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ORIGINAL ARTICLE

Cross-sectional and longitudinal association of serum alanine aminotransaminase and γ-glutamyltransferase with metabolic syndrome in middle-aged and elderly Chinese people

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Abstract

Background: Although associations of the liver enzymes alanine aminotransaminase (ALT) and γ-glutamyltransferase (GGT) with metabolic syndrome (MetS) are well recognized, whether they are independent of insulin resistance and which enzyme is more effective are yet to be clarified.
Methods: A total of 5404 subjects aged ≥40 years were recruited from two urban communities in Shanghai for cross-sectional analyses. A subgroup of 681 participants without MetS at baseline was included in the longitudinal analyses. Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR), and the modified National Cholesterol Education Program Adult Treatment Panel III criteria were adopted to diagnose MetS.
Results: Both GGT and ALT were strongly and positively associated with MetS risks in simple and multivariate analyses. Further adjustment for HOMA-IR and ALT did not change the association of GGT and MetS materially, whereas adjustment for HOMA-IR and GGT substantially attenuated the ALT–MetS association. In longitudinal analyses, risks of developing MetS were increased across GGT quartiles in a dose-dependent manner after extensive adjustments (odds ratios were 1.00, 1.38, 1.62, and 2.29 for GGT, quartile 1 through quartile 4; P for trend = 0.01). In contrast, ALT was no longer associated with MetS development after final adjustment for GGT (P for trend = 0.09).
Conclusions: Our study confirmed significant and independent associations of GGT and ALT with MetS in adult Chinese people. Moreover, GGT might be more effective for indicating the future development of MetS.

Keywords: alanine aminotransaminase, insulin resistance, metabolic syndrome, γ-glutamyltransferase.

Significant findings of the study

The significant associations of the liver enzymes ALT and GGT with metabolic syndrome were independent of insulin resistance measured with HOMA-IR. GGT was superior to ALT for indicating the future development of metabolic syndrome.

What this study adds

It confirmed a significant and independent association of liver enzymes with metabolic syndrome, and demonstrated a better relationship between GGT and metabolic syndrome than ALT.

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Introduction

Metabolic syndrome (MetS), which is a cluster of various cardiometabolic disorders including hypertension, obesity, dyslipidemia and glucose intolerance, has affected 20–25% of the world's adult population. Individuals with MetS are at high risk for cardiovascular diseases and have a doubled cardiovascular-associated mortality compared with those without the syndrome.[1]

Non-alcoholic fatty liver disease (NAFLD), which is caused by excess deposition of fat in the liver, is now regarded as the hepatic manifestation of MetS.[2] NAFLD, diagnosed on the basis of a raised alanine aminotransaminase (ALT; >40 IU/L) after exclusion of other known causes of elevated liver enzymes, was reported to be predictive of developing diabetes and MetS.[3] Moreover, an elevated ALT level within its reference range, which is also known as a "high-normal" ALT level, is also associated with increased risks of both diabetes and MetS.[4,5] Meanwhile, γ-glutamyltransferase (GGT), another frequently adopted surrogate biomarker for NAFLD, has also been well investigated in epidemiological studies. A growing body of evidence supports the notion that a high-normal GGT concentration is a strong risk marker for metabolic disorders and cardiovascular diseases.[6–11] However, the question as to whether the association between elevated liver enzymes and MetS is independent of insulin resistance either has not been well addressed[12] or has controversial answers: the Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort reported that the association of GGT and MetS was dependent on insulin resistance rather than other confounding factors;[10] whereas the Insulin Resistance Atherosclerosis Study (IRAS) showed that a significant association of ALT and MetS remained after adjustment for a wide range of covariates, including directly measured insulin sensitivity and acute insulin response from the frequently sampled intravenous glucose tolerance test.[5] Besides, few studies have compared different liver enzymes for their associations with MetS; therefore, this study aims to cross-sectionally and longitudinally investigate the association of liver enzymes, including ALT and GGT, with the risks of MetS adjusted for insulin resistance, and to compare GGT and ALT in association with MetS in an adult Chinese population.

Methods

Study subjects

Cross-sectional study

The study subjects were recruited from two nearby communities (Youyi and Songnan) in the Baoshan district in the city of Shanghai between 2004 and 2008. Altogether, there were 5847 subjects aged ≥40 years who participated in the cross-sectional study. The detailed information about subject selection has been described previously.[13,14] Questionnaires requesting information about lifestyle and medical history, anthropometric measurements, a 75-g oral glucose tolerance test, and blood and urine sampling were collected from each participant. A total of 443 subjects were excluded from the present analysis due to missing information on MetS status (n = 120) or serum ALT concentrations (n = 1), known liver diseases such as hepatitis, cirrhosis or malignancy (n = 32), and alcohol consumption exceeding 30 g/day (n = 290), which is considered as heavy drinking.[15] Thus, a total of 5404 subjects were eventually included in the cross-sectional analysis.

Follow-up study

In 2008, we conducted a follow-up examination for those subjects who were first investigated in 2005. Of 963 non-MetS subjects at baseline, 692 (72% response rate) received the same examinations as that at baseline in the follow-up visit. After excluding 11 subjects with missing data on MetS status at follow up, a total of 681 participants were finally included in the longitudinal analysis.

The study protocol was approved by the Institutional Review Board of Rui-Jin Hospital and informed consent was obtained from each participant.

Data collection

The approaches for collection of medical history, anthropometric characteristics and biochemical measurements were consistent at baseline and at follow up. The history of chronic diseases and current use of medication, including antihypertensive drugs, were recorded. A family history of diabetes was defined as having a mother, father, sister, brother, son, or daughter with diagnosed diabetes. The smoking or drinking status was defined as "current" if a subject had smoked cigarettes or consumed alcohol regularly in past 6 months, or "ever" if a subject quit smoking or drinking more than 6 months ago, or "never" if a subject had never started regular smoking or drinking during their lifetime. The information about alcohol consumption included the type of alcoholic beverage and the usual amount consumed daily. Physical activity at leisure time was estimated using the short form of the International Physical Activity Questionnaire by adding questions on the duration of mild/moderate/vigorous activities per day.[16] Levels of leisure-time

activity were categorized as low, medium, and high by the corresponding tertiles of the entire study population. Waist circumference was measured at the umbilical level. Body mass index (BMI) was calculated as body weight in kilograms divided by body height squared in meters (kg/m^2). Blood pressure was measured at the non-dominant arm in a seated position three times consecutively at 1-minute intervals after at least five minutes' rest using an automated electronic device (OMRON Model HEM-752; Omron, Dalian, China). The three readings were averaged for analysis. All participants were informed to fast for at least 10 hours before blood samples were collected.

Plasma glucose, serum ALT, GGT, triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were measured using an autoanalyser (CX-7 Biochemical Autoanalyser; Beckman Coulter, Brea, CA, USA). The white blood cell (WBC) count was determined using an automated cell counter. Serum insulin was measured by a radioimmunoassay (Sangon, Shanghai, China). The index of homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the formula: HOMA-IR = fasting insulin concentration (mIU/L) × fasting plasma glucose concentration (mmol/L)/22.5.

MetS definition

The MetS definition was based on the National Cholesterol Education Program Adult Treatment Panel III criteria[17] with modification on waist circumference cut-off to be more appropriate for an Asian population.[18] A subject was diagnosed to have MetS when three or more of the following were satisfied: (i) blood pressure ≥130/85 mmHg or taking antihypertensive drugs; (ii) waist circumference ≥90 cm in men and ≥80 cm in women; (iii) triglyceride level ≥1.69 mmol/L (150 mg/dL); (iv) HDL cholesterol level < 1.03 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women; and (v) fasting glucose level ≥6.1 mmol/L (110 mg/dL) or confirmed diagnosis of type 2 diabetes.

Statistical analysis

Statistical analysis was performed using SAS version 8.1 (SAS Institute, Cary, NC, USA). Continuous variables were presented as mean ± SD or median (interquartile range) for skewed variables. Categorical variables were shown in proportions. The following skewed variables were logarithmically transformed before analysis: fasting insulin, HOMA-IR, triglycerides, ALT, and GGT.

In cross-sectional analysis, the study population was divided into four quarters on the basis of GGT or ALT distributions. Sex-specific quartiles for GGT concentrations were: < 20, 20–27, 27–40, and ≥40 IU/L for men, and < 16, 16–21, 21–32, and ≥32 IU/L for women; and those for ALT concentrations were: < 12, 12–16, 16–25, and ≥25 IU/L for men, and < 11, 11–15, 15–23, and ≥23 IU/L for women. Linear regression analysis was used to test for trends across GGT or ALT groups with or without adjustment for age, sex, BMI, or community by fitting quantitative variables (1–4, representing four different groups of either GGT or ALT) for the four groups. Logistic regression models were used to assess the univariate and multivariate-adjusted relative risks of MetS and the individual components for each quartile, compared with the reference group (quartile 1 or the lowest quartile). In the adjustment, sex (male/female), community (Youyi/Songnan), occupation (eleven groups), educational level (five groups), family history of diabetes (yes/no), smoking status (never/ever/current), drinking status (never/ever/current), and leisure-time physical activity (low/medium/high) were fitted as categorical variables. Age, BMI, ln(HOMA-IR), ln(ALT) (adjusted for GGT quartiles), and ln(GGT) (adjusted for ALT quartiles) were fitted as continuous variables. Tests of linear trend across increasing quartiles of GGT or ALT were conducted by treating the quartiles as a continuous variable. Results were presented as odds ratios (OR) and 95% confidence intervals (CI).

In longitudinal analysis, one-way analysis of variance was used to analyze statistical differences adjusted for age and sex amongst baseline characteristics of the study participants according to metabolic status at follow up. Logistic regression models were used to evaluate the association of serum GGT or ALT with development of MetS adjusted for the same variables as cross-sectional analysis, except the variable "community". The relationship between GGT and the incidence of each MetS component was also analyzed using logistic regression analysis adjusted for age and sex in participants free of this component abnormality at baseline.

Significance tests were two-tailed and a *P*-value of < 0.05 was considered to be statistically significant.

Results

Cross-sectional analysis

Characteristics of the participants

Clinical and biochemical characteristics of the participants according to baseline GGT and ALT quartiles are shown in Tables 1 and 2. Subjects with higher GGT

Table 1 General characteristics of the study population by γ-glutamyltransferase (GGT) quartiles

	Quartiles				*P*-values for trend	
Variable	1	2	3	4	Unadjusted	Adjusted*
GGT (IU/L)	14 (12–16)	20 (18–22)	28 (24–31)	50 (41–68)		
n	1305	1377	1363	1359		
Age (years)	60.8 ± 10.3	62.0 ± 10.0	62.4 ± 9.5	61.5 ± 9.5	0.044	–
Female, *n* (%)	813 (62.3)	911 (66.2)	866 (63.5)	864 (63.6)	0.86	–
BMI (kg/m^2)	23.9 ± 3.2	25.0 ± 3.4	25.8 ± 3.7	26.5 ± 3.8	<0.0001	–
Current smoking, *n* (%)	193 (14.8)	190 (13.8)	233 (17.1)	251 (18.5)	0.0013	0.0001
Current drinking, *n* (%)	95 (7.3)	139 (10.1)	164 (12.0)	194 (14.3)	<0.0001	<0.0001
Waist circumference (cm)	82.4 ± 9.2	85.4 ± 9.1	87.7 ± 9.4	89.7 ± 9.5	<0.0001	<0.0001
Systolic BP (mmHg)	134 ± 22	139 ± 23	142 ± 22	143 ± 22	<0.0001	<0.0001
Diastolic BP (mmHg)	76 ± 10	78 ± 10	80 ± 10	81 ± 10	<0.0001	<0.0001
Fasting BG (mmol/L)	5.45 ± 1.40	5.80 ± 1.70	6.07 ± 1.91	6.50 ± 2.15	<0.0001	<0.0001
2h post-load BG (mmol/L)	8.16 ± 4.75	9.19 ± 4.88	10.29 ± 5.25	11.63 ± 5.62	<0.0001	<0.0001
Fasting insulin (mIU/L)	4.84 (3.10–7.32)	6.31 (3.82–9.67)	7.79 (4.70–12.10)	9.53 (5.81–14.46)	<0.0001	<0.0001
HOMA-IR	1.14 (0.70–1.77)	1.52 (0.88–2.47)	1.92 (1.17–3.22)	2.55 (1.48–4.20)	<0.0001	<0.0001
Total cholesterol (mmol/L)	4.82 ± 0.92	5.01 ± 0.96	5.18 ± 0.94	5.35 ± 1.08	<0.0001	<0.0001
HDL (mmol/L)	1.42 ± 0.34	1.38 ± 0.35	1.37 ± 0.32	1.35 ± 0.33	<0.0001	0.20
Triglycerides (mmol/L)	1.09 (0.79–1.49)	1.34 (0.93–1.94)	1.55 (1.12–2.13)	1.86 (1.27–2.70)	<0.0001	<0.0001
White blood cell (×10^9/L)	5.80 ± 1.60	6.13 ± 1.56	6.23 ± 1.62	6.30 ± 1.63	<0.0001	<0.0001
ALT (IU/L)	12 (11–16)	14 (10–19)	16 (12–24)	25 (16–39)	<0.0001	<0.0001
Prevalence of MetS, *n* (%)	310 (23.8)	575 (41.8)	731 (53.6)	869 (63.9)	<0.0001	<0.0001

Data are mean ± SD, median (interquartile range) for skewed variables, or proportions for categorical variables.
**P* values for trend across groups were adjusted for age, sex, community, and BMI.
ALT, alanine aminotransaminase; BG, blood glucose; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome.

Table 2 General characteristics of the study population by alanine aminotransaminase (ALT) quartiles

	Quartiles				*P*-values for trend	
Variable	1	2	3	4	Unadjusted	Adjusted*
ALT (IU/L)	9 (7–10)	13 (11–14)	19 (17–21)	33 (27–44)		
n	1326	1349	1354	1375		
Age (years)	63.6 ± 10.1	61.4 ± 10.0	61.5 ± 9.7	60.3 ± 9.2	<0.0001	–
Female, *n* (%)	725 (54.7)	967 (71.7)	850 (62.8)	912 (66.3)	<0.0001	–
BMI (kg/m^2)	24.4 ± 3.4	24.7 ± 3.5	25.5 ± 3.6	26.6 ± 3.8	<0.0001	–
Current smoking, *n* (%)	240 (18.1)	188 (13.9)	214 (15.8)	225 (16.4)	0.47	0.10
Current drinking, *n* (%)	166 (12.5)	125 (9.3)	143 (10.6)	158 (11.5)	0.66	0.91
Waist circumference (cm)	83.6 ± 8.8	84.5 ± 9.5	87.2 ± 9.3	89.8 ± 9.8	<0.0001	<0.0001
Systolic BP (mmHg)	139 ± 23	138 ± 23	140 ± 22	142 ± 22	<0.0001	<0.0001
Diastolic BP (mmHg)	78 ± 11	78 ± 10	79 ± 10	81 ± 10	<0.0001	<0.0001
Fasting BG (mmol/L)	5.95 ± 1.61	5.75 ± 1.78	5.88 ± 1.85	6.25 ± 2.10	<0.0001	<0.0001
2h post-load BG (mmol/L)	8.78 ± 4.54	9.12 ± 5.32	9.96 ± 5.22	11.42 ± 5.62	<0.0001	<0.0001
Fasting insulin (mIU/L)	4.80 (2.63–8.30)	5.91 (3.70–9.00)	7.09 (4.70–10.16)	10.06 (6.55–14.79)	<0.0001	<0.0001
HOMA-IR	1.20 (0.66–2.27)	1.41 (0.84–2.30)	1.73 (1.12–2.72)	2.59 (1.61–4.23)	<0.0001	<0.0001
Total cholesterol (mmol/L)	4.83 ± 0.97	5.11 ± 1.00	5.13 ± 0.94	5.30 ± 1.01	<0.0001	<0.0001
HDL (mmol/L)	1.42 ± 0.38	1.41 ± 0.34	1.36 ± 0.32	1.33 ± 0.30	<0.0001	0.21
Triglycerides (mmol/L)	1.21 (0.84–1.73)	1.33 (0.93–1.97)	1.46 (1.02–2.10)	1.72 (1.21–2.50)	<0.0001	<0.0001
White blood cell (×10^9/L)	5.96 ± 1.74	6.05 ± 1.51	6.18 ± 1.54	6.28 ± 1.64	<0.0001	0.084
GGT (IU/L)	20 (16–26)	20 (15–28)	24 (18–33)	37 (25–57)	<0.0001	<0.0001
Prevalence of MetS, *n* (%)	447 (33.7)	543 (40.3)	634 (46.8)	861 (62.6)	<0.0001	<0.0001

Data are mean ± SD, median (interquartile range) for skewed variables, or proportions for categorical variables.
**P* values for trend across groups were adjusted for age, sex, community, and BMI.
BG, blood glucose; BMI, body mass index; BP, blood pressure; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome.

concentrations were more likely to be current smokers or drinkers. Nearly all the metabolic risk factors, including BMI, waist circumference, blood pressure, fasting and 2h post-load blood glucose, fasting insulin, HOMA-IR, TC and triglycerides, increased significantly with incrementing GGT and ALT quartiles, whereas HDL levels decreased markedly (all $P < 0.0001$). WBC counts also had a significant and positive relationship with GGT and ALT concentrations. These associations remained significant after adjustment for age, sex, community and BMI, with the exception of associations of HDL with GGT and ALT, and of WBC with ALT. The prevalence of MetS increased significantly with increasing GGT and ALT levels, both before and after adjustment (all $P < 0.0001$).

Associations of serum GGT and ALT with MetS

Elevated serum GGT was strongly associated with an increased risk of MetS in both simple and multivariate analyses, in the total study population and in males and females alone (Table 3). Adjustment for HOMA-IR attenuated the association between GGT and MetS, and adding ALT to the model slightly attenuated the association further, but the strong and positive association still remained (all *P*-values for trend < 0.0001). Moreover, the magnitude of the association of GGT with MetS was consistently greater than that of ALT with MetS (Table 4). Adjustment for GGT greatly reduced the ALT–MetS association in all participants and in females, and substantially attenuated the association toward null in males (*P*-value for trend = 0.28; Table 4).

Elevated serum GGT was also independently associated with increased risk of each individual MetS component except low HDL after full adjustment, including HOMA-IR and ALT (all *P*-values for trend < 0.01; Fig. 1a). The risk of high blood pressure increased by 33% with each 1-SD increment of logarithmically transformed GGT, and that of central obesity by 65%, high triglycerides by 141%, and high blood glucose by 75% (all $P < 0.001$). In comparison, elevated ALT was not significantly associated with increased risk of any MetS component after adjustment for a wide range of confounding variables, including serum GGT (all *P*-values for trend > 0.05; Fig. 1b).

Longitudinal analysis

Baseline characteristics of participants by MetS status at follow up

Of the 681 non-MetS subjects at baseline, 180 (26.4%) developed MetS in 3.5 years. The participants who

Table 3 Prevalence rates and relative risks for metabolic syndrome by γ-glutamyltransferase (GGT) quartiles

	Quartiles				*P*-values
GGT	1	2	3	4	for trend
Total (*n* = 5404)					
Cases/subjects number (%)	310/1305 (23.8)	575/1377 (41.8)	731/1363 (53.6)	869/1359 (63.9)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	2.30 (1.95–2.72)	3.71 (3.14–4.38)	5.69 (4.81–6.74)	<0.0001
Model 2	1.00	1.94 (1.61–2.33)	2.88 (2.39–3.47)	4.37 (3.61–5.29)	<0.0001
Model 3	1.00	1.63 (1.34–1.98)	2.14 (1.76–2.61)	2.77 (2.26–3.39)	<0.0001
Model 4	1.00	1.59 (1.31–1.94)	2.02 (1.65–2.48)	2.44 (1.95–3.07)	<0.0001
Male (*n* = 1950)					
Cases/number at risk (%)	115/492 (23.4)	159/466 (34.1)	226/497 (45.5)	278/495 (56.2)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	1.70 (1.28–2.25)	2.73 (2.08–3.59)	4.20 (3.19–5.52)	<0.0001
Model 2	1.00	1.48 (1.06–2.05)	2.14 (1.56–2.95)	3.46 (2.50–4.79)	<0.0001
Model 3	1.00	1.23 (0.88–1.74)	1.73 (1.24–2.42)	2.42 (1.72–3.41)	<0.0001
Model 4	1.00	1.22 (0.87–1.72)	1.70 (1.20–2.39)	2.33 (1.59–3.41)	<0.0001
Female (*n* = 3454)					
Cases/number at risk (%)	195/813 (24.0)	416/911 (45.7)	505/866 (58.3)	591/864 (68.4)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	2.66 (2.17–3.28)	4.43 (3.59–5.47)	6.86 (5.53–8.51)	<0.0001
Model 2	1.00	2.16 (1.71–2.71)	3.24 (2.57–4.09)	4.82 (3.80–6.12)	<0.0001
Model 3	1.00	1.83 (1.44–2.33)	2.30 (1.80–2.94)	2.88 (2.23–3.72)	<0.0001
Model 4	1.00	1.78 (1.39–2.26)	2.12 (1.65–2.73)	2.41 (1.81–3.22)	<0.0001

Model 1, unadjusted; Model 2, adjusted for age, sex, community, occupation, educational level, family history of diabetes, smoking status, drinking status, leisure-time activity and BMI; Model 3, model 2 plus adjustment for HOMA-IR; Model 4, model 3 plus adjustment for alanine aminotransaminase (ALT).

Table 4 Prevalence rates and relative risks for metabolic syndrome by alanine aminotransaminase (ALT) quartiles

ALT	Quartiles 1	2	3	4	*P*-values for trend
Total (*n* = 5404)					
Cases/number at risk (%)	447/1326 (33.7)	543/1349 (40.3)	634/1354 (46.8)	861/1375 (62.6)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	1.33 (1.13–1.55)	1.73 (1.48–2.02)	3.29 (2.81–3.86)	<0.0001
Model 2	1.00	1.53 (1.26–1.85)	1.77 (1.45–2.16)	3.26 (2.64–4.03)	<0.0001
Model 3	1.00	1.45 (1.18–1.78)	1.53 (1.24–1.90)	2.17 (1.73–2.72)	<0.0001
Model 4	1.00	1.30 (1.05–1.60)	1.27 (1.01–1.58)	1.44 (1.12–1.86)	0.014
Male (*n* = 1950)					
Cases/subjects number (%)	175/601 (29.1)	126/382 (33.0)	215/504 (42.7)	262/463 (56.6)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	1.20 (0.91–1.58)	1.81 (1.41–2.32)	3.17 (2.46–4.09)	<0.0001
Model 2	1.00	1.14 (0.82–1.59)	1.42 (1.04–1.94)	2.43 (1.74–3.40)	<0.0001
Model 3	1.00	1.12 (0.79–1.57)	1.25 (0.90–1.74)	1.72 (1.21–2.45)	0.0027
Model 4	1.00	1.00 (0.71–1.42)	1.08 (0.77–1.52)	1.24 (0.84–1.85)	0.28
Female (*n* = 3454)					
Cases/number at risk (%)	272/725 (37.5)	417/967 (43.1)	419/850 (49.3)	599/912 (65.7)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	1.26 (1.04–1.54)	1.62 (1.32–1.98)	3.19 (2.60–3.91)	<0.0001
Model 2	1.00	1.82 (1.42–2.34)	2.10 (1.60–2.75)	3.97 (2.99–5.28)	<0.0001
Model 3	1.00	1.69 (1.29–2.21)	1.79 (1.34–2.39)	2.52 (1.86–3.42)	<0.0001
Model 4	1.00	1.50 (1.15–1.98)	1.44 (1.07–1.95)	1.62 (1.15–2.28)	0.032

Model 1, unadjusted; Model 2, adjusted for age, sex, community, occupation, educational level, family history of diabetes, smoking status, drinking status, leisure-time activity and BMI; Model 3, model 2 plus adjustment for HOMA-IR; Model 4, model 3 plus adjustment for γ-glutamyltransferase (GGT).

progressed to MetS were more likely to be females and had an unfavorable risk profile at baseline compared with non-progressors, including higher BMI and waist circumference, elevated systolic and diastolic blood pressure, increased concentrations of fasting and 2h-post-load glucose and fasting insulin, higher HOMA-IR, triglycerides and WBC count, and lower HDL after adjustment for age and sex (all $P < 0.01$; Table 5). In particular, the progressors had significantly higher serum ALT and GGT concentrations (both $P < 0.001$).

Baseline GGT and ALT in association with the development of MetS

As shown in Table 6, the risk of developing MetS was enhanced dramatically with increasing quartiles of serum GGT. Although the final adjustment of ALT for GGT quartiles attenuated the GGT–MetS association, serum GGT levels were still strongly and independently associated with risks of MetS development in a dose-dependent manner (odds ratios were 1.00, 1.38, 1.62, and 2.29 for quartiles 1, 2, 3, and 4, respectively; *P*-value for trend = 0.01). Age- and sex-adjusted relative risks for developing high blood glucose and high triglycerides were also elevated with increasing serum GGT concentrations (both *P*-values for trend < 0.05; Table 7). In contrast, although the trend for increased MetS risk across incrementing ALT quartiles was significant after adjustment for demographic and anthropometric variables and HOMA-IR, the addition of GGT to the adjustment diminished the significance of the ALT–MetS association (*P*-value for trend = 0.09; Table 6).

Discussion

The present study has evaluated serum liver enzymes, including GGT and ALT, as risk markers for MetS and its component disorders in the middle-aged and elderly Chinese population. The major findings of our study are: (i) both high-normal serum GGT and ALT are associated with increased risk of developing MetS after adjustment for a broad spectrum of metabolic risk factors, including insulin resistance measured by HOMA-IR; and (ii) the association of GGT with MetS was more significant compared with ALT. It indicated that serum GGT is possibly a better risk marker of MetS than ALT.

To our knowledge, this is the first study to investigate the association of different liver enzymes with the risk of developing MetS in the Chinese population. Although elevated circulating concentrations of liver

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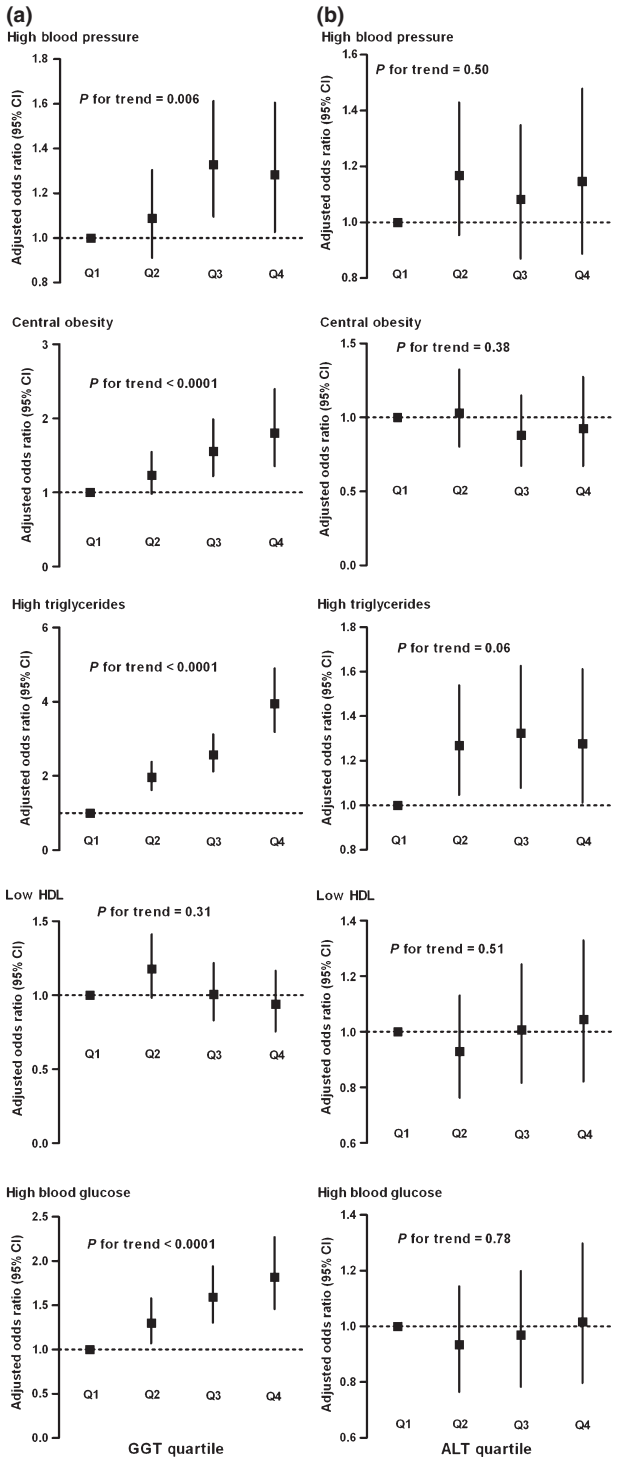

Figure 1 Relative risks for each individual metabolic syndrome component by (a) γ-glutamyltransferase (GGT) and (b) alanine aminotransaminase (ALT) quartiles. Odds ratios were adjusted for age, sex, community, occupation, educational level, family history of diabetes, smoking status, drinking status, leisure-time activity, body mass index, HOMA-IR, and ALT (for GGT) or GGT (for ALT). HDL, high-density lipoprotein.

Table 5 Baseline characteristics of participants, according to metabolic status at follow-up

Baseline variable	Metabolic status at follow-up		
	Non-MetS	MetS	*P* value*
n	501	180	
Age (years)	61.6 ± 9.2	61.7 ± 9.6	0.58
Female, *n* (%)	289 (57.7)	121 (67.2)	0.02
Current smoking, *n* (%)	77 (15.4)	19 (10.6)	0.64
Current drinking, *n* (%)	67 (13.4)	17 (9.4)	0.64
BMI (kg/m^2)	23.6 ± 3.0	25.6 ± 2.8	<0.0001
Waist circumference (cm)	79.8 ± 7.5	84.8 ± 8.5	<0.0001
Systolic BP (mmHg)	132 ± 22	140 ± 22	<0.0001
Diastolic BP (mmHg)	77 ± 10	81 ± 10	<0.0001
Fasting BG (mmol/L)	5.59 ± 0.90	5.97 ± 1.19	<0.0001
2h post-load BG (mmol/L)	7.05 ± 2.43	8.39 ± 2.96	<0.0001
Fasting insulin (mIU/L)	3.5 (1.9–6.9)	5.2 (2.6–8.5)	0.0064
HOMA-IR	0.87 (0.45–1.66)	1.31 (0.67–2.21)	0.0005
Total cholesterol (mmol/L)	4.77 ± 0.82	4.75 ± 0.92	0.30
HDL (mmol/L)	1.62 ± 0.37	1.47 ± 0.33	<0.0001
Triglycerides (mmol/L)	0.97 (0.72–1.29)	1.26 (0.94–1.59)	<0.0001
White blood cell (×10^9/L)	5.52 ± 1.38	5.83 ± 1.47	0.0056
ALT (IU/L)	9 (8–11)	10 (8–14)	<0.0001
GGT (IU/L)	20 (16–27)	23 (18–32)	0.0001

Data are mean ± SD, median (interquartile range) for skewed variables, or proportions for categorical variables.
**P* values were adjusted for age and sex.
ALT, alanine aminotransaminase; BG, blood glucose; BMI, body mass index; BP, blood pressure; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome.

enzymes are not gold-standard measures of NAFLD, it is well recognized that NAFLD is the most common cause of chronically increased transaminase levels after excluding other possible causes of liver injury, such as excess alcohol consumption and virus infection.[19] Therefore, elevated GGT and ALT could be reliable surrogate measures of NAFLD in large population studies. The significant relationship between elevated GGT and ALT concentrations and increased MetS risks independent of insulin resistance in our study was consistent with some, but not all, investigations conducted in different populations.[5,10] The discrepancy might be due to different liver enzymes investigated, varied sample size and follow-up durations, which could result in different statistical power and different measures of insulin resistance, that is, using HOMA-IR in the

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Table 6 Incidence rates and relative risks for development of metabolic syndrome by baseline γ-glutamyltransferase (GGT) or alanine aminotransaminase (ALT)

	Quartiles				*P*-values for trend
	1	2	3	4	
GGT					
Cases/number at risk (%)	22/144 (15.3)	43/186 (23.1)	52/178 (29.2)	63/173 (36.4)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	1.67 (0.95–2.94)	2.29 (1.31–4.00)	3.18 (1.83–5.50)	<0.0001
Model 2	1.00	1.47 (0.81–2.66)	1.79 (1.00–3.23)	2.67 (1.49–4.81)	0.0006
Model 3	1.00	1.41 (0.77–2.56)	1.73 (0.95–3.14)	2.67 (1.47–4.84)	0.0006
Model 4	1.00	1.38 (0.76–2.52)	1.62 (0.89–2.97)	2.29 (1.20–4.35)	0.01
ALT					
Cases/number at risk (%)	27/142 (19.0)	37/187 (19.8)	41/159 (25.8)	75/193 (38.9)	<0.0001
Odds ratio (95% CI)					
Model 1	1.00	1.05 (0.61–1.83)	1.48 (0.85–2.56)	2.71 (1.63–4.51)	<0.0001
Model 2	1.00	0.75 (0.41–1.36)	1.04 (0.58–1.86)	1.75 (1.01–3.05)	0.0042
Model 3	1.00	0.72 (0.40–1.31)	0.99 (0.55–1.79)	1.69 (0.97–2.96)	0.0057
Model 4	1.00	0.69 (0.38–1.26)	0.93 (0.51–1.68)	1.38 (0.75–2.53)	0.09

Model 1, unadjusted; Model 2, adjusted for age, sex, occupation, educational level, family history of diabetes, smoking status, drinking status, leisure-time activity, and BMI; Model 3, model 2 plus adjustment for HOMA-IR; Model 4, model 3 plus adjustment for ALT (for GGT) or GGT (for ALT).

Table 7 Sex- and age-adjusted odds ratios for development of metabolic syndrome (MetS) components by baseline γ-glutamyltransferase (GGT)

	GGT quartiles				*P* values for trend
MetS components	1	2	3	4	
High blood pressure (*n* = 285)					
Cases/number at risk (%)	18/57 (31.6)	42/94 (44.7)	32/68 (47.1)	27/66 (40.9)	0.35
Odds ratio (95% CI)	1.00	2.02 (0.99–4.11)	2.19 (1.03–4.67)	1.55 (0.72–3.31)	0.35
Central obesity (*n* = 463)					
Cases/number at risk (%)	25/110 (22.7)	38/139 (27.3)	31/109 (28.4)	35/105 (33.3)	0.090
Odds ratio (95% CI)	1.00	1.07 (0.58–1.97)	1.35 (0.71–2.57)	1.65 (0.87–3.11)	0.082
High triglycerides (*n* = 621)					
Cases/number at risk (%)	8/136 (5.9)	23/175 (13.1)	15/162 (9.3)	24/148 (16.2)	0.028
Odds ratio (95% CI)	1.00	2.42 (1.04–5.65)	1.60 (0.65–3.92)	3.39 (1.45–7.90)	0.018
Low high-density lipoprotein (*n* = 630)					
Cases/number at risk (%)	23/136 (16.9)	30/166 (18.1)	28/165 (17.0)	33/163 (20.3)	0.52
Odds ratio (95% CI)	1.00	1.01 (0.55–1.85)	0.97 (0.53–1.79)	1.27 (0.70–2.30)	0.46
High blood glucose (*n* = 541)					
Cases/number at risk (%)	13/124 (10.5)	13/143 (9.1)	24/142 (16.9)	29/132 (22.0)	0.0020
Odds ratio (95% CI)	1.00	0.87 (0.38–1.96)	1.76 (0.85–3.64)	2.42 (1.19–4.92)	0.0022

present study and DESIR cohort whereas frequently sampled intravenous glucose tolerance tests were applied to directly measure insulin sensitivity in IRAS.

In recent years, NAFLD has become the most common liver injury worldwide, affecting 15–30% of Western and Eastern populations.[20,21] Fan et al.[21] reported that approximately 20.8% of adults in Shanghai presented with fatty liver, among whom >90% were non-alcoholic fatty liver. The cross-sectional survey also demonstrated a strong association between ultrasound-diagnosed NAFLD and the risk factors characteristic of MetS. Although the advanced stage of NAFLD, including non-alcoholic steatohepatitis, could progress to fibrosis, cirrhosis, and liver failure, the majority of NAFLD progressors had a substantially increased risk of developing metabolic disorders.[22] Insulin resistance, as the core issue of all component disorders of MetS, is also the principle pathophysiological mechanism of NAFLD. The increase of hepatic fat content resulted in the impaired suppression of endogenous glucose production by insulin,[23] which was notable in our study, as elevated serum GGT

values predicted fasting hyperglycemia. Moreover, HOMA-IR, a direct and reliable measure of insulin resistance in the fasting state,[24] also showed a positive and significant association with GGT and ALT after adjustment for age, sex, BMI, and community ($r = 0.25$, $P < 0.0001$; $r = 0.24$, $P < 0.0001$, respectively). The risk of insulin resistance increased across GGT and ALT quartiles.

In our study, GGT was a better risk indicator of MetS than ALT, which is a more specific liver enzyme for NAFLD. In fact, a recent meta-analysis by Fraser et al.[25] also reported a better predictive value of GGT than ALT for type 2 diabetes. Apart from metabolic disorders, a high-normal GGT level was also associated with an increased risk of cardiovascular diseases and all-cause mortality. In the present study, the WBC count, one major component of the inflammatory process, was increased with elevated GGT concentrations rather than ALT, and the association of WBC with GGT was significant after adjustment for age, sex, community, BMI, and HOMA-IR ($r = 0.05$, $P = 0.00001$); therefore, elevated GGT could also be a marker of subclinical inflammation. Furthermore, *in-vitro* studies have showed that GGT participated in the maintenance of intracellular antioxidant defenses by mediating extracellular glutathione into the cells, and thus played an important role in the intracellular antioxidative system. In addition, the concentration-response relationship of GGT with markers of oxidative stress, such as F2-isoprostanes, was demonstrated in humans. GGT was histologically detected within the coronary plaque,[26] which provided evidence that GGT participated directly in oxidation in the plaque and therefore in atherogenesis. Hence, elevated serum GGT could also be an effective indicator of oxidative stress, a causal factor of MetS in the long run.

Several limitations of our study should be addressed. The longitudinal study only included a relatively small number of participants and had a comparatively short duration of follow up, which would attenuate the association toward null and cause the estimate conservative. However, a strong and causal relation between elevated liver enzymes and increased MetS risk was still demonstrated in the longitudinal study. Although the subjects with a history of heavy drinking and other liver diseases were excluded from the present analysis, participants with undiagnosed liver dysfunction, including especially hepatitis B, could not be ruled out. Serum testing for hepatitis B surface antigen is warranted if available.

Our findings have important clinical and public implications, given the fact that the number of people with NAFLD or MetS has been growing at an alarming speed in China in recent years. Subjects who have unexplained, chronically-elevated liver enzymes, especially GGT, might have to be screened and closely followed up for the development of MetS. The simplicity of GGT measurement and its availability in routine clinical practice suggest that this enzyme activity could be included in future MetS prediction algorithms.

In conclusion, this community-based study demonstrated a significant and independent association of liver enzymes with MetS in the adult Chinese population, both cross-sectionally and longitudinally. Moreover, a high-normal serum GGT value is a good risk indicator for the future development of MetS.

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Author contributions

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Yu Xu, Yu-fang Bi, Min Xu, Guang Ning, and Xiao-ying Li. *Acquisition of data*: Yu Xu, Yu-fang Bi, Min Xu, Yun Huang, Wen-ying Lu, and Yi-fu Gu. *Analysis and interpretation of data*: Yu Xu, Yu-fang Bi, Min Xu, and Xiao-ying Li. *Drafting of the manuscript*: Yu Xu and Xiao-ying Li. *Critical revision of the manuscript*: Yu Xu, Min Xu, Yu-fang Bi, Xiao-ying Li, and Guang Ning. *Statistical analysis*: Yu Xu, Min Xu, and Yun Huang.

Disclosure

The authors report there is nothing to disclose.

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