INTRODUCTION

Metabolic syndrome (MS) refers to a cluster of interrelated risk factors that include hypertension, obesity, hyperglycemia, and dyslipidemia. Evidence suggests that MS can increase the risks for cardiovascular disease, type 2 diabetes, and all-cause mortality. At present, there are approximately 1/3 adults in the United States and 1/5 adults in China with MS. With the increasing prevalence of sedentary behavior and obesity, the prevalence of MS will continue to increase. The prevention and treatment of MS had become urgent. Serum alanine aminotransferase (ALT) is a marker of liver injury and is commonly used to identify non-alcoholic fatty liver disease, which is considered as a hepatic component of MS. The relationship between ALT and MS was studied by a number of researchers. Some epidemiological studies suggested that elevated ALT levels can increase the risk of MS and...
its related diseases, such as cardiovascular disease and diabetes. On the other hand, Janiĉko, et al. showed that people with elevated ALT are not at an increased risk of MS and its components, compared with people with normal ALT. The upper normal limit of serum ALT level is set on 40 U/L on average, ranging from 30–50 U/L, which is used to discriminate people with diseased liver from general people. However, there are some people with nonalcoholic fatty liver disease or/and MS, whose ALT levels are still within the reference interval. Several studies have reported that elevation of ALT level within the reference interval is associated with a higher prevalence of MS; however, the association between ALT and MS might differ by ethnicity and gender. Little is known, meanwhile, of the detailed dose-response relationship of ALT levels within the reference interval and MS in different genders. Studies to test whether a linear dose-response relationship or a threshold effect is present are warranted.

Accordingly, we conducted logistic regression analyses and restricted cubic spline models to evaluate the association of ALT levels within the reference interval with MS and dose-response relationships in different genders to provide some evidence for prevention and control of MS.

MATERIALS AND METHODS

Study population
Subjects for this study were selected from who attended routine health check-ups at the Health Management Center of Shengli Oilfield Central Hospital in Dongying City, located in eastern China, from January 2006 to March 2012. A total of 16621 subjects who met all the following conditions were included in our study: 1) aged 18 years or more; 2) serum ALT levels in the reference interval (≤40 U/L); and 3) clinical data on measurements of ALT level and related indicators to diagnose MS. If a person attended two or more health check-ups during the 6 years, we used the latest health examination data in this cross-sectional study.

Subjects were excluded from analysis if they had a positive test for hepatitis B virus surface antigen or hepatitis C virus antibody. Those with a history of viral hepatitis, liver cirrhosis, liver carcinoma, or autoimmune liver disease were also excluded from this study. Additionally, we further excluded people with serious disease, such as renal failure, heart failure, and malignancy. Finally, 16028 people (6372 women and 9656 men) were included in our study. This study was approved by the Ethics Committee of School of Public Health, Shandong University, and informed oral consent was obtained from each participant.

Measurements
All subjects underwent a standardized interview, anthropometric measurements, and blood biochemical analysis. The standardized interview obtained information on age, medical history, and lifestyle behaviors (including smoking and drinking). The medical history included diseases of hypertension, diabetes, liver disease, and cancer. Smoking was defined as smoking any tobacco product continuously or cumulatively for more than 6 months during their lifetime and at least once within the past 30 days. Drinking was defined as consumption of any kind of alcohol beverage averagely once a week, but excluding occasionally drinking during festivals.

The anthropometric measurements evaluated weight, height, body mass index (BMI), and blood pressure. Height and weight were measured on subjects with light clothing and no shoes. BMI was calculated by dividing weight (kg) by the height (m) squared. Blood pressure was measured twice from the right arm by a calibrated mercury sphygmomanometer after at least 5 minutes of rest in a comfortable sitting position.

Blood samples were collected under at least 12 hours fasting conditions. Blood biochemical tests to determined serum levels of ALT, fasting blood-glucose (FPG), triglyceride (TG), total cholesterol (T-Ch), high density lipoprotein cholesterol (HDL-C), serum creatinine (Cr), uric acid (UA), and total bilirubin (TBIL) were performed using an automatic analyzer (Hitachi 7170; Hitachi, Tokyo, Japan). White blood cell counts (WBC) were measured by a CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, IL, USA). In addition, hepatitis B virus surface antigen and hepatitis C virus antibody were tested by the enzyme-linked immunosorbent assay (ELISA).

Definition of metabolic syndrome
In this study, MS was defined according to the criteria proposed by China Diabetes Society (CDS). The criteria for MS were three or more of the following risk factors: 1) overweight or obesity, BMI ≥25.0 kg/m²; 2) hypertension, systolic blood pressure (SBP) ≥140 mm Hg, or diastolic blood pressure (DBP) ≥90 mm Hg, or previous diagnosis of hypertension; 3) dyslipidemia, TG ≥1.7 mmol/L, or low HDL-C (<0.9 mmol/L in men, <1.0 mmol/L in women); 4) hyperglycemia, FPG ≥6.1 mmol/L (110 mg/dL), or 2 h post-meal glucose (PG) ≥7.8 mmol/L (140 mg/dL), or previous diagnosis with hyperglycemia.

Statistical analysis
Data are presented as means±standard deviation (SD) for normally distributed continuous variables and as proportions for categorical variables. According to variable distributions using histograms, skewed variables are expressed as medians (interquartile range). To compare differences in general characteristics between the quartiles of ALT, One-Way Analysis of Variance or Kruskal-Wills H test was used for continuous variables, and Pearson χ² test was used for categorical variables. Linear regression analysis was used to test for trend across the four groups of ALT levels. Logistic regression analyses were used to compute the odds ratios (OR) for MS and its components in higher quartiles, compared with the lowest quartile of ALT lev-
els. Considering biological mechanisms and the habits of statistical analysis, regular analysis variables and variables with p less than 0.10 in univariate analysis were entered into the multiple analysis. The dose-response relationship between ALT and MS was explored by restricted cubic spline analyses with 5 knots at percentiles 5%, 25%, 50%, 75%, and 95% of the distribution, and percentile 25% was the reference ALT level. Restricted cubic spline analyses were performed by SAS 9.3 (SAS Institute, Cary, NC, USA) and all other statistical analyses were conducted using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Two-sided p<0.05 was considered statistically significant.

RESULTS

General characteristics

This study included 16028 subjects, with 6372 females and 9656 males, aged 18–85 years old. The prevalence of MS in the total population was 13.7% (6.4% for females and 18.4% for males).

Compared with females, males had higher levels of ALT and a higher prevalence of MS (p<0.001). The general characteristics of participants stratified by ALT quartiles in different genders are presented in Table 1 and Table 2. Subjects in the higher ALT quartiles tended to have higher levels of diagnostic indexes of MS in both genders, except for HDL-C which decreased with increasing ALT level.

Table 1. General Characteristics Stratified by ALT Quartiles in Women

| Variables | Quartile 1 (n=1716) | Quartile 2 (n=1848) | Quartile 3 (n=1435) | Quartile 4 (n=1373) | p value | p for trend
|-----------|---------------------|---------------------|---------------------|---------------------|---------|-------------|
| MS (%)    | 2.0                 | 4.2                 | 7.0                 | 14.3                | <0.001  | <0.001      |
| Smoking (%) | 0.1               | 0.5                 | 0.6                 | 0.7                 | 0.038   | 0.009       |
| Drinking (%) | 0.1               | 0.3                 | 0.6                 | 0.6                 | 0.110   | 0.018       |
| ALT (U/L) | 9.00 (8.00−10.00)   | 13.00 (13.00−14.00) | 18.00 (17.00−19.00) | 25.00 (23.00−30.00) | <0.001  | <0.001      |
| Age (years) | 38.10±10.40       | 40.81±11.54         | 42.48±12.00         | 43.90±12.16         | <0.001  | <0.001      |
| BMI (kg/m²) | 21.69±2.77        | 22.46±3.06          | 22.99±3.26          | 24.02±3.66          | <0.001  | <0.001      |
| SBP (mm Hg) | 117.25±16.84      | 120.83±18.66        | 124.15±20.36        | 128.30±22.43        | <0.001  | <0.001      |
| DBP (mm Hg) | 73.09±10.58       | 75.51±11.01         | 76.13±12.05         | 78.47±12.95         | <0.001  | <0.001      |
| FPG (mmol/L) | 4.80 (4.60–5.10)  | 4.80 (4.60–5.10)    | 4.90 (4.60–5.30)    | 5.00 (4.70–5.40)    | <0.001  | <0.001      |
| T-Ch (mmol/L) | 4.44±0.84       | 4.60±0.88           | 4.77±0.91           | 4.94±1.01           | <0.001  | <0.001      |
| HDL-C (mmol/L) | 1.42±0.28      | 1.40±0.28           | 1.42±0.31           | 1.37±0.30           | 0.001   | 0.007       |
| TG (mmol/L) | 0.76 (0.56–1.03)  | 0.84 (0.62–1.20)    | 0.95 (0.68–1.38)    | 1.13 (0.77–1.74)    | <0.001  | <0.001      |
| VLDL (mmol/L) | 5.79±1.44       | 5.85±1.42           | 6.01±1.50           | 6.16±1.64           | <0.001  | <0.001      |
| UA (umol/L) | 229.51±49.69     | 237.88±54.46        | 245.51±51.59        | 258.51±63.13        | <0.001  | <0.001      |
| Cr (umol/L) | 55.58±10.95      | 57.00±10.78         | 57.26±11.35         | 57.21±12.61         | <0.001  | <0.001      |
| T-Bil (umol/L) | 12.26±4.71      | 12.55±5.00          | 12.81±5.09          | 12.38±4.79          | 0.018   | 0.240       |

MS, metabolic syndrome; ALT, alanine aminotransferase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting blood-glucose; T-Ch, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; WBC, white blood cell count; UA, uric acid; Cr, serum creatinine; T-Bil, total bilirubin.

Risk of MS and its components by ALT

Table 3 and Table 4 list results of logistic regression analyses for the presence of MS and its components in relation to the quartiles of ALT level in different genders. Higher ALT level was associated with higher prevalence of MS and its three components (hypertension overweight/obesity and dyslipidemia) in both sexes. The OR of MS increased to 4.830 for women and 3.168 for men in the highest quartile, compared with the ALT levels in the lowest quartile, after adjustment for multiple confounders. However, the risk of hyperglycemia was positively associated with ALT level in women, but not in men.

Dose-response association between ALT and MS

Restricted cubic spline analyses, with adjustment for the same variables in multiple logistic regression analyses, indicated a positive dose-response relationship between the risk of MS and ALT level in women and men, and all tests for overall association were significant. The estimated shapes of the associations are shown (Figs. 1–4). In univariate analyses, a non-linear relationship of the risk of MS with ALT level was found in both genders (p for nonlinearity <0.0001 in women and 0.0072 in men). In multivariable analyses, the relationship between the risk of MS and ALT level was nonlinear in women (p for nonlinearity=0.0327), but linear in men (p for nonlinearity=0.0659).
### Table 2. General Characteristics Stratified by ALT Quartiles in Men*

| Variables               | Quartile 1 (n=2545) | Quartile 2 (n=2296) | Quartile 3 (n=2601) | Quartile 4 (n=2214) | p value  | p for trend † |
|-------------------------|---------------------|---------------------|---------------------|---------------------|----------|--------------|
| MS (%)                  | 10.4                | 14.8                | 20.5                | 29.1                | <0.001   | <0.001       |
| Smoking (%)             | 32.5                | 31.6                | 32.8                | 34.1                | 0.342    | 0.184        |
| Drinking [%]            | 39.2                | 41.2                | 43.2                | 44.8                | 0.001    | <0.001       |
| ALT (U/L) ‡             | 13.00 (11.00–15.00) | 19.00 (18.00–20.00) | 25.00 (23.00–26.00) | 33.00 (31.00–36.00) | <0.001   | <0.001       |
| SBP (mmHg)              | 129.92±19.31        | 131.37±19.07        | 133.90±18.93        | 134.80±18.57        | <0.001   | <0.001       |
| BMI (kg/m²)             | 81.07±12.66         | 82.32±12.70         | 84.45±12.70         | 85.77±13.03         | <0.001   | <0.001       |
| FPG (mmol/L) †          | 5.00 (4.70–5.40)    | 5.06 (4.70–5.50)    | 5.10 (4.70–5.50)    | 5.10 (4.80–5.60)    | <0.001   | 0.001        |
| T-CH (mmol/L) ‡         | 4.63±0.86           | 4.76±0.90           | 4.86±0.89           | 4.95±0.91           | <0.001   | <0.001       |
| HDL-C (mmol/L) ‡        | 1.26±0.27           | 1.22±0.27           | 1.19±0.27           | 1.15±0.26           | <0.001   | <0.001       |
| TG (mmol/L) †           | 1.05 (0.76–1.51)    | 1.24 (0.86–1.78)    | 1.42 (1.00–2.05)    | 1.62 (1.14–2.45)    | <0.001   | <0.001       |
| WBC (10³/µL) ‡          | 6.27±1.57           | 6.45±1.61           | 6.63±1.65           | 6.79±1.72           | <0.001   | <0.001       |
| UA (umol/L) ‡           | 320.89±66.27        | 336.00±71.58        | 343.21±69.03        | 356.73±73.63        | <0.001   | <0.001       |
| Cr (umol/L) ‡           | 76.17±13.21         | 75.13±12.38         | 75.46±12.51         | 75.06±12.31         | 0.015    | 0.013        |
| TBLI (umol/L) ‡         | 16.07±6.52          | 16.24±6.28          | 15.82±6.15          | 15.52±5.90          | 0.001    | <0.001       |

MS, metabolic syndrome; ALT, alanine aminotransferase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting blood-glucose; T-CH, total cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; WBC, white blood cell count; UA, uric acid; Cr, serum creatinine; TBLI, total bilirubin.

*ALT quartiles in men were as follows: ≤16.0 U/L, 16.1–21.0 U/L, 21.1–28.0 U/L, 28.1–40.0 U/L. 1Categorical variable expressed as percentages. Pearson χ² test was used to test the difference between four groups, 2Skewed variable expressed as medians (interquartile range). Kruskal-Wallis H test was used, 3Normally distributed continuous variable expressed as means±SD. One-way analysis of Variance was used, 4Linear regression analysis was used to test for the trend across the four groups.

### Table 3. Logistic Regression for the Presence of MS in Relation to ALT Quartiles

| ALT quartiles * | OR (95% CI) for MS in women | OR (95% CI) for MS in men |
|-----------------|-----------------------------|--------------------------|
|                 | Unadjusted                  | Adjusted†                 | Unadjusted                  | Adjusted†                 |
| Quartile 1      | 1.000                       | 1.000                     | 1.000                       | 1.000                     |
| Quartile 2      | 2.151 (1.429–3.238)         | 1.451 (0.847–2.488)       | 1.490 (1.255–1.770)         | 1.306 (1.078–1.583)       |
| Quartile 3      | 3.746 (2.523–5.561)         | 2.817 (1.699–4.670)       | 2.218 (1.882–2.599)         | 1.975 (1.651–2.362)       |
| Quartile 4      | 8.287 (5.715–12.016)‡        | 4.830 (2.980–7.828)‡      | 3.529 (2.017–6.126)‡         | 3.168 (2.649–3.790)‡      |

MS, metabolic syndrome; ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval; WBC, white blood cell count; UA, uric acid; Cr, serum creatinine; TBLI, total bilirubin.

*Gender-specific quartiles of ALT: women (≤11.0, 11.1–15.0, 15.1–20.0, 20.1–40.0 U/L), men (≤16.0, 16.1–21.0, 21.1–28.0, 28.1–40.0 U/L). 1Adjusted for age, smoking, drinking, WBC, UA and TBLI. 2The value of OR was statistically significant, p < 0.05.

### DISCUSSION

In this study, we conducted a cross-sectional study to explore the relationship between ALT levels within the reference interval (<40 U/L) and MS in a large-scale adult Chinese population. We found a positive relationship between ALT levels within the reference interval and the prevalence of MS and most of its components in both sexes, after adjustment for potentially confounders. The OR of MS monotonously increased with increasing levels of ALT in both genders, although the relationship had several differences in women and men.

ALT is a specific liver enzyme and a marker of liver damage, restricted to the cytoplasm of hepatocytes. A few studies of Korean and Israeli populations found that increased ALT levels within the reference interval are associated with an increased risk of MS. The present study in Chinese adults is in accordance with these articles. Compared with ALT levels in the lowest quartile, the OR of MS in the highest ALT groups increased to 4.830 and 3.168 in women and men, respectively. Our study supports that elevated ALT level even within the reference interval can increase the risk of MS.

Different from previous studies, this paper analyzed the dose-response relationship between ALT levels within the reference interval and MS in different genders. This study found that elevated ALT levels among the reference interval are positively and monotonously associated with an increased risk of MS in both genders. The detail dose-response curve was positive and linear in men, but positive and non-linear in women. The reason for the difference is not clear. Menopause status may be an explanation. Polotsky reported that the incidence

https://doi.org/10.3349/ymj.2017.58.1.158
### Table 4. Multiple Logistic Regression for the Presence of the Components of MS in Relation to ALT Quartiles

| ALT quartiles | Hypertension | Overweight/obesity | Hyperglycemia | Dyslipidemia | Hypertension | Overweight/obesity | Hyperglycemia | Dyslipidemia |
|---------------|--------------|--------------------|---------------|--------------|--------------|--------------------|---------------|--------------|
|               | OR (95% CI) in women | OR (95% CI) in men |               |              | OR (95% CI) in women | OR (95% CI) in men |               |              |
| Quartile 1    | 1.000        | 1.000              | 1.000         | 1.000        | 1.000        | 1.000              | 1.000         | 1.000        |
| Quartile 2    | 1.277 (0.996–1.637) | 1.277 (1.013–1.609) | 1.412 (0.874–2.828) | 1.247 (0.942–1.649) | 0.881 (0.765–1.015) | 1.576 (1.376–1.803) | 1.031 (0.830–1.281) | 1.408 (1.211–1.637) |
| Quartile 3    | 1.483 (1.151–1.911) | 1.613 (1.275–2.041) | 1.739 (1.084–2.789) | 1.602 (1.211–2.120) | 1.191 (1.039–1.366) | 2.133 (1.870–2.434) | 1.014 (0.821–1.252) | 1.944 (1.685–2.244) |
| Quartile 4    | 1.972 (1.538–2.528) | 2.026 (1.607–2.554) | 2.086 (1.324–3.323) | 2.423 (1.853–3.168) | 1.345 (1.163–1.554) | 3.154 (2.736–3.635) | 1.185 (0.952–1.475) | 2.415 (2.080–2.802) |

MS, metabolic syndrome; ALT, alanine aminotransferase; OR, odds ratio; CI, confidence interval; WBC, white blood cell count; UA, uric acid; Cr, serum creatinine; TBIL, total bilirubin.

*Gender-specific quartiles of ALT: women (≤11.0, 11.1–15.0, 15.1–20.0, 20.1–40.0 U/L), men (≤16.0, 16.1–21.0, 21.1–28.0, 28.1–40.0 U/L). Adjusted for age, smoking, drinking, WBC, UA, Cr, TBIL and the components of MS other than the analyzed component.*

The value of OR was statistically significant, p<0.05.

MS increases markedly during perimenopause and early menopause. Metabolic changes are associated with menopausal transition. Lacking information on menopausal status in our study, we stress that this speculation needs confirmation in future research.

# Alanine Aminotransferase and Metabolic Syndrome

Previous studies have indicated that ALT elevation in the absence of liver disease is strongly associated with insulin resistance and obesity, which is commonly considered as the hepatic component of MS. ALT is as important an enzyme as the hepatic component of MS.

In our study, we stress that this speculation needs confirmation in future research.
A previous study has reported that CDS criteria and IDF criteria are in good accordance. Meanwhile, considering the fact that our database lacks waist circumference information, CDS criteria might make our estimation more precise. Although there may be a slight difference by using different criteria to diagnose MS, the difference would hardly change the noted dose-response trends in the relationship between ALT and MS.

There are some limitations in this study. First, the participants of our study were enrolled from a hospital for routine health check-ups who mainly work in enterprises, institutions, factories, and for government. Therefore, there is a question as to whether the present findings could be applicable to other groups of people, such as farmers. Second, we had no detailed data on alcohol consumption, and thus, we could not exclude alcohol abusers. However, ALT levels among alcohol abusers are usually higher than 40 U/L, and our subjects only included ALT levels in the reference interval. Therefore, the influence of alcohol abusers would be limited. Finally, this study was a cross-sectional study, and could not delineate the temporal association of ALT with MS or identify a causal relationship. Prospective research and clinical trials are needed to validate the present results in the future.

In conclusion, we found a positive dose-response relationship between ALT levels within the reference interval and the risk of MS in both genders. Elevated ALT levels, even within the reference interval, may reflect early dysmetabolic changes and a greater risk for MS.

ACKNOWLEDGEMENTS

We are indebted to the members of the Health Management Center of Shengli Oilfield Central Hospital in Dongying City. They have provided invaluable help with the data collection.

REFERENCES

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Dona-
to KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.

2. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poizier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113-32.

3. Khang YH, Cho SI, Kim HR. Risks for cardiovascular disease, stroke, ischemic heart disease, and diabetes mellitus associated with the metabolic syndrome using the new harmonised definition: findings from nationally representative longitudinal data from an Asian population. Atherosclerosis 2010;213:579-85.

4. Mozumdar A, Ligouri G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999-2006. Diabetes Care 2011;34:216-9.

5. Xi B, He D, Hu Y, Zhou D. Prevalence of metabolic syndrome and its influencing factors among the Chinese adults: the China Health and Nutrition Survey in 2009. Prev Med 2013;57:867-71.

6. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. Exerc Sport Sci Rev 2010;38:105-13.

7. James PT. Obesity: the worldwide epidemic. Clin Dermatol 2004;22:276-80.

8. Schindhelm RK, Diamant M, Dekker JM, Tushuizen ME, Teerlink T, Heine RJ. 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.

9. Goessling W, Massaro JM, Vasan RS, D’Agostino RB Sr, Ellison RC, Fox CS. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. Gastroenterology 2008;135:1935-44, 1944.e1.

10. Janičko M, Veselény E, Orenčák R, Huslák R, Fedáčko J, Dražilová S, et al. Redefining the alanine aminotransferase upper limit of normal improves the prediction of metabolic syndrome risk. Eur J Gastroenterol Hepatol 2015;27:405-11.

11. Kim HC, Choi KS, Jang YH, Shin HW, Kim DJ. Normal serum aminotransferase levels and the metabolic syndrome: Korean National Health and Nutrition Examination Surveys. Yonsei Med J 2006;47:542-50.

12. Suh SY, Choi SE, Ahn HY, Yang HM, Kim YI, Sung NJ. The association between normal alanine aminotransferase levels and the metabolic syndrome: 2005 Korean National Health and Nutrition Examination Survey. Metabolism 2009;58:1731-6.

13. Steinvil A, Shapira I, Ben-Bassat OK, Cohen M, Vered Y, Berliner S, et al. The association of higher levels of within-normal-limits liver enzymes and the prevalence of the metabolic syndrome. Cardiovasc Diabetol 2010;9:30.

14. Bethel MA, Deedwania P, Levitt NS, Schmitz O, Huntsman-Labeld A, Califf RM, et al. Metabolic syndrome and alanine aminotransferase: a global perspective from the NAVIGATOR screening population. Diabet Med 2009;26:1204-11.

15. Liu Z, Que S, Ning H, Wang L, Peng T. Elevated alanine aminotransferase is strongly associated with incident metabolic syndrome: a meta-analysis of prospective studies. PLoS One 2013;8:e60596.

16. WHO. Guidelines for controlling and monitoring the tobacco epidemic. Geneva: World Health Organization; 1998.

17. Ma G, Zhu D, Hu X, Luan D, Kong L, Yang X. [The drinking practice of people in China]. Acta Nutrimenta Sinica 2005;27:362-65.

18. Wang X, Yang F, Bots ML, Guo WY, Zhao B, Hoes AW, et al. Prevalence of the metabolic syndrome among employees in Northeast China. Chin Med J 2015;128:1989-93.

19. Desquillet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med 2010;29:1037-57.

20. Polotsky HN, Polotsky AJ. Metabolic implications of menopause. Semin Reprod Med 2010;28:826-34.

21. Murphy MJ, Metcalf BS, Voss LD, Jeffery AN, Kirkby J, Mallam KM, et al. Girls at five are intrinsically more insulin resistant than boys: The Programming Hypotheses Revisited--The EarlyBird Study (EarlyBird 6). Pediatrics 2004;113(1 Pt 1):82-6.

22. Ehnh MC, Karnoub MC, Sakal H, Gottschalk K, Holt DC, Weber JL, et al. Genomewide search for type 2 diabetes susceptibility genes in four American populations. Am J Hum Genet 2000;66:1871-81.

23. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98:960-7.

24. Tarantino G, Finelli C. What about non-alcoholic fatty liver disease as a new criterion to define metabolic syndrome?. World J Gastroenterol 2013;19:3375-84.

25. Gariani K, Philippe J, Jornayvaz FR. Non-alcoholic fatty liver disease and insulin resistance: from bench to bedside. Diabetes Metab 2013;39:16-26.

26. Sookoian S, Pirolo CJ. Alanine and aspartate aminotransferase and glutamine-cycling pathway: their roles in pathogenesis of metabolic syndrome. World J Gastroenterol 2012;18:3775-81.

27. Hanley AJ, Wagenknecht LE, Festa A, D’Agostino RB Jr, Haffner SM. Alanine aminotransferase and directly measured insulin sensitivity in a multiethnic cohort: the Insulin Resistance Atherosclerosis Study. Diabetes Care 2007;30:1819-27.

28. Yamada J, Tomiyama H, Yambe M, Koji Y, Motobe K, Shiina K, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Atherosclerosis 2006;189:198-205.

29. Lee SH, Kim KN, Kim KM, Joo NS. Irritable bowel syndrome may be associated with elevated alanine aminotransferase and metabolic syndrome. Yonsei Med J 2016;57:146-52.

30. Harrison SA. HCV therapy in 2006: down with ALT levels, in with fibrosis. J Hepatol 2006;44:624-6.

31. Wu WC, Wu CY, Wang YJ, Hung HH, Yang HI, Kao WY, et al. Updated thresholds for serum alanine aminotransferase level in a large-scale population study composed of 34 346 subjects. Aliment Pharmacol Ther 2012;36:560-8.

32. Prati D, Taioi E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase. Ann Intern Med 2002;137:1-10.

33. Kunde SS, Lazenby AJ, Clements RH, Abrams GA. Spectrum of non-alcoholic fatty liver disease in relation to type 2 diabetes mellitus and cardiovascular disease. Yonsei Med J 2016;57:146-52.

34. Wei D, Chen T, Li J, Gao Y, Ren Y, Zhang X, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Atherosclerosis 2006;189:198-205.