Lipid indices as simple and clinically useful surrogate markers for insulin resistance in the U.S. population

Juncheol Lee1,9, Bongyoung Kim2,9, Wonhee Kim3, Chiwon Ahn4, Hyun Young Choi3, Jae Guk Kim3, Jihoon Kim5, Hyungoo Shin6, Jun Goo Kang7,8 & Shinje Moon7,8

This study aimed to compare the accuracy of novel lipid indices, including the visceral adiposity index (VAI), lipid accumulation product (LAP), triglycerides and glucose (TyG) index, TyG-body mass index (TyG-BMI), and TyG-waist circumference (TyG-WC), in identifying insulin resistance and establish valid cutoff values. This cross-sectional study used the data of 11,378 adults, derived from the United States National Health and Nutrition Examination Survey (1999–2016). Insulin resistance was defined as a homeostasis model assessment-insulin resistance value above the 75th percentile for each sex and race/ethnicities. The area under the curves (AUCs) were as follows: VAI, 0.735; LAP, 0.796; TyG index, 0.723; TyG-BMI, 0.823, and; TyG-WC, 0.822. The AUCs for TyG-BMI and TyG-WC were significantly higher than those for VAI, LAP, and TyG index (vs. TyG-BMI, p < 0.001; vs. TyG-WC, p < 0.001). The cutoff values were as follows: VAI: men 1.65, women 1.65; LAP: men 42.5, women 42.5; TyG index: men 4.665, women 4.575; TyG-BMI: men 135.5, women 135.5; and TyG-WC: men 461.5, women 440.5. Given that lipid indices can be easily calculated with routine laboratory tests, these values may be useful markers for insulin resistance risk assessments in clinical settings.

Insulin resistance (IR) is a pathological situation, in which there is a lack of physiological response to insulin acting on peripheral tissues1–3. Insulin resistance reduces glucose utilization in the muscles and fats and increases gluconeogenesis in the liver, leading to metabolic and hemodynamic disturbances known as metabolic syndrome, which is a major risk factor for coronary heart disease and cerebrovascular disease1–7. Considering the prevalence of insulin resistance and metabolic syndromes, it would be necessary to detect insulin resistance early even in healthy individuals8.

Insulin resistance was initially evaluated using the pancreatic suppression test, hyperinsulinemic euglycemic clamp technique (HIEG clamp), or minimal model approximation of the metabolism of glucose (MAMMG)9–11. However, these methods are invasive, complicated, expensive, and difficult to use clinically12. For these reasons, indices that measure insulin resistance indirectly have been developed. The homeostasis model for IR (HOMA-IR), which uses fasting blood glucose levels and insulin concentration as variables, was developed in 1985 and has been widely used to estimate IR13. However, a significant drawback of HOMA-IR is the lack of a standard assay for the measurement of fasting insulin concentration14. Therefore, considering these concerns regarding standardization, the HOMA-IR has a significant limitation in establishing an overall acceptable reference value. Furthermore, while several studies have defined IR as a value greater than the 75th percentile value of the HOMA-IR in individuals without diabetes mellitus, the reported cutoff values vary widely, ranging from 2.0 to 3.812,15–19. Given that the measurement of fasting insulin concentration is cumbersome and expensive, the HOMA-IR is not routinely measured in the clinical setting20.

Therefore, insulin-free equations for estimating IR, such as lipid indices, were developed. Lipid indices include visceral adiposity index (VAI), lipid accumulation product (LAP), and triglycerides and glucose (TyG) index21–25.

1Department of Emergency Medicine, Armed Forces Capital Hospital, Seongnam, Republic of Korea. 2Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea. 3Department of Emergency Medicine, Hallym University, Chuncheon, Republic of Korea. 4Department of Emergency Medicine, College of Medicine, Chung-Ang University, Seoul, Republic of Korea. 5Department of Thoracic and Cardiovascular Surgery, Hallym University College of Medicine, Chuncheon, Republic of Korea. 6Department of Emergency Medicine, College of Medicine, Hanyang University Guri Hospital, Guri, Republic of Korea. 7Department of Internal Medicine, Hallym University, Chuncheon, Republic of Korea. 8Division of Endocrinology and Metabolism, Hallym University College of Medicine, 1, Hallymhoeak-gil, Chuncheon-si, Gangwon-do 24252, Republic of Korea. 9These authors contributed equally: Juncheol Lee and Bongyoung Kim. *email: kjg0804@empas.com; sinjei1129@gmail.com
These parameters were proposed as a useful surrogate measure of insulin resistance. In addition, several studies have evaluated modified indices that combine TyG index and obesity indices such as body mass index (BMI) and waist circumference (WC). However, limited evidence is available regarding the discriminatory accuracy and cutoff values of these novel lipid indices for detecting insulin resistance.

Therefore, this study aimed to compare the accuracy of novel lipid indices in identifying insulin resistance using a representative sample of the US population and establish valid cutoff values for IR.

**Results**

The study included 11,378 adults (men 5478, women 7900; mean age, 40 years) from the National Health and Nutrition Examination Survey (NHANES) 1999–2016 (Fig. 1). Participants’ demographic and clinical characteristics were compared based on the presence or absence of IR, and the results are shown in Table 1. Age, BMI,
WC, and blood pressure were higher in participants with insulin resistance. In addition, blood tests demonstrated high values of fasting glucose, hemoglobin A1C, fasting insulin, total cholesterol, and triglycerides, and low value of high-density lipoprotein (HDL) cholesterol, in participants with IR. Data (median with interquartile range) of each parameter according to race/ethnicity and sex are summarized in Table 2.

The receiver operating characteristic (ROC) curve for IR is presented in Fig. 2. The AUC was 0.723 for TyG index and 0.735 for VAI (Table 3). The AUC of LAP (0.796) was significantly higher than that of TyG index (p < 0.001). However, the AUCs of TyG-BMI (0.823) and TyG-WC (0.822) were significantly higher than that of LAP (vs. TyG-BMI, p < 0.001; vs. TyG-WC, p < 0.001). Subgroup analysis according to sex and race/ethnicities showed that TyG-BMI and TyG-WC had the highest AUC in every subgroup. Further analysis using 1:1 propensity score matching (PSM) data with age, sex, and race/ethnicities showed similar results (Table 3). The cutoff values of each lipid index were as follows: VAI: men 1.65, women 1.65; LAP: men 42.5, women 42.5; TyG index: men 4.665, women 4.575; TyG-BMI: men 135.5, women 135.5; and TyG-WC: men 461.5, women 440.5. The

Table 2. Distribution of indirect parameters for insulin resistance according to race/ethnicity and sex. IQR interquartile range, HOMA-IR homeostasis model assessment-insulin resistance, VAI visceral adiposity index, LAP lipid accumulation product, TyG index triglycerides and glucose index, BMI body mass index, WC waist circumference. *Other race included non-Hispanic Asian and multi-racial Americans.

| Indirect parameters for insulin resistance | Total (Median IQR) | Hispanic (Median IQR) | Non-Hispanic white (Median IQR) | Non-Hispanic black (Median IQR) | Other race* (Median IQR) |
|------------------------------------------|--------------------|-----------------------|-------------------------------|-------------------------------|------------------------|
| HOMA-IR                                  |                    |                       |                               |                               |                        |
| Men                                      | 1.98 (1.27–3.24)   | 2.34 (1.49–3.62)     | 1.86 (1.20–3.07)              | 1.82 (1.14–3.18)              | 1.94 (1.18–2.96)      |
| Women                                    | 1.87 (1.21–3.06)   | 2.24 (1.46–3.44)     | 1.60 (1.05–2.53)              | 2.17 (1.40–3.59)              | 1.59 (1.05–2.53)      |
| VAI                                      |                    |                       |                               |                               |                        |
| Men                                      | 1.4 (0.8–2.3)      | 1.6 (1.0–2.7)        | 1.4 (0.9–2.5)                 | 1.0 (0.6–1.5)                 | 1.3 (0.8–2.3)         |
| Women                                    | 1.4 (0.9–2.2)      | 1.7 (1.0–2.6)        | 1.4 (0.9–2.3)                 | 1.0 (0.7–1.7)                 | 1.2 (0.8–2.1)         |
| LAP                                      |                    |                       |                               |                               |                        |
| Men                                      | 38 (20–66)         | 45 (26–72)           | 41 (23–72)                    | 26 (14–47)                    | 30 (14–56)            |
| Women                                    | 35 (20–63)         | 43 (24–71)           | 34 (19–63)                    | 31 (18–52)                    | 25 (14–47)            |
| TyG index                                |                    |                       |                               |                               |                        |
| Men                                      | 4.64 (4.45–4.85)   | 4.70 (4.52–4.90)     | 4.65 (4.47–4.85)              | 4.52 (4.34–4.7)               | 4.64 (4.46–4.87)      |
| Women                                    | 4.535 (4.35–4.74)  | 4.62 (4.42–4.81)     | 4.55 (4.37–4.75)              | 4.41 (4.26–4.59)              | 4.50 (4.33–4.72)      |
| TyG-BMI                                  |                    |                       |                               |                               |                        |
| Men                                      | 125 (108–144)      | 131 (114–147)        | 125 (108–144)                 | 120 (104–143)                 | 115 (100–133)         |
| Women                                    | 122 (103–147)      | 129 (111–151)        | 118 (100–143)                 | 130 (108–155)                 | 106 (91–127)          |
| TyG-WC                                   |                    |                       |                               |                               |                        |
| Men                                      | 446 (391–499)      | 456 (409–503)        | 455 (400–510)                 | 416 (364–483)                 | 416 (365–466)         |
| Women                                    | 415 (362–477)      | 431 (381–488)        | 408 (358–473)                 | 421 (365–483)                 | 374 (332–436)         |

Figure 2. Receiver operating characteristic (ROC) curves of lipid indices for insulin resistance.
VAI uses BMI, WC, and triglyceride and HDL cholesterol levels to evaluate IR and was proposed by Amato et al. using the NHANES data. LAP is calculated using WC and fasting triglyceride levels. In a previous study conducted by Amato et al., VAI showed a significant inverse correlation with insulin sensitivity measured using a HIEG clamp, providing evidence that VAI can be a surrogate marker for IR21. In addition, VAI was reported to be associated with the glucose distribution rate evaluated through the HIEG clamp test in a study on patients with type 1 diabetes mellitus (DM)26, and it was shown to be inversely correlated with HIEG clamp tested insulin sensitivity in studies conducted on women with polycystic ovary syndrome27. How-ever, most of these studies using the HIEG clamp test had a small sample, and the clinical application of VAI and LAP requires an investigation of appropriate cutoff values through large scale population-based studies. In addition to studies measuring insulin resistance directly, there are numerous studies on the accuracy of VAI and LAP. Although the mechanism through which lipid indices cause IR remains unclear, numerous studies have reported that glucolipotoxicity is a key mechanism in the modulation of IR32,33. Ectopic lipid accumulation increases hepatic lipogenesis and leads to IR in the liver and hyperlipidemia38–40. In addition, macrophage infiltration into white adipose tissue increases lipolysis, which stimulates hepatic triglyceride synthesis, thereby, promoting hyperlipidemia34. Macrophage-induced lipolysis in white adipose tissue also leads to increased hepatic gluconeogenesis and results in hyperglycemia through increased fatty acid delivery to the liver, which results in increased glycerol conversion to glucose41-43.

**Discussion**

In this study, we investigated the discriminatory accuracy of novel lipid indices for IR and confirmed that LAP showed significantly higher AUC than TyG index and VAI. There was a significant increase in AUC when BMI or WC was combined with TyG index, exhibiting an even higher discriminatory accuracy than that of LAP. Another important aspect of this study is that the cutoff value of each parameter for IR was presented using large-scale data, facilitating the clinical application of each parameter.

Table 3. Area under the curve for each parameter for insulin resistance according to race/ethnicity and sex. HOMA-IR homeostasis model assessment-insulin resistance, VAI visceral adiposity index, LAP lipid accumulation product, TyG index triglycerides and glucose index, BMI body mass index, WC waist circumference, AUC area under the curve, PSM propensity score matching with age, sex, and race/ethnicity.

|                | AUC (95% CI) | AUC (95% CI) | AUC (95% CI) | AUC (95% CI) | AUC (95% CI) |
|----------------|-------------|-------------|-------------|-------------|-------------|
| **Total**      | 0.735 (0.725–0.746) | 0.796 (0.787–0.805) | 0.723 (0.712–0.733) | 0.823 (0.814–0.832) | 0.822 (0.813–0.831) |
| **Men**        | 0.735 (0.720–0.750) | 0.800 (0.787–0.813) | 0.727 (0.712–0.742) | 0.829 (0.816–0.841) | 0.828 (0.816–0.841) |
| **Women**      | 0.735 (0.721–0.750) | 0.793 (0.780–0.806) | 0.726 (0.711–0.741) | 0.819 (0.807–0.832) | 0.825 (0.813–0.837) |
| **Hispanics**  |             |             |             |             |             |
| Men            | 0.733 (0.706–0.760) | 0.788 (0.764–0.812) | 0.730 (0.702–0.757) | 0.824 (0.801–0.847) | 0.818 (0.795–0.841) |
| Women          | 0.718 (0.691–0.745) | 0.773 (0.749–0.797) | 0.711 (0.684–0.738) | 0.818 (0.796–0.840) | 0.814 (0.792–0.837) |
| **Non-Hispanic Whites** |             |             |             |             |             |
| Men            | 0.754 (0.731–0.776) | 0.82 (0.801–0.839) | 0.742 (0.720–0.765) | 0.847 (0.829–0.865) | 0.852 (0.833–0.870) |
| Women          | 0.759 (0.737–0.780) | 0.814 (0.795–0.833) | 0.753 (0.731–0.774) | 0.840 (0.822–0.858) | 0.842 (0.824–0.860) |
| **Non-Hispanic Blacks** |             |             |             |             |             |
| Men            | 0.733 (0.698–0.768) | 0.815 (0.785–0.845) | 0.730 (0.696–0.765) | 0.823 (0.793–0.853) | 0.829 (0.801–0.858) |
| Women          | 0.722 (0.689–0.755) | 0.778 (0.748–0.809) | 0.710 (0.676–0.744) | 0.795 (0.765–0.825) | 0.810 (0.781–0.839) |
| **Other race** |             |             |             |             |             |
| Men            | 0.734 (0.687–0.781) | 0.794 (0.750–0.837) | 0.712 (0.663–0.761) | 0.808 (0.761–0.855) | 0.830 (0.787–0.872) |
| Women          | 0.773 (0.729–0.818) | 0.824 (0.783–0.864) | 0.758 (0.711–0.805) | 0.846 (0.808–0.885) | 0.847 (0.808–0.885) |
| **PSM data**   |             |             |             |             |             |
| Total          | 0.732 (0.719–0.745) | 0.790 (0.778–0.802) | 0.716 (0.703–0.729) | 0.818 (0.807–0.829) | 0.818 (0.807–0.828) |
| Men            | 0.726 (0.707–0.745) | 0.789 (0.772–0.805) | 0.718 (0.698–0.737) | 0.819 (0.803–0.835) | 0.818 (0.802–0.833) |
| Women          | 0.737 (0.719–0.755) | 0.792 (0.776–0.809) | 0.722 (0.704–0.740) | 0.817 (0.802–0.833) | 0.827 (0.812–0.842) |

cutoff values with their corresponding sensitivity, specificity, and odds ratio (OR) of insulin resistance according to sex and race/ethnicities are summarized in Table 4.
Table 4. Cutoff values for each parameter and their corresponding sensitivity, specificity, and odds ratios for insulin resistance. *Adjusted for Age, race, smoking status, and blood pressure. † Other race included non-Hispanic Asian and multi-racial Americans.
with various races/ethnicities. Nonetheless, to accurately assess the correlation of IR with TyG-BMI and TyG-WC, verification through the HIEG clamp test is required as has been performed for HOMA-IR and TyG index.

The present study has several strengths. This study is the largest to evaluate the performance of the novel lipid indices to identify insulin resistance in the general US population. In addition, this study conducted various subgroup analyses of IR, with age, sex, and PSM data, to minimize the bias caused by heterogeneity due to demographic characteristics. Moreover, it is important to propose valid cutoff values for each lipid index so that they can be used as a reference in clinical settings for identifying groups at risk for IR. To the best of our knowledge, this is the first study that evaluated the performance and cutoff values of TyG-BMI and TyG-WC in a non-Asian population. However, considering that this is a cross-sectional study, further prospective studies are required to validate the relationship between each surrogate measure and cardiovascular risk factors.

Conclusion
The present study supports the clinical relevance of novel lipid indices in identifying IR in the general US population. Considering that lipid indices can be easily calculated with routine laboratory tests, they can be useful markers of insulin resistance risk assessments in clinical settings. Moreover, the cutoff values presented in our study may be useful in interpreting the results of lipid indices for IR.

Methods
Study population. The NHANES is a cross-sectional study that uses a representative sample of the population living in the United States. The NHANES, administered by the Centers for Disease Control and Prevention every two years, consists of health and nutrition surveys, physical examinations, and laboratory tests. Of the 92,062 individuals who participated in the NHANES between 1999 and 2016, 11,378 adult participants were included in this study after excluding those who were aged < 20 years (n = 42,550), those with missing or incomplete anthropometric and fasting laboratory data (n = 28,694), those on medication for dyslipidemia and hypertension (n = 6598), those with DM, CVD, stroke, cancer, chronic liver disease, and estimated glomerular filtration rate < 60 ml/min/1.73 m² (n = 2842) (Fig. 1).

Anthropometric and laboratory measurements. Waist circumference was measured using a flexible tape between the uppermost lateral border of the right ilium and that of the left ilium. BMI was defined as the weight in kilograms divided by the height in meters squared (kg/m²). Blood pressure was measured 3 times in the sitting position, with at least 5 min of rest in between each reading. The mean value of the three recorded blood pressure readings was used in this study. Fasting blood glucose and lipid levels were measured using the enzymatic method, and fasting insulin was measured using an immune-enzymometric assay. Detailed sample collection and processing instructions are described in the NHANES Laboratory Procedures Manual.

Calculation of parameters for insulin resistance. Parameters for insulin resistance were calculated as follows:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin (µIU/mL)} \times \text{fasting glucose (mmol/L)}}{22.5},
\]

\[
\text{VAI} = \left(\frac{\text{WC (cm)}}{39.68 + (1.88 \times \text{BMI})}\right) \times \left(\frac{\text{triglycerides (mmol/L)}}{1.03}\right) \\
\times \left(\frac{1.31}{\text{HDL-C (mmol/L)}}\right) \text{ for men, or (WC in centimeter)/(36.58 + (1.89 \times \text{BMI}))} \\
\times \left(\frac{\text{triglycerides (mmol/L)}}{0.81}\right) \times \left(\frac{1.51}{\text{HDL-C (mmol/L)}}\right) \text{ for women},
\]

\[
\text{LAP} = \left(\frac{\text{WC in centimeter} − 65}\right) \times \left(\frac{\text{triglycerides (mmol/L)}}{\text{for men, or (WC (cm) − 58)}}\right) \\
\times \left(\frac{\text{triglycerides (mmol/L)}}{\text{for women}},
\]

\[
\text{TyG index} = \ln{\left(\frac{\text{fasting glucose (mg/dL)}}{\text{triglycerides (mg/dL)}}\right)} / 2,
\]

\[
\text{TyG - BMI} = \ln{\left(\frac{\text{fasting glucose (mg/dL)} \times \text{triglycerides (mg/dL)}}{\text{BMI}}\right)} / 2,
\]

\[
\text{TyG - WC} = \ln{\left(\frac{\text{fasting glucose (mg/dL)} \times \text{triglycerides (mg/dL)}}{\text{WC (cm)}}\right)} / 2.
\]

We define IR as a HOMA-IR value above the 75th percentile for each race/ethnicity and sex (Hispanics: Men > 3.62, Women > 3.44; Non-Hispanic Whites: Men > 3.07, Women > 2.53; Non-Hispanic Blacks: Men > 3.18, Women > 3.59; other race: Men > 2.96, Women > 2.53).

Statistical analysis. Data were presented as mean with standard deviation, or number with prevalence (%) of IR status. Between groups, the differences were determined using t-tests and a Pearson chi-square test. The values of each lipid index for IR were presented as median and interquartile range. To compare the relative diagnostic strength of each lipid index for insulin resistance, AUC was compared using the ROC curve; de Long’s test was used to identify the surrogate measures that were significantly superior for insulin resistance. The cutoff value of each lipid index was determined as the value with the highest Youden index score. Considering the heterogeneity of demographic characteristics such as sex and race/ethnicities, subgroup analyses for IR were
performed. Further analysis was performed by 1:1 PSM with nearest-neighbor 1-to-1 matching. Furthermore, OR of HOMA-IR defined IR was checked using the multivariate logistic regression models based on the estimated cutoff values. Statistical analysis was performed using IBM SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA) and R ver. 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). The results were considered statistically significant if the p-value was less than 0.05.

**Ethics statement.** This study was approved by the institutional review board of Kangnam Sacred Heart Hospital (IRB No. HKS 2017-07-007) and the NHANES was approved by the Research Ethics Review Board of the National Center for Health Statistics, US Centers for Disease Control and Prevention (NHANES 1999–2004, Protocol #98-12; NHANES 2005–2010, Protocol #2005–06; NHANES 2011–2016, Protocol #2011-17). All participants volunteered and provided written informed consent before enrolment. All participants’ records were anonymized before being accessed by the authors. All methods were carried out in accordance with the principles contained in the Declaration of Helsinki.

Received: 27 August 2019; Accepted: 8 December 2020
Published online: 27 January 2021

**References**

1. Ascaso, J. F. et al. Diagnosing insulin resistance by simple quantitative methods in subjects with normal glucose metabolism. *Diabetes Care* **26**, 3320–3325 (2003).
2. Hanefeld, M. The metabolic syndrome: Roots, myths, and facts. In *The Metabolic Syndrome* (eds Hanefeld, M. & Leonhardt, W.) 13–24 (Gustav Fischer, Portland, 1997).
3. Samuel, V. T. & Shulman, G. I. Mechanisms for insulin resistance: Common threads and missing links. *Cell Metab.* **13**, 13–24 (2011).

**References**

1. Bergman, R. N., Prager, R., Volund, A. & Olefsky, J. M. Equivalence of the insulin sensitivity index in man derived by the minimal model method and the euglycemic glucose clamp. *J. Clin. Invest.* **79**, 787–790 (1987).
2. Greenfield, M. S. et al. Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. *Diabetes* **30**, 387–392 (1981).

3. Du, T. Role of insulin resistance associated with compensatory hyperinsulinemia in ischemic stroke. *Stroke* **27**, 37–43 (1996).
4. Miller, W. G. Insulin resistance in the pathogenesis of type 2 diabetes. *J. Transl. Med.* **9**, e98–e100 (2011).
5. Vasques, A. C. TyG index performs better than HOMA in a Brazilian population: A hyperglycemic clamp validated study. *Diabetes Res. Clin. Pract.* **93**, e98–e100 (2011).
6. Er, L. K. et al. Triglyceride glucose-body mass index is a simple and clinically useful surrogate marker for insulin resistance in nondiabetic individuals. *PLoS ONE* **11**, e0149731 (2016).
7. Zheng, S. et al. Triglyceride glucose-waist circumference, a novel and effective predictor of diabetes in first-degree relatives of type 2 diabetes patients: Cross-sectional and prospective cohort study. *J. Transl. Med.* **14**, 260 (2016).
31. Lim, J., Kim, J., Koo, S. H. & Kwon, G. C. Comparison of triglyceride glucose index, and related parameters to predict insulin resistance in Korean adults: An analysis of the 2007–2010 Korean National Health and nutrition examination survey. PLoS ONE 14, e0212963 (2019).
32. Bickerton, A. S. et al. Preferential uptake of dietary fatty acids in adipose tissue and muscle in the postprandial period. Diabetes 56, 168–176 (2007).
33. Samuel, V. T. & Shulman, G. I. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. J. Clin. Invest. 136, 12–22 (2016).
34. Dresner, A. et al. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. J. Clin. Investig. 103, 253–259 (1999).
35. Yu, C. et al. Mechanism by which fatty acids inhibit activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. J. Biol. Chem. 277, 50230–50236 (2002).
36. Irani, S. I., Ruckeman, N. B., Schmiede, F. & Boden, G. Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IκB-α. Diabetes 51, 2005–2011 (2002).
37. Szendroedi, J. et al. Role of diacylglycerol activation of PKCθ in lipid-induced muscle insulin resistance in humans. Proc. Natl. Acad. Sci. U.S.A. 111, 9597–9602 (2014).
38. Kim, J. K. et al. Glucose toxicity and the development of diabetes in mice with muscle specific inactivation of GLUT4. J. Clin. Investig. 108, 153–160 (2001).
39. Petersen, K. F. et al. The role of skeletal muscle insulin resistance in the pathogenesis of the metabolic syndrome. Proc. Natl. Acad. Sci. U.S.A. 104, 12587–12594 (2007).
40. Petersen, K. F. et al. Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. J. Clin. Investig. 109, 1345–1350 (2002).
41. Perry, R. J. et al. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. Cell 160, 745–758 (2015).
42. Perry, R. J. et al. Leptin reverses diabetes by suppression of the hypothalamic-pituitary-adrenal axis. Nat. Med. 20, 759–763 (2014).
43. Previs, S. F., Cline, G. W. & Shulman, G. I. A critical evaluation of mass isotopomer distribution analysis of gluconeogenesis in vivo. Am. J. Physiol. 277, E154–E160 (1999).
44. Oh, J. Y., Sung, Y. A. & Lee, H. J. The visceral adiposity index as a predictor of insulin resistance in young women with polycystic ovary syndrome. Obesity(Lips Silver Spring) 21, 1690–1694 (2013).
45. Ramezani Tehrani, F., Minooee, S. & Azizi, F. Comparison of various adiposity indexes in women with polycystic ovary syndrome and normo-ovulatory non-hirsute women: A population-based study. Eur. J. Endocrinol. 171, 199–204 (2017).
46. Huang, X. et al. Body fat indices as effective predictors of insulin resistance in obese/non-obese polycystic ovary syndrome women in the Southwest of China. Endocrine 65, 81–85 (2019).
47. Abruzzese, G. A. et al. Lipid accumulation product (LAP) and visceral adiposity index (VAI) as markers of insulin resistance and metabolic associated disturbances in young argentine women with polycystic ovary syndrome. Horm. Metab. Res. 49, 23–29 (2017).
48. Li, S. et al. The role of the triglyceride (triaclylglycerol) glucose index in the development of cardiovascular events: A retrospective cohort analysis. Sci. Rep. 9, 7320 (2019).
49. Kim, B. et al. The cut-off values of surrogate measures for insulin resistance in the Korean population according to the Korean genomic and epidemiology study (KOGES). PLoS ONE 13, e0206994 (2018).
50. Lee, S. H. et al. Predicting the development of diabetes by using triglycerides and glucose: The Chungju metabolic disease cohort (CMC) study. PLoS ONE 9, e90430 (2014).
51. Kershaw, E. E. & Flier, J. S. Adipose tissue as an endocrine organ. J. Clin. Endocrinol. Metab. 89, 2548–2556 (2004).
52. Matsuda, M. & Shimomura, I. Increased oxidative stress in obesity: Implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer. Obes. Res. Clin. Pract. 7, e330–341 (2013).
53. Kahn, S. E., Hull, R. L. & Utschneider, K. M. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 444, 840–846 (2006).
54. Zhang, S. et al. Triglyceride glucose-body mass index is effective in identifying nonalcoholic fatty liver disease in nonobese subjects. Medicine (Baltimore) 96, e7041 (2017).
55. Gu, Q. et al. Associations of triglyceride-glucose index and its derivatives with hyperuricemia risk: A cohort study in Chinese general population. Int. J. Endocrinol. 2020, 3214716 (2020).
56. Ramdas Nayak, V. K., Nayak, K. R., Vidyasagar, S. & Rekha, P. Predictive performance of traditional and novel lipid combined anthropometric indices to identify prediabetes. Diabetes Metab. Syndr. 14, 1265–1272 (2020).
57. Centers for Disease Control and Prevention. The National Health and Nutrition Examination Survey (NHANES) MEC Laboratory Procedures Manual (2016). https://www.cdc.gov/nchs/data/nhanes/2015-2016/manuals/2016_mec_laboratory_procedures_manual.pdf. Accessed 18 January 2021.
58. Morales-Gurrola, G. et al. The triglycerides and glucose index is associated with cardiovascular risk factors in metabolically obese normal-weight subjects. J. Clin. Investig. 43, 995–1000 (2020).
59. Ho, D. E., Imai, K., King, G. & Stuart, E. A. MatchIt: Nonparametric preprocessing for parametric causal inference. J. Stat. Softw. 42, 1–28 (2011).

Author contributions
S.M. and J.G.K. contributed to the research design; W.K., C.A., H.Y.C., J.G.K., J.K. and H.S. participated in the design and performance of the research and data analysis; S.M., B.K., J.G.K. and J.L. wrote the main manuscript text and S.M. prepared Figs. 1 and 2. All authors reviewed the manuscript. Correspondence and requests for materials should be addressed to J.G.K. or S.M.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to J.G.K. or S.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
