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Serum γ-glutamyltransferase level and metabolic syndrome in children and adolescents: Korean National Health and Nutrition Examination Survey

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ABSTRACT

Aims/Introduction: Serum γ-glutamyltransferase (GGT) is positively related to cardiometabolic diseases, such as type 2 diabetes mellitus, hypertension and metabolic syndrome (MetS), in adult populations. Our aim was to investigate whether serum GGT is independently associated with MetS and its components in a nationally representative sample of Korean children and adolescents.

Materials and Methods: The study included data from 1,618 participants (867 boys, 751 girls) aged 10–18 years from the 2010–2011 Korean National Health and Nutrition Examination Survey. MetS was diagnosed by the 2007 International Diabetes Federation criteria for children and adolescents. Participants were stratified using a cut-off value of the 75th percentile of serum GGT levels (19 IU/L for boys, 15 IU/L for girls). The odds ratios and 95% confidence intervals for MetS and its components were determined with multiple logistic regression analyses.

Results: The mean values of most cardiometabolic variables were significantly higher in the upper stratum. Except for low high-density lipoprotein cholesterol in boys and elevated blood pressure in girls, participants in the upper GGT stratum had significantly higher odds of MetS and its components than those in the lower stratum. The multivariate-adjusted odds ratios for MetS for the upper stratum were 5.79 (95% confidence interval 1.21–27.02) in boys and 6.20 (95% confidence interval 1.71–22.47) in girls, after adjusting for age, household income and residential area.

Conclusions: Serum GGT was positively associated with MetS and its components in Korean children and adolescents. Serum GGT could be a useful measure for identifying children and adolescents with MetS.

INTRODUCTION

Metabolic syndrome (MetS), which is a cluster of metabolic abnormalities that include abdominal obesity, high blood pressure, glucose intolerance and dyslipidemia, is a risk factor for type 2 diabetes mellitus, cardiovascular disease and certain cancers[1,2]. All these diseases are leading causes of mortality in adults; however, abnormalities of components of MetS are observed during childhood and can persist into adulthood[3,4]. With the ongoing obesity epidemic among children and adolescents, MetS is important in public health perspectives in this population[5,6]. Thus, biomarkers for the identification of individuals with MetS or at risk for MetS development among the pediatric population are crucial for better management of this syndrome.

The membrane-bound glycoprotein, γ-glutamyltransferase (GGT), is a microsomal enzyme that carries out a key function in extracellular catabolism of glutathione (γ-L-glutamyl-L-cysteinyl-glycine), which is a significant anti-oxidant against oxidative stress and free radicals, and is responsible for maintaining glutathione homeostasis[7]. GGT is present in serum and on the

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outer surface of most human cells, especially in tissues that carry out transport functions, such as the bile duct and kidneys[8].

Although an increase in the GGT level has traditionally been recognized as a marker of hepatobiliary disease or inordinate alcohol consumption[8,9], recent epidemiological research has shown that the serum GGT level can be used to predict the development of cardiometabolic diseases, such as hypertension[10], insulin resistance[11], type 2 diabetes mellitus[12] and MetS[13], in adults. However, few studies have examined the relationship between the serum GGT level and MetS in the general pediatric population. Although a previous study examined the association between the serum GGT level and insulin resistance in obese children, the study focused on only overweight/obese children and did not include a non-obese pediatric population[14]. Therefore, the present study aimed to investigate the association between the serum GGT level and MetS in a nationally representative sample of Korean children and adolescents.

METHODS

Survey overview and study population

The present cross-sectional study utilized data collected from the 2010–2011 Korean National Health and Nutrition Examination Survey (KNHANES), which was carried out by the Korea Centers for Disease Control and Prevention[15]. The KNHANES is a nationwide, representative, population-based survey carried out to evaluate the health and nutrition status of Koreans. The target population of the KNHANES was the civilian non-institutionalized people of Korea. The sampling units were composed of families that were selected through a stratified, multistage probability sampling design based on sex distribution, geographic area and age. Sampling weights that were representative of the probability of being sampled were allocated to each participant to ensure that the results represented the overall Korean population.

Of the 2,018 children and adolescents aged 10–18 years who participated in the 2010–2011 KNHANES, we excluded those who had not fasted for 12 h before blood sampling (n = 191), those with missing data (n = 181) and those who had a serum GGT level higher than the upper limit of the normal range (n = 26). We also excluded individuals with positive serological findings for hepatitis B (n = 2). Finally, 1,618 participants (867 boys and 751 girls) were included in the final analysis. Written informed consent was acquired from all citizens who agreed to participate. The KNHANES was approved by the Korea Centers for Disease Control and Prevention Institutional Review Board (approval numbers: 2010-02CON-21-C and 2011-02CON-06-C). Additionally, this study complied with the ethical principles of the Declaration of Helsinki.

Measurement of anthropometric and laboratory data

Educated medical staff carried out the anthropometric measurements following a standardized procedure. Height and bodyweight were obtained to the nearest 0.1 cm and 0.1 kg, respectively, while participants wore light clothing without shoes. The body mass index (BMI) was computed as weight (kg) divided by the square of height (m^2). BMI z-scores were determined with the modified lambda, mu, sigma statistical method applied in the growth charts issued by the Korean Pediatric Society in 2007[16]. Waist circumference (WC) was obtained to the nearest 0.1 cm at the midpoint between the iliac crest and the lower border of the rib cage at the end stage of natural expiration. Blood pressure (BP) was obtained on the right arm three separate times at 5-min intervals with a typical mercury sphygmomanometer (Baumanometer; W.A. Baum Co., Inc., Copiague, NY, USA), and the mean of the second and third assessments was used in the analysis.

Venous blood was drawn from the antecubital vein in each participant after a minimum 12-h fast. Fasting plasma glucose, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, aspartate aminotransferase, alanine aminotransferase and GGT levels were determined with an automatic analyzer (Hitachi 7600; Hitachi Co., Tokyo, Japan). White blood cell (WBC) count was analyzed using an automated blood cell counter (XE-2100D; Sysmex, Kobe, Japan).

Definition of clinical variables

MetS was diagnosed by the 2007 International Diabetes Federation consensus definition of MetS in children and adolescents[17]. According to the International Diabetes Federation definition, MetS, as an entity, is not diagnosed in children below the age of 10 years, and an individual aged ≥10 years can be diagnosed with MetS when abdominal obesity is noted along with at least two of the following four factors: (i) TG ≥150 mg/dL; (ii) HDL-C <40 mg/dL for girls aged <16 years and boys of all ages, and HDL-C <50 mg/dL for girls aged ≥16 years; (iii) systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg; and (iv) fasting plasma glucose ≥100 mg/dL. Abdominal obesity was defined as a WC ≥90th percentile for age and sex for individuals aged <16 years, and a WC ≥90 cm and ≥80 cm for boys and girls, respectively, aged ≥16 years. The cut-off value for WC in individuals <16 years was based on the 2007 Korean Children and Adolescents Growth Standard[16]. Overweight was defined as BMI in the 85–95th percentile for age and sex, and obesity was defined as a BMI ≥95th percentile for age and sex according to the 2007 Korean Children and Adolescents Growth Standard[16]. Participants were divided into an upper and a lower stratum according to a cut-off value of the 75th percentile of serum GGT, which in the present study was 19 IU/L for boys and 15 IU/L for girls, respectively.

Statistical analysis

Sampling units were obtained from a stratified, multistage, probability sampling design that was based on the sex, age and geographical area of participants, using household registries. The characteristics of the study participants were assessed using a weighted t-test for continuous variables, and a weighted

χ^2-test for categorical variables. Age-adjusted mean serum GGT values were obtained by carrying out analysis of covariance (ANCOVA) according to the number of MetS components. To determine the clinical application of serum GGT in predicting MetS, the receiver operating characteristic (ROC) curves of serum GGT for MetS diagnosis were derived, and the area under the ROC curve was calculated for boys and girls. The odds ratios and 95% confidence intervals (95% CI) for abdominal obesity, elevated BP, high fasting plasma glucose, high TG, low HDL-C and MetS were determined with multiple logistic regression analysis after adjusting for potential confounding factors. All statistical analyses were carried out with SPSS version 24 (IBM Corporation, Chicago, IL, USA). A *P*-value <0.05 was considered significant.

RESULTS

Table 1 shows the characteristics of study participants. The mean values of most cardiometabolic variables, such as BMI, BMI z-score, WC, waist-to-height ratio, total cholesterol, TG, low-density lipoprotein cholesterol levels and WBC count, were significantly higher in the upper stratum of GGT than in the lower stratum.

Table 2 presents the prevalence of MetS and each of its components. The overall prevalence rate of MetS according to the International Diabetes Federation definition was 1.7% among boys and 2.7% among girls. The prevalence of abdominal obesity and low HDL-C was higher in girls than in boys, whereas elevated BP was more prevalent in boys than in girls. The prevalence of MetS and most of its components was significantly higher in the upper stratum of GGT than in the lower stratum in both boys and girls.

The age-adjusted mean GGT levels according to the number of MetS components are presented in Figure 1. The age-adjusted mean GGT level increased progressively with the presence of each additional MetS component in both boys and girls (*P* for trend <0.001). The mean GGT levels were 15.9, 18.7, 26.4 and 31.1 IU/L in boys, and 12.4, 12.8, 15.5 and 19.1 IU/L in girls, with 0, 1, 2 and ≥3 MetS components, respectively.

Figure 2 illustrates the ROC curves of serum GGT for MetS. The area under the ROC curve was 0.823 (95% CI 0.701–0.946) in boys and 0.752 (95% CI 0.605–0.898) in girls, respectively.

Table 3 presents the prevalence risk of MetS and its components according to GGT level. In comparison with participants in the lower stratum of GGT, those in the upper stratum of GGT had significantly higher odds of MetS and its components except for low HDL-C in boys and elevated BP in girls. The multivariate-adjusted odds ratios for MetS in the upper stratum

Table 1 | Characteristics of study participants

	Boys	Girls	*P*-value	Boys			Girls		
				GGT ≤18 IU/L	GGT ≥19 IU/L	*P*-value	GGT ≤14 IU/L	GGT ≥15 IU/L	*P*-value
Unweighted (*n*)	867	751		641	226		569	182	
Age (years)	14.3 (0.1)	14.2 (0.1)	0.569	13.9 (0.1)	15.1 (0.2)	<0.001	14.0 (0.1)	14.6 (0.3)	0.051
BMI (kg/m²)	20.9 (0.2)	20.4 (0.2)	0.048	19.9 (0.1)	23.5 (0.3)	<0.001	19.8 (0.1)	22.2 (0.5)	<0.001
BMI z-score	–0.04 (0.05)	0.04 (0.05)	0.263	-0.27 (0.05)	0.54 (0.10)	<0.001	–0.13 (0.05)	0.50 (0.15)	<0.001
Overweight (%)	11.1 (1.2)	11.0 (1.4)	0.980	7.2 (1.1)	21.1 (3.1)	<0.001	10.5 (1.6)	12.6 (2.7)	0.468
Obesity (%)	7.0 (1.1)	8.3 (1.3)	0.477	1.9 (0.6)	20.3 (3.4)	<0.001	3.6 (0.9)	21.8 (4.2)	<0.001
WC (cm)	71.5 (0.4)	67.6 (0.4)	<0.001	68.8 (0.4)	78.5 (0.9)	<0.001	66.0 (0.4)	71.9 (1.1)	<0.001
Waist-to-height ratio	0.43 (0.00)	0.43 (0.00)	0.267	0.42 (0.00)	0.47 (0.01)	<0.001	0.42 (0.00)	0.46 (0.01)	<0.001
SBP (mmHg)	109.4 (0.5)	103.8 (0.5)	<0.001	107.9 (0.5)	113.2 (0.9)	<0.001	103.6 (0.5)	104.4 (0.8)	0.384
DBP (mmHg)	67.5 (0.4)	65.5 (0.4)	<0.001	66.7 (0.5)	69.5 (0.8)	0.003	65.1 (0.4)	66.5 (0.7)	0.068
FPG (mg/dL)	89.2 (0.3)	88.3 (0.30)	0.028	89.0 (0.3)	89.6 (0.6)	0.407	88.1 (0.3)	89.2 (0.7)	0.159
Total cholesterol (mg/dL)	153.1 (1.3)	162.7 (1.2)	<0.001	150.7 (1.3)	159.6 (3.0)	0.005	159.5 (1.3)	171.9 (2.7)	<0.001
TG (mg/dL)	80.6 (2.2)	85.5 (2.4)	0.117	73.6 (2.2)	98.8 (4.8)	<0.001	80.7 (2.6)	99.4 (5.2)	0.001
HDL-C (mg/dL)	48.3 (0.4)	50.5 (0.4)	<0.001	48.9 (0.4)	47.0 (0.7)	0.019	51.1 (0.5)	48.8 (0.8)	0.010
LDL-C (mg/dL)	91.4 (1.8)	97.5 (1.5)	0.010	87.8 (1.7)	99.3 (3.4)	0.017	93.2 (1.4)	108.0 (3.4)	<0.001
AST (IU/L)	20.7 (0.4)	17.1 (0.2)	<0.001	18.9 (0.2)	25.4 (1.1)	<0.001	16.7 (0.2)	18.2 (0.4)	0.001
ALT (IU/L)	18.6 (0.8)	11.5 (0.3)	<0.001	12.9 (0.3)	33.3 (2.6)	<0.001	10.4 (0.2)	14.6 (0.8)	<0.001
WBC count (cells/μL)	6,130 (71)	6,150 (71)	0.898	5,930 (74)	6,650 (146)	0.001	6,050 (82)	6,420 (116)	0.007
Household income (US$/month)	4,602 (300)	4,384 (315)	0.565	4,431 (323)	5,048 (665)	0.400	4,299 (379)	4,633 (454)	0.557
Residence in rural area (%)	17.2 (2.9)	18.2 (3.3)	0.651	18.9 (3.3)	12.6 (3.1)	0.055	19.6 (3.4)	14.3 (4.8)	0.245

Data are presented as mean (standard error) or percentage (standard error). *P*-values were obtained by using weighted one-way ANOVA for continuous variables or weighted χ^2-test for categorical variables. US$1 = 1,000 Korean won. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; GGT, γ-glutamyltransferase; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, triglycerides; WBC, white blood cell; WC, waist circumference.

Table 2 | Prevalence of metabolic syndrome and its components

	Boys	Girls	*P*-value	Boys			Girls		
				GGT ≤18 IU/L	GGT ≥19 IU/L	*P*-value	GGT ≤14 IU/L	GGT ≥15 IU/L	*P*-value
MetS (%)	1.7 (0.6)	2.7 (0.8)	0.273	0.6 (0.4)	4.5 (1.7)	0.001	1.2 (0.6)	6.8 (2.6)	0.003
Abdominal obesity (%)	7.9 (1.1)	12.0 (1.5)	0.026	2.3 (0.6)	22.6 (3.4)	<0.001	7.2 (1.4)	25.8 (4.1)	<0.001
Elevated BP (%)	5.6 (1.1)	0.5 (0.3)	<0.001	3.2 (0.9)	11.9 (3.1)	<0.001	0.6 (0.4)	1.0 (0.8)	0.636
High FPG (%)	6.1 (1.0)	5.7 (1.0)	0.769	4.9 (1.0)	9.1 (2.9)	0.043	4.4 (0.9)	9.6 (3.0)	0.041
High TG (%)	8.7 (1.4)	8.5 (1.3)	0.920	5.2 (1.2)	17.7 (3.5)	<0.001	6.6 (1.3)	13.9 (3.1)	0.010
Low HDL-C (%)	18.1 (1.7)	25.0 (2.3)	0.010	16.8 (1.8)	21.5 (3.1)	0.141	20.1 (2.4)	38.9 (4.7)	<0.001

Data are presented as percentage (standard error). *P*-values were obtained by using weighted χ^2-test. BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; GGT, γ-glutamyltransferase; MetS, metabolic syndrome; TG, triglycerides.

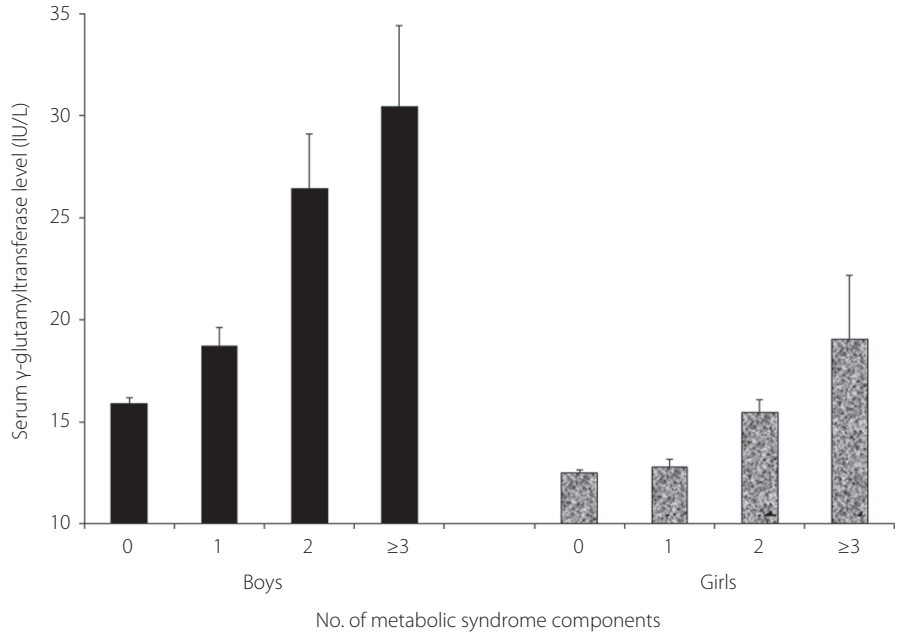

Figure 1 | Age-adjusted mean serum γ-glutamyltransferase levels by the number of components of metabolic syndrome (error bars represent standard error of the mean). Black columns represent data for boys, and shaded columns represent data for girls.

of GGT were 5.79 (95% CI 1.21–27.02) in boys and 6.20 (95% CI 1.71–22.47) in girls after adjusting for age, household income and residential area.

DISCUSSION

In the present representative sample of Korean children and adolescents, the serum GGT level was positively associated with MetS after adjusting for potential confounding factors. These findings are consistent with the results of previous studies showing that GGT is a predictor of MetS in adults[13], and show that this association also exists in the pediatric population. Recently, serum GGT level has been reported to be associated with MetS in children and adolescents. Kong *et al.*[18] reported that serum GGT elevation was associated with MetS and its components in Chinese children and adolescents. However, in that study, sex-related differences were not fully considered, and separate analyses for both sexes were not carried out. As serum GGT levels differed significantly by sex in the present study, sex-specific analyses models would be more appropriate. In this regard, the present study confirmed that the associations between serum GGT levels and MetS can be applied to both boys and girls, through sex-specific multiple logistic regression analyses.

There were sex-related differences in the prevalence of some components of MetS. Although the mechanism underlying these differences is unclear, hormonal differences (such as sex hormones) between boys and girls might explain this phenomenon. Previous studies have shown that sex hormones and sex hormone-binding globulin levels differ between boys and

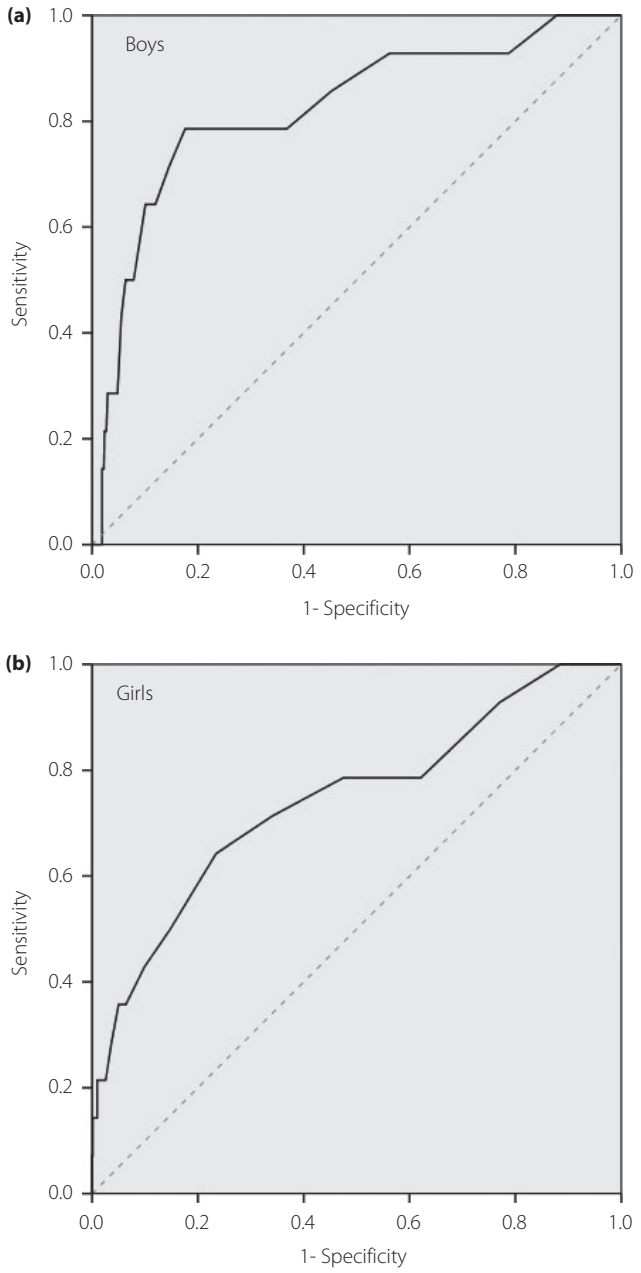

Figure 2 | Receiver operating characteristic curves of γ-glutamyltransferase for metabolic syndrome in (a) boys and (b) girls. The area under the receiver operating characteristic curve was 0.823 (95% confidence interval 0.701–0.946) in boys and 0.752 (95% confidence interval 0.605–0.898) in girls.

girls in the pubertal stage[19], and are differentially associated with lipid profile in boys and girls[20–22].

There are several possible mechanisms for the significant association between the serum GGT level and MetS in children and adolescents. An increase in the GGT level could indicate an increase in fat infiltration in the liver, and a higher GGT level has been frequently observed in non-alcoholic fatty liver disease[23]. Non-alcoholic fatty liver disease is increasingly being regarded as a manifestation of MetS and insulin resistance[24,25]. Fat infiltration in the liver has been shown to bring about insulin resistance, and result in the overproduction of both glucose and very low-density lipoprotein cholesterol, which can cause hyperglycemia, hypertriglyceridemia, low HDL-C levels and hypertension[26–29].

Another possible factor to be considered is chronic low-grade inflammation. Insulin resistance and the related MetS are increasingly being recognized as subclinical inflammatory states[30,31]. Inflammatory markers, such as the WBC count, interleukin-6 and C-reactive protein, are believed to be independent predictors of type 2 diabetes mellitus and cardiovascular disease[32,33]. Furthermore, growing evidence suggests that GGT might be an inflammatory marker[34]. Indeed, in the current study, the WBC count was considerably higher in participants in the upper GGT stratum than in those in the lower GGT stratum. Furthermore, oxidative stress has been suggested as a possible mechanism linking a high GGT level with MetS. As GGT is responsible for maintaining glutathione homeostasis, a high GGT level could be an indicator of high oxidative stress levels[35]. These findings show that the association between GGT and MetS might be explained by oxidative stress and low-grade, chronic inflammation.

Several limitations should be considered when interpreting the present findings. First, this study applied a cross-sectional design, making it hard to set up a causal relationship between GGT and MetS in children and adolescents. Although a considerable relationship between GGT and MetS was noted in the current study, it remains unclear whether GGT is a risk factor directly included in the development of MetS or simply an epiphenomenon. Future prospective research is warranted to substantiate the causal relationship between GGT and MetS in children and adolescents. Second, serum GGT levels are elevated in some autoimmune disorders[36,37]; however, we could not consider this aspect because the secondary data from the KNHANES used in the present study did not include data pertaining to the presence of autoimmune disorders. Finally, we did not consider the physiological effect of puberty on insulin resistance. Studies have shown that children and adolescents experience transient insulin resistance during puberty[38]. Unfortunately, because data on the pubertal stage were not included in the KNHANES dataset, the pubertal stage of the participants was not directly considered in our analysis. However, to minimize the influence of this limitation, we analyzed data by sex and involved age as a confounding variable in the multiple logistic regression analysis. Further research is required to elucidate the relationship between the serum GGT level and MetS according to pubertal stage, with a comparison between boys and girls. Despite these potential limitations, the results of the present study have good general applicability owing to the use of a nationally representative sample of children and adolescents in Korea. Additionally, the large sample of healthy participants of both sexes strengthens the reliability of the findings.

Table 3 | Multivariate-adjusted odds ratios and 95% confidence intervals for metabolic syndrome and its components according to γ-glutamyltransferase level in boys and girls

	Boys		Girls	
	GGT ≤18 IU/L	GGT ≥19 IU/L	GGT ≤14 IU/L	GGT ≥15 IU/L
MetS	1 (reference)	5.79 (1.21–27.02)	1 (reference)	6.20 (1.71–22.47)
Abdominal obesity	1 (reference)	14.60 (7.22–29.50)	1 (reference)	4.45 (2.43–8.13)
Elevated BP	1 (reference)	3.07 (1.34–7.01)	1 (reference)	3.82 (0.33–44.58)
High FPG	1 (reference)	2.60 (1.09–6.17)	1 (reference)	2.70 (1.18–6.22)
High TG	1 (reference)	3.69 (1.86–7.31)	1 (reference)	2.45 (1.26–4.76)
Low HDL-C	1 (reference)	1.31 (0.86–1.98)	1 (reference)	2.61 (1.69–4.03)

Data are presented as odds ratio (95% confidence interval). Odds ratios for metabolic syndrome (MetS), abdominal obesity (defined as a waist circumference ≥90th percentile for age and sex for individuals aged <16 years, and having a waist circumference ≥90 cm for boys and ≥80 cm for girls, respectively, aged ≥16 years), elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic BP ≥85 mmHg), high fasting plasma glucose (FPG; FPG ≥100 mg/dL), high triglycerides (TG; TG ≥150 mg/dL) and low high-density lipoprotein cholesterol (HDL-C; HDL-C <40 mg/dL for girls aged <16 years and boys of all ages, and HDL-C <50 mg/dL for girls aged ≥16 years) were determined by using multiple logistic regression analysis after adjusting for age, household income and residential area. GGT, γ-glutamyltransferase.

In conclusion, serum GGT was positively associated with MetS and its components in Korean children and adolescents. The present findings make a contribution to our insight of the relationship between serum GGT and MetS and its components in children and adolescents. This study suggests that serum GGT, which is a marker of inflammation and oxidative stress, could be a helpful measure for identifying children and adolescents with MetS.

DISCLOSURE

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Proportion of Upper GGT stratum (GGT ≥19 IU/L).