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Association Between Elevated Liver Enzymes and Metabolic Syndrome Among Thai Adults

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Abstract

Background—To examine the relation between elevated liver marker concentrations (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [ALP]) and risk of metabolic syndrome (MetS).

Methods—This cross-sectional study was comprised of 1,391 Thai participants (451 men and 940 women) receiving annual health check-ups. Multivariable logistic regression procedures were used to estimate odds ratios (OR) and 95% confidence intervals (95%CI) of MetS risk according to quartiles of each liver marker concentration with the lowest quartile specified as the referent group.

Results—Overall, mean concentrations of AST, ALT and ALP increased and mean AST:ALT ratio decreased with increasing presence of metabolic abnormalities (p-value=0.059 for AST in men, all other p-values <0.001). After adjusting for confounders, men with ALT concentrations in the extreme quartiles (>40 units/L), had a 2.77-fold increased risk of MetS (95%CI: 1.18–6.53), as compared with men who had values in the lowest quartile (≤21 units/L). The OR for extreme quartiles of ALP concentrations was 3.72 (95%CI: 1.49–9.29). In women, elevated ALT concentrations were also associated with MetS risk. Those with the highest ALT concentrations (>23 units/L) had a 2.55-fold increased risk of MetS (95%CI: 1.22–5.35) compared to women with concentrations ≤13 units/L.

Conclusions—These findings add to an emerging body of literature that suggests elevated liver enzymes may be related with MetS risk. However, prospective studies are needed to more fully determine the practical value of elevated liver enzymes as a clinical risk predictor of MetS and related disorders among Thai adults.

Keywords

Epidemiology; Liver Enzymes; Metabolic Syndrome; Risk Factors

Introduction

Metabolic syndrome (MetS), also known as insulin resistance syndrome, is a collection of metabolic abnormalities that increases the risk of coronary heart disease and type 2 diabetes [1–4]. While excessive abdominal fat and insulin resistance are major characteristics of the disorder, a host of other abnormalities including elevated blood pressure and dyslipidemia (decreased high density lipoprotein-cholesterol (HDL-C), elevated low density lipoprotein cholesterol (LDL-C), and hypertriglyceridemia) are also indicative of MetS [5]. Whilst some individuals are genetically predisposed to such metabolic abnormalities as insulin resistance and obesity, external factors like alcohol consumption, smoking, a sedentary lifestyle, and diets high in highly refined carbohydrates and saturated fats are associated with increased risks of MetS [2].

Recent research has brought attention to nonalcoholic fatty liver disease (NAFLD) as possibly being a phenotypic outcome of MetS [6–10]. Characteristic symptoms of NAFLD range from hepatic steatosis, which is the abnormal retention of fat in the liver, to nonalcoholic steatohepatitis (NASH). NAFLD can further result in liver cirrhosis, fibrosis, liver failure, and hepatocellular carcinoma [8, 10]. Marchesini et al [10] were among the first to identify an association between MetS and NAFLD. Since then, an increasing number of investigators have explored risks of metabolic abnormalities in relation to increased concentrations of various liver enzymes, including γ -glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and high-sensitivity C-reactive protein (CRP, an inflammation marker) [7–9, 11–14].

The prevalence of NAFLD is high among populations residing in western countries. Notably, up to 20% of liver test abnormalities are due to NAFLD [9]. More critically, a worldwide increase in obesity, type 2 diabetes, and cardiovascular disease is predicted [2]. While the risks of MetS have been recognized in developed countries, however, there is limited awareness of the risks and prevalence of metabolic disorders, such as NAFLD, in the Asia-Pacific region. Several studies have investigated metabolic disorders in the region including, Japan [9], where NAFLD was present in 15% of subjects. A study conducted in Indonesia indicated that hepatic steatosis was evident in 30% of subjects [15]. In Taiwan, where 3D body scans were performed on study participants, investigators reported that the prevalence of MetS was 16.6% [16]. This finding is largely consistent with studies conducted in Korea [2, 17] and China [18]. Collectively, available prevalence studies suggest that metabolic disorders including NAFLD and MetS are prevalent among Asians. However, to date, the relationship between elevated liver enzymes and MetS remains unexplored. Therefore, we sought to assess the extent to which, if at all, there are associations between elevated liver enzymes and MetS in a population of Thai adults receiving annual health exams.

Methods

Study Population and Data Collection

We conducted a cross-sectional study of 1,608 patients (536 men and 1072 women) who participated in annual health examinations at the Mobile Health Checkup Unit of King

Chulalongkorn Memorial Hospital in Bangkok, Thailand during the period of December 2006 through February 2007. Each year, Chulalongkorn Memorial Hospital provides on-site annual health examinations to professional and office workers of approximately 45 private companies and governmental agencies in and around Bangkok. Given that blood chemistry evaluations are not routinely measured on all participants under the age of 35 years, this research was restricted to those participants who were ≥ 35 years of age at the time of annual health examination. Eligible participants were asked to provide information about their age, marital status, occupation, educational attainment, medical history, use of anti-hypertensive, anti-diabetic, or lipid lowering medications, smoking status, alcohol consumption habits, and physical activity. Participants underwent routine clinical physical examinations which included collection of venous blood samples after an overnight fast, and measurement of height, weight, waist circumference and resting blood pressures. Standing height was determined without shoes and measured to the nearest 0.5 centimeter. Weight was determined without shoes and with participants lightly clothed. Weight was measured using an automatic electronic scale (Seca, Inc., Hamburg, Germany) to the nearest 100 grams. Waist circumference was measured with a heavy-duty inelastic plastic fiber tape measure to the nearest 0.5 centimeter while the subject stood balanced on both feet, with the feet touching each other and both arms hanging freely. Measurement was taken midway between the inferior margin of the last rib and the iliac crest at the end of expiration [19]. Systolic and diastolic blood pressures, measured using an automatic sphygmomanometer (UDEX-IIa, UEDA, Corp., Tokyo, Japan), were taken in the seated position after participants rested for at least 5 minutes.

Patients taking anti-hypertensive, anti-diabetic, or lipid lowering medications were excluded from further consideration. Hence a total of 1,391 participants (451 men and 940 women) remained for analysis. All participants provided informed consent; and the research protocol was reviewed and approved by the Ethical Committee of Faculty of Medicine, Chulalongkorn University, and the Human Subjects Division, University of Washington.

Laboratory Analyses

Serum triglyceride (TG) concentrations were determined using standardized enzymatic glycerol phosphate oxidase assay procedures. High density lipoprotein-cholesterol (HDL-C) was measured by a chemical precipitation technique using dextran sulfate. Fasting plasma glucose (FPG) concentrations were determined using the hexokinase method. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were measured using standard clinical methods with an automated Hitachi 912 Analyzer (Boehringer, Mannheim, Germany). All assays were completed without knowledge of participants' medical history. Plasma lipids, lipoproteins and glucose concentrations were reported as mg/dL. Liver enzyme concentrations were reported as units/L.

Analytical Variable Specification

Metabolic syndrome (MetS) was defined using a modified version of the ATP III criteria [1]. Briefly, four of the five MetS components were defined using the following ATP III categorizations: 1) raised blood pressure $\geq 130/85$ mmHg; 2) raised triglyceride ≥ 150 mg/dl; 3) reduced high-density lipoprotein-cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl

in women; 4) raised fasting plasma glucose ≥ 100 mg/dl. The fifth component, waist circumference (WC) was defined based on specific values specified for South Asians [20]. Men with WC ≥ 90 cm and women with WC ≥ 80 cm were classified as having a central obesity in this study population. Consistent with the ATP III diagnostic criteria for MetS, participants with three of any of the five components were classified as having MetS.

In order to estimate the risk of MetS according to varying concentrations of liver enzymes, participants were characterized into approximate quartile for each enzyme. Categories were defined for men and women separately. Among men, inter-quartile cut points were 22, 25, 31 units/L for AST; 21, 28, 40 units/L for ALT; 0.71, 0.89, 1.14 for AST:ALT ratio; and 58, 67, 80 units/L for ALP. The corresponding inter-quartile cut points for women were 18, 21, 25 units/L for AST; 13, 17, 23 units/L for ALT; 0.98, 1.21, 1.47 for AST:ALT ratio; and 50, 61, 73 units/L for ALP.

Statistical Analyses

All statistical analyses were performed separately for men and women. Frequency distributions of socio-demographic, behavioral and clinical characteristics were examined. Participants were divided into five groups according their number of metabolic abnormalities (i.e., numbers of positive MetS parameters: 0, 1, 2, 3 and ≥ 4 components). Group-specific mean (and standard deviations: SD) for each liver enzyme was then computed and summarized. Statistical significance for monotonic trends in mean liver enzyme concentrations across groups was assessed using linear regression analytic procedures. Associations of liver enzymes with each component of MetS were determined using the using Spearman's rank correlation coefficients. Univariate and multivariable logistic regression procedures were employed to calculate unadjusted odds ratios (OR) to assess the risk of MetS according to varying concentrations of each liver enzyme. Confounding factors were evaluated on the basis of their hypothesized relationship with the covariates of interest and with MetS [21]. Confounding was empirically assessed by entering covariates into a logistic regression model one at a time, and by comparing the adjusted and unadjusted ORs. Final logistic regression models included those covariates which altered unadjusted ORs by at least 10% [21]. All statistical analyses were performed using SPSS (version 14.0, SPSS Inc. Chicago, IL, USA) software. All reported p-values are two tailed, and confidence intervals were calculated at the 95% level.

Results

The socio-demographic and clinical characteristics of study subjects, stratified by gender, are presented in Table I. Overall, study subjects were middle-aged with a mean of 45.7 years for men and 46.3 years for women. Participants were also well educated. A majority of both men and women had at least a bachelor's degree (70.9% of men and 81.7% of women). Approximately 39% of men reported being consumers of alcohol <10 g/day, while 10.4% reported ≥ 10 g/day. Only 14.6% of women reported being consumers of alcohol. More men were also smokers, both current and previous, as compared to women (37.5% and 5.3%, respectively). A majority of subjects had BMI of 18.5–24.9 kg/m² (57.6% of men and 63.7% of women).

The degree to which increasing concentrations of liver markers are related with the presence of increasing numbers of metabolic abnormalities, represented by increasing number of MetS components, are presented in Table II. Overall, mean concentrations of AST, ALT and ALP increased with increasing MetS components, while mean AST:ALT ratio was inversely related with number of MetS components. Trends were greater in magnitude among women than among men. Most notably, mean concentrations of ALT increased almost 3-fold, from 17.4 units/L in women without metabolic abnormalities to 50.4 units/L in women with 4 MetS components. While this trend was weaker in men, there was still a notable 1.7-fold increase in ALT mean concentrations, from 27.7 units/L in men without MS components to 47.6 units/L in men with 4 MetS components (p-value <0.001 for both men and women). The smallest change in liver enzymes between those without metabolic abnormalities and those with 4 MetS components was evident for mean AST concentration in men (p-value=0.059). In women, the smallest change was noted for mean ALP concentration increase between women without MS and women with 4 MetS components (p-value <0.001).

The results of Spearman's correlation analysis for associations between various liver markers and MetS components are presented in Table III. Overall in men, AST, ALT and ALP were most strongly positively correlated with plasma triglyceride concentrations. ALT was the liver marker most strongly positively associated with metabolic abnormalities. However, unlike men, the strongest positive correlations of ALT and ALP were noted with waist circumference in women. While ALP appeared least correlated with MetS components in men, ALP was the liver marker most positively correlated with blood pressure and fasting plasma glucose in women.

Results from logistic regression analyses of the risk of MetS for those in the 2nd, 3rd, and 4th quartiles of the various liver marker concentrations when compared to those in the 1st quartile are presented in Table IV. After adjusting for age, education, smoking status, drinking status, body mass index and level of physical activity, subjects in the 2nd, 3rd, and 4th quartile of ALT and ALP were at an increased risk for metabolic syndrome outcome when compared to those with concentrations in the 1st quartile. For both men and women, increasing quartiles of AST concentration were not statistically significantly associated with increased risks of MetS. Most notably in men, subjects in the 4th quartile of ALP had a 3.72-fold increased risk of MetS compared with those who had ALP concentrations in the 1st quartile. However, in women, there were no statistically significant increased risks of MetS according to increased concentrations of ALP. Women with ALP concentrations in the 4th quartile had a 1.53-fold increased risk of MetS, though this association did not reach statistical significance (95% CI 0.67–3.49).

We repeated logistic regression analyses after excluding participants who reported consuming alcohol. Results from these restricted analyses were similar to those reported above. For example, men with high ALT concentration (>40 units/L) had a 2.17-fold increased risk of MetS (95%CI: 0.64–10.13) as compared with men who had low ALT concentration (<21 units/L). This measure of association was similar to the 2.77-fold (95%CI: 1.18–6.53) increased estimated for the entire study population. The OR for MetS among women with high ALT concentration (>23 units/L) was 2.56 (95%CI: 1.17–5.60) in

the restricted analysis. The corresponding OR in the analysis of the entire study population was 2.55 (95%CI: 1.22–5.35).

Discussion

Results from this cross-sectional study indicate that increased liver marker concentrations are associated with an increased MetS risk. Statistically significant positive linear trends were noted between elevated AST, ALT, and ALP concentrations and the presence of increasing numbers of metabolic abnormalities. Significant correlations between liver markers AST, ALT and ALP and MetS components were also observed. Results of this study indicate that elevated ALT concentrations are associated with increases in risk for MetS in both men and women. In addition, while elevated ALP was associated with increased MetS risk in men, no such association was evident among women.

Our findings of elevated MetS risk with increasing ALP concentrations are supported by few previous studies. Hanley et al reported that subjects in the upper quartile of ALP had a 2.88-fold increased risk of incident metabolic syndrome compared with those in the lowest quartile (95%CI 1.24–4.20) [11]. However, the association between elevated ALT concentrations and increased MetS risk observed in this study is consistent with a number of previous studies that have demonstrated elevated liver enzymes (including AST, ALT, GGT, and CRP) to be related to an increased risk of MetS and related disorders [11, 14, 22, 23]. In particular, our results support Hanley et al's [11] finding of elevated ALT concentrations associated with increased risks for incident MetS. More generally, this study adds to a growing body of literature demonstrating the prevalence of metabolic disorders in the Asia-Pacific region, including studies in Thailand [24], Taiwan [16], Korea [17, 25], China [18] and Japan [14] providing further support for the recognition of the global impact of metabolic disorders such as MetS.

The exact pathophysiological mechanism of how increased liver markers are related to MetS remains elusive. Moreover, we cannot infer any directionality when relating liver enzymes and components of MetS, such as insulin resistance, from our cross sectional study. As suggested by Hanley et al [11], one possible explanation is that elevated liver markers are indicative of excess fat deposition in the liver, which is a characteristic symptom of NAFLD. Another possible explanation is that elevated liver enzymes indicate liver inflammation, as suggested by Nakanishi et al [14]. Still further, Patel et al [22] reported that in addition to excess visceral adiposity, liver enzymes and MetS risk may be linked with NAFLD and hepatic insulin resistance. Wong et al [26] also reported that most Chinese with histology-proven NAFLD had features of the metabolic syndrome, while Malik et al reported that the full histological spectrum of NAFLD was seen in their patients and the majority of patients were insulin resistant, centrally obese and either diabetic or had impaired glucose tolerance [27]. As reported by the authors, excess visceral fat may facilitate increased hepatic lipogenesis and triglyceride-rich lipoprotein secretion. Further, central obesity may increase insulin resistance as a result of increased expression of proinflammatory adipocytokines and decreased expression of insulin-sensitizing and anti-inflammatory adiponectin. The resulting increase in oxidative stress may be associated with elevated liver enzymes.

This study has several potential limitations. First, as the study population is comprised of highly educated middle-aged university employees, thus results may not be generalizable to the general Thai population. However, the prevalence of MetS in our study population (13.5%) was comparable to estimates from other studies conducted in Thailand (15.0%, 17.7%) [24, 28]. Second, we excluded those commonly used medications which may influence the association between elevated liver markers and risk for metabolic syndrome. We do not have detailed information on other medications and chemical substances that can induce liver enzyme. However, the proportion of subjects who use such medications is expected to be small. Third, because of self-reporting and the lack of quantitative measures of behavioral characteristics such as smoking, drinking, and physical activity, some error and resulting residual confounding by these covariates and others including participants' viral hepatitis status cannot be excluded.

Forth, the cross-sectional design of our study does not allow us to determine the directionality of observed associations. We are not able to determine if altered liver enzyme is a cause or consequence of MetS. Available literature, however, indicate that elevated liver enzymes in subjects without MetS may be a predictor of future developed MetS [11, 29, 30]. For example, Hanley et al [11], in their prospective study with 5.2 years of follow-up study, reported that elevated liver marker concentrations predicted subsequent development of MetS. Lastly, causal inferences from our study are limited given the absence of rigorous, objective measures of liver health, such as the use of ultrasonography or liver biopsies, (to determine hepatic steatosis inflammation and fibrosis). Measuring liver enzyme concentrations at only a single time-point may have led to some misclassification. Future prospective studies with serial measures of liver enzymes, ultrasonographic assessments for fatty liver, and a more comprehensive assessment of participants' exposure to hepatotoxic chemicals will overcome these limitations and will expand the literature.

Despite potential limitations, our cross-sectional study of Thai adults supports the increasingly recognized association between elevated liver enzymes and MetS risk. Notably, it is the first study to report an association between elevated liver markers and increased risk for MetS among Thais. The predicted global increase in metabolic abnormalities, such as MetS, may place millions at risk for cardiovascular disease and type 2 diabetes [7]. This warrants special attention to preventative measures, which may help to ease the financial burden on health care systems and to preserve a decent quality of life for millions. The ease and non-invasive nature of obtaining liver markers from patients at risk for MetS, makes the incorporation of liver markers in diagnosing and predicting MetS a promising and feasible possibility. However, further prospective cohort studies are needed to determine the clinical predictive value of using liver markers to predict MetS and cardiovascular disease risk. In particular, a prospective study to determine the association between elevated liver markers and incident MetS, type 2 diabetes and hypertension among Thais may be an appropriate next step.

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Table I

Socio-demographic and clinical characteristics of study participants.

Characteristics	Men (N=451)		Women (N=940)	
	n ^a	%	n ^a	%
Age (Years)				
<40	116	25.7	169	18.0
40–49	193	42.8	454	48.3
50–59	127	28.2	305	32.4
60	15	3.3	12	1.3
Mean ± SD	45.7 ± 7.3		46.3 ± 6.5	
Education				
<Bachelor degree	129	29.1	170	18.3
Bachelor degree	90	20.3	388	41.7
Master degree	88	19.8	217	23.3
PhD degree	137	30.9	156	16.8
Previous smoker	81	18.1	34	3.7
Current smoker	87	19.4	15	1.6
Never drinker	227	50.7	794	85.4
<10 g/day	174	38.8	128	13.8
10–30 g/day	32	7.1	8	0.9
>30 g/day	15	3.3	0	0.0
Components of MetS				
Waist circumference (cm)	85.2 ± 9.1		74.7 ± 9.6	
Triglyceride (mg/dL)	156.9 ± 136.2		92.9 ± 47.9	
HDL-cholesterol (mg/dL)	53.4 ± 13.4		64.9 ± 16.0	
Systolic blood pressure (mmHg)	126.5 ± 17.3		118.9 ± 16.9	
Diastolic blood pressure (mmHg)	79.0 ± 10.9		71.9 ± 10.5	
Fasting plasma glucose (mg/dL)	94.7 ± 28.4		87.4 ± 15.6	
Liver markers				
AST (units/L)	28.9 ± 19.3		22.7 ± 10.4	
ALT (units/L)	35.5 ± 35.5		20.8 ± 15.4	
AST: ALT ratio	1.0 ± 0.4		1.3 ± 0.8	
ALP (units/L)	70.3 ± 19.4		63.0 ± 18.1	

^a Number may not be added up to the total number due to missing data

Table II

Evaluation of mean ($\pm$ standard deviation) concentrations of liver markers in relation to number of metabolic abnormalities used to define metabolic syndrome.

Liver Marker	Number of Metabolic Abnormalities				Trend Test p-value
	0	1	2	3	4
Men	n = 133	n = 142	n = 81	n = 58	n = 26
AST (units/L)	27.4 $\pm$ 22.5	27.9 $\pm$ 21.2	28.7 $\pm$ 9.8	30.7 $\pm$ 11.9	35.2 $\pm$ 22.1
					0.059
ALT (units/L)	27.7 $\pm$ 18.6	33.6 $\pm$ 50.5	38.9 $\pm$ 22.8	44.6 $\pm$ 30.2	47.6 $\pm$ 28.1
					<0.001
AST: ALT ratio	1.1 $\pm$ 0.3	1.0 $\pm$ 0.4	0.9 $\pm$ 0.4	0.8 $\pm$ 0.3	0.8 $\pm$ 0.2
					<0.001
ALP (units/L)	66.8 $\pm$ 18.0	70.1 $\pm$ 20.8	70.2 $\pm$ 18.1	74.5 $\pm$ 17.4	79.6 $\pm$ 21.4
					0.001
Women	n = 427	n = 261	n = 130	n = 68	n = 32
AST (units/L)	21.8 $\pm$ 11.0	22.1 $\pm$ 8.3	23.5 $\pm$ 8.8	23.6 $\pm$ 9.0	33.8 $\pm$ 19.3
					<0.001
ALT (units/L)	17.4 $\pm$ 8.9	20.1 $\pm$ 15.1	23.1 $\pm$ 12.6	26.8 $\pm$ 15.8	50.4 $\pm$ 41.7
					<0.001
AST: ALT ratio	1.4 $\pm$ 1.0	1.3 $\pm$ 0.5	1.2 $\pm$ 0.5	1.0 $\pm$ 0.3	0.8 $\pm$ 0.3
					<0.001
ALP (units/L)	57.6 $\pm$ 15.1	65.4 $\pm$ 18.8	68.6 $\pm$ 16.8	72.7 $\pm$ 22.7	74.2 $\pm$ 16.2
					<0.001

Spearman correlation coefficients from analysis of associations of liver markers with metabolic abnormalities that define metabolic syndrome.

Table III

Liver markers	WC	TG	HDL-C	SBP	DBP	FPG
Men						
AST	0.160 ^b	0.230 ^b	-0.014	0.132 ^b	0.100 ^a	0.103 ^a
ALT	0.340 ^b	0.356 ^b	-0.220 ^b	0.160 ^b	0.140 ^b	0.228 ^b
AST: ALT ratio	-0.379 ^b	-0.339 ^b	0.321 ^b	-0.140 ^b	-0.134 ^b	-0.247 ^b
ALP	0.093 ^a	0.179 ^b	-0.100 ^a	0.109 ^a	0.086	0.093 ^a
Women						
AST	0.106 ^b	0.175 ^b	0.013	0.050	0.026	0.006
ALT	0.310 ^b	0.284 ^b	-0.178 ^b	0.189 ^b	0.117 ^b	0.150 ^b
AST: ALT ratio	-0.373 ^b	-0.276 ^b	0.268 ^b	-0.230 ^b	-0.154 ^b	-0.210 ^b
ALP	0.362 ^b	0.247 ^b	-0.084 ^a	0.233 ^b	0.179 ^b	0.206 ^b

^a p < 0.05,

^b p < 0.001

WC = waist circumference; TG = triglyceride; HDL = high-density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose

Table IV

Adjusted odds ratio (OR) and 95% confidence interval (CI) of metabolic syndrome risk according to varying concentrations of liver markers.

Liver markers		Men		Women		
	OR ^a	95%CI	Liver markers		OR ^a	95%CI
AST (units/L)						
22	1.00	Reference	18	1.00	Reference	
23–25	1.45	(0.59–3.58)	19–21	1.06	(0.52–2.15)	
26–31	1.63	(0.68–3.91)	22–25	0.90	(0.44–1.84)	
>31	1.83	(0.75–4.45)	>25	1.53	(0.80–2.92)	
<i>p for trend = 0.188</i>		<i>p for trend = 0.284</i>				
ALT (units/L)						
21	1.00	Reference	13	1.00	Reference	
22–28	0.91	(0.33–2.55)	14–17	0.66	(0.27–1.63)	
29–40	1.69	(0.70–4.06)	18–23	1.85	(0.82–4.15)	
>40	2.77	(1.18–6.53)	>23	2.55	(1.22–5.35)	
<i>p for trend = 0.007</i>		<i>p for trend < 0.001</i>				
AST: ALT ratio						
0.71	1.00	Reference	0.98	1.00	Reference	
0.72–0.89	0.54	(0.26–1.14)	0.99–1.21	0.35	(0.19–0.64)	
0.90–1.14	0.32	(0.14–0.74)	1.22–1.47	0.24	(0.11–0.53)	
>1.14	0.31	(0.12–0.79)	>1.47	0.19	(0.07–0.49)	
<i>p for trend = 0.004</i>		<i>p for trend < 0.001</i>				
ALP (units/L)						
58	1.00	Reference	50	1.00	Reference	
59–67	3.06	(1.20–7.82)	51–61	0.90	(0.37–2.18)	
68–80	3.07	(1.18–8.00)	62–73	1.12	(0.48–2.59)	
>80	3.72	(1.49–9.29)	>73	1.53	(0.67–3.49)	
<i>p for trend = 0.011</i>		<i>p for trend = 0.162</i>				

^a Adjusted for age, education, smoking status, alcohol intake, body mass index and level of physical activity. Separate models were estimated for men and women.