

Triglyceride–Glucose Index Predicts Cardiovascular Outcome in Metabolically Unhealthy Obese Population: A Nationwide Population–Based Cohort Study

Yun Kyung Cho^{1,†}, Hwi Seung Kim^{2,3}, Joong–Yeol Park^{2,3}, Woo Je Lee^{2,3}, Ye–Jee Kim⁴, Chang Hee Jung^{2,3,*}

¹Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang; ²Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul; ³Asan Diabetes Center, Asan Medical Center, Seoul; ⁴Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Background: This study assesses the prognostic value of the triglyceride–glucose (TyG) index for cardiovascular (CV) risk in subgroups based on metabolic health and obesity status.

Methods: Originally, 514,866 participants were enrolled from the Korean National Health Insurance Service–National Health Screening Cohort. The study participants were categorized into four groups: metabolically healthy non-obese (MHNO), metabolically unhealthy non-obese (MUNO), metabolically healthy obese (MHO), and metabolically unhealthy obese (MUO). The TyG index was calculated using the following formula: $\ln(\text{fasting triglyceride [mg/dL]} \times \text{fasting plasma glucose [mg/dL]} / 2)$. Participants were followed from 2009 to 2015 for CV events and CV mortality according to the TyG index.

Results: After exclusions, the final study cohort contained 292,206 people. During the follow-up, 9,138 CV events and 1,163 CV deaths were documented. When the high and low TyG groups were compared, the high TyG group had a substantially increased risk of CV events among the MUNO and MUO participants (multivariable-adjusted hazard ratio [HR], 1.18; 95% confidence interval [CI], 1.07–1.30 and 1.27 [1.14–1.42], respectively). In participants with MUO status, CV mortality was also significantly increased in the high TyG group compared with the corresponding low TyG group (multivariable-adjusted HR, 1.48; 95% CI, 1.13–1.93). In contrast, a high TyG index was not related to CV mortality in the MHNO, MHO, and MUNO groups.

Conclusion: The predictive value of the TyG index can vary across populations. Among MUO participants, the TyG index was significantly and positively correlated with unfavorable CV outcomes.

Key words: Cardiovascular disease risk, Cardiovascular mortality, Metabolic syndrome, Obesity, Triglyceride–glucose index

Received November 20, 2021
Reviewed December 29, 2021
Accepted May 12, 2022

*Corresponding author
Chang Hee Jung

 <https://orcid.org/0000-0003-4043-2396>

Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-1418
Fax: +82-2-3010-6962
E-mail: chjung0204@gmail.com

[†]Current affiliation: Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

INTRODUCTION

Insulin resistance (IR) is a major risk factor for cardiovascular (CV) disease (CVD) and metabolic disorders such as obesity, type 2 diabetes, dyslipidemia, and hypertension.^{1–3} Recently, the triglyceride–glucose (TyG) index, the product of triglyceride (TG) and fasting plasma glucose (FPG) levels, has been introduced as a surrogate marker for IR.^{4,6} Previous studies have found a link between

IR and major CVD risk factors such as type 2 diabetes and hypertension.^{7,8} Furthermore, a higher plasma TyG index was reported to be associated with an increased incidence of CVD, irrespective of other conventional CVD risk factors.¹

Obesity is also a significant risk factor for CV morbidity. However, it has been suggested that the prognosis of persons with obesity is largely influenced by their metabolic health status.^{9–11} Previous studies have consistently found that metabolic unfitnes increases

CV risk and mortality in individuals with obesity.^{9,12} The TyG index might be a helpful predictor of CV risk in persons with obesity because it is a surrogate measure of IR, and IR is a primary pathophysiology that links obesity with poor CV outcomes.

Nonetheless, to our knowledge, no one has investigated the link between the TyG index and CV risk in relation to both metabolic health and obesity profiles. Therefore, in this study, we evaluate the predictive value of the TyG index for CV risk and examine its differential value in subgroups divided according to metabolic health status and the presence of obesity.

METHODS

Study population

Our analyses used data from the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) 2002–2015. The detailed structure and content of the database are described in Supplementary Material 1 and a previous publication.¹³ The index period was set between January 1, 2009, and December 31, 2010, because NHIS-HEALS started to include some lipid profile parameters that are needed to define metabolic health in 2009.¹³ Of the 514,866 total participants, those who died or had a

previous history of admission for a CV event before the end of the index period were excluded. Heavy alcohol drinkers were further excluded from the study population. The study cohort finally contained 292,206 participants, as described in Fig. 1. This study was approved by the Institutional Review Board of Asan Medical Center (No. 2021-0777). As this study was based on the results of the NHIS-HEALS, in which all data were fully anonymized and de-identified for all analyses, specific informed consent was not obtained from each participant.

Definitions of metabolic health and obesity

According to their metabolic health and obesity status, the participants were categorized into four groups: (1) metabolically healthy non-obese (MHNO), (2) metabolically unhealthy non-obese (MUNO), (3) metabolically healthy obese (MHO), and (4) metabolically unhealthy obese (MUO).^{14,15} The criteria used to define obesity and metabolic health are described in Supplementary Material 2.

TyG index

The TyG index was calculated using the following formula: $\ln(\text{fasting TG [mg/dL]} \times \text{FPG [mg/dL]}/2)$.¹⁶ The study population (the entire cohort and the subgroups based on metabolic health and obesity status) was divided into three groups according to the TyG index. The lowest quartile (Q1) was defined as the group with a low TyG index; the second and third quartiles (Q2 and Q3) were defined as the group with a middle TyG index; and the highest quartile (Q4) was defined as the group with a high TyG index.

Definitions of incident CV events and CV mortality

Admissions for myocardial infarction or stroke (ischemic or hemorrhagic) in hospital discharge records between January 1, 2011, and December 31, 2015, were defined as CV events. Participants were included if their International Classification of Diseases 10th revision (ICD-10) codes for a principal or subsidiary diagnosis included myocardial infarction or stroke. A detailed list of the ICD-10 codes is provided in Supplementary Material 3. CV mortality was defined as deaths caused by circulatory system diseases (I00-99) according to the 7th Korean Standard Classification of Diseases and Causes of Death, which is based on the ICD-10, as

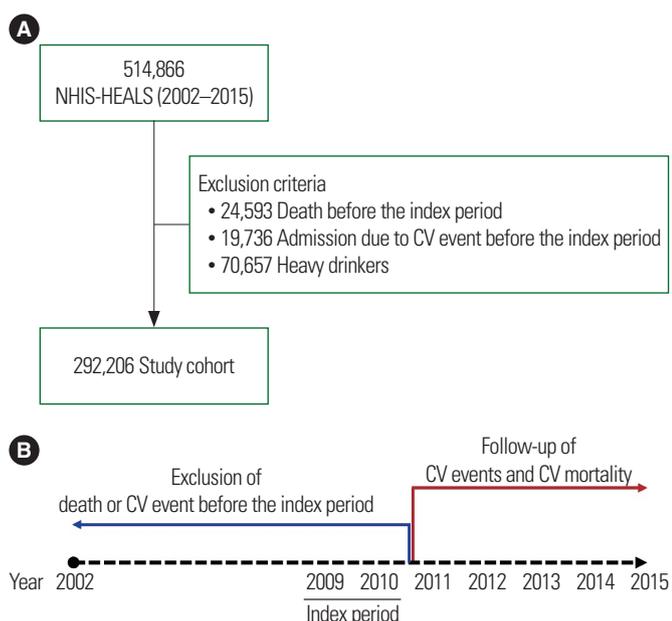


Figure 1. Study design and participants. (A) Selection of study participants. (B) Study design. NHIS-HEALS, National Health Insurance Service-Health Screening Cohort; CV, cardiovascular.

provided by the Korean National Statistical Office.

Statistical analysis

Cox proportional hazards analyses were performed to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for CV events and CV mortality. Multivariate-adjusted models were adjusted for age, sex, smoking habits (non-, ex-, or current smoker), alcohol drinking (non-, mild, or moderate drinker), physical activi-

ty (0, 1–2, 3–4, or ≥ 5 times per week), waist circumference, estimated glomerular filtration rate (eGFR), gamma-glutamyl transpeptidase level, low-density lipoprotein cholesterol level, and the use of anti-diabetic, anti-hypertensive, lipid-lowering, and antiplatelet agents. The group of participants in the lowest quartile of the TyG index in the entire cohort and in each metabolic health and obesity subgroup was used as the reference. SAS Enterprise Guide software (version 7.1; SAS Institute Inc., Cary, NC, USA) was used

Table 1. Characteristics of study participants according to the TyG quartiles

Variable	Total	Low TyG	Middle TyG	High TyG	P
Number	292,206	73,070 (25.0)	146,121 (50.0)	73,015 (25.0)	-
Sex (% men)	43.8	36.3	43.0	52.7	<0.001
Age (yr)	59.7±8.8	58.6±8.8	60.0±8.9	60.0±8.7	<0.001
BMI (kg/m ²)	24.0±2.9	23.0±2.8	24.1±2.9	25.0±2.9	<0.001
WC (cm)	81.7±8.4	78.0±8.0	81.8±8.0	85.1±7.7	<0.001
Systolic BP (mmHg)	125.9±15.3	121.6±15.0	126.1±15.1	129.6±15.1	<0.001
Diastolic BP (mmHg)	77.8±9.9	75.2±9.7	77.9±9.8	80.1±9.8	<0.001
Smoking (%)					<0.001
Current smoker	11.7	7.6	11.3	16.9	
Ex-smoker	14.6	11.7	14.5	17.7	
Non-smoker	70.4	77.5	70.9	62.2	
Drinking (%)					<0.001
None	70.5	72.8	71.1	66.9	
Mild	21.2	19.8	20.8	23.2	
Moderate	5.4	4.3	5.0	7.1	
Physical activity (%)					<0.001
None	28.8	26.2	28.9	31.1	
1–2 times/wk	21.4	19.9	21.4	23.0	
3–4 times/wk	20.8	22.6	20.7	20.2	
≥ 5 times/wk	26.5	29.7	26.4	23.3	
Anti-diabetic medication (%)	11.1	4.1	8.7	22.7	<0.001
Anti-hypertensive medication (%)	41.7	32.1	42.2	50.2	<0.001
Lipid-lowering medication (%)	22.1	13.3	21.5	32.0	<0.001
Antiplatelet use (%)	20.5	14.6	20.7	26.1	<0.001
FPG (mg/dL)	101.4±25.0	91.0±11.4	98.6±16.1	117.3±38.5	<0.001
TG (mg/dL)	139.1±86.9	66.3±15.5	122.2±29.0	245.6±105.4	<0.001
HDL-C (mg/dL)	53.9±26.6	59.5±19.5	53.8±23.9	48.7±35.3	<0.001
LDL-C (mg/dL)	122.4±38.6	117.9±34.1	125.8±36.8	120.3±45.3	<0.001
TC (mg/dL)	203.1±37.8	191.0±34.3	203.6±36.4	214.3±40.0	<.0001
AST (U/L)	26.4±17.7	25.4±18.8	25.9±15.8	28.3±19.7	<0.001
ALT (U/L)	25.2±19.3	21.7±18.8	24.5±18.0	30.0±21.1	<0.001
GGT (U/L)	32.0±39.9	23.7±27.6	30.1±34.8	44.1±54.6	<0.001
eGFR (mL/min/1.73 m ²)	79.6±19.0	82.5±18.3	79.4±18.9	77.1±19.7	<0.001
TyG index	8.7±0.6	8.0±0.3	8.7±0.2	9.5±0.4	<0.001

Values are presented as mean ± standard deviation unless otherwise indicated.

TyG, triglyceride–glucose; BMI, body mass index; WC, waist circumference; BP, blood pressure; FPG, fasting plasma glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; eGFR, estimated glomerular filtration rate.

for the statistical analyses. Detailed information about the statistical analyses is provided in Supplementary Material 4.

RESULTS

Baseline clinical and biochemical characteristics

Table 1 shows the baseline characteristics of the entire study cohort. After exclusions, the final study cohort contained 292,206 people. Compared with the low TyG group, the middle and high TyG groups had a less favorable risk profile, with higher glucose levels, poorer lipid profiles, and a higher waist circumference and body mass index (all $P < 0.001$). These groups also contained more smokers and alcohol drinkers (both $P < 0.001$), and the groups with a higher TyG index were less physically active than the low TyG index groups (all $P < 0.001$). The TyG index exhibited an inverse association with eGFR and high-density lipoprotein cholesterol (all $P < 0.001$).

Risk of CV events according to the TyG index

Table 2 shows the HRs for CV events according to the TyG index in the total population and the metabolic health and obesity

subgroups. In the entire population, 9,138 CV events were documented. The HRs for CV events were substantially higher in the middle and high TyG groups (HR [95% CI], 1.34 [1.26–1.41] and 1.74 [1.64–1.84], respectively) than in the low TyG group. The association between the TyG index and CV event risk remained significant after adjusting for other confounders (multivariate-adjusted HR [95% CI], 1.10 [1.03–1.16] in the middle TyG group and 1.26 [1.18–1.34] in the high TyG group).

Thereafter, we assessed the relationship between the TyG index and incident CV event rate in the subgroups divided by metabolic health and obesity status. The multivariate-adjusted HR for incident CV events was significantly increased by a high TyG index in participants with the MUNO and MUO phenotypes (multivariate-adjusted HRs [95% CI] in the high TyG group: 1.18 [1.07–1.30] in the MUNO subjects and 1.27 [1.14–1.42] in the MUO subjects). In the MHNO and MHO groups, no significant association was found between the TyG index and incident CV events after full adjustment (multivariate-adjusted HR [95% CI] of high TyG index: 1.14 [1.00–1.30] in the MHNO group and 1.13 [0.90–1.41] in the MHO group). Subgroup analyses by sex revealed similar findings in terms of CV events, with a greater CV event risk in the high TyG

Table 2. Hazard ratios for the CV event according to TyG index in total population and in obese metabolic health subgroups

TyG index	Total	MHNO	MHO	MUNO	MUO
Event					
Low (Q1)	2.32 (1,694/73,070)	1.76 (430/24,484)	2.11 (157/7,447)	3.67 (852/23,201)	3.52 (628/17,837)
Middle (Q2–Q3)	3.10 (4,524/146,121)	2.12 (1,045/49,204)	2.36 (352/14,910)	3.90 (1,810/46,394)	3.78 (1,348/35,693)
High (Q4)	4.00 (2,920/73,015)	2.26 (555/24,556)	2.34 (174/7,445)	4.38 (1,016/23,195)	4.32 (771/17,840)
Unadjusted					
Low (Q1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Middle (Q2–Q3)	1.34 (1.26–1.41)	1.21 (1.08–1.35)	1.12 (0.93–1.36)	1.06 (0.98–1.16)	1.08 (0.98–1.18)
High (Q4)	1.74 (1.64–1.84)	1.29 (1.14–1.46)	1.12 (0.90–1.39)	1.20 (1.10–1.31)	1.24 (1.12–1.38)
Age and sex-adjusted					
Low (Q1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Middle (Q2–Q3)	1.21 (1.14–1.28)	1.12 (1.00–1.26)	1.07 (0.89–1.29)	1.09 (1.01–1.18)	1.11 (1.01–1.22)
High (Q4)	1.58 (1.48–1.67)	1.22 (1.08–1.39)	1.11 (0.89–1.38)	1.30 (1.19–1.42)	1.37 (1.24–1.53)
Multivariable adjusted*					
Low (Q1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Middle (Q2–Q3)	1.10 (1.03–1.16)	1.07 (0.95–1.19)	1.06 (0.88–1.28)	1.06 (0.99–1.15)	1.08 (0.98–1.18)
High (Q4)	1.26 (1.18–1.34)	1.14 (1.00–1.30)	1.13 (0.90–1.41)	1.18 (1.07–1.30)	1.27 (1.14–1.42)

Values are presented as percent (number) or hazard ratio (95% confidence interval).

*Adjusted for baseline age, sex, smoking, alcohol drinking, physical activities, waist circumference, estimated glomerular filtration rate, gamma-glutamyl transpeptidase, low-density lipoprotein cholesterol level, and use of anti-diabetic medication, anti-hypertensive medication, lipid-lowering agents and antiplatelets.

CV, cardiovascular; TyG, triglyceride–glucose; MHNO, metabolically healthy non-obese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese; Q, quartile.

groups that was more noticeable in MUO participants in both sexes (Supplementary Tables 1 and 2).

CV mortality according to the TyG index

Table 3 shows the HRs for CV mortality based on the TyG index in the total population and the metabolic health and obesity subgroups. During follow-up, 1,163 CV deaths were reported. We

found that a high TyG index was related to higher CV mortality only in MUO participants (multivariate-adjusted HR [95% CI], 1.48 [1.13–1.93]). A high TyG index did not increase the CV mortality rate in the other groups (MHO, MHNO, and MUNO). Although the HRs did not reach statistical significance after adjustments, we did observe an inverse relationship between the TyG index and CV mortality in non-obese populations (multivariate-ad-

Table 3. Hazard ratios for the CV mortality according to TyG in total population and in obese metabolic health subgroups

TyG index	Total	MHNO	MHO	MUNO	MUO
Event					
Low (Q1)	0.49 (357/73,070)	0.39 (95/24,484)	0.27 (20/7,447)	0.84 (196/23,201)	0.53 (95/17,837)
Middle (Q2–Q3)	0.55 (806/146,121)	0.43 (214/49,204)	0.33 (49/14,910)	0.80 (371/46,394)	0.58 (206/35,693)
High (Q4)	0.67 (490/73,015)	0.35 (86/24,556)	0.17 (13/7,445)	0.72 (166/23,195)	0.80 (142/17,840)
Unadjusted					
Low (Q1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Middle (Q2–Q3)	1.12 (0.99–1.27)	1.12 (0.88–1.42)	1.23 (0.73–2.07)	0.95 (0.80–1.13)	1.08 (0.85–1.38)
High (Q4)	1.37 (1.19–1.57)	0.90 (0.67–1.20)	0.66 (0.33–1.32)	0.85 (0.69–1.04)	1.51 (1.16–1.95)
Age and sex-adjusted					
Low (Q1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Middle (Q2–Q3)	0.99 (0.87–1.12)	1.00 (0.79–1.28)	1.11 (0.66–1.87)	1.01 (0.85–1.20)	1.13 (0.88–1.44)
High (Q4)	1.25 (1.09–1.44)	0.89 (0.66–1.19)	0.65 (0.32–1.30)	1.02 (0.83–1.26)	1.74 (1.34–2.26)
Multivariable adjusted*					
Low (Q1)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Middle (Q2–Q3)	0.88 (0.78–1.00)	0.99 (0.77–1.26)	1.05 (0.62–1.78)	0.99 (0.83–1.18)	1.08 (0.85–1.38)
High (Q4)	0.96 (0.83–1.11)	0.91 (0.67–1.23)	0.65 (0.32–1.33)	0.95 (0.76–1.18)	1.48 (1.13–1.93)

Values are presented as percent (number) or hazard ratio (95% confidence interval).

*Adjusted for baseline age, sex, smoking, alcohol drinking, physical activities, waist circumference, estimated glomerular filtration rate, gamma-glutamyl transpeptidase, low-density lipoprotein cholesterol level, and use of anti-diabetic medication, anti-hypertensive medication, lipid-lowering agents and antiplatelets.

CV, cardiovascular; TyG, triglyceride–glucose; MHNO, metabolically healthy non-obese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese; Q, quartile.

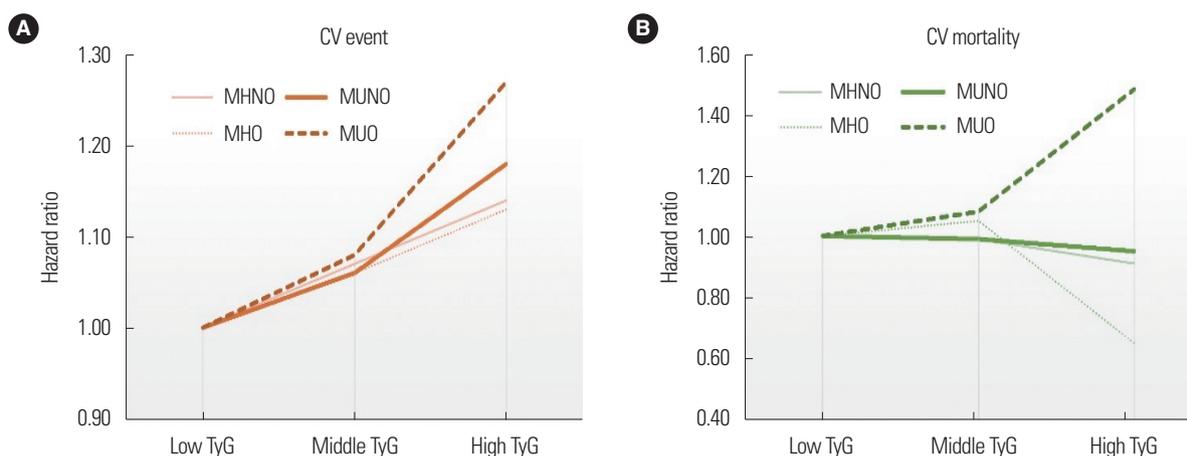


Figure 2. Summary of the implication of the triglyceride–glucose (TyG) index on cardiovascular (CV) outcomes according to metabolic health and obesity subgroups. (A) CV event. (B) CV mortality. MHNO, metabolically healthy non-obese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese.

justed HR [95% CI] of the high TyG groups: 0.91 [0.67–1.23] in the MHNO population and 0.65 [0.32–1.33] in the MUNO population). Subgroup analyses by sex demonstrated similar trends in general. Specifically, among MUO men, CV mortality in the high TyG group was significantly higher than that in the low TyG group (multivariate-adjusted HRs [95% CI], 1.83 [1.27–2.66]). However, in women, we observed only a nonsignificant increase in CV mortality in the high TyG group (multivariate-adjusted HR [95% CI], 1.14 [0.78–1.68]) (Supplementary Tables 3 and 4). The associations between the TyG index and incident CV events and CV mortality in the subgroups divided by the metabolic health and obesity phenotypes are summarized in Fig. 2.

DISCUSSION

We investigated the link between the TyG index and CV risk using data from a large-scale nationwide cohort. Even after controlling for traditional CV risk factors, a high TyG index was found to be associated with a significantly increased risk of future CV events. In our subgroup analysis, this association was particularly evident among MUO participants. The association between a high TyG index and CV mortality was observed only among MUO participants. Our results suggest that the predictive significance of the TyG index varies among subpopulations based on metabolic health and obesity status.

Obesity confers an increased risk of metabolic diseases such as diabetes, dyslipidemia, and hypertension,¹⁷ all of which are well-established risk factors for CVD. Metabolic syndrome is a complex of three or more of the above-mentioned disorders that increases the risk of future CVD.¹⁸ However, not all persons with obesity have associated metabolic abnormalities. In fact, metabolic syndrome affects only a subset of persons with obesity. In this context, MHO refers to the healthier phenotype presented by certain individuals with obesity, whereas MUO refers to the high-risk phenotype associated with obesity-induced metabolic derangement.¹⁹

Although the CV outcomes of the MHO phenotype are still controversial, it is irrefutable that persons with an MUO phenotype are at an increased risk of CVD.^{9,12,20,21} The major determinant of cardiometabolic fate that discriminates the MUO phenotype from the MHO phenotype is IR.¹⁷ Previous investigations have

suggested that IR is a strong predictor of CVD.^{22–26} A meta-analysis of approximately five million participants showed that the relative risk of CVD increased more with every 1 standard deviation increase in the homeostasis model assessment of IR (HOMA-IR) index than with a 1 standard deviation increase in fasting glucose or fasting insulin level.²⁷ Therefore, a marker for assessing IR in the obese population could be a useful predictor of future CV risk.

The TyG index, computed by multiplying TG and FPG, has demonstrated excellent sensitivity and specificity in detecting IR.^{4,16,28} De Fronzo's hyperinsulinemic–euglycemic clamp (HEC) technique is widely considered to be the gold standard approach for evaluating IR.²⁸ However, that approach is inappropriate for clinical use due to its cost and ethical considerations.²⁸ According to Guerrero-Romero et al.,¹⁶ the TyG index has high sensitivity and specificity and can be beneficial for detecting persons with decreased insulin sensitivity. A hyperglycemic clamp–validated study found a substantial association between TyG and IR, with higher performance than the HOMA-IR index.²⁹

Furthermore, several investigations have shown that the TyG index could be a surrogate marker for the risk of CVD. In the Vascular Metabolic CUN cohort, a higher TyG index correlated substantially with a higher risk of CVD development independent of confounding factors, and adding the TyG index to the Framingham risk score improved its predictive power for future CVD.³⁰ Recently, a Korean research group demonstrated that people with an elevated TyG index were more likely than others to suffer from myocardial infarction and stroke in the future.³¹ In line with those prior studies, our results support the close association between a high TyG index and a considerably increased risk of CV events and CV mortality. We further discovered that, particularly in people with the MUO phenotype, the TyG index had an excellent prognostic value for CV outcomes. To the best of our knowledge, this study is the first to demonstrate a particular metabolic health and obesity subgroup in which the TyG index is particularly effective in predicting incident CV events and CV mortality. Although the precise mechanism cannot be explained by our analyses, the predictive value of the TyG index might be greater in MUO participants, or insulin-resistant participants, because this index reflects the level of IR. That is, IR might have a considerable clinical effect on CV outcomes. Other risk factors, such as age, blood pressure, and chronic

inflammation, might be more significant contributors to CV risk in insulin sensitive individuals, such as metabolically healthy and lean people, than in people with IR.

Inevitably, this investigation had some limitations. First, our definition of CV events is based on claims data and might not be completely reliable, although we defined the outcomes by combining diagnosis and prescription history to improve accuracy. Second, we are unable to provide data supporting the advantages of the TyG index over HEC. Third, the number of events and the mortality rates might be underestimated due to the relatively short follow-up duration. Fourth, our subgroup analyses revealed that in women, CV mortality in the high TyG group was not significantly higher than that in the low TyG group, whereas men with a high TyG index were at a higher risk of CV death than the referent group. However, because the number of participants in the subgroup analyses was nearly halved, the discrimination power of the TyG index might have been compromised; the differential implications of the TyG index by sex need to be further investigated with a larger population. Nevertheless, this study's strengths can compensate for those limitations. We assessed the predictive efficacy of the TyG index for CV risk in different subgroups divided by metabolic health and obesity status, which allowed us to identify the subpopulation in which this index can be most effectively applied.

In conclusion, this study analyzed nationwide population-based cohort data and found that a higher TyG index is associated with a higher risk of CV events. Our findings also show that the TyG index has a high predictive value for CV risk in individuals with the MUO phenotype. Given the convenience of the TyG index, which can be easily calculated using TG and FPG levels, we recommend the application of this index in CV risk prediction, particularly in patients with the MUO phenotype.

CONFLICTS OF INTEREST

Chang Hee Jung is an editorial board member of the journal; however, he was not involved in the peer reviewer selection, evaluation, or decision process for this article. No other potential conflicts of interest relevant to this article were reported.

ACKNOWLEDGMENTS

This work was supported by a 2020 JOMES Research Acceleration Award from the Korean Society for the Study of Obesity.

AUTHOR CONTRIBUTIONS

Study concept and design: CHJ; acquisition of data: YKC, HSK, and JL; analysis and interpretation of data: YJK; drafting of the manuscript: YKC; critical revision of the manuscript: HSK, JYP, WJL, YJK, and CHJ; statistical analysis: YKC and YJK; obtained funding: YKC; administrative, technical, or material support: YJK; and study supervision: CHJ.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found online at <https://doi.org/10.7570/jomes21086>.

REFERENCES

1. Barzegar N, Tohidi M, Hasheminia M, Azizi F, Hadaegh F. The impact of triglyceride-glucose index on incident cardiovascular events during 16 years of follow-up: Tehran Lipid and Glucose Study. *Cardiovasc Diabetol* 2020;19:155.
2. Ginsberg HN. Insulin resistance and cardiovascular disease. *J Clin Invest* 2000;106:453-8.
3. Jeppesen J, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C, Madsbad S. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease: a population-based study. *J Am Coll Cardiol* 2007;49:2112-9.
4. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord* 2008;6:299-304.
5. Abbasi F, Reaven GM. Comparison of two methods using plasma triglyceride concentration as a surrogate estimate of insulin action in nondiabetic subjects: triglycerides \times glucose versus triglyceride/high-density lipoprotein cholesterol. *Metabolism* 2011;60:1673-6.

6. Toro-Huamanchumo CJ, Urrunaga-Pastor D, Guarnizo-Poma M, Lazaro-Alcantara H, Paico-Palacios S, Pantoja-Torres B, et al. Triglycerides and glucose index as an insulin resistance marker in a sample of healthy adults. *Diabetes Metab Syndr* 2019;13:272-7.
7. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 1990;113:909-15.
8. Wang F, Han L, Hu D. Fasting insulin, insulin resistance and risk of hypertension in the general population: a meta-analysis. *Clin Chim Acta* 2017;464:57-63.
9. Cho YK, Kang YM, Yoo JH, Lee J, Park JY, Lee WJ, et al. Implications of the dynamic nature of metabolic health status and obesity on risk of incident cardiovascular events and mortality: a nationwide population-based cohort study. *Metabolism* 2019;97:50-6.
10. Stefan N, Häring HU, Schulze MB. Metabolically healthy obesity: the low-hanging fruit in obesity treatment? *Lancet Diabetes Endocrinol* 2018;6:249-58.
11. Jung CH, Lee WJ, Song KH. Metabolically healthy obesity: a friend or foe? *Korean J Intern Med* 2017;32:611-21.
12. Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Januszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. *J Am Coll Cardiol* 2014;63:1071-8.
13. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. *BMJ Open* 2017;7:e016640.
14. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-97.
15. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157-63.
16. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity: comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 2010;95:3347-51.
17. Iacobini C, Pugliese G, Blasetti Fantauzzi C, Federici M, Menini S. Metabolically healthy versus metabolically unhealthy obesity. *Metabolism* 2019;92:51-60.
18. Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? *Circulation* 2003;108:1546-51.
19. Després JP. Body fat distribution and risk of cardiovascular disease: an update. *Circulation* 2012;126:1301-13.
20. Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically healthy obese and incident cardiovascular disease events among 3.5 million men and women. *J Am Coll Cardiol* 2017;70:1429-37.
21. Bell JA, Hamer M, Batty GD, Singh-Manoux A, Sabia S, Kivimäki M. Incidence of metabolic risk factors among healthy obese adults: 20-year follow-up. *J Am Coll Cardiol* 2015;66:871-3.
22. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, et al. Insulin sensitivity and atherosclerosis. *Circulation* 1996;93:1809-17.
23. Isomaa B, Almgren P, Tuomi T, Forsén B, Lahti K, Nissén M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683-9.
24. Bonora E, Formentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care* 2002;25:1135-41.
25. Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in Caucasian subjects from the general population: the Bruneck study. *Diabetes Care* 2007;30:318-24.
26. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. *Diabetes Care* 2002;25:1177-84.

27. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One* 2012;7:e52036.
28. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol* 2014;13:146.
29. Vasques AC, Novaes FS, de Oliveira Mda S, Souza JR, Yamanaka A, Pareja JC, et al. TyG index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. *Diabetes Res Clin Pract* 2011;93:e98-100.
30. Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martínez JA. The TyG index may predict the development of cardiovascular events. *Eur J Clin Invest* 2016;46:189-97.
31. Hong S, Han K, Park CY. The triglyceride glucose index is a simple and low-cost marker associated with atherosclerotic cardiovascular disease: a population-based study. *BMC Med* 2020;18:361.