The cut-off values of surrogate measures for insulin resistance in the Korean population according to the Korean Genome and Epidemiology Study (KOGES)

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Abstract

Objective

The current methods available for determining insulin resistance are complicated; hence, they are only applicable to small-scale studies. Therefore, this study aimed to classify the characteristics of surrogate measures for insulin resistance and establish valid cut-off values for predicting the development of type 2 diabetes mellitus (DM) in Korean populations.

Methods

This prospective study included 7,643 participants aged 40–69 years from the Ansung-Ansan cohort database (2001–2012). Four surrogate measures, namely homeostasis model assessment-insulin resistance (HOMA-IR), visceral adiposity index (VAI), lipid accumulation product (LAP), and triglycerides and glucose (TyG) index, were analyzed. We analyzed each measure using receiver operating characteristic (ROC) curve for the development of type 2 DM. The cut-off value was determined as the value with the highest Youden index score in the specificity dominant area.

Results

The area under the curve (AUC) was 0.566 (95% confidence interval [CI], 0.548–0.583) for HOMA-IR, 0.622 (95% CI, 0.605–0.639) for VAI, 0.642 (95% CI, 0.625–0.658) for LAP, and 0.672 (95% CI, 0.656–0.687) for TyG index. The AUC of TyG index was significantly higher than that of HOMA-IR, VAI, and LAP (p < 0.001). The cut-off value was 2.54 (sensitivity 36.8%; specificity 73.1%; hazard ratio [HR], 1.41, 95% CI, 1.25–1.59) for HOMA-IR, 2.54

(sensitivity 50.4%; specificity 68.8%; HR, 1.75, 95% CI, 1.55–1.96) for VAI, 36.6 (sensitivity 59.2%; specificity 63.9%; HR, 1.87, 95% CI, 1.64–2.14) for LAP, and 4.69 (sensitivity 62.1%; specificity 63.1%; HR, 2.17, 95% CI, 1.92–2.45) for TyG index.

Conclusions

The TyG index was a better predictor for DM than HOMA-IR. VAI and LAP showed the modest predictability for DM. The TyG index could be a useful supplementary method for identifying individuals at risk for insulin resistance and DM development.

Introduction

Variable degrees of insulin resistance and impaired insulin secretion are major pathophysiological characteristics of type 2 diabetes mellitus (DM) [1]. Insulin resistance is characterized by a reduced physiological response of target tissues to normal levels of insulin and results in decreased glucose utilization in muscle and fat, as well as increased gluconeogenesis in the liver [2–4]. Understanding the contribution of insulin resistance to the pathogenesis of type 2 DM is important for establishing preventive measures and determining optimal therapeutic approaches. Unfortunately, the current methods (e.g., pancreatic suppression test, hyperinsulinemic-euglycemic [HIEG] clamp technique, and minimal model approximation of the metabolism of glucose [MMAMG]) available for determining insulin resistance are complicated, invasive, and expensive; hence, they are only applicable to small-scale studies [5–8]. Instead, indirect indices, such as homeostasis model assessment-insulin resistance (HOMA-IR), visceral adiposity index (VAI), lipid accumulation product (LAP), or triglycerides and glucose (TyG) index, are widely accepted for epidemiological or clinical studies because of their technical simplicity [9, 10, 11]. However, valid cut-off values of the indices used in predicting DM have not been fully evaluated yet. Hence, this study aimed to determine the characteristics of surrogate measures for insulin resistance in Korean populations and establish valid cut-off values for predicting DM.

Materials and methods

Study populations

The Ansung-Ansan cohort study is an ongoing prospective study that started in 2001 with support from the National Genome Research Institute in Korea's Center for Disease Control and Prevention. Detailed information on the study design and procedures is available in a previous report [12].

A population-based sample of male and female Koreans aged 40–69 years were enrolled from the following two sites: Ansung, which is a rural community with approximately 190,000 residents and Ansan, which is a rural community with approximately 693,000 residents [13]. A total of 10,038 participants (5,018 from Ansung and 5,020 from Ansan) underwent a baseline health examination at the Ajou University Medical Center and the Korea University Ansan Hospital from June 2001 to January 2003. Follow-up examinations were conducted biennially. Data from the baseline survey and five subsequent surveys (I-VI: 2001–2012) were analyzed in the present study. We excluded the following participants: those with incomplete data, those with lipid lowering medications and those with a clinical history of DM at the baseline examination (Fig 1). In total, 7,643 participants were eligible for this study.
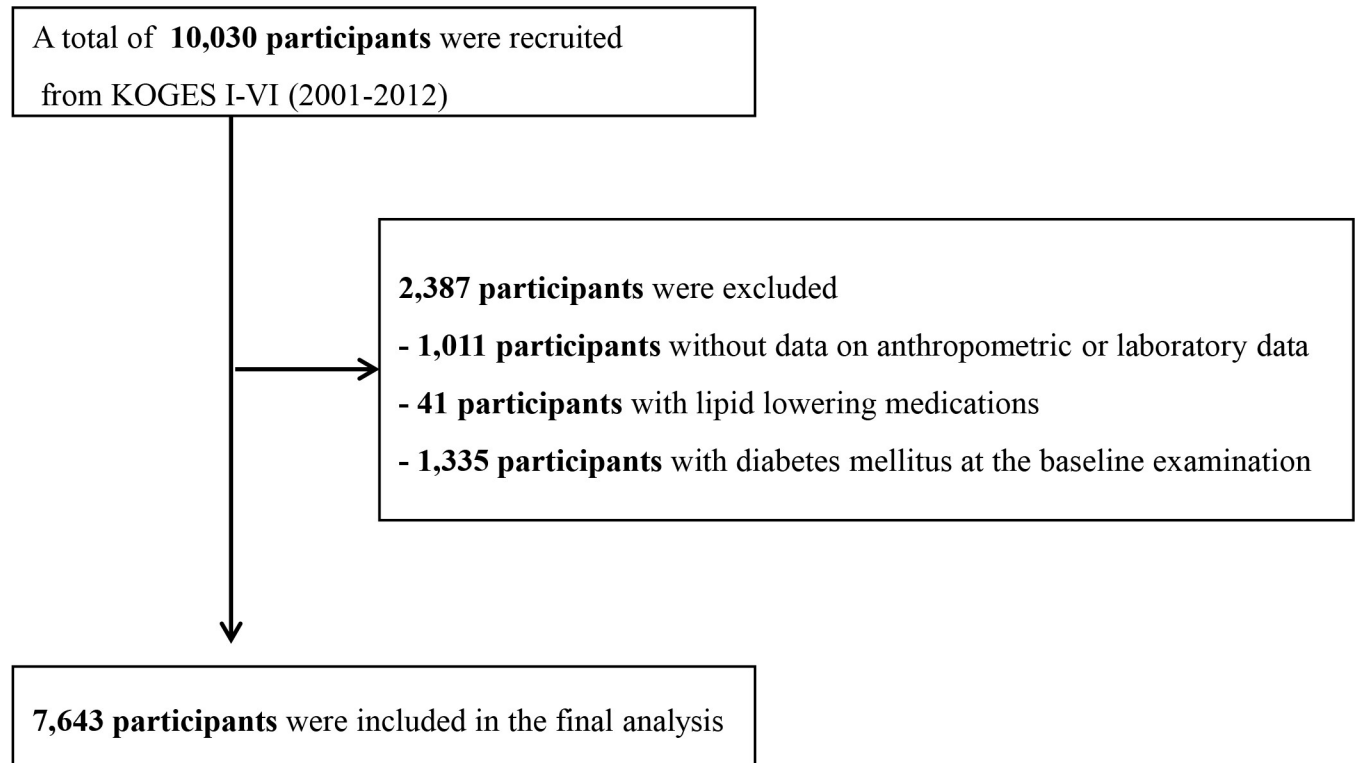
A total of **10,030 participants** were recruited from KOGES I-VI (2001-2012)

2,387 participants were excluded

- **1,011 participants** without data on anthropometric or laboratory data

- **41 participants** with lipid lowering medications

- **1,335 participants** with diabetes mellitus at the baseline examination

7,643 participants were included in the final analysis

Fig 1. Flowchart showing the final selection. KOGES, The Korean Genome and Epidemiology study.

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Clinical and laboratory measurements

Waist circumference was measured at the end of normal expiration using flexible tape at the narrowest point between the lowest border of the rib cage and the uppermost lateral border of the iliac crest. Height and body weight were measured to the nearest 0.1 cm and 0.2 kg, respectively. Blood pressure was measured in the sitting position after at least 5 minutes of rest. Blood samples were obtained after an overnight fast of at least 8 hours, and biochemical assays, including plasma glucose, total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C), were measured using the ADVIA 1650 chemistry analyzer (Bayer HealthCare Ltd., Tarrytown, NY, USA). Hemoglobin A1c (HbA1c) level was measured using high-performance liquid chromatography (Variant II; BioRad Laboratories, Hercules, CA, USA).

Definitions

A patient was deemed to have DM if he/she had at least one of the following conditions: the fasting glucose concentration was $\geq$126 mg/d, glucose concentration was $\geq$200 mg/dL in an oral 75-g 2-hour glucose tolerance test, HbA1c was $\geq$6.5%, and the use of glucose-lowering medication. A structured questionnaire was used to investigate regarding the use of glucose-lowering medication.

Insulin resistance was evaluated using HOMA-IR, VAI, LAP, and TyG index. The formulas for HOMA-IR and TyG index were as follows:

$$HOMA - IR = \text{fasting insulin } (\mu IU/mL) \times \text{fasting glucose } (mmol/L)/22.5$$

$$VAI = (\text{waist circumference (cm)}/(39.68 + (1.88 \times \text{Body mass index (BMI)}))) \times (\text{triglycerides (mmol/L)}/1.03) \times (1.31/\text{HDL} - \text{C (mmol/L)}) \text{ for men, or (waist circumference}$$
$$(\text{cm})/(36.58 + (1.89 \times \text{BMI}))) \times (\text{triglycerides (mmol/L)}/0.81) \times (1.51/\text{HDL} - \text{C (mmol/L)}) \text{ for women,}$$

$$LAP = (\text{waist circumference (cm)} - 65) \times (\text{triglycerides (mmol/L)}) \text{ for men, or (waist circumference (cm)} - 58) \times (\text{triglycerides (mmol/L)}) \text{ for women}$$

$$\text{TyG index} = Ln\ (\text{fasting glucose (mg/dL)} \times \text{triglycerides (mg/dL)})/2.$$

Statistical analysis

Summary statistics are presented as mean and standard deviation (SD) or prevalence (%). The values of each surrogate measure for insulin sensitivity were presented by the 10th, 25th, 50th, 75th, and 90th percentile. We analyzed each measure of insulin resistance using receiver operating characteristic (ROC) curve to estimate the predictive ability for the development of DM in 10 years. We performed the de Long's test to identify which surrogate measures for insulin resistance were significantly superior. The cut-off value of each surrogate measure was determined as the value with the highest Youden index score in the specificity dominant area. Multivariate Cox proportional hazards regression models were constructed to evaluate the hazards ratio (HR) and 95% confidence interval [CI] for DM. Follow-up duration was calculated as the time from the first anthropometric and clinical measures to either the date of development of DM or the end of follow-up (December 31, 2012). In addition, OR for DM according to the continuous value of each measure was analyzed using restricted cubic spline splits with five knots.

Analyses were carried out using SPSS, version 25.0 (IBM, Armonk, NY, USA) and the statistical package R (version 3.3.2, R Foundation for Statistical Computing). The significance levels were set at 0.05.

Ethics statement

The protocol of the study was approved by the institutional review board of Kangnam Sacred Heart Hospital (IRB No. HKS 2017-07-007), and all participants gave written informed consent. All participants' records were anonymized before being accessed by the authors, and all methods were carried out in accordance with the approved guidelines and regulations.

Results

Baseline characteristics

Overall, data from 7,643 participants were assessed (3,603 males and 4,040 females). Among them, 17.1% (1,306) had newly diagnosed DM during the 10-year follow-up period. Table 1 summarizes baseline anthropometric, clinical, and biochemical characteristics of the participants.

The distribution of surrogate measures for insulin resistance at baseline examination are summarized in Table 2.

Cut-off values of surrogate measures for insulin resistance

The ROC for newly developed DM in 10 years according to each measure is presented in Fig 2. The AUC was 0.566 (95% CI, 0.548–0.583) for HOMA-IR, 0.622 (95% CI, 0.605–0.639) for

Table 1. Baseline characteristics of participants according to incident DM.

Characteristics	Total participants (N = 7,643)
Age, years	51.7 ± 8.8
Male sex, n (%)	3,603 (47.1)
Smoking, n (%)	3,044 (40.3)
BMI, Kg/m^2	24.4 ± 3.1
Energy intake, Kcal/day	1,967.7 ± 720.8
Physical activity*, n (%)	4,649 (62.6)
Hypertension, n (%)	2,271 (29.7%)
Systolic BP, mmHg	120.5 ± 17.9
Diastolic BP, mmHg	79.9 ± 11.4
HbA1c, %	5.5 ± 0.3
Fasting glucose, mg/dL	82.7 ± 8.5
Fasting insulin, μIU/mL	7.6 ± 4.8
Total cholesterol, mg/dL	189.6 ± 34.2
HDL Cholesterol, mg/dL	44.9 ± 10.0
Triglycerides, mg/dL	154.8 ± 94.0
HOMA-IR	1.6 ± 1.0
VAI	2.5 ± 1.9
LAP	38.5 ± 31.9
TyG index	4.7 ± 0.2

Data were presented as means ± SD or number (%)

* Participants who engaged in physical activity for at least 30 minutes per day

Abbreviations: BMI; body mass index; BP, blood pressure; HbA1c; hemoglobin A1c; HDL; high-density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance; TyG index; triglycerides and glucose index

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VAI, 0.642 (95% CI, 0.625–0.658) for LAP, and 0.672 (95% CI, 0.656–0.687) for TyG index. The AUC of TyG index was significantly higher than that of HOMA-IR, VAI, and LAP (p < 0.001). The AUC of VAI was similar with that of LAP (p = 0.115) while higher than that of HOMA-IR (p value < 0.001). The AUC of each measure was higher in women than in men.

The cut-off values with their corresponding sensitivity, specificity, and HR are summarized in Table 3. In the restricted cubic spline regression, each surrogate measure showed a dose-dependent relationship with the risk of DM (Fig 3).

Discussion

In this community-based prospective cohort, we confirmed that TyG index was a better predictor for DM compared with VAI, LAP and HOMA-IR. VAI and LAP showed modest predictability for DM while HOMA-IR scarcely predicted DM.

Table 2. Distribution of surrogate measures for insulin resistance at baseline examination.

Indirect index	Percentile				
	10th	25th	50th	75th	90th
HOMA-IR	0.64	1.03	1.40	1.92	2.48
VAI	0.97	1.34	2.00	3.05	4.67
LAP	10.7	17.9	30.2	49.7	75.7
TyG index	4.37	4.49	4.64	4.81	4.99

Abbreviations: HOMA-IR: homeostasis model assessment-insulin resistance; VAI: visceral adiposity index; LAP: lipid accumulation product; TyG index: triglycerides and glucose index
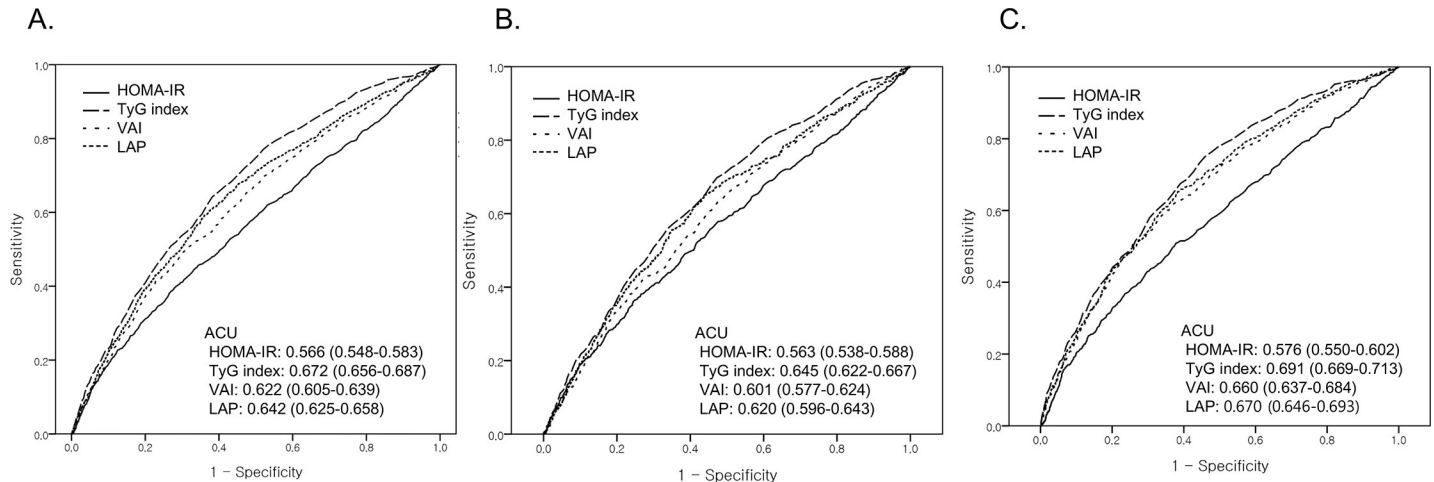
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Fig 2. ROC curves of incident diabetes mellitus in 10 years based on each surrogate measure for insulin resistance. A. Total; **B.** Men; **C.** Women.

HOMA-IR is a well-known robust tool for the assessment of insulin resistance and is associated with the development of DM [14–16]. The present study shows dose dependent association between HOMA-IR and the risk of DM. However, the AUC value was much lower than those in previous studies. According to studies conducted in Iran, China, and Korea, the AUC value of HOMA-IR was approximately 0.7–0.8 [17–19]. Interestingly, a significant decline of the diagnostic performance of HOMA-IR for type 2 DM was observed with aging [19]. Several previous studies showed a decline in the AUC of HOMA-IR for metabolic syndrome in elderly individuals as well [20, 21]. Considering that the participants of our study were older than those of previous studies, such differences might arise from age-related effects.

It is important to estimate a valid cut-off value for the clinical use of HOMA-IR. Although a number of studies suggested the cut-off values, there is great variability. In several population-based studies, the cut-off values of HOMA-IR were made based on the percentile criterion (75 -90th percentile according to studies) of values in the general population [22–24]. However, considering the distribution of HOMA-IR varied according to participants' demographic characteristics such as age, sex and race, it is difficult to estimate the optimal cut-off value with the percentile criterion. For example, the 75th percentile of HOMA-IR was 2.53 in healthy Koreans, while 1.6 in healthy Iranians, 2.0 in healthy Swedish men and 3.8 in French men [20, 22–24]. In addition, it is unclear whether the proposed cutoff values of HOMA-IR based on the percentile criterion could predict clinically relevant outcomes [15, 20, 21].

In order to resolve such doubts, several studies were conducted to determine the valid cut-off value of HOMA-IR for predicting the development of DM. Despite the fact that DM

Table 3. Cut-off values with their corresponding sensitivity, specificity, and hazard ratio (HR).

Surrogate measures	Cut-off value	Sensitivity	Specificity	HR (95% CI)*
HOMA-IR	1.83	38.6	73.1	1.41 (1.25–1.59)
VAI	2.54	50.4	68.8	1.75 (1.55–1.96)
LAP	36.6	59.2	63.9	1.87 (1.64–2.14)
TyG index	4.69	62.1	63.1	2.17 (1.92–2.45)

Abbreviations: HOMA-IR: homeostasis model assessment-insulin resistance; TyG index; triglycerides and glucose index; HR: hazard ratio

*Adjusted for age, sex, BMI, smoking and hypertension, physical activity, energy intake
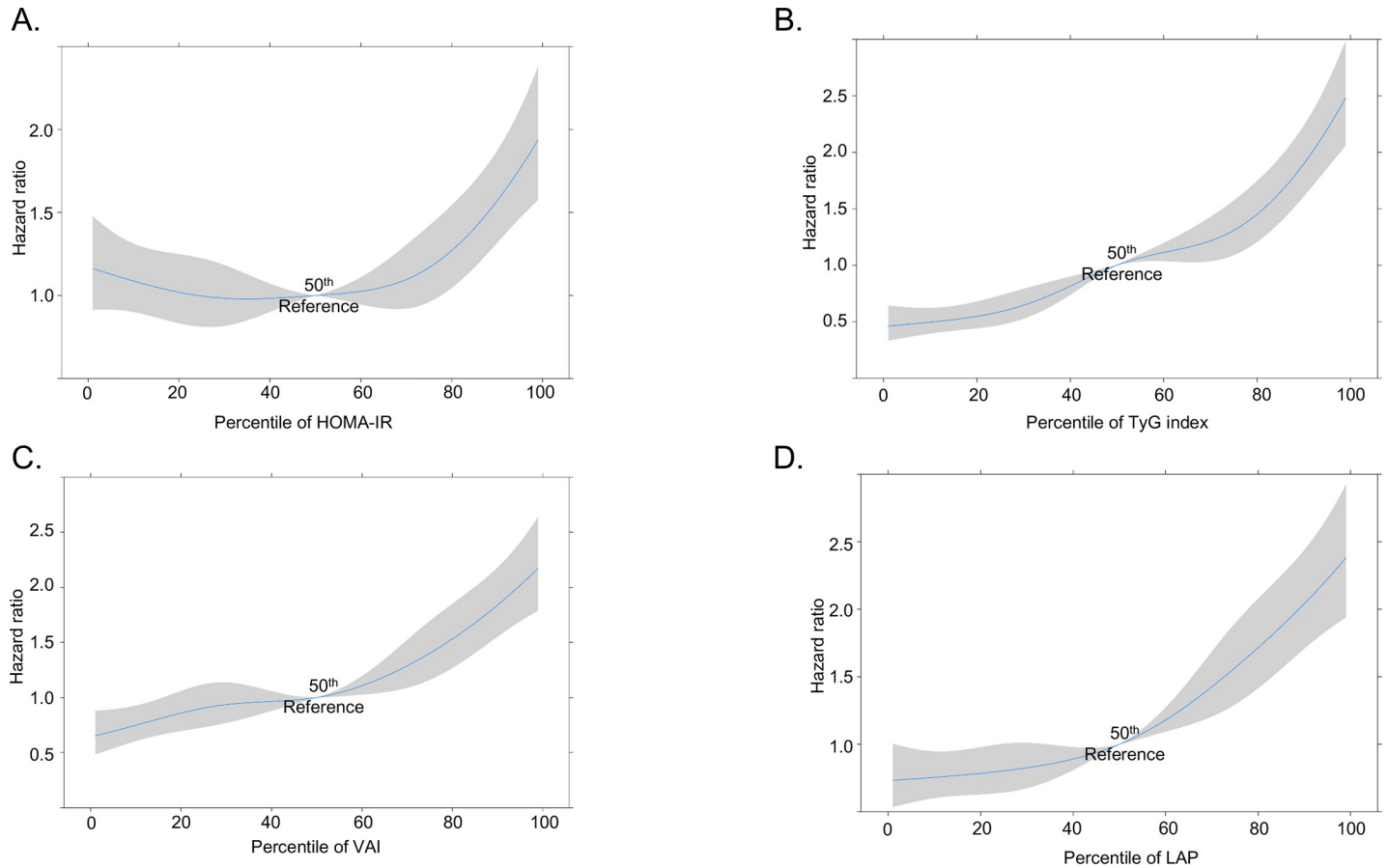
Fig 3. The odds ratio for DM according to the percentile of each surrogated measure. A. HOMA-IR; B. VAI; C. LAP; D. TyG index Abbreviations: HOMA-IR: homeostasis model assessment-insulin resistance; VAI: visceral adiposity index; LAP: lipid accumulation product; TyG index: triglycerides and glucose index.

develops over a long period of time, most of the studies were cross-sectional and may have contained various confounding factors [25–27]. Limited data regarding HOMA-IR cut-off values were obtained from longitudinal studies. Ghasemi et al. suggested that the cut-off value of HOMA-IR was 2.17 (sensitivity 50%, specificity 76.7%) for males and 1.85 (sensitivity 75.9%, specificity 58.3%) for females [17]. According to Lee et al., the cut-off value of HOMA-IR was 1.97 (sensitivity 65.5%, specificity 82.9%) [18]. The results obtained in our study are consistent with those obtained in these studies. However, considering the low sensitivity of HOMA-IR for DM in the present study, this cut-off value has limitations for the application to clinical settings.

One significant drawback of HOMA-IR is that a standard assay for measurement of fasting insulin is absent. To overcome this, insulin-free equations for estimating insulin resistance have been developed. One well-known useful insulin-free surrogate measure is the triglycerides and glucose (TyG) index [10]. It is a more simple and inexpensive method compared with insulin-based surrogate measures. TyG is well correlated with the gold standard methods for insulin resistance such as HIEG clamp or MMAMG [10, 28]. Moreover, there was a modest correlation between the TyG index and insulin stimulated glucose uptake during insulin suppression testing [29]. Several population-based studies demonstrated that high TyG index was associated with DM, hypertension, nonalcoholic fatty liver disease, and atherosclerosis [30–35]. However, there have been few studies to estimate the cut-off value of TyG index for

predicting development of DM. Guerrero-Romero et al. suggested that the best value of the TyG index for diagnosis of insulin resistance was 4.68 using the HIEG clamp test with a small sample size; this cut-off value is similar to our findings [10]. We suggest our results could support the cut-off value from the study of Guerrero-Romero et al. To the best of our knowledge, this is the first study to estimate a valid cut-off value of TyG index using data from a population-based longitudinal study.

Notably, we found that TyG index had better predictive power for development of DM, compared with HOMA-IR. The correlation between HIEG clamp test and TyG index is known to be comparable with the correlation between HIEG clamp test and HOMA-IR [28, 36]. However, a direct comparison between TyG index and HOMA-IR regarding their ability to predict DM development has not performed yet. Therefore, another significance of the present study is providing evidence of clinical usefulness of TyG index for identifying individuals at risk for DM. Regarding low cost and universal use of blood glucose and triglycerides tests, the TyG index can be a good supplementary test measure for insulin resistance.

Interestingly, the AUC of the surrogate measures differed by sex. This result is consistent with those of a previous study [17, 19]. Considering that estrogens promote peripheral fat storage, whereas androgens promote the accumulation of visceral abdominal fat, the alteration of sex hormone might affect the insulin resistance and the diagnostic performance of each measure for type 2 DM [37].

The main strength of this study was the data source, the Ansung-Ansan Cohort, which is a long-term (10-year follow-up), community-based cohort. Despite this strength, the present study has some limitations. First, because this study was performed among Korean adults, the result might not be applicable to other ethnicities. Second, the study lacks in directly comparing the surrogate measure and gold standard methods for insulin resistance such as HIEG clamp or MMAMG. Further studies are necessary for this issue.

In conclusion, TyG index was better predictor for DM compared with HOMA-IR. VAI and LAP showed modest predictability for DM. TyG index could be used as a simple and supplementary method to identify individuals at risk for insulin resistance and DM development.

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Author Contributions

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Formal analysis: Shinje Moon.

Funding acquisition: Shinje Moon.

Methodology: Bongyoung Kim, Wonhee Kim, Chiwon Ahn, Juncheol Lee, Jae Guk Kim, Jihoon Kim, Hyungoo Shin, Jae Myung Yu, Shinje Moon.

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Writing – original draft: Bongyoung Kim, Hyun Young Choi, Shinje Moon.

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