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 cancers1,2. All these diseases are leading causes of mortality in adults; however, abnormalities of components of MetS are observed during childhood and can persist into adulthood3,4. With the ongoing obesity epidemic among children and adolescents, MetS is important in public health perspectives in this population5,6. 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 homeostasis7. GGT is present in serum and on the
outer surface of most human cells, especially in tissues that carry out transport functions, such as the bile duct and kidneys.

Although an increase in the GGT level has traditionally been recognized as a marker of hepatobiliary disease or inordinate alcohol consumption, recent epidemiological research has shown that the serum GGT level can be used to predict the development of cardiometabolic diseases, such as hypertension, type 2 diabetes mellitus, and MetS, 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. 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. 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 body weight 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 (m²). 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. 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. 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. 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. 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
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                                 | P-value |
|         | GGT ≤18 IU/L                          | GGT ≥19 IU/L                          |         | GGT ≤14 IU/L                          | GGT ≥15 IU/L                          |         |
| Unweighted (n) | 867 | 751 | 0.569 | 641 | 226 | <0.001 | 569 | 182 | 0.051 |
| Age (years) | 143 (0.1) | 142 (0.1) | 0.569 | 139 (0.1) | 151 (0.2) | <0.001 | 140 (0.1) | 146 (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) | 785 (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) | 695 (0.8) | 0.003 | 65.1 (0.4) | 655 (0.7) | 0.068 |
| FPG (mg/dL) | 892.3 (0.3) | 883.3 (0.3) | 0.028 | 890.3 (0.3) | 896.6 (0.6) | 0.407 | 881.0 (0.3) | 892.0 (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) | 99.5 (5.2) | 0.001 |
| HDL-C (mg/dL) | 483.0 (0.4) | 505.0 (0.4) | <0.001 | 489.0 (0.4) | 470.7 (0.7) | 0.019 | 51.1 (0.5) | 488.8 (0.8) | 0.010 |
| LDL-C (mg/dL) | 91.4 (1.8) | 97.5 (1.5) | 0.010 | 87.8 (1.7) | 993.3 (3.4) | 0.017 | 93.2 (1.4) | 1080.4 (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) | 182.4 (0.2) | 0.001 |
| ALT (IU/L) | 186.8 (0.8) | 115.3 (0.3) | <0.001 | 129.3 (0.3) | 333.2 (2.6) | <0.001 | 10.4 (0.2) | 146.0 (0.8) | <0.001 |
| WBC count (cells/µL) | 6,130 (71) | 6,150 (71) | 0.989 | 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 (325) | 5,048 (665) | 0.400 | 4,299 (379) | 4,633 (454) | 0.557 |

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 χ²-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.
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, 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. 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 girls.
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. Non-alcoholic fatty liver disease is increasingly being regarded as a manifestation of MetS and insulin resistance. 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.

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. 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. Furthermore, growing evidence suggests that GGT might be an inflammatory marker. 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. 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; 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. 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.

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.
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.

REFERENCES
1. Wilson PW, D’Agostino RB, Parise H, et al. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. Circulation 2005; 112: 3066–3072.
2. Esposito K, Chiodini P, Colao A, et al. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 2012; 35: 2402–2411.
3. Moriarty-Kelsey M, Daniels SR. Childhood obesity is the fuel that fires adult metabolic abnormalities and cardiovascular disease. Child Obes (Formerly Obesity and Weight Management) 2010; 6: 250–256.
4. Morrison JA, Friedman LA, Wang P, et al. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. J Pediatr 2008; 152: 201–206.
5. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014; 384: 766–781.
6. Friend A, Craig L, Turner S. The prevalence of metabolic syndrome in children: a systematic review of the literature. Metab Syndr Relat Disord 2013; 11: 71–80.
7. Stark AA, Porat N, Volohonsky G, et al. The role of gamma-glutamyl transpeptidase in the biosynthesis of glutathione. BioFactors 2003; 17: 139–149.
8. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001; 38: 263–355.
9. Hannuksela ML, Lissansantti MK, Nissinen AE, et al. Biochemical markers of alcoholism. Clin Chem Lab Med 2007; 45: 953–961.
10. Liu CF, Gu YT, Wang HY, et al. Gamma-glutamyltransferase level and risk of hypertension: a systematic review and meta-analysis. PLoS ONE 2012; 7: e48878.
11. Ryoo JH, Oh CM, Kim HS, et al. Clinical association between serum gamma-glutamyltransferase levels and the development of insulin resistance in Korean men: a 5-year follow-up study. Diabet Med 2014; 31: 455–461.
12. Ko SH, Baeg MK, Han KD, et al. Increased liver markers are associated with higher risk of type 2 diabetes. World J Gastroenterol 2015; 21: 7478–7487.
13. Liu CF, Zhou WN, Fang NY. Gamma-glutamyltransferase levels and risk of metabolic syndrome: a meta-analysis of prospective cohort studies. Int J Clin Pract 2012; 66: 692–698.
14. Lee SY, Sung E, Chang Y. Elevated serum gamma-glutamyltransferase is a strong marker of insulin resistance in obese children. Int J Endocrinol 2013; 2013: 578693.
15. Korea Centers for Disease Control and Prevention. Korean National Health and Nutrition Examination Survey. Available from: http://knhanes.cdc.go.kr/knhanes. Last accessed April 2, 2017.
16. Korea Centers for Disease Control and Prevention and Korean Pediatrics Society. 2007 Korean Children and Adolescents Growth Standard. Available from: https://www.cdc.go.kr/CDC. Last accessed April 2, 2017.
17. Zimmert P, Albert KG, Kaufman F, et al. The metabolic syndrome in children and adolescents – an IDF consensus report. Pediatr Diabetes 2007; 8: 299–306.
18. Kong AP, Choi KC, Ho CS, et al. Associations of uric acid and gamma-glutamyltransferase (GGT) with obesity and components of metabolic syndrome in children and adolescents. Pediatr Obes 2013; 8: 351–357.

19. Agirbasli M, Agaoglu NB, Orak N, et al. Sex hormones and metabolic syndrome in children and adolescents. Pediatr Obes 2013; 8: 351–357.

20. Garces C, Oya I, Lasuncion MA, et al. Sex hormone-binding globulin and lipid profile in pubertal children. Metabolism 2010; 59: 166–171.

21. Yasui T, Uemura H, Irahara M, et al. Associations of endogenous sex hormones and sex hormone-binding globulin with lipid profiles in aged Japanese men and women. Clin Chim Acta 2008; 398: 43–47.

22. Bottner A, Kratzsch J, Muller G, et al. Gender differences of adiponectin levels develop during the progression of puberty and are related to serum androgen levels. J Clin Endocrinol Metab 2004; 89: 4053–4061.

23. Tahan V, Canbakaln B, Balci H, et al. Serum gamma-glutamyltranspeptidase distinguishes non-alcoholic fatty liver disease at high risk. Hepatogastroenterology 2008; 55: 1433–1438.

24. Penke M, Kiess W, Giorgis T. Non-alcoholic fatty liver disease in children and adolescents. J Pediatr Endocrinol Metab 2016; 29: 1329–1330.

25. Boyraz M, Hatipoglu N, Sari E, et al. Non-alcoholic fatty liver disease in obese children and the relationship between metabolic syndrome criteria. Obes Res Clin Pract 2014; 8: e356–e363.

26. Seppala-Lindoos A, Vehkavaara S, Hakkinen AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metab 2002; 87: 3023–3028.

27. Tiikkainen M, Tamminen M, Hakkinen AM, et al. Liver-fat accumulation and insulin resistance in obese women with previous gestational diabetes. Obes Res 2002; 10: 859–867.

28. Adiels M, Taskinen MR, Packard C, et al. Overproduction of large VLDL particles is driven by increased liver fat content in man. Diabetologia 2006; 49: 755–765.

29. Kikuchi A, Takamura T. Where does liver fat go? A possible molecular link between fatty liver and diabetes. J Diabetes Investig 2017; 8: 152–154.

30. Can U, Buyukinan M, Guzelant A, et al. Investigation of the inflammatory biomarkers of metabolic syndrome in adolescents. J Pediatr Endocrinol Metab 2016; 29: 1277–1283.

31. Warnberg J, Marcos A. Low-grade inflammation and the metabolic syndrome in children and adolescents. Curr Opin Lipidol 2008; 19: 11–15.

32. Lee CD, Folsom AR, Nieto FJ, et al. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. Am J Epidemiol 2001; 154: 758–764.

33. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286: 327–334.

34. Shin YH, Kim KE, Kim KE, et al. Relationship between serum gamma-glutamyltransferase level and leukocyte count in Korean children and adolescents. Scand J Clin Lab Invest 2015; 75: 177–182.

35. Lee DH, Blomhoff R, Jacobs Jr DR. Is serum gamma-glutamyltransferase a marker of oxidative stress? Free Radic Res 2004; 38: 535–539.

36. Lozovoy MA, Simao AN, Oliveira SR, et al. Relationship between iron metabolism, oxidative stress, and insulin resistance in patients with systemic lupus erythematosus. Scand J Rheumatol 2013; 42: 303–310.

37. Czaja AJ. Cholestatic phenotypes of autoimmune hepatitis. Clin Gastroenterol Hepatol 2014; 12: 1430–1438.

38. Moran A, Jacobs Jr DR, Steinberger J, et al. Insulin resistance during puberty: results from clamp studies in 357 children. Diabetes 1999; 48: 2039–2044.

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).