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Comparison of Lipid-Derived Markers for Metabolic Syndrome in Youth: Triglyceride/HDL Cholesterol Ratio, Triglyceride-Glucose Index, and non-HDL Cholesterol

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Triglyceride/high-density lipoprotein (HDL) cholesterol ratio (TG/HDL-C), triglyceride-glucose index (TyG), and non-HDL cholesterol level (non-HDL-C) have been proposed as surrogate markers for predicting metabolic syndrome (MetS). This study investigated whether these lipid-derived surrogate markers can predict MetS in Korean children and adolescents. Data from 1,814 participants were analyzed from the 2013-2016 Korean National Health and Nutrition Examination Survey. MetS was defined using three sets of criteria: Cook et al. (MetS1), de Ferranti et al. (MetS2), and the International Diabetes Federation (MetS3). The prevalence of MetS1, MetS2, and MetS3 was 4.6%, 11.3%, and 2.7%, respectively. In receiver operating characteristic curve analysis of MetS and lipid-derived surrogate markers, TG/HDL-C (0.937 for MetS1, 0.894 for MetS2, and 0.897 for MetS3) had the largest area under the curve (AUC), followed by TyG (0.906 for MetS1, 0.864 for MetS2, and 0.887 for MetS3), and non-HDL-C (0.752 for MetS1, 0.708 for MetS2, and 0.703 for MetS3) (all $P < 0.001$). The cutoff values for detecting MetS with TG/HDL-C, TyG, and non-HDL-C were 2.64, 8.52, and 111.6 for MetS1; 2.23, 8.47, and 110.7 for MetS2; and 2.64, 8.74, and 110.8 for MetS3, respectively. In conclusion, TG/HDL-C and TyG were similarly predictive of MetS. We propose using TG/HDL-C and TyG as surrogate markers for assessing MetS in Korean children and adolescents.

Keywords: adolescents; metabolic syndrome; triglyceride-glucose index; triglyceride to high-density lipoprotein cholesterol ratio
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Introduction

The prevalence of overweight and obesity in children and adolescents has increased worldwide because of increased consumption of high-calorie foods and a sedentary lifestyle (Han et al. 2010). Among children, obesity is the major cause of insulin resistance (IR), which is associated with metabolic and cardiovascular complications, such as glucose intolerance, type 2 diabetes, dyslipidemia, metabolic syndrome (MetS), and atherosclerosis. Obesity in childhood leads to obesity in adulthood and chronic disease (Dietz 1998). The spectrum of cardiovascular diseases (CVDs) is now becoming more relevant in children and adolescents, considering the recent rise in obesity and the range of obesity related complications (Cote et al. 2013).

More recently, useful surrogate markers that could help predict cardiovascular events have been reported. Several surrogate markers, including the triglyceride-glu-

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cose index (TyG), non-high-density lipoprotein cholesterol level (non-HDL-C), and triglyceride/HDL cholesterol ratio (TG/HDL-C), have been assessed with regard to IR and predicting the development of MetS in adults.

Elevated serum TG level leads to a decrease in insulin sensitivity by interfering with muscle glucose metabolism (Kelley and Goodpaster 2001). As an indirect index, the TyG has been used in some adult studies (Vasques et al. 2011; Du et al. 2014). The TyG is based on fasting TG and glucose, rather than fasting insulin and glucose. Considering the high cost incurred by insulin measurements and the absence of a standard measurement method, clinical application of the TyG is convenient. However, there have been few relevant pediatric studies in Korea; moreover, there minimal reference criteria are available in Korea. Non-HDL-C is total cholesterol level minus HDL-C level and includes all atherogenic cholesterols, such as low-density lipoprotein (LDL), lipoprotein (a), intermediate-density lipoprotein, and the very-low-density lipoprotein remnant (Cui et al. 2001). The non-HDL-C is reportedly an accurate predictor of CVD (Pischon et al. 2005). The TG/HDL-C has been suggested as a measure to identify overweight individuals with IR (McLaughlin et al. 2003). In recent studies, the TG/HDL-C has been associated with cardiovascular mortality (Hadaegh et al. 2009). The commonly used biomarker TG/HDL-C has been recently proposed as a marker to reflect cardiometabolic status and predict increased risks of metabolic and cardiovascular complications in adults and children (Salazar et al. 2012).

To our knowledge, there is no consensus regarding whether specific surrogate markers are suitable for predicting MetS or CVD. The most useful surrogate markers for predicting MetS, CVD, and IR remain controversial. No clear guidelines or universally accepted cutoffs are available for most of the main surrogate markers (Levy-Marchal et al. 2010).

A series of robust findings have indicated that the lipid profile of children is affected by different parameters, including age, sex, pubertal stage, and ethnicity. The present study analyzed large-scale data to determine whether the aforementioned lipid-derived surrogate markers could be useful for predicting MetS in Korean children and adolescents.

Materials and Methods

Study participants

This study examined data obtained from the Korean National Health and Nutrition Examination Survey (KNHANES) (2013-2016). The KNHANES is a nationally representative surveillance system that has been conducted cross-sectionally since 1998 by the Korea Centers for Disease Control and Prevention (KCDC) and the Ministry of Health and Welfare. A multi-stage clustered probability design was applied for the KNHANES sampling among non-institutionalized Korean citizens.

In total, 31,098 individuals were enrolled in the KNHANES from 2013 to 2016. In the present study, 3,201 participants aged 10-18 years were considered as potential participants. Among them, 1,387 individuals were excluded because they met one or more of the following criteria: no record of fasting time or fasting time < 12 h (n = 1,082) and absence of data regarding MetS components (n = 708). In total, 1,814 participants (938 boys and 876 girls) met the necessary conditions and were included in the present study (Fig. 1). Fasting insulin levels were measured only in 2015 (n = 422).

The KNHANES was approved by the Institutional Review Board of the KCDC and the KCDC Bioethics

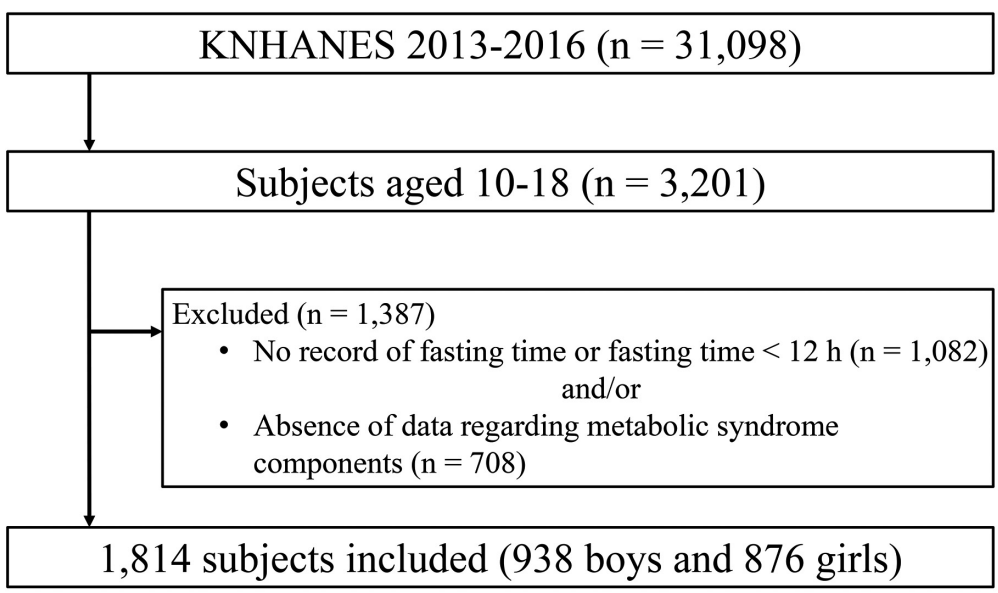

Fig 1. Flow chart of the study population selection process.
KNHANES, Korea National Health and Nutrition Examination Survey.

Committee (approval numbers: 2013-07CON-03-4C, 2013-12ESP-03-5C, and 2015-02CON-21-C). Informed consent was obtained from all participants, including children and adolescents or their legal guardian(s) or parent(s), before data collection for the KNHANES. The requirement for review of the present study was waived by the Institutional Review Board of Inje University Ilsan Paik Hospital. All procedures were performed in accordance with the tenets of the Declaration of Helsinki.

Anthropometric and laboratory measurements

Anthropometric measures were calculated for all participants by trained personnel. Height was determined to the nearest 0.1 cm using a stadiometer (Seca 225, Seca, Hamburg, Germany). Weight was measured to the nearest 0.1 kg using an electronic balance (GL-6000-20, G-tech, Seoul, Korea). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Height, weight, and BMI were converted to z-scores for age and sex, using the 2017 Korean National Growth Chart (Kim et al. 2018a). Waist circumference was measured using a flexible tape and determined to the nearest 0.1 cm at the midpoint between the lowest margin of the rib and the uppermost border of the iliac crest during expiration. Blood pressure (BP) was measured using a mercury sphygmomanometer [Baumanometer Wall Unit 33 (0850), W.A. Baum, New York, NY, USA] after participants had rested for 5 min in a sitting position. All BP measurements were collected on the right arm three times with a cuff appropriate for the arm circumference. The mean values of the second and third measurements of systolic BP and diastolic BP were used for subsequent analyses.

Blood samples were collected from all participants by trained nurses following an overnight fast. Drawn samples were transported to the Central Laboratory after proper preparation and analyzed within 24 h. Plasma glucose, total cholesterol, HDL-C, TG, and alanine transaminase levels were measured using a Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Direct LDL cholesterol measurements that were determined by the automatic analyzer were used when available (participants eligible for sampling of heavy metal levels or with TG levels ≥ 200 mg/dL); if such measurements were unavailable, the Friedwald formula was used if the TG level was < 400 mg/dL. Glycated hemoglobin was measured using high-performance liquid chromatography (HLC-723G8; Tosoh, Tokyo, Japan), which is the certified method in the National Glycohemoglobin Standardization Program. Fasting insulin levels were measured using an electrochemiluminescence immunoassay using Elecsys Insulin (Roche, Mannheim, Germany), then analyzed with the Cobas 8000 modular analyzer (Roche).

Definition of MetS

Overweight and obesity were defined as BMIs in the 85-< 95th percentile and ≥ 95th percentile for corresponding age and sex, respectively (Kim et al. 2018a). We used the three definitions for MetS that are most commonly used in children and adolescents. Two were proposed by Cook et al. (2003) (MetS1) and de Ferranti et al. (2004) (MetS2); they were based on criteria established by the National Cholesterol Education Program/Adult Treatment Panel-III, modified for pediatric age. The third definition was proposed by the International Diabetes Federation (IDF) (MetS3) (Zimmet et al. 2007). The three definitions are summarized in Table 1.

The TG/HDL-C was calculated as TG level (mg/dL) divided by HDL-C level (mg/dL). Non-HDL-C was calculated as total cholesterol (mg/dL) – HDL-C (mg/dL). The TyG was calculated as the natural logarithm (ln) of the product of plasma glucose and TG using the following formula: ln (TG [mg/dL] × fasting glucose [mg/dL]/2) (Simental-Mendia et al. 2008). IR was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR). The HOMA-IR score was calculated using the following formula: fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5 (Matthews et al. 1985).

Table 1. Criteria and definition for metabolic syndrome in children and adolescents.

Criteria/Components	Cook et al. (MetS1) (Cook et al. 2003)	de Ferranti et al. (MetS2) (de Ferranti et al. 2004)	IDF (10-16 yr)* (MetS3) (Zimmet et al. 2007)	IDF (Adults) (MetS3) (Zimmet et al. 2007)
Central obesity (WC)	≥ 90th percentile	> 75th percentile	≥ 90th percentile	≥ 90 cm in men ≥ 85 cm in women
Fasting glucose	≥ 110 mg/dL	≥ 110 mg/dL	≥ 100 mg/dL	≥ 100 mg/dL
Blood pressure	≥ 90th percentile	> 90th percentile	systolic ≥ 130 mmHg diastolic ≥ 85 mmHg	systolic ≥ 130 mmHg diastolic ≥ 85 mmHg
Triglycerides	≥ 110 mg/dL	≥ 100 mg/dL	≥ 150 mg/dL	≥ 150 mg/dL
HDL-cholesterol	≤ 40 mg/dL	< 50 mg/dL (girls) < 45 mg/dL (boys)	< 40 mg/dL	< 40 mg/dL in men < 50 mg/dL in women
Definition of MetS	≥ 3 among 5 criteria	≥ 3 among 5 criteria	central obesity and ≥ 2 other criteria	central obesity and ≥ 2 other criteria

*For adolescents older than 16 years, the IDF criteria for adults were used.
IDF, International Diabetes Federation; WC, waist circumference; HDL, high density lipoprotein; MetS, metabolic syndrome

Statistical analyses

Statistical analyses were performed using Stata 16.1 software (StataCorp LP, College Station, TX, USA). In accordance with the KNHANES design, appropriate weights for each sample were applied for all analyses. The distribution of continuous variables was examined for skewness and kurtosis; parameters were logarithmically transformed, when appropriate. Data are presented as the weighted mean ± standard error for continuous variables or the number of participants with a weighted percent. Total cholesterol level, TG level, HDL-C level, non-HDL-C, TG/HDL-C, and HOMA-IR score were log-transformed for the analyses; they are presented as the geometric mean ± standard error. Student's *t*-test for continuous variables and the chi-squared test for categorical variables were performed to compare the means and proportions between groups. Logistic regression analysis was performed to calculate the relevant odds ratio with a 95% confidence interval (CI) for a possible association between MetS and the lipid-derived surrogate markers: TG/HDL-C, TyG, and non-HDL-C. Linear regression analysis was also used to calculate possible pairwise associations between markers: TG/HDL-C vs. TyG, TG/HDL-C vs. non-HDL-C, and TyG vs. non-HDL-C. To validate the power of the lipid-derived surrogate markers as predictors of MetS and IR, the area under the curve (AUC) was calculated from the receiver operating characteristic (ROC) curve (Akobeng 2007). The best cutoff point was determined using the Euclidean index (geometric distance) in which the cutoff value corresponds to the point on the ROC curve that is closest to the left-hand corner of the ROC space. To minimize the Euclidean index, as defined by $d^2 = FNF^2 + FPF^2 = (1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$, FNF and FPF were the false negative and false positive fractions, respectively (Hajian-Tilaki 2018). P-values < 0.05 were considered statistically significant.

Results

Anthropometric and biochemical characteristics of the participants

The general characteristics of the study participants are shown in Table 2. The mean age of the participants was 14.2 ± 0.1 years, and the mean BMI was 21.1 ± 0.1 kg/m^2. Overall, 9.4% of the participants (10.0% of boys and 8.8% of girls) were overweight, while 12.3% of the participants (13.3% of boys and 11.2% of girls) were obese. The prevalence of overweight and obesity was higher in boys than girls. Furthermore, boys had elevated systolic BP, fasting glucose level, and alanine transaminase level, whereas girls had elevated total cholesterol, TG, HDL-C, and non-HDL-C levels.

The highest prevalence of MetS was 11.3% (12.5% in boys and 10.1% in girls) using the MetS2 criteria (de Ferranti et al. 2004); the lowest prevalence was 2.7% (2.6% in boys and 2.7% in girls) using the MetS3 (Zimmet et al. 2007). The prevalence of MetS using the MetS1 criteria (Cook et al. 2003) was 4.6% (5.3% in boys and 3.8% in girls).

Associations between lipid-derived surrogate markers

Fig. 2A-C shows pairwise correlations of the three lipid-derived surrogate markers. The TyG and TG/HDL-C had a strong positive correlation ($r^2 = 0.89$, $P < 0.001$) (Fig. 2A).

Lipid-derived surrogate markers for predicting MetS

The ROC curves of the lipid-derived surrogate markers for MetS, as determined using each of the three criteria, are shown in Fig. 3. Following MetS ROC analyses of the lipid-derived surrogate markers (Table 3), the TG/HDL-C exhibited AUCs of 0.937 (95% CI 0.936-0.938) using the MetS1 criteria (Cook et al. 2003); 0.894 (95% CI 0.893-0.894) using the MetS2 criteria (de Ferranti et al. 2004); and 0.897 (95% CI 0.896-0.898) using the MetS3 criteria (Zimmet et al. 2007). Furthermore, the TyG exhibited AUCs of 0.906 (95% CI 0.905-0.907) using the MetS1 criteria (Cook et al. 2003); 0.864 (95% CI 0.864-0.865) using the MetS2 criteria (de Ferranti et al. 2004); and 0.887 (95% CI 0.886-0.889) using the MetS3 criteria (Zimmet et al. 2007). Thus, the TG/HDL-C and TyG showed good prediction power for MetS.

Discussion

This validation study used nationally representative data to investigate the usefulness of lipid-derived surrogate markers, the TG/HDL-C, TyG, and non-HDL-C, to predict MetS. We applied three different definitions of MetS that are generally used in clinical practice. The results showed that the TG/HDL-C and TyG were predictive of MetS in Korean children and adolescents.

To our knowledge, this is the first study to analyze the correlations of these three lipid-derived surrogate markers with MetS in children and adolescents. Although some studies have analyzed the associations of specific lipid-derived surrogate markers with MetS or IR, no study has performed simultaneous comparative analyses of these three lipid-derived surrogate markers with MetS (Chu et al. 2019; Katsa et al. 2019).

To determine a valid cutoff value, we performed a MetS ROC curve analysis. Because there is no consensus regarding the diagnosis of MetS in children and adolescents, we used the three different definitions of MetS that are most commonly used in children and adolescents, then estimated cutoff values for each definition.

TG is correlated with insulin secretion in normoglycemic and prediabetic individuals. Childhood obesity induces increased hepatic production of fasting TG and decreased HDL-C level; these abnormalities are most marked in children and central obesity (Freedman et al. 1989). Hypertriglyceridemia caused by visceral fat is related to the increased flux of free fatty acids to the liver, which decreases hepatic insulin sensitivity and increases hepatic glucose output; these changes are associated with IR, lead-

Table 2. Anthropometric and biochemical characteristics in study participants.

		Total (n = 1,814, 100%)	Boys (n = 938, 51.0%)	Girls (n = 876, 49.0%)	P-value
Estimated population		3,118,340	1,591,164	1,527,176	-
Age (years)		14.2 ± 0.1	14.1 ± 0.1	14.3 ± 0.1	0.338
Body mass index (kg/m^2)		21.0 ± 0.1	21.3 ± 0.1	20.8 ± 0.1	< 0.001
Body mass index z-score		0.09 ± 0.04	0.04 ± 0.06	0.14 ± 0.05	0.170
Obesity	Normal (%)	1,411 (78.36%)	708 (76.7%)	703 (80.0%)	
	Overweight (%)	188 (9.4%)	106 (10.0%)	82 (8.8%)	0.302
	Obese (%)	215 (12.3%)	124 (13.3%)	91 (11.2%)	
Waist circumference (cm)		70.8 ± 0.3	72.8 ± 0.4	68.6 ± 0.3	< 0.001
Systolic blood pressure (mm Hg)		108.3 ± 0.3	110.6 ± 0.4	105.9 ± 0.4	< 0.001
Diastolic blood pressure (mm Hg)		66.0 ± 0.2	66.1 ± 0.3	65.8 ± 0.3	0.479
Total cholesterol (mg/dL)		158.6 ± 0.7	154.0 ± 0.9	163.6 ± 1.0	< 0.001
Triglyceride (mg/dL)		74.3 ± 1.0	72.0 ± 1.4	76.7 ± 1.3	0.012
HDL-C (mg/dL)		51.1 ± 0.3	50.1 ± 0.3	52.3 ± 0.4	< 0.001
TG/HDL-C		1.45 ± 0.02	1.44 ± 0.03	1.47 ± 0.03	0.549
TyG		8.11 ± 0.01	8.08 ± 0.02	8.13 ± 0.02	0.072
Non-HDL-C (mg/dL)		105.8 ± 0.7	102.2 ± 0.9	109.6 ± 1.0	< 0.001
Insulin (μIU/mL)		11.1 ± 0.4	10.4 ± 0.5	11.7 ± 0.5	0.042
Fasting glucose (mmol/L)		5.07 ± 0.02	5.11 ± 0.01	5.03 ± 0.02	0.001
HOMA-IR		2.49 ± 0.09	2.37 ± 0.12	2.62 ± 0.11	0.107
HbA1c (%)		5.43 ± 0.01	5.45 ± 0.01	5.42 ± 0.01	0.074
Serum ALT (IU/L)		15.6 ± 0.4	18.6 ± 0.8	12.4 ± 0.4	< 0.001
MetS1 (%)		80 (4.6%)	50 (5.3%)	30 (3.8%)	0.184
MetS2 (%)		207 (11.3%)	119 (12.5%)	88 (10.1%)	0.073
MetS3 (%)		43 (2.7%)	23 (2.6%)	20 (2.7%)	0.911

Data were expressed as weight mean ± standard error or number of cases (weighted percent).
HDL-C, high density lipoprotein cholesterol; TG/HDL-C, triglyceride/HDL cholesterol ratio; TyG, triglyceride-glucose index; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycated hemoglobin; ALT, alanine transaminase; MetS1, metabolic syndrome by Cook et al. (2003); MetS2, metabolic syndrome by de Ferranti et al. (2004); MetS3, metabolic syndrome by International Diabetes Federation (Zimmet et al. 2007).
Total cholesterol, triglyceride, HDL-C, non-HDL-C, TG/HDL-C, TyG, insulin, and HOMA-IR were log-transformed and expressed as geometric mean ± standard error.
Insulin and HOMA-IR were measured in 422 subjects.

ing to impaired glucose tolerance and diabetes. Furthermore, hypertriglyceridemia induces *β*-cell dysfunction by *de novo* formation of ceramide and increased nitric oxide production (Shimabukuro et al. 1998). IR is reportedly associated with higher levels of TG in children with obesity (Jiang et al. 1995).

The recently introduced lipid profile measure TG/HDL-C may be a better predictor of small, dense LDL, which is atherogenic lipoprotein particle with robust ability to predict coronary heart disease; moreover, small, dense LDL has been associated with an increased risk of CVD (Onat et al. 2010). In a study performed in the USA, the TG/HDL-C was an independent predictor of arterial stiffness in adolescents and adults aged 10-26 years (Urbina et al. 2013). In addition, a large Italian study reported that the TG/HDL-C is a simple and effective tool to detect children and adolescents with atherogenic dyslipidemia and cardiometabolic risk (Di Bonito et al. 2015). In the Italian study, individuals with a TG/HDL-C ≥ 2.2 were at high risk of preclinical signs of organ damage. Another study in the USA demonstrated that Caucasian children and adolescents with a TG/HDL-C ≥ 2.27 were at a high risk of IR (Giannini et al. 2011). IR is one of the main mechanisms involved in MetS, which is a significant risk factor for CVD. Thus, individuals with a TG/HDL-C ≥ 2.27 are presumably at risk of CVD (Giannini et al. 2011). The highest 75th percentile of the TG/HDL-C ratio was 2.39 in boys and 2.49 in girls among Korean children and adolescents (Shim et al. 2016). The highest 75th percentile of the TG/HDL-C in both sexes ranged between 2.2 and 2.7; these values were previously associated with a high risk of CVD in children and adolescents (Seo and Kim 2017).

In 2010, the TyG (rather than the euglycemic-hyperinsulinemic clamp) was suggested as a useful surrogate measure for IR in healthy adults (Guerrero-Romero et al. 2010). In the Chungju Metabolic Disease cohort study, the TyG

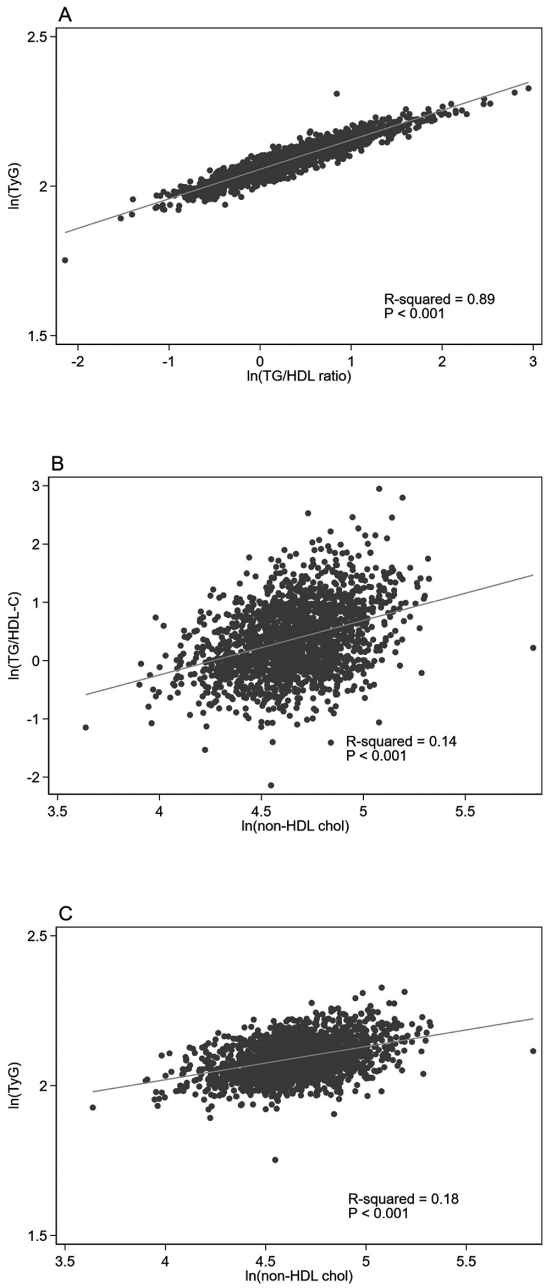

Fig 2. Correlation between lipid-derived surrogate markers. A. Correlation between triglyceride/high-density lipoprotein cholesterol ratio (TG/HDL-C) and triglyceride-glucose index (TyG). B. Correlation between non-high-density lipoprotein cholesterol level (non-HDL-C) and TG/HDL-C. C. Correlation between non-HDL-C and TyG. All variables were log-transformed due to skewed distribution.

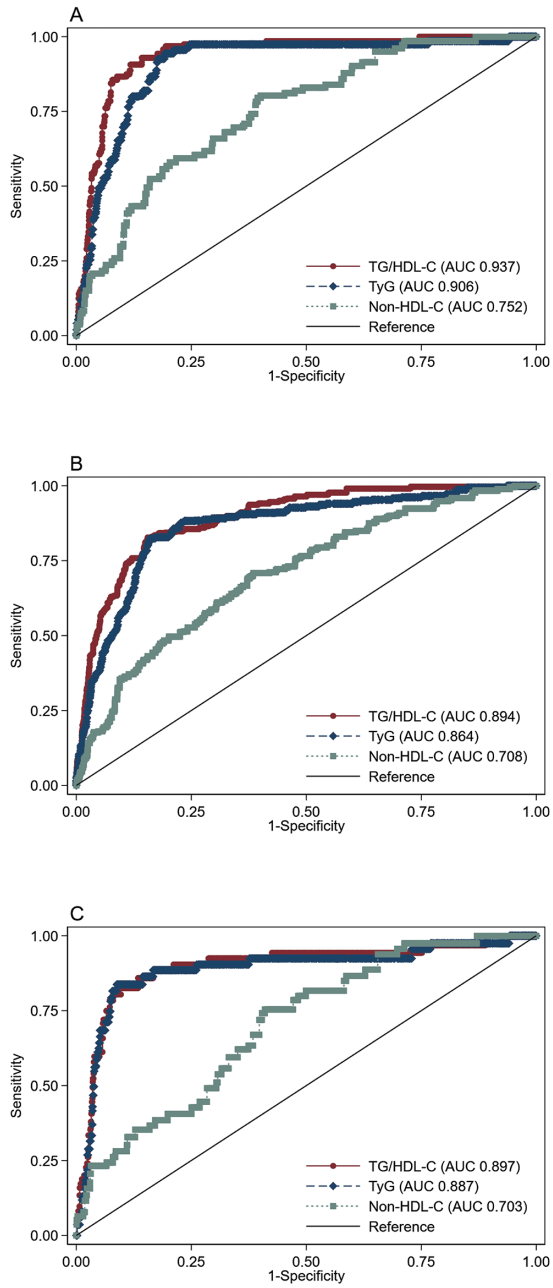

Fig. 3. Receiver operating characteristic curves of lipid-derived surrogate markers for predicting 3 different definitions of metabolic syndrome (MetS).
Outcome variables were MetS1 (A), MetS2 (B), and MetS3 (C).
MetS1, metabolic syndrome by Cook et al. (2003); MetS2, metabolic syndrome by de Ferranti et al. (2004); MetS3, metabolic syndrome by International Diabetes Federation (Zimmet et al. 2007); TG/HDL-C, triglyceride/high-density lipoprotein cholesterol ratio; TyG, triglyceride-glucose index; non-HDL-C, non-high-density lipoprotein cholesterol level.

was correlated with HOMA-IR score (r = 0.4; P < 0.001), and the TyG cutoff value for diagnosis of IR was 8.18 (Kang et al. 2017). The HOMA-IR score is a simple tool to estimate insulin sensitivity and is appropriate for use in large epidemiological studies. However, it requires data regarding fasting insulin levels; collection of these data may be hindered by poor reproducibility, the need for standardization, and a generally high cost. In contrast, the TyG does not require an insulin assay or TG testing, and it is less expensive than insulin testing. In addition, the enzymatic

Table 3. Receiver operating characteristic curve analysis of lipid-derived surrogate markers for predicting 3 different definitions of metabolic syndrome and insulin resistance.

Definition	Variable	AUC	95% CI	P-value	Cutoff	Sensitivity (%)	Specificity (%)
MetS1	TG/HDL-C	0.937	0.936-0.938	< 0.001	2.64	90.6	88.2
	TyG	0.906	0.905-0.907		8.52	92.6	82.2
	Non-HDL-C	0.752	0.751-0.753		111.6	79.5	60.6
MetS2	TG/HDL-C	0.894	0.893-0.894	< 0.001	2.23	82.8	84.5
	TyG	0.864	0.864-0.865		8.47	82.4	84.1
	Non-HDL-C	0.708	0.707-0.709		110.7	70.9	61.5
MetS3	TG/HDL-C	0.897	0.896-0.898	< 0.001	2.64	85.9	65.6
	TyG	0.887	0.886-0.889		8.74	83.7	91.2
	Non-HDL-C	0.703	0.701-0.705		110.8	75.4	59.0

AUC, area under the curve; CI, confidence interval; TG/HDL-C, triglyceride/high density lipoprotein cholesterol ratio; TyG, triglyceride-glucose index; MetS1, metabolic syndrome by Cook et al. (2003); MetS2, metabolic syndrome by de Ferranti et al. (2004); MetS3, metabolic syndrome by International Diabetes Federation (Zimmet et al. 2007).

method to measure TG is standardized, which facilitates reproducibility in all clinical laboratories. In a study based on the 2005-2013 KNHANES, cutoff values of the TyG were suggested based on three different MetS criteria (Moon et al. 2017). The optimal cutoff values using the different definitions were 8.45 (sensitivity 94.4%, specificity 79.3%) using the MetS1 criteria (Cook et al. 2003); 8.35 (sensitivity 86.2%, specificity 77.5%) using the MetS2 (de Ferranti et al. 2004); and 8.55 (sensitivity 89.8%, specificity 83.1%) using the MetS3 criteria (Zimmet et al. 2007). These results and the AUC values are similar to the findings in the present study. Furthermore, the study by Moon et al. (2017) was similar to the present study which included a comparative analysis of the TyG according to the three different definitions of MetS for adolescents based on the KNHANES. According to the another recent study, TyG and modified TyG indices are simple and valuable predictor of IR in youth (Song et al. 2021). However, the present study included participants aged 10-18 years, which is an age range representative of Korean children and adolescents. Furthermore, the three different lipid-derived surrogate markers were compared simultaneously. In addition, because the prevalence of obesity has markedly increased in recent years, the results based on recent data (KNHANES 2013-2016) are more useful than results based on older data (2005-2013 or 2007-2010).

The non-HDL-C reflects the cholesterol content in all potential atherogenic lipoproteins, including LDL-C, very-low-density lipoprotein remnants, and chylomicron remnants. Non-HDL-C measurement has a distinct advantage in pediatrics because it does not require fasting. The non-HDL-C was reportedly more effective for prediction of CVDs, compared with the LDL-C level, particularly when TG levels are elevated; the most recent guidelines recommend that the non-HDL-C should be targeted to manage cardiovascular risk (Miller et al. 2011; Smith et al. 2011). In the Bogalusa Heart study, non-HDL-C was equivalent to or better than other lipoprotein measurements, including LDL-C levels, for identification of subclinical atherosclerosis among individuals aged 24-48 years (Frontini et al. 2007). In guidelines regarding childhood and adolescent cardiovascular health, non-HDL-C has been recommended as a screening tool for childhood dyslipidemia defined as a non-HDL-C of ≥ 145 mg/dL (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung and Blood Institute 2011). A study of children and adolescents aged 12-19 years in the USA demonstrated that non-HDL-C are significantly associated with MetS, which is significantly associated with CVDs in adulthood (Li et al. 2011). Non-HDL-C of 120 mg/dL and 150 mg/dL for male and female Korean children and adolescents represent the threshold between borderline high and high risk of MetS (Kim et al. 2018b).

Serum lipids are affected by age, sex, ethnicity, nutritional status, pubertal stage, and physical activity. Overall, measurements of these three lipid-derived surrogate markers are inexpensive and their values are easy to calculate. However, they are not specific to a single disease and a single cutoff is not available. These markers are affected by changes in the lipid profile components according to age, sex, pubertal stage, and infections.

In the present study, the cutoff values of the TG/HDL-C for MetS were 2.64 using the MetS1 criteria (Cook et al. 2003), 2.23 using the MetS2 criteria (de Ferranti et al. 2004), and 2.64 using the MetS3 criteria (Zimmet et al. 2007). These values are consistent with the 75th-90th percentiles of the TG/HDL-C in Korean children and adolescents (Shim et al. 2016).

Several studies have suggested cutoff values for the lipid-derived surrogate markers for MetS or IR; however, the study populations and resulting values have varied among studies. A previous study performed in overweight Korean children and adolescents demonstrated that the TG/HDL-C was independently associated with IR (Yoo et al. 2017). However, that study had a retrospective, single-cen-

ter design; it also only analyzed overweight individuals. Notably, the TG/HDL-C was positively associated with IR in adolescents aged 12-18 years in the 2007-2010 KNHANES data. Previous epidemiological studies in adult populations have reported that a high TG/HDL-C is positively correlated with HOMA-IR score and is an independent predictor of cardiometabolic events (Hadaegh et al. 2009; Kang et al. 2012). Several studies have suggested the TG/HDL-C offers a marker of cardiovascular risk and IR in children and adolescents (Di Bonito et al. 2012; de Giorgis et al. 2014; Hirschler et al. 2015). However, most of these studies have either focused on children and adolescents with obesity or have used a small sample size, such that they were not representative of the general pediatric population. A recent study found no evidence that the TG/HDL-C is a useful predictor of IR (Bridges et al. 2016). The TyG appears to be a more useful screening tool than HOMA-IR score when determining MetS risk (Kim et al. 2016). Both the TyG and HOMA-IR score reflect IR in healthy adults (Simental-Mendia et al. 2008); compared with the HOMA-IR score, the TyG is better associated with carotid atherosclerosis in adult populations (Irace et al. 2013). The TyG was better correlated with IR, compared with HOMA-IR score, in a hyperinsulinemic-euglycemic clamp validated study involving an adult population (Vasques et al. 2011). In children and adolescents, the TyG is significantly associated with insulin sensitivity when compared with the hyperinsulinemic-euglycemic clamp, regardless of obesity status (Rodriguez-Moran et al. 2017). Furthermore, the TyG has high diagnostic concordance with the HOMA-IR score in children from the general population (Rodriguez-Moran et al. 2017). These studies suggest that the previously mentioned surrogate markers, which are generally simple and easy to obtain, might be helpful to predict MetS. However, the most appropriate marker remains controversial.

This study had a potential limitation that should be considered when interpreting the results. This study used a cross-sectional design, which hindered identification of causal relationships between the lipid-derived surrogate markers and MetS. Although significant relationships involving the TG/HDL-C, TyG, and MetS existed in the present study, it remains unclear whether the TG/HDL-C or TyG are risk factors involved in the development of MetS; alternatively, they may comprise epiphenomena. No long-term follow-up studies have evaluated lipid-derived surrogate markers throughout a lifetime, which is a further limitation of the use of these markers in clinical practice. No data are available regarding the possible role of the ratio as a predictive factor in future MetS risk. Therefore, longitudinal studies are needed to verify whether lipid-derived surrogate markers are the most appropriate markers to predict future MetS development

In conclusion, the TG/HDL-C and TyG had similar power for prediction of MetS in Korean children and adolescents, and our findings suggest that the TG/HDL-C and TyG are useful for screening or prediction of MetS in Korean children and adolescents. Therefore, if the TG/HDL-C or TyG is higher than the cutoff value, further investigation should be considered for diagnosis of MetS and active efforts to prevent MetS are required. Additionally, further long-term prospective follow-up studies are needed to investigate potential causal roles of the lipid-derived surrogate markers in the onset of MetS.

Conflict of Interest

The authors declare no conflict of interest.

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