±2.9	23.7±3.2	25.2±3.8	<0.001
Waist circumference (cm)	75.7±8.8	79.3±9.4	82.5±10.3	0.003
SBP (mmHg)*	114.9±14.4	117.2±15.2	121.8±18.8	0.013
DBP (mmHg)*	72.6±9.4	73.9±9.3	76.6±11.8	0.039
MAP (mmHg)*	86.7±10.2	88.3±10.4	91.7±12.9	0.014
Triglycerides (mmol/l)	0.93 (0.89-0.97)	1.13 (1.07-1.19)	1.50 (1.42-1.60)	<0.001
HDL cholesterol (mmol/l)	1.43±0.35	1.37±0.37	1.28±0.39	0.009
LDL cholesterol (mmol/l)	3.17±0.80	3.21±0.74	3.37±0.86	0.026
Fasting glucose (mmol/l)	5.03 (4.96-5.10)	5.22 (5.12-5.31)	5.47 (5.34-5.61)	<0.001
HOMA-IR	1.34 (1.27-1.41)	1.71 (1.60-1.83)	2.31 (2.16-2.48)	<0.001
Fibrinogen (g/l)	2.90±0.57	2.92±0.51	3.04±0.62	0.158
CRP (mg/l)	0.40 (0.36-0.45)	0.60 (0.54-0.67)	0.82 (0.74-0.91)	<0.001
ALP (U/l)	61.4 (59.6-63.2)	69.2 (67.2-71.3)	77.3 (74.7-80.0)	<0.001
ALT (U/l)	15.9 (15.1-16.6)	19.9 (19.0-20.9)	30.5 (28.5-32.7)	<0.001
AST (U/l)	19.6 (19.0-20.2)	21.5 (20.9-22.2)	26.3 (25.0-27.6)	<0.001
Current smoking (%)	12.4	15.3	14.5	0.351
Hypertension (%)	14.8	21.9	39.1	<0.001

Data are expressed as mean±SD or geometric mean (95% CI) unless otherwise stated.

P for trend was adjusted for age, sex, and BMI, where appropriate.

*Subjects on anti-hypertensive medication were excluded from analysis.

Table 4

Association with incident hypertension in CRISPS-3 (n=708).

Liver enzyme	**Unadjusted model**		**Model 1**		**Model 2**	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
ALP tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.89 (1.11-3.22)	0.019	1.60 (0.88-2.90)	0.124	1.48 (0.79-2.77)	0.218
Tertile 3	2.98 (1.79-4.95)	<0.001	1.66 (0.94-2.94)	0.083	1.48 (0.80-2.74)	0.212
P for trend		<0.001		0.185		0.385
ALP, U/l*	1.49 (1.21-1.83)	<0.001	1.14 (0.90-1.43)	0.283	1.08 (0.82-1.42)	0.593
ALT tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.44 (0.87-2.36)	0.153	1.36 (0.78-2.40)	0.279	1.19 (0.65-2.18)	0.566
Tertile 3	1.82 (1.11-2.98)	0.017	1.59 (0.91-2.77)	0.104	1.30 (0.69-2.43)	0.416
P for trend		0.057		0.260		0.714
ALT, U/l*	1.26 (1.05-1.51)	0.012	1.32 (1.05-1.67)	0.018	1.20 (0.92-1.56)	0.181
AST tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.11 (0.68-1.81)	0.674	1.01 (0.58-1.77)	0.968	1.12 (0.63-2.02)	0.697
Tertile 3	1.66 (1.03-2.66)	0.037	1.44 (0.82-2.50)	0.202	1.47 (0.82-2.64)	0.198
P for trend		0.080		0.332		0.408
AST, U/l*	1.22 (1.03-1.46)	0.026	1.20 (0.96-1.49)	0.105	1.15 (0.91-1.45)	0.256
GGT tertile						
Tertile 1	1.00 (referent)		1.00 (referent)		1.00 (referent)	
Tertile 2	1.54 (0.90-2.63)	0.115	1.28 (0.69-2.35)	0.434	1.16 (0.60-2.22)	0.661
Tertile 3	2.81 (1.69-4.66)	<0.001	2.93 (1.63-5.24)	<0.001	2.68 (1.36-5.26)	0.004

P for trend		<0.001		<0.001		0.004
GGT, U/l*	1.36 (1.13-1.62)	0.001	1.43 (1.14-1.79)	0.002	1.38 (1.05-1.81)	0.020

For ALP, the cut-off values for tertiles 1, 2, and 3 are ≤67, 68-81 and ≥82 U/l in men, and ≤54, 55-70 and ≥71 U/l in women, respectively.

For ALT, the cut-off values for tertiles 1, 2, and 3 are ≤19, 20-31 and ≥32 U/l in men, and ≤13, 14-19 and ≥20 U/l in women, respectively.

For AST, the cut-off values for tertiles 1, 2, and 3 are ≤20, 21-25 and ≥26 U/l in men, and ≤17, 18-22 and ≥23 U/l in women, respectively.

For GGT, the cut-off values for tertiles 1, 2, and 3 are ≤19, 20-30 and ≥31 U/l in men, and ≤13, 14-19 and ≥20 U/l in women, respectively.

Model 1: Adjusted for age, sex, and systolic blood pressure at baseline and follow-up duration.

Model 2: Further adjusted for baseline BMI, triglycerides, HDL cholesterol, HOMA-IR, CRP, fibrinogen, current smoking, and change in BMI.

*ORs are expressed in term of per SD of the log-transformed unit.