

# Normal Serum Aminotransferase Levels and the Metabolic Syndrome: Korean National Health and Nutrition Examination Surveys

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Increasing evidence suggests an association between elevated serum aminotransferase level and the metabolic syndrome. However, the significance of relatively low levels of aminotransferase in relation to the metabolic syndrome has not been fully investigated in the general population. We investigated the association between serum aminotransferase level and the metabolic syndrome using data from a nationwide survey in Korea. We measured serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels and metabolic conditions among 9771 participants aged 20 or more in the 1998 and 2001 Korean National Health and Nutrition Examination Surveys. Metabolic syndrome was defined according to NCEP-ATP III criteria with a modified waist circumference cutoff (men > 90 cm; women > 80 cm). Serum aminotransferase level, even within normal range, was associated with the metabolic syndrome independent of age, body mass index, waist circumference, smoking, and alcohol intake. Compared with the lowest level (< 20 IU/L), the adjusted odds ratios (95% CI) for an AST level of 20-29, 30-39, 40-49 and  $\geq$  50 IU/L were 1.10 (0.85-1.42), 1.37 (1.02-1.83), 1.62 (1.08-2.43), and 2.25 (1.47-3.44) in men, and 1.18 (0.99-1.41), 1.43 (1.29-1.83), 1.71 (1.09-2.68), and 2.14 (1.20-3.80) in women, respectively. Corresponding odds ratios for ALT levels were 1.27 (0.99-1.63), 1.69 (1.28-2.23), 2.17 (1.58-2.99), and 2.65 (1.96-3.58) in men, and 1.44 (1.22-1.70), 1.65 (1.26-2.15), 2.94 (1.93-4.47), and 2.25 (1.54-3.30) in women, respectively. In conclusion, elevated serum aminotransferase levels, even in the normal to near normal range, are associated with features

of the metabolic syndrome.

**Key words:** Metabolic syndrome, aspartate aminotransferase, alanine aminotransferase, non-alcoholic fatty liver disease

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is an increasingly recognized condition that has accompanied the recent increase in obesity.<sup>1-3</sup> and is also known to be associated with various cardiovascular risk factors including central obesity, type 2 diabetes, dyslipidemia, and high blood pressure.<sup>2,4-9</sup> Moreover, it has been suggested that NAFLD can be considered a hepatic consequence of the metabolic syndrome.<sup>10-14</sup> Patients with fatty liver disease usually have elevated serum aminotransferase activity, and so aminotransferase assays are widely used to monitor liver function in people with metabolic syndrome.<sup>12</sup> It has been suggested, however, that the use of current definitions of normal serum aminotransferase levels may underestimate the prevalence of liver disease, because normal aminotransferase levels cannot rule out the existence of liver disease.<sup>15-17</sup> The significance of serum aminotransferase level, including within the normal to near normal range, needs to be reviewed in relation to the metabolic syndrome, and the need for a full investigation in the general population still remains. Accordingly, we investigated the independent association between serum aminotransferase level and the metabolic syndrome in a representative Korean population.

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## MATERIALS AND METHODS

### Study population

The Korean National Health and Nutrition Examination Surveys were conducted in non-institutionalized Korean civilians in 1998 and 2001. A stratified multistage probability sampling design was used, with selection made from sampling units based on geographical area, sex, and age groups using household registries. A total of 13,451 individuals (7945 in 1998 and 5506 in 2001) aged 20 years or more completed the health examinations. Among them, 11,282 people fasted for at least eight hours before their blood samples were obtained. We excluded 549 people who tested positive for Hepatitis B (HBsAg), and 95 pregnant women. We also excluded 389 people who reported consuming at least 50 g of alcohol per day. In the end, 9771 people (4019 men and 5752 women) were eligible for our analyses.

### Data collection

Anthropometric measurements including height, weight, and waist and hip circumference were conducted by well-trained examiners on individuals wearing light clothing. Waist circumference was measured to the nearest 0.1 cm at the midpoint between the lower borders of the rib cage and the iliac crest. A standard mercury sphygmomanometer was used to measure the blood pressure of each individual in a sitting position after a 10-minute rest period. Systolic and diastolic blood pressures were measured at phase I and V Korotkoff sounds, respectively. Two readings of systolic and diastolic blood pressure were recorded and the average was used for data analysis. Blood samples were obtained after an overnight fasting period and subsequently analyzed at a central certified laboratory. Serum glucose, total cholesterol, triglyceride, high density lipoprotein (HDL)-cholesterol, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were measured by an autoanalyzer (Hitachi 747, Tokyo, Japan). Smoking and alcohol consumption habits and current medication status were determined by a self-administered questionnaire. Non-drinkers were people who reported

that they never or almost never (less than once a month) consumed alcoholic beverages. For drinkers, daily alcohol intake was calculated by multiplying the frequency of drinking and the amount consumed in one sitting.

### Definition of the metabolic syndrome

The metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), except for abdominal obesity by waist circumference.<sup>18</sup> We used a modified waist circumference cutoff of > 90 cm in men and > 80 cm in women.<sup>19</sup> Hence, in the present study, individuals having three or more of the five following criteria were defined as having the metabolic syndrome: 1) high blood pressure ( $\geq 130/85$  mmHg) or anti-hypertensive medication, 2) elevated fasting blood glucose ( $\geq 6.1$  mmol/L) or anti-diabetic medication, 3) hypertriglyceridemia ( $\geq 1.7$  mmol/L), 4) low HDL-cholesterol (men, <1.0 mmol/L; women, <1.3 mmol/L), and 5) abdominal obesity by waist circumference (men, > 90 cm; women, > 80 cm).

### Statistical analysis

We compared clinical and biochemical characteristics between men and women using student's t-test or  $\chi^2$  test. Spearman correlation coefficients among the metabolic risk factors and aminotransferase levels were calculated in men and women separately. The sex-specific prevalence of abnormal metabolic conditions and the metabolic syndrome were calculated by the level of AST and ALT. Independent association between serum aminotransferase level and the metabolic syndrome was investigated using serial logistic regression models. First, we estimated the age-adjusted odds ratio for the metabolic syndrome by serum aminotransferase levels. Second, we adjusted for age, body mass index, cigarette smoking and alcohol intake. Finally, waist circumferences were adjusted in addition to all of the variables in the second model. In order to assess the possible confounding effects of alcohol intake, we investigated the association between ALT and the metabolic syndrome by drinking status.

## RESULTS

Clinical characteristics and laboratory data of the 4019 men and 5752 women are shown in Table 1. Mean age was 44.7 years for men and 45.6 years for women ( $p = 0.009$ ), but mean body mass index was the same for both sexes. Compared with women, men had higher waist circumference, blood pressure, fasting glucose, triglyceride, AST and ALT levels, but lower HDL-cholesterol levels. Among the study participants, 6.6% were taking anti-hypertensive medications, and 2.6% were taking anti-diabetic medications. Of men, 61.5%

were current smokers, as were 5.7% of women. Regular alcohol drinkers comprised 64.8% of men and 28.1% of women.

Serum aminotransferase levels were correlated with most metabolic risk factors, except there was no association ( $p = 0.982$ ) between AST level and HDL-cholesterol level in women. Compared to AST level, serum ALT level was more closely associated with body mass index, waist circumference, and fasting blood glucose level (Table 2). Prevalence of central obesity, high blood pressure, high fasting blood glucose, and hypertriglyceridemia increased according to the increase of

**Table 1.** Clinical and Biochemical Characteristics of 4019 Men and 5752 Women

Characteristics	Men (n = 4019)	Women (n = 5752)	<i>p</i> for difference*
Mean ± SD			
Age (yr)	44.7 ± 15.1	45.6 ± 15.8	0.009
Body mass index, kg/m <sup>2</sup>	23.3 ± 3.0	23.3 ± 3.3	0.805
Waist circumference, cm	83.2 ± 8.3	78.4 ± 9.5	< 0.001
Systolic blood pressure, mmHg	126.7 ± 18.1	122.6 ± 20.6	< 0.001
Diastolic blood pressure, mmHg	80.4 ± 11.3	75.9 ± 11.4	< 0.001
Fasting glucose, mmol/L	5.59 ± 1.47	5.51 ± 1.47	0.008
Total cholesterol, mmol/L	4.87 ± 0.94	4.87 ± 0.95	0.924
Triglyceride, mmol/L	1.61 ± 0.82	1.31 ± 0.69	< 0.001
HDL-cholesterol, mmol/L	1.19 ± 0.29	1.29 ± 0.30	< 0.001
Aspartate aminotransferase, IU/L	28.1 ± 21.0	23.0 ± 8.9	< 0.001
Alanine aminotransferase, IU/L	29.9 ± 20.7	20.1 ± 12.9	< 0.001
Number (%)			
Anti-hypertensive medication	203 (5.1)	441 (7.7)	< 0.001
Anti-diabetic medication	91 (2.3)	163 (2.8)	0.082
Cigarette smoking			
Nonsmoker	786 (19.6)	5311 (92.3)	< 0.001
Ex-smoker	762 (19.0)	111 (1.9)	
Current smoker	2471 (61.5)	330 (5.7)	
Alcohol intake			
Nondrinker	1414 (35.2)	4138 (71.9)	< 0.001
Drinker	2605 (64.8)	1614 (28.1)	

\*Student's t-test for continuous variables, and  $\chi^2$ -test for categorical variables.  
HDL, high density lipoprotein.

**Table 2.** Correlation Among Metabolic Risk Factors and Serum Aminotransferase Levels

	BMI	WC	SBP	DBP	Total cholesterol	Triglyceride	HDL-cholesterol	FBS	AST	ALT
BMI	-	0.818	0.196	0.266	0.261	0.343	-0.270	0.146	0.123	0.353
WC	0.836	-	0.248	0.290	0.284	0.384	-0.280	0.188	0.161	0.340
SBP	0.311	0.403	-	0.660	0.133	0.169	0.028*	0.137	0.175	0.117
DBP	0.289	0.334	0.750	-	0.182	0.213	0.001 <sup>†</sup>	0.079	0.163	0.197
Total cholesterol	0.267	0.329	0.311	0.272	-	0.354	0.112	0.140	0.156	0.220
Triglyceride	0.332	0.413	0.346	0.281	0.424	-	-0.375	0.139	0.189	0.293
HDL-cholesterol	-0.220	-0.246	-0.112	-0.078	0.127	-0.421	-	-0.045 <sup>‡</sup>	0.105	-0.068
FBS	0.234	0.281	0.235	0.162	0.182	0.213	-0.110	-	0.095	0.141
AST	0.149	0.223	0.280	0.220	0.254	0.217	0.001 <sup>§</sup>	0.118	-	0.682
ALT	0.298	0.340	0.252	0.235	0.251	0.262	-0.051	0.190	0.683	-

Figures are Spearman correlation coefficients for men in the upper right of the table, for women in the lower left of the table. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein; FBS, fasting blood sugar; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

All correlations were significant with  $p < 0.001$ , except for \* $p = 0.077$ ; <sup>†</sup> $p = 0.954$ ; <sup>‡</sup> $p = 0.004$ ; <sup>§</sup> $p = 0.928$ .

**Table 3.** Prevalence (%) of Metabolic Abnormalities by Serum Aminotransferase Level

Metabolic abnormality	Aspartate aminotransferase (IU/L)					$p$ for trend	Alanine aminotransferase (IU/L)					$p$ for trend
	<20	20-29	30-39	40-49	≥50		<20	20-29	30-39	40-49	≥50	
Men												
Waist circumference > 90 cm	14.8	18.3	25.7	35.8	28.6	<0.001	10.6	16.7	25.8	33.1	41.6	<0.001
Blood pressure ≥ 130/85 mmHg*	34.4	43.8	51.8	55.3	65.9	<0.001	39.0	43.4	48.6	53.9	55.6	<0.001
Fasting blood glucose ≥ 6.1 mmol/L*	15.2	17.9	23.5	28.8	30.8	<0.001	15.2	17.6	22.3	23.5	31.4	<0.001
Triglyceride ≥ 1.7 mmol/L	26.8	35.0	47.8	54.0	55.5	<0.001	25.2	34.0	44.3	55.5	61.6	<0.001
HDL-cholesterol < 1.0 mmol/L	34.8	31.6	27.9	28.8	21.4	<0.001	27.8	29.0	33.6	35.6	37.1	<0.001
Women												
Waist circumference > 80 cm	30.8	44.7	53.9	61.5	66.7	<0.001	31.7	52.2	62.5	73.3	67.4	<0.001
Blood pressure ≥ 130/85 mmHg*	21.0	38.7	50.3	48.1	54.3	<0.001	27.1	43.5	43.5	54.0	50.6	<0.001
Fasting blood glucose ≥ 6.1 mmol/L*	12.8	17.8	22.7	29.6	39.5	<0.001	12.5	22.4	22.4	26.7	33.1	<0.001
Triglyceride ≥ 1.7 mmol/L	16.7	25.4	32.7	40.0	42.0	<0.001	17.5	30.9	30.9	43.3	39.3	<0.001
HDL-cholesterol < 1.3 mmol/L	54.7	52.3	55.8	56.3	53.1	0.916	52.3	54.4	54.4	60.0	57.9	0.002

\*Including people on anti-hypertensive/anti-diabetic medication.

HDL, high density lipoprotein.

serum AST level. The prevalence of low serum HDL-cholesterol was negatively associated with AST level in men, but not in women. On the

contrary, serum ALT level was positively associated with all five metabolic abnormalities in both sexes (Table 3).

**Table 4.** Independent Associations between Serum Aminotransferase Level and the Metabolic Syndrome

Aminotransferase level	People (n)	Metabolic syndrome (n)	Odds ratio (95% confidence interval) for metabolic syndrome		
			Age-adjusted	Multivariate adjusted (1)*	Multivariate adjusted (2)†
<b>Men</b>					
AST < 20 IU/L	776	118 (15.2%)	1.00	1.00	1.00
20-29 IU/L	2053	415 (20.2%)	1.29 (1.03 - 1.62)	1.13 (0.88 - 1.45)	1.10 (0.85 - 1.42)
30-39 IU/L	793	218 (27.5%)	1.90 (1.47 - 2.44)	1.44 (1.09 - 1.91)	1.37 (1.02 - 1.83)
40-49 IU/L	215	77 (35.8%)	2.74 (1.94 - 3.86)	1.70 (1.15 - 2.51)	1.62 (1.08 - 2.43)
≥ 50 IU/L	182	66 (36.3%)	2.70 (1.87 - 3.88)	2.52 (1.67 - 3.81)	2.25 (1.47 - 3.44)
Total	4019	894 (22.2%)			
ALT < 20 IU/L	1250	154 (12.3%)	1.00	1.00	1.00
20-29 IU/L	1306	246 (18.8%)	1.65 (1.32 - 2.07)	1.32 (1.04 - 1.67)	1.27 (0.99 - 1.63)
30-39 IU/L	664	180 (27.1%)	2.98 (2.33 - 3.81)	1.89 (1.44 - 2.47)	1.69 (1.28 - 2.23)
40-49 IU/L	362	125 (34.5%)	4.40 (3.32 - 5.83)	2.41 (1.77 - 3.29)	2.17 (1.58 - 2.99)
≥ 50 IU/L	437	189 (43.3%)	6.57 (5.05 - 8.54)	3.16 (2.36 - 4.23)	2.65 (1.96 - 3.58)
Total	4019	894 (22.2%)			
<b>Women</b>					
AST < 20 IU/L	2096	367 (17.5%)	1.00	1.00	1.00
20-29 IU/L	2832	867 (30.6%)	1.31 (1.12 - 1.52)	1.25 (1.06 - 1.48)	1.18 (0.99 - 1.41)
30-39 IU/L	608	264 (40.5%)	1.62 (1.30 - 2.01)	1.47 (1.16 - 1.86)	1.43 (1.29 - 1.83)
40-49 IU/L	135	64 (47.4%)	2.40 (1.63 - 3.55)	1.81 (1.17 - 2.80)	1.71 (1.09 - 2.68)
≥ 50 IU/L	81	44 (54.3%)	3.38 (2.06 - 5.54)	2.53 (1.46 - 4.37)	2.14 (1.20 - 3.80)
Total	5752	1588 (27.6%)			
ALT < 20 IU/L	3529	683 (19.4%)	1.00	1.00	1.00
20-29 IU/L	1495	549 (36.7%)	1.97 (1.70 - 2.28)	1.58 (1.35 - 1.86)	1.44 (1.22 - 1.70)
30-39 IU/L	400	178 (44.5%)	2.90 (2.30 - 3.66)	1.89 (1.46 - 2.44)	1.65 (1.26 - 2.15)
40-49 IU/L	150	86 (57.3%)	5.66 (3.93 - 8.13)	3.40 (2.26 - 5.11)	2.94 (1.93 - 4.47)
≥ 50 IU/L	178	92 (51.7%)	4.79 (3.43 - 6.70)	2.54 (1.76 - 3.67)	2.25 (1.54 - 3.30)
Total	5752	1588 (27.6%)			

\*Adjusted for age, body mass index, smoking, and alcohol intake; † Adjusted for age, body mass index, smoking, alcohol intake, and waist circumference.

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Age-adjusted odds ratios for the metabolic syndrome increased progressively according to serum aminotransferase levels. The positive association between aminotransferase level and the metabolic syndrome was observed even within the normal range of aminotransferase levels. When adjusted for age, body mass index, smoking

and alcohol intake, the association between aminotransferase level and metabolic syndrome was attenuated but still highly significant. Even after additional adjustment for waist circumference, the association between aminotransferase level and metabolic syndrome still remained (Table 4). We assessed the association between

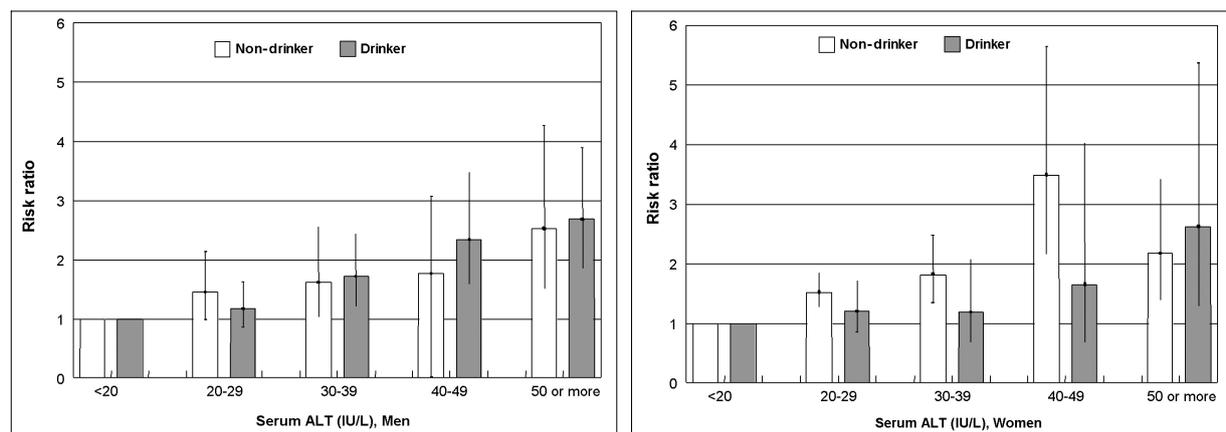


Fig. 1. Association between serum alanine aminotransferase level and metabolic syndrome by alcohol drinking status. Odds ratios with 95% confidence intervals (vertical lines) are adjusted for age, body mass index, waist circumference, and smoking status.

ALT and the metabolic syndrome in non-drinkers and drinkers separately. The positive association between serum ALT level and the metabolic syndrome was not different by alcohol intake (Fig. 1).

In a further analysis, we compared the relative significance of individual liver enzymes by including AST and ALT in the same model. In that model, the metabolic syndrome was significantly associated only with ALT level ( $p < 0.001$  for both sexes), but not with AST level ( $p = 0.272$  for men and 0.240 for women).

## DISCUSSION

We found a positive association between serum aminotransferase level and the metabolic syndrome in Korean adults. Recent epidemiologic studies have also reported an association between aminotransferase elevation and the metabolic syndrome.<sup>20-30</sup> This association has been observed in various populations, including obese people,<sup>26,27</sup> elderly men,<sup>28</sup> postmenopausal women,<sup>29</sup> and even adolescents.<sup>30</sup> Although similar findings have already been reported in some Korean populations,<sup>22,29,30</sup> the present study showed a significant association between aminotransferase level and the metabolic syndrome in a nationally representative Korean population. Another more important finding of this study is that the association was observed even in the normal to near normal

range of aminotransferase levels, in a dose-related manner.

The most probable explanation for the association between serum aminotransferase level and the metabolic syndrome is NAFLD. NAFLD is the most common cause of unexplained aminotransferase elevations in Western populations, and even in some Asian populations.<sup>2,31</sup> A growing body of evidence supports an association between NAFLD and the metabolic syndrome.<sup>3,7,10-14,30-35</sup> Recent studies have added evidence that insulin resistance, a key component of the metabolic syndrome, may contribute to the development of NAFLD.<sup>7,13,36,37</sup> Central obesity may be an underlying cause of insulin resistance and can also contribute to the development of NAFLD.<sup>11,37-39</sup> Compared with adipose tissue in other sites, visceral adipose tissue is more resistant to insulin, and the associated relative hyperinsulinemia promotes lipogenesis in the liver.<sup>40,41</sup> Visceral adipose tissue is also known to be a potent modulator of insulin action on hepatic glucose production and gene expression.<sup>42</sup> In the present study, serum aminotransferase levels had a dose-related association with metabolic syndrome even after adjustment for body mass index and waist circumference. The significance of central obesity in the connection between liver dysfunction and the metabolic syndrome may differ by ethnicity, as differences in the adverse effects of obesity between different ethnicities have been reported.<sup>43,44</sup> Further studies are required to inves-

tigate ethnic and regional differences in the relationship between liver disease and the metabolic syndrome.

Other conditions which can increase aminotransferase activity may also be associated with the metabolic syndrome.<sup>31</sup> The serum aminotransferase assay is a sensitive screening tool for the detection of liver disease, but it cannot provide information on the underlying causes of liver damage. Alcohol-related liver disease can be associated with the metabolic syndrome. Heavy drinkers tend to have an adverse cardiovascular risk profile, including high blood pressure, central obesity, and unhealthy lifestyle. We did not include current heavy drinkers for the analysis, and past history of alcohol consumption was also not considered. We could not exclude other causes of aminotransferase elevation, such as C-viral hepatitis and iron overload. It is unlikely that other causes of liver disease severely affected the relationship between aminotransferase levels and the metabolic syndrome. A recent study found that the association between metabolic risk factors and ALT elevation was similar in subjects with and without identifiable causes of chronic liver disease, including viral hepatitis, excessive alcohol use, and increased iron saturation.<sup>45</sup> Some systemic diseases and medications may also elevate serum aminotransferase levels. Accordingly, we performed further analysis after excluding 963 people who were receiving hormone replacement therapy or medications for hypertension, diabetes mellitus, liver disease, and/or renal disease during the month before examinations. We still found a strong association between serum aminotransferase level and the metabolic syndrome, even in the normal to near normal range of aminotransferase. Compared with levels below 20 IU/L, the adjusted odds ratios for an ALT level of 20-29, 30-39, 40-49 and  $\geq 50$  IU/L were 1.38, 1.76, 2.24 and 3.01 in men and 1.49, 1.73, 3.05 and 2.40 in women, respectively ( $p < 0.05$  for all). These results demonstrate that other causes of aminotransferase elevations did not alter the outcomes of this study.

In the present study, serum ALT level was more closely associated with the metabolic syndrome than AST level. In addition to that, only ALT level was significantly associated with the metabolic

syndrome when both enzymes were simultaneously investigated in a single model. This finding is in agreement with previous studies, and can be explained by higher specificity of ALT to liver disease.

Serum aminotransferase assays have been widely used to identify NAFLD and other liver diseases. But the cutoff level that discriminates between healthy and diseased livers has not been clearly defined. The upper normal limit of serum aminotransferase is set on average at 40 IU/L, ranging from 30-50 IU/L.<sup>17,46</sup> However, this normal range was calculated from a supposedly healthy reference population, which probably included people with mild to moderate chronic liver disease. Several previous studies have demonstrated that serum aminotransferase level, even within the normal range, may be associated with morbidity and mortality.<sup>15-17,22,29,47</sup> The progressive linear association between serum aminotransferase level and the metabolic syndrome suggests that people with high normal aminotransferase levels may need further investigation for the presence of fatty liver disease. Adjustment of the normal limit of serum aminotransferase should be considered for the monitoring of liver function in people with the metabolic syndrome. In most Western regions, the aminotransferase assay has been less useful as a mass-screening tool, because the prevalence of liver disease is lower than in East Asian or African countries. However, considering the increasing prevalence of the metabolic syndrome and its association with liver dysfunction, the significance of the serum aminotransferase assay needs to be re-evaluated.

The present study also has several possible limitations. First, we had only one measurement of aminotransferase. Aminotransferase activity is a sensitive marker of liver dysfunction, but its specificity in detection of liver diseases is low because it can be elevated temporarily in various conditions. This limitation would serve to attenuate the magnitude of the association toward the null; thus, our results can probably be considered as conservative estimates. Second, there is the possibility of confounding effects by viral and alcoholic liver diseases. We excluded people who were positive for HBsAg, but could not rule out

the effects of other types of viral hepatitis. We did not include heavy drinkers in the analysis and statistically controlled the effects of alcohol consumption, but the possibility of residual confounding influence still exists. Finally, this study could not investigate the causal relationship between serum aminotransferase levels and the metabolic syndrome because of its cross-sectional design. Further prospective studies are needed to establish the temporal relationship between aminotransferase level and the metabolic syndrome, and to discover the underlying mechanism of the relationship.

In conclusion, serum aminotransferase levels even in the normal or near normal range are associated with features of the metabolic syndrome in Korean men and women.

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