Letter to the Editor

Serum Alanine Aminotransferase Is Associated with Metabolic Syndrome and 10-year Risk of Cardiovascular Disease*

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Metabolic syndrome (MetS) is a cluster of metabolic disorders including obesity, hypertension, hyperglycemia, elevated triglyceride levels, and low high-density lipoprotein cholesterol (HDL-C) levels. In recent years, the prevalence of MetS[1] has increased dramatically worldwide. Several researchers have found that elevated ALT is associated with increased risks of MetS, CVD, and T2DM[2]. Some studies have revealed that elevated ALT levels within the normal interval are associated with a higher prevalence of MetS and CVD, although the relationships between ALT and MetS and CVD may differ according to ethnicity and gender.

Based on the previously reported association between MetS and cardiovascular morbidity and mortality, we conducted this study to evaluate the association of ALT levels within the reference interval with MetS and risk of developing CVD among Chinese adults aged 40 years and older.

We conducted a population-based cross-sectional survey in Jiading District, Shanghai, China from March 2010 to August 2010. A total of 10,569 adults aged 40 years and older were invited to join this survey by trained community workers using the door-to-door invitation method. A total of 10,375 residents (participation rate, 98.2%) agreed to participate and signed informed consent forms. The study was conducted with the approval of the Institutional Review Board of Ruijin Hospital, which is affiliated to Shanghai Jiao Tong University School of Medicine[3]. Subjects who met the following criteria were excluded from this study: (1) History of virus hepatitis, liver cirrhosis, liver carcinoma, or autoimmune liver disease (n = 375); (2) missing information to diagnose MetS (n = 19); (3) missing information on ALT level (n = 3); (4) ALT > 40 U/L; and (5) current alcohol intake[4] (n = 986). Finally, a total of 8,300 individuals (5,805 women and 2,495 men) were considered eligible for the analysis.

All subjects underwent a standardized interview, anthropometric measurements, and blood biochemical analysis. A standard questionnaire was used to obtain information on sociodemographics, medical history, family history, and lifestyle behaviors by trained doctors through face-to-face interviews[3]. Using an interviewer-assisted questionnaire, we also collected information on CVDs *via* open-ended questions: 'Has a doctor or other health professional ever told you that you have coronary heart disease, stroke, or myocardial infarction?' Medical records from relevant hospitalizations or emergency department visits were inspected by two physicians who were blind to the self-reported data. We grouped CVDs (reported coronary heart disease, stroke, or myocardial infarction) in the analysis.

Participants who smoked cigarettes regularly over the past 6 months were defined as current smokers. Current drinking was defined as regular consumption of any kind of alcoholic beverage over the past 6 months. The International Physical Activity Questionnaire was used to estimate physical activity by collecting information on intensity, duration, and frequency of physical activity[5].

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Anthropometric measurements were performed by experienced nurses in accordance with a standard protocol. The height and weight of subjects wearing light clothing and no shoes were measured. BMI was calculated by dividing weight (in kilograms) by the square of height (in meters). Waist circumference was measured at the umbilical level while standing. Blood pressure was determined using an automated electronic device (OMRON Model HEM-752 FUZZY; Omron Company, Dalian, China) while sitting; measurements were taken three times consecutively at 1 min intervals after the subject had been sitting for 5 min. The three readings of systolic (SBP) and diastolic (DBP) BP were averaged and recorded for analysis. Plasma glucose concentrations were assayed using the glucose oxidase or hexokinase method within 2 hours after blood sample collection using an autoanalyzer (Modular P800; Roche, Basel, Switzerland). Serum insulin, serum ALT, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglycerides (TG) were also measured using an autoanalyzer (Modular E170; Roche)[3].

The upper limit of ALT is 40 U/L; this limit is generally used to discriminate individuals with liver disease from the general population[6]. Participants were divided according to ALT level into four groups of 2.5-13.2, 13.3-17.1, 17.2-22.7, and 22.8-40.0 U/L. Overweight was defined as a BMI of 25.0-29.9 kg/m^2, and obesity was defined as a BMI of 30.0 kg/m^2 or higher according to World Health Organization definitions. Dyslipidemia was diagnosed according to the modified National Cholesterol Education Program-Adult Treatment Panel III (NCEP/ATP III) as hypercholesterolemia, TC ≥ 6.22 mmol/L (240 mg/dL), hypertriglyceridemia, TG ≥ 2.26 mmol/L (200 mg/dL), high LDL-C, LDL-C ≥ 4.14 mmol/L (160 mg/dL), and low HDL-C, HDL-C < 1.04 mmol/L (40 mg/dL)[7]. NCEP/ATP III MetS criteria for Asian populations were used to diagnose MetS[7]. An individual who had three or more of the following components was diagnosed to have MetS: (1) Waist circumference ≥ 90 cm in men and ≥ 80 cm in women; (2) serum TG ≥ 150 mg/dL (1.69 mmol/L) and/or HDL-C < 40 mg/dL (1.03 mol/L) in men and 50 mg/dL (1.29 mmol/L) in women or on antihyperlipidemic medications; (3) blood pressure ≥ 130/85 mmHg or on antihypertensive medications; and (4) serum fasting glucose ≥ 110 mg/dL (6.10 mmol/L) or on hypoglycemic medications.

Estimated 10-year ASCVD risk scores were calculated using the new Pooled Cohort Risk Assessment Equations according to the recommendations of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. The age range of study participants in the analysis for 10-year ASCVD risk was 40-79 years. An ASCVD score ≥ 7.5% was considered to indicate high 10-year risk of ASCVD among participants without previous CVD[7].

Data are presented as mean ± standard deviation for normally distributed continuous variables and as number (proportions) for categorical parameters. Logistic regression analyses were used to evaluate the relationships between ALT within the normal range and MetS, previous CVDs, and 10-year ASCVD risk. The results of logistic regression analysis are presented as odds ratio (*OR*) and 95% *CI*. The dose-response relationship between ALT and MetS was explored by restricted cubic spline analyses with four knots at the 5th, 25th, 50th, and 95th percentiles of the distribution; here, the 25th percentile was considered the reference ALT level. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Two-sided $P < 0.05$ was considered to indicate statistical significance. We tested *P* values for trends through the quartiles of ALT level by treating it as an ordinal variable.

A total of 8,300 subjects with a mean age of 58.7 ± 9.8 years were included in the current study; of the sample population, 30.06% were men. The prevalence of MetS was 26.49% (30.06% in women and 18.20% in men), 8.27% of the participants reported having CVDs, and 3,134 (42.08%) had an increased estimated 10-year risk of a first hard ASCVD event.

The general characteristics of the study population classified by ALT level quartiles are presented in Table 1. Subjects in higher ALT quartile groups tended to have higher levels of BMI, WC, current smoking status, SBP, DBP, FPG, 2h-PPG, TG, TC, LDL-C, uric acid, serum creatinine, and prevalence of MetS than those in lower quartile groups.

Estimates of the risk of MetS according to ALT level quartiles are shown in Table 2. Higher ALT levels were associated with increased risk of MetS. After adjusting for age, sex, BMI, current smoking status, educational attainment, physical activity, uric acid, creatinine, and family history of diabetes, logistic regression analysis revealed that participants in the third and fourth serum ALT quartiles were associated with a higher risk of MetS compared with those in the first quartile (*OR*, 95% *CI*: 1.32, 1.13-1.53; 1.92, 1.65-2.25) (*P* for trend < 0.0001).

Estimates of the risk of prevalent MetS components according to ALT level quartiles are shown in Supplementary Table S1, available in www.besjournal.com. Multivariate logistic regression analysis indicated that, compared with individuals at the bottom quartile of serum ALT level,

Table 1. Baseline Characteristics of the Study Population According to Alanine Aminotransferase Quartiles (*N* = 8,300)

Characteristis	Serum ALT (U/L)				*P* for Trend
	Quartile 1 (*n* = 2,055)	Quartile 2 (*n* = 2,097)	Quartile 3 (*n* = 2,068)	Quartile 4 (*n* = 2,080)	
ALT, U/L, mean (range)	10.7 (2.5-13.2)	15.2 (13.3-17.1)	19.6 (17.2-22.7)	28.9 (22.8-40.0)	< 0.0001
Age, y	58.05 ± 11.11	59.00 ± 9.60	59.39 ± 9.28	58.45 ± 8.97	0.0004
Male, *n* (%)	376 (18.30)	542 (25.85)	694 (33.56)	883 (42.45)	< 0.0001
BMI, kg/m^2	23.75 ± 3.02	24.56 ± 2.97	25.38 ± 3.21	26.10 ± 3.27	< 0.0001
WC, cm	78.49 ± 8.10	80.55 ± 8.31	83.06 ± 8.51	85.22 ± 8.89	< 0.0001
Current smoker, *n* (%)	193 (9.39)	274 (13.07)	334 (16.15)	420 (20.19)	< 0.0001
SBP, mmHg	137.4 ± 20.9	140.0 ± 20.1	142.7 ± 19.6	143.1 ± 20.0	< 0.0001
DBP, mmHg	80.2 ± 10.2	81.4 ± 10.0	82.8 ± 10.0	84.0 ± 10.2	< 0.0001
FPG, mmol/L	5.3 ± 1.3	5.4 ± 1.3	5.5 ± 1.4	5.7 ± 1.7	< 0.0001
2h-PPG, mmol/L	7.5 ± 3.6	7.8 ± 3.9	8.3 ± 4.2	8.9 ± 4.6	< 0.0001
TG, mmol/L	1.38 ± 0.94	1.52 ± 1.17	1.70 ± 1.28	1.96 ± 1.54	< 0.0001
TC, mmol/L	5.18 ± 0.92	5.35 ± 0.99	5.40 ± 1.03	5.44 ± 1.08	< 0.0001
HDL-C, mmol/L	1.37 ± 0.30	1.36 ± 0.31	1.32 ± 0.31	1.28 ± 0.33	< 0.0001
LDL-C, mmol/L	3.09 ± 0.81	3.21 ± 0.86	3.25 ± 0.89	3.26 ± 0.87	< 0.0001
Uric acid, mmol/L	264.62 ± 80.26	280.20 ± 83.42	296.33 ± 88.63	318.33 ± 93.20	< 0.0001
Creatinine, mmol/L	59.29 ± 19.10	59.91 ± 13.04	61.84 ± 22.84	63.06 ± 15.52	< 0.0001
Physical activity (moderate to vigorous), *n* (%)	285 (13.87)	319 (15.21)	301 (14.56)	293 (14.09)	0.9929
Education status (high school or above), *n* (%)	499 (24.28)	419 (19.98)	403 (19.49)	433 (20.82)	0.0056
Family history of diabetes, *n* (%)	206 (10.07)	213 (10.18)	238 (11.53)	242 (11.67)	0.0440
Metabolic syndrome, *n* (%)	358 (17.42)	475 (22.65)	582 (28.14)	784 (37.69)	< 0.0001

Note. Data are means ± standard deviation (SD) for continuous variables and as number (proportions) for categorical parameters. ALT, alanine aminotransferase; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting blood-glucose; 2-h PPG, 2h postprandial plasma glucose; TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Table 2. Odds Ratio (*OR*) and 95% Confidence Intervals (*CI*s) for Risk of Metabolic Syndrome According to Alanine Aminotransferase Quartiles (*N* = 8,300)

Item	Serum ALT (U/L)				*P* for Trend
	Quartile 1 (*n* = 2,055)	Quartile 2 (*n* = 2,097)	Quartile 3 (*n* = 2,068)	Quartile 4 (*n* = 2,080)	
Cases, *n*	530	648	803	1,031	
Prevalence, %	25.79	30.90	38.83	49.57	< 0.0001
Model 1	1.00	1.29 (1.12-1.47)	1.83 (1.60-2.09)	2.83 (2.48-3.22)	< 0.0001
Model 2	1.00	1.34 (1.17-1.54)	2.04 (1.78-2.34)	3.60 (3.13-4.13)	< 0.0001
Model 3	1.00	1.10 (0.94-1.28)	1.37 (1.18-1.59)	2.11 (1.81-2.45)	< 0.0001
Model 4	1.00	1.08 (0.93-1.26)	1.32 (1.13-1.53)	1.92 (1.65-2.25)	< 0.0001

Note. Model 1, unadjusted; Model 2: Adjusted for age and sex; Model 3: Adjusted for age, sex, BMI, current smoking status, education attainment and physical activity; Model 4: Adjusted for age, sex, BMI, current smoking status, education attainment, physical activity, uric acid, creatinine and family history of diabetes. ALT, alanine aminotransferase.

those in the highest quartile were associated with an increased risk of high blood pressure (*OR* = 1.31, 95% *CI*: 1.12-1.54), hypertriglyceridemia (*OR* = 2.46, 95% *CI*: 2.12-2.86), and high fasting glucose (*OR* = 1.82, 95% *CI*: 1.52-2.18) (all *P* < 0.0001).

The association between serum ALT level and CVD was evaluated. A total of 686 (8.27%) subjects had a history of CVD, including 240 (9.62%) men and 446 (7.68%) women. Elevated serum ALT was associated with an increased risk of CVDs.

The prevalence numbers of self-reported CVDs in the first, second, third, and fourth quartiles were 164 (7.98%), 175 (8.35%), 169 (8.17%), and 178 (8.56%), respectively. The estimated 10-year risk of a first hard ASCVD event was evaluated in participants free of CVDs (*n* = 7,448, Table 3; Supplementary Figure S1, available in www.besjournal.com), and a total of 3,134 (42.08%) participants revealed an ASCVD risk score ≥ 7.5%. Multivariate-adjusted *OR*s (95% *CI*) of ASCVD risk score ≥ 7.5% associated with the ALT quartiles in the first, second, third and fourth quartiles were 1.00, 0.97 (0.68-1.39), 1.28 (0.90-1.82), and 1.82 (1.26-2.63), respectively (*P* for trend < 0.0001; Table 3).

We conducted a cross-sectional study to explore the relationship between serum ALT levels within the reference interval (< 40 U/L) with MetS and 10-year risk of a first hard ASCVD event in the middle-aged and elderly Chinese. After adjustment for potential confounders, we found positive associations between serum ALT level within the reference interval and MetS and 10-year risk of a first hard ASCVD event.

ALT, a specific liver enzyme and marker of liver damage, is restricted to the cytoplasm of hepatocytes[8]. Our study indicates that elevated ALT levels, even when within the reference interval, are associated with increased risk of MetS and 10-year risk of ASCVD.

While the mechanisms underlying the association between ALT and MetS and its related diseases, such as CVDs, have not been fully clarified, the clear association between MetS and CVD may offer some explanation for this phenomenon. Unexplained ALT elevation is commonly caused by non-alcoholic fatty liver disease, which is associated with insulin resistance, obesity, and CVD; in fact, this disease is commonly considered the hepatic component of MetS[2]. However, Sookoian and Pirola[9] argued that the glutamine-cycling pathway may be involved in the development of MetS. ALT is an important enzyme in this cycling. Researchers have speculated that abnormal ALT levels may reflect the risk of MetS before the liver becomes fatty.

Insulin resistance may be another mechanism explaining the association between ALT and MetS. Some studies have indicated that insulin resistance, a major risk factor of MetS and CVD, is associated with ALT[10]. Moreover, endothelial dysfunction and oxidative stress in adipocytes are two potential mechanisms of the association between ALT and CVD[10]. Assays for ALT are simple, inexpensive, sensitive, and specific for liver injury. The current upper normal limit of ALT level is 40 U/L. However,

Table 3. Association between Alanine Aminotransferase Quartiles and Cardiovascular Diseases in Middle-aged and Elderly Chinese Adults

Variables	Serum ALT (U/L)				*P* for Trend
	Quartile 1 (*n* = 2,055)	Quartile 2 (*n* = 2,097)	Quartile 3 (*n* = 2,068)	Quartile 4 (*n* = 2,080)	
Cardiovascular diseases (*N* = 8,300)					
Case percentage (%)	164 (7.98%)	175 (8.35%)	169 (8.17%)	178 (8.56%)	0.5654
Age-adjusted *OR* (95% *CI*)	1.00	1.07 (0.85-1.34)	1.03 (0.81-1.30)	1.19 (0.94-1.49)	0.4688
Multivariate adjusted *OR* (95% *CI*)[†]	1.00	1.03 (0.81-1.30)	0.91 (0.71-1.15)	0.91 (0.71-1.17)	0.6664
ASCVD risk score ≥ 7.5%[††] (*N* = 7,448)					
Case percentage (%)	586 (32.06%)	717 (38.10%)	869 (46.62%)	962 (51.33%)	< 0.0001
Age-adjusted *OR* (95% *CI*)	1.00	1.24 (1.03-1.48)	1.98 (1.65-2.37)	3.29 (2.74-3.94)	< 0.0001
Multivariate adjusted *OR* (95% *CI*)[†]	1.00	0.97 (0.68-1.39)	1.28 (0.90-1.82)	1.82 (1.26-2.63)	< 0.0001

Note. [†]Multivariable model adjusted for age, sex, BMI, current smoking status, education attainment, physical activity, SBP, TG, HDL-C, lipid-lowering treatment, antidiabetic treatment, antihypertensive treatment. [††]Analysis was carried out in participants ages 40-79 years old, free of CVD (*N* = 7,448) and individuals with ASCVD score ≥ 7.5% were identified as at high risks for 10-year ASCVD. *OR*, odds ratio; *CI*, confidence interval; ALT indicates alanine aminotransferase; BMI, body mass index; SBP, systolic blood pressure; TG, triglyceride; HDL-C, high density lipoprotein cholesterol.

several studies have shown that many people with MetS and NAFLD have ALT levels within the current reference interval; thus, reducing the upper limit of normal has been proposed. Updating the upper limit could help improve the identification of subjects with subclinical liver disease and at high risk of developing metabolic diseases, such as MetS. However, several researchers also suggest that reducing the upper limit of ALT level may increase healthcare expenditures and cause undue stress. Our results indicate that the risk of MetS and 10-year risk of ASCVD increase with increasing ALT level within the reference interval. Thus, elevated ALT levels, even in the reference interval, may reflect early dysmetabolic changes and greater risks of MetS and CVD.

Our research involved analysis of a large sample size, but some limitations must be noted. First, this study is a cross-sectional study and cannot delineate the temporal associations of ALT with MetS and CVD or identify a causal relationship. Prospective research and clinical trials are needed to validate the present results. Second, our study was performed among a middle-aged and elderly Chinese population; thus, results should be carefully interpreted for other ages and ethnical populations. Third, we may have over- (or under)-estimated the 10-year ASCVD risk in the Chinese population by using ASCVD risk scores, which were established in American populations by the ACC/AHA. The ASCVD risk equations used in this study may require validation to determine their suitability for Chinese populations. Fourth, aggregation effects, such as family members with similar genes and inclination to develop the same diseases, may exist among the subjects; thus, data that are not completely independent of each other were not excluded in the current study. Further analysis is needed to verify the independent associations found in our study. Finally, information on cardiovascular diseases was obtained through self-reports, which may lead to inevitable recall bias.

In conclusion, we found a positive relationship between ALT levels within the reference interval and the risk of MetS and the 10-year risk of ASCVD among the middle-aged and elderly Chinese. Elevated ALT levels, even when within the reference interval, may reflect early dysmetabolic changes, greater risks of MetS, and greater 10-year risks of ASCVD. Further investigations are needed to validate this association and the underlying mechanisms.

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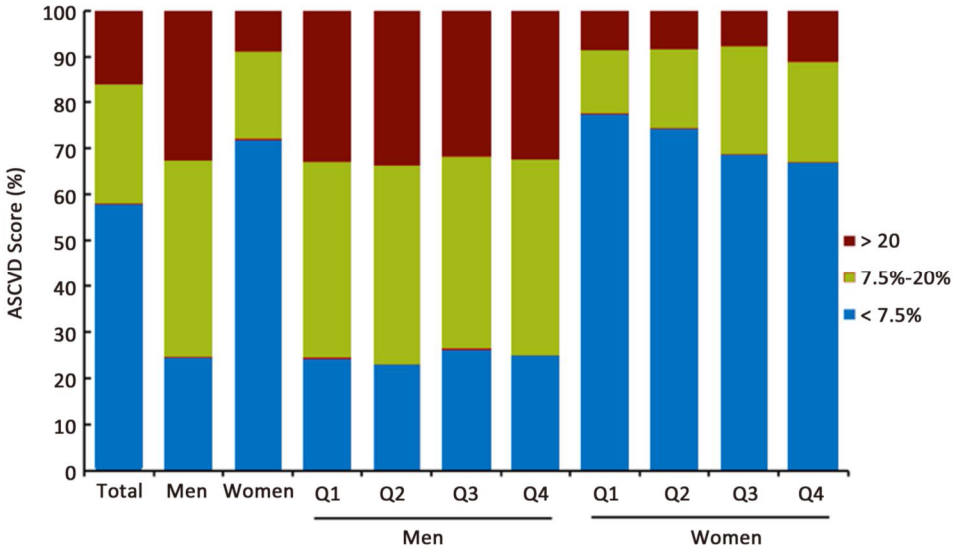
REFERENCES

1. Aguilar M, Bhuket T, Torres S, et al. Prevalence of the metabolic syndrome in the United States, 2003-2012. JAMA, 2015; 313, 1973-4.
2. Schindhelm RK, Diamant M, Dekker JM, et al. Alanine aminotransferase as a marker of non-alcoholic fatty liver disease in relation to type 2 diabetes mellitus and cardiovascular disease. Diabetes Metab Res Rev, 2006; 22, 437-43.
3. Lu J, Zhang J, Du R, et al. Age at menarche is associated with the prevalence of non-alcoholic fatty liver disease later in life. J Diabetes, 2017; 9, 53-60.
4. Kuzhandai velu V, Jyothirmayi B, Kumar JS. Insulin resistance and alanine amino transaminase (ALT) levels in first degree relatives of type 2 diabetes mellitus. Diabetes Metab Syndr, 2011; 5, 143-7.
5. Du R, Cheng D, Lin L, et al. Association between serum CA 19-9 and metabolic syndrome: A cross-sectional study. J Diabetes, 2017; 9, 1040-7.
6. Lee Y, Han KD, Jung JJ, et al. Upper Normal Alanine Aminotransferase Range and Insulin Resistance in Korean Adolescents: Korean National Health and Nutrition Examination Survey, 2009-2010. Dig Dis Sci, 2016; 61, 1700-6.
7. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation, 2002; 106, 3143-421.
8. Liu Z, Que S, Xu J, et al. Alanine aminotransferase-old biomarker and new concept: a review. Int J Med Sci, 2014; 11, 925-35.
9. Sookoian S, Pirola CJ. Alanine and aspartate aminotransferase and glutamine-cycling pathway: their roles in pathogenesis of metabolic syndrome. World J Gastroenterol, 2012; 18, 3775-81.
10. Schindhelm RK, Dekker JM, Nijpels G, et al. Alanine aminotransferase predicts coronary heart disease events: a 10-year follow-up of the Hoorn Study. Atherosclerosis, 2007; 191, 391-6.



Supplementary Figure S1. Distribution of estimated 10-year risk for a first hard atherosclerotic cardiovascular diseases (ASCVD) event in middle-aged and elderly Chinese adults without CVD, stratified by sex and alanine aminotransferase quartiles. (*n* = 7,448).

Supplementary Table S1. Odds Ratio (*OR*) and 95% Confidence Intervals (*CI*s) of the Components of Metabolic Syndrome by Alanine Aminotransferase Quartiles (*N* = 8,300)

Characteristis	Serum ALT (U/L)				*P* Value
	Quartile 1 (*n* = 2,055)	Quartile 2 (*n* = 2,097)	Quartile 3 (*n* = 2,068)	Quartile 4 (*n* = 2,080)	
Central obesity					
Case percentage, *n* (%)	741 (36.06)	888 (42.35)	1,036 (50.10)	1,155 (55.53)	< 0.0001
Age-adjusted *OR* (95% *CI*)	1.00	1.28 (1.13-1.46)	1.75 (1.54-1.98)	2.21 (1.95-2.51)	< 0.0001
Multivariate adjusted *OR* (95% *CI*)*	1.00	0.98 (0.82-1.18)	1.08 (0.90-1.30)	1.17 (0.96-1.41)	0.0712
High blood pressure					
Case percentage (%)	1,324 (64.43)	1,478 (70.48)	1,587 (76.74)	1,646 (79.13)	< 0.0001
Age-adjusted *OR* (95% *CI*)	1.00	1.22 (1.07-1.40)	1.67 (1.45-1.93)	2.07 (1.79-2.40)	< 0.0001
Multivariate adjusted *OR* (95% *CI*)*	1.00	1.05 (0.91-1.21)	1.24 (1.06-1.44)	1.31 (1.12-1.54)	< 0.0001
Hypertriglyceridemia					
Case percentage (%)	427 (20.78)	587 (27.99)	725 (35.06)	961 (46.20)	< 0.0001
Age-adjusted *OR* (95% *CI*)	1.00	1.47 (1.27-1.70)	2.03 (1.77-2.34)	3.27 (2.85-3.75)	< 0.0001
Multivariate adjusted *OR* (95% *CI*)*	1.00	1.35 (1.16-1.56)	1.70 (1.47-1.97)	2.46 (2.12-2.86)	< 0.0001
Low high-density lipoprotein cholesterol					
Case percentage (%)	733 (35.67)	699 (33.33)	767 (37.09)	840 (40.38)	< 0.0001
Age-adjusted *OR* (95% *CI*)	1.00	0.91 (0.80-1.03)	1.07 (0.95-1.22)	1.23 (1.08-1.39)	< 0.0001
Multivariate adjusted *OR* (95% *CI*)*	1.00	0.85 (0.74-0.97)	0.96 (0.84-1.10)	1.06 (0.92-1.22)	< 0.0001
High fasting glucose					
Case percentage (%)	256 (12.46)	318 (15.16)	369 (17.84)	514 (24.71)	< 0.0001
Age-adjusted *OR* (95% *CI*)	1.00	1.24 (1.04-1.48)	1.49 (1.25-1.78)	2.35 (1.99-2.78)	< 0.0001
Multivariate adjusted *OR* (95% *CI*)*	1.00	1.14 (0.95-1.37)	1.22 (1.02-1.47)	1.82 (1.52-2.18)	< 0.0001

Note. *Multivariable model adjusted for age, sex, BMI, current smoking status, education attainment, physical activity, uric acid, creatinine and family history of diabetes. ALT indicates alanine aminotransferase; BMI, body mass index.