# Triglyceride-Glucose Index and HOMA-IR in Young Adulthood and Risk of Incident Congestive Heart Failure: The CARDIA Study

**Xianghui Zeng** ( 303992796@qq.com )
Southern Medical University Nanfang Hospital https://orcid.org/0000-0002-2307-1149

**Haobin Zhou**
Southern Medical University Nanfang Hospital

**Yuting Xue**
Southern Medical University Nanfang Hospital

**Xiao Wang**
Southern Medical University Nanfang Hospital

**Qiong Zhan**
Southern Medical University Nanfang Hospital

**Yujia Bai**
Southern Medical University Nanfang Hospital

**Xingfu Huang**
Southern Medical University Nanfang Hospital

**Qingchun Zeng**
Southern Medical University Nanfang Hospital

**Hao Zhang**
Southern Medical University Nanfang Hospital

**Zhuang Ma**
Southern Medical University Nanfang Hospital

**Hao Ren**
Southern Medical University Nanfang Hospital

**Dingli Xu**
Southern Medical University Nanfang Hospital

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# Abstract

**Background:** Triglyceride-glucose (TyG) index and homeostasis model assessment-insulin resistance (HOMA-IR) are related to insulin resistance (IR). The aim of this study was to assess the association between triglyceride-glucose index / HOMA-IR within young adults and congestive heart failure (CHF), and to explore whether triglyceride-glucose index can replace HOMA-IR as a surrogate marker for insulin resistance in predicting the risk of CHF.

**Methods:** A total of 4992 participants between the ages of 18 and 30 were enrolled from the Coronary Artery Risk Development in Young Adults (CARDIA) investigation (from 1985 to 1986 [year 0]). Cox proportional hazard regression analysis was conducted for assessing correlations between baseline TyG index / HOMA-IR and congestive heart failure events, together with Receiver Operating Characteristic (ROC) Curve employed for scrutinizing TyG index / HOMA-IR and he risk of CHF.

**Results:** During the 31-year follow-up period, 64 (1.3%) out of the 4992 participants developed congestive heart failure. In multivariable Cox proportional hazards models, adjusted for confounding factors for CHF, increased risk of CHF was associated with per-unit increase in TyG index (hazard ratio [HR] 2.8; 95% confidence interval [CI], 1.7-4.7) and HOMA-IR (HR 1.2; 95%CI, 1.1-1.3). Kaplan-Meier curve analysis showed that participants in the TyG index and HOMA-IR index Q4 group had a higher risk of congestive heart failure than those in the Q1 group. The area under curve (AUC) for TyG index and HOMA-IR consisted of 0.67 (95% CI, 0.6-0.742) and 0.675 (95%CI, 0.604-0.746), respectively. There were no significant differences between TyG index and HOMA-IR for AUC (P = 0.986).

**Conclusions:** TyG index and HOMA-IR are independent risk factors for CHF. The TyG index can replace HOMA-IR in young adulthood as a surrogate marker for IR to predict the risk of CHF.


# Background

Congestive heart failure is a global issue within the public-health scenario and it is also the main causative agent for mortality [1, 2]. Many risk parameters, including diabetes, hypertension and coronary heart disease, are considered to be intimately related to heart failure [2]. Consequently, it is very imperative to identify early any risk factors for heart failure, followed by timely treatment, in order to prevent / regulate any progress to heart failure. There is a close interplay between insulin resistance and the etiology and clinical manifestation of heart failure [3]. IR is very common in patients with heart failure [4, 5]. The biological effects of exacerbated insulin resistance can, in turn, lead to the development or exacerbation of heart failure [6–8]. Multipole investigations demonstrated that IR is an independent risk factor for heart failure [9–11]. Consequently, early diagnosis of IR can predict the manifestation of future heart failure events. Methods for evaluating IR includes the euglycemic-hyperinsulinemic clamp test, the quantitative insulin sensitivity check index, HOMA-IR, 1/insulin, Matusda index, among others [12]. Although the euglycemic-hyperinsulinemic clamp test is considered to be an accurate and reliable method for the assessment of IR, such a test is time consuming, complex and carried an elevated

financial running cost, rendering it a challenge for such a test to be implemented and promoted within routine clinical practice [13, 14]. HOMA-IR has become the most commonly used indicator for clinical assessment of IR [15]. Triglyceride glucose index derived from triglyceride and glucose, which was recently proposed as reliable and inexpensive biomarker for predicting IR (as an alternative to euglycemic-hyperinsulinemic clamp test and HOMA-IR evaluation), have been used within the clinical setting and subject to focus by cardiovascular disease researchers [16, 17]. Recent investigations provided further evidence for the clinical manifestation risk of CHF, together with hypertension, ischemic stroke, arteriosclerosis, diabetes and coronary heart disease is correlated with TyG index [18–21]. However, it is unclear whether the TyG index can predict the occurrence of heart failure. In order to answer this question, this study focused on the cohort from the CARDIA study to longitudinally observe whether there was an association between the TyG index / HOMA-IR, and CHF. In addition, this study evaluated whether the triglyceride-glucose index could replace HOMA-IR as the main classifier of insulin resistance for predicting CHF event risk.

# Methods

### Study population

The CARDIA multi-center randomized, prospective cohort study was conducted from 1985 to 1986 (year 0), enrolling 5115 African-American and Caucasian aged from 18 to 30 from across the general population or selected census areas within four research centers in the USA. All participants were investigated at years 2, 5, 7, 10, 15, 20, 25 and 30, respectively. The institutional review committee from each research center accepted the research scheme and informed consent from all individual cohort participants was obtained in writing.The baseline data for this study used the 0-year examination data, for a total of 5,114 participants (one patient withdrew consent). Following the exclusion of patients with incomplete clinical data (missing fasting blood glucose, triglyceride, insulin, missing endpoint records), a total of 4992 patients formed part of the final analytical queue (Additional file: Fig. S1). Patientss were grouped into four groups, depending on TyG index quartiles.

### TyG index, HOMA-IR and CHF

Participants at 0 year fasted for at least eight hours, immediately followed by blood collection using an EDTA vacuum vessel. Consequrently, plasma was isolated and frozen at -70°C prior to shipping to the laboratory using dry ice. Glucose was determined at baseline using hexokinase UV, calibrated, and followed by enzymatic analysis of triglyceride levels [22]. The TyG index was determined as:Ln (fasting triglycerides (mg/dL) × fasting blood glucose (mg/dL)/2) [23]. HOMA-IR was determined as: fasting blood glucose (mmol/L) × fasting serum insulin (μU/mL)/22.5 [24].

Diagnostic validation of CHF necessitated a finalized CHF diagnosis by a physician, together with the implementation of CHF clinical management protocols during the patient hospitalization period (i.e. diuretic/s + digoxin / Glycerin tri-nitrate, hydralazine, ACE-inhibitor/s or angiotensin receptor blocker/s). All patients were monitored until an endpoint of August 2017.

## Covariates

Covariates included in the present analysis were obtained through established protocols / quality assurance processes throughout all centers involved [25]. Education level was stratified as ≤ 12 years (up to high school degree), 13 to 16 years (up to graduate educational level), and ≥ 13 years (representing>high school education). Smoking-status was stratified as present and present non-smoking (including past and never smoking). Hypertension was deemed present upon a systolic blood pressure of ≥ 130 mmHg, diastolic blood pressure of ≥ 90 mmHg, or current consumption of anti-hypertension drug/s [26]. Obesity was deemed present upon a body mass index (BMI) ≥ 30 [27]. The dietary modification study equation for renal disease diet was implemented in this study in order to estimate the glomerular filtration rate (eGFR) within serum creatinine: eGFR (mL/min/1.73m$^2$) = 175 × standardized Scr$^{-1.154}$ × age$^{-0.203}$ × 1.212 [if African-American] × 0.742 [if female].Participants with eGFR < 60mL/min/1.73m$^2$ were deemed to have chronic kidney disease (CKD) [28, 29]. Detailed descriptions of measurements for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, serum creatinine, and fasting plasma glucose for all participants were previously published.

## Statistical analyses

Normally distributed continuous data were represented by mean±SD, while non-normally distributed continuous data were represented by median (inter-quartile range). Categorical variables reported percentage frequency. Participants were classified into four groups according to the quartiles of the TyG index. Wilcoxon or Kruskal–Wallis test were employed for analyzing group variations for continuous variables, while Chi-square test was employed for categorical variables. Smooth curve fittings and scatter plots were used to address the relationship between TyG index and HOMA-IR. The Cox proportional-hazard regression model was employed to determine HR and 95% CI for CHF events by quartiles of TyG index, and HOMA-IR, respectively. The proportional hazard assumption was evaluated by visualization of Schoenfeld residuals, where such analytical outcomes indicated no evidence of assumption breaches (Additional file: Table S1). Multi-collinearity was investigated using variance inflation factors, while TC was removed as a significant variance inflation factor (≥ 5) . Three models were fitted: model 1 was not adjusted; model 2 was adjusted for age, sex, and race; model 3 was adjusted for variables included in model 2 and education level, smoking status, hypertension, diabetes mellitus, hypercholesteremia, systolic and diastolic blood pressure, obesity, CKD, HDL-C and LDL-C. Trend P values were evaluated by a median value within each quartile, as a continuous variable. Kaplan–Meier curve data outcomes were employed for determining cumulative incidence of CHF events through both TyG index and HOMA-IR quartiles, with estimation variations being comparatively analyzed through log-rank protocols. The ROC curve and area under the curve were used to assess both TyG index-based and HOMA-IR-based capacity for predicting CHF event risk during follow-up. The participants were divided into subgroups according to sex, race, education, obesity, smoking status, hypertension and CKD status.The results were scrutinized following adjustments for age, sex, race, education, obesity, smoking status, hypertension, diabetes mellitus, hypercholesteremia, CKD, LDL-C, HDL-C, except for the subgroup variable. All statistical analyses

were conducted using R® software (version 4.0.3, http://www. R-project.org/). The study deemed that P values less than 0.05 (bilateral) conferred statistical significance.

# Results

Baseline characteristics of participants

Table 1 showed the baseline characteristics for the total-participating patient cohort, together with the quartile TyG index. During a median (IQR) follow-up of 31 (30.8–31.2) years, 64 out of 4,992 participants (1.3%) developed CHF, with an annual incidence of 41.4 / 100,000 individuals. With the increase in the quartile of the TyG index of participants, the CHF events increased significantly, from 20.7 / 100,000 individuals in quartile Q1 to 82.7 / 100,000 in quartile Q4. The median (IQR) of the TyG index quartiles were 7.3 (7.1-7.4), 7.7 (7.6-7.8), 8.0 (7.9-8.1) and 8.4 (8.3-8.7), respectively. With decreasing quartiles of TyG index, prevalence of obesity, hypercholesteremia, hypertension and current smoking were progressively higher (all P <0.001), paralleling the progressive increase of triglycerides, systolic and diastolic blood pressure, HOMA-IR, insulin, HDL-C, LDL-C, TC and fasting blood glucose (all P <0.001). Conversely, the proportion of females and caucasians was progressively lower with increasing quartiles of TyG index (all P <0.001).

Table 1
Clinical characteristics of the study population according to TyG index

| Variables | Overall | Quartiles of TyG index | | | | P-value |
|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | |
| No. of participants | 4992 | 1247 | 1246 | 1251 | 1248 | |
| TyG index | 7.8 (7.5-8.2) | 7.3 (7.1-7.4) | 7.7 (7.6-7.8) | 8.0 (7.9-8.1) | 8.4 (8.3-8.7) | <0.001 |
| Age,year | 25.0 (22.0-28.0) | 25.0 (22.0-28.0) | 25.0 (22.0-28.0) | 25.0 (22.0-28.0) | 26.0 (23.0-28.0) | <0.001 |
| Female,n(%) | 2721 (54.5%) | 807 (64.7%) | 737 (59.1%) | 676 (54.0%) | 501 (40.1%) | <0.001 |
| Caucasian, n(%) | 2562 (51.3%) | 754 (60.5%) | 680 (54.6%) | 618 (49.4%) | 510 (40.9%) | <0.001 |
| More high school,n(%) | 2989 (60.0%) | 745 (59.9%) | 747 (60.0%) | 765 (61.2%) | 732 (58.8%) | 0.681 |
| Obesity,n(%) | 578 (11.6%) | 77 (6.2%) | 105 (8.5%) | 148 (11.8%) | 248 (20.0%) | <0.001 |
| Systolic BP,mmHg | 110.0 (103.0-118.0) | 107.0 (101.0-115.0) | 108.0 (102.0-116.0) | 110.0 (104.0-118.0) | 113.0 (106.0-121.0) | <0.001 |
| Diastolic BP,mmHg | 68.0 (62.0-75.0) | 67.0 (62.0-72.0) | 67.0 (62.0-74.0) | 69.0 (63.0-75.0) | 70.0 (64.0-77.0) | <0.001 |
| Current smoking,n(%) | 1521 (30.5%) | 296 (23.8%) | 387 (31.1%) | 378 (30.2%) | 460 (36.9%) | <0.001 |
| Diabetes mellitus,n(%) | 37 (0.7%) | 7 (0.6%) | 6 (0.5%) | 6 (0.5%) | 18 (1.5%) | <0.001 |
| Hypertension ,n(%) | 975 (19.5%) | 182 (14.6%) | 185 (14.8%) | 263 (21.0%) | 345 (27.6%) | <0.001 |
| Hypercholesteremia,n(%) | 102 (2.1%) | 16 (1.3%) | 15 (1.2%) | 24 (2.0%) | 47 (3.9%) | <0.001 |
| CKD,n(%) | 159 (3.2%) | 34 (2.7%) | 35 (2.8%) | 42 (3.4%) | 48 (3.8%) | 0.351 |

Values are presented as Median (Q1-Q3) or number (%).

Definition of abbreviations: BMI, body mass index; Systolic BP, systolic blood pressure; Diastolic BP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TyG, Triglyceride-glucose; TC, total cholesterol; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance; CHF, chronic heart failure.

| Variables | Overall | Quartiles of TyG index | | | | P-value |
|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | |
| HDL-C,mg/dL | 52.0 (44.0-61.0) | 56.0 (50.0-66.0) | 54.0 (47.0-63.0) | 51.0 (44.0-59.0) | 44.0 (37.0-53.0) | <0.001 |
| TC,mg/dL | 174.0 (153.0-197.0) | 163.0 (144.0-182.0) | 169.0 (150.0-189.8) | 176.0 (157.0-200.0) | 188.0 (167.0-214.0) | <0.001 |
| LDL-C,mg/dL | 106.0 (87.0-127.0) | 97.0 (80.0-115.0) | 102.0 (85.0-121.0) | 110.0 (91.0-131.5) | 119.0 (97.0-140.0) | <0.001 |
| Triglycerides,mg/dL | 62.0 (45.0-84.0) | 38.0 (32.5-42.0) | 53.0 (49.0-58.0) | 71.0 (66.0-78.0) | 108.0 (93.0-140.0) | <0.001 |
| Fasting lucose,mg/dL | 81.0 (77.0-87.0) | 78.0 (74.0-83.0) | 81.0 (76.0-85.0) | 82.0 (78.0-87.0) | 85.0 (80.0-91.0) | <0.001 |
| HOMA-IR | 1.8 (1.2-2.7) | 1.4 (1.0-2.0) | 1.6 (1.1-2.4) | 1.9 (1.3-2.7) | 2.4 (1.5-3.6) | <0.001 |
| Insulin,μU/ mL | 8.8 (6.1-13.0) | 7.3 (5.1-10.2) | 8.1 (5.8-11.6) | 9.3 (6.4-13.5) | 11.2 (7.4-16.9) | <0.001 |
| Follow-up time,years | 31.0 (30.8-31.2) | 31.0 (30.8-31.2) | 31.0 (30.8-31.2) | 31.0 (30.8-31.2) | 31.0 (30.8-31.2) | <0.001 |
| CHF | 64 (1.3%) | 8 (0.6%) | 10 (0.8%) | 14 (1.1%) | 32 (2.6%) | <0.001 |
| Incidence rate per 100000 | 41.4 | 20.7 | 25.9 | 36.1 | 82.7 | <0.001 |
| Values are presented as Median (Q1-Q3) or number (%). | | | | | | |
| Definition of abbreviations: BMI, body mass index; Systolic BP, systolic blood pressure; Diastolic BP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TyG, Triglyceride-glucose; TC, total cholesterol; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance; CHF, chronic heart failure. | | | | | | |

# The association between TyG index and HOMA-IR

The scatter plots and smooth curve fittings in Fig. 1 demonstrated the relationship between TyG index and HOMA-IR, where the TyG index was intimately linked to HOMA-IR ($R = 0.339$, $P < 0.001$).

# Risk of CHF event predicted by TyG index and HOMA-IR

On competing risk analysis, the cumulative CHF incidence among the TyG index and HOMA-IR quartile were illustrated in Fig. 2. Participants in the quartile of the TyG index Q4 were at elevated risk of CHF

events in comparison to the Q1 group throughout the clinical monitoring timeframe (log-rank test, P < 0.001; Fig. 2(a)). Similar results were observed for HOMA-IR, Fig. 2(b).

Risk of CHF events was increased, with per-unit increase in TyG index and HOMA-IR illustrated in Table 2. Within the non-adjusted model (model 1), per-unit increase inTyG index correlated to a 3 - fold increase for the risk of CHF (HR 3.0, 95% CI 2.1-4.4). In model 2, adjusted according to race, sex and age, per-unit increase in TyG index elevated the risk of CHF by 3.4 - fold (HR 3.4, 95% CI 2.3-5.0). In model 3, risk of CHF event with per-unit increase in TyG index was still considerable also post-modification for possible confounding factors, with the HR being 2.8 - fold (HR 2.8, 95% CI 1.7-4.7). HRs for HOMA-IR Models 1, 2 and 3 were 1.2, 1.2, and 1.2, respectively (P<0.001). Risk of CHF events was still significant, based on the triglyceride-glucose index and the quartile of HOMA-IR (P trend < 0.001).

Table 2
HR and 95% confidence intervals for CHF according to TyG index and HOMA-IR

| Variables | HR(95%CI) | | |
|---|---|---|---|
| | Model 1 | Model 2 | Model 3 |
| Quartiles of TyG index | | | |
| Q1 | 1 (Reference) | 1 (Reference) | 1 (Reference) |
| Q2 | 1.3 (0.5, 3.2) | 1.3(0.51, 3.3) | 1.2 (0.5, 3.1) |
| Q3 | 1.8 (0.8, 4.3) | 2.0 (0.8, 4.6) | 1.7 (0.7, 4.1) |
| Q4 | 4.2 (2.0, 9.1) | 4.8 (2.2, 10.6) | 3.4 (1.4, 8.0) |
| P trend | <0.001 | <0.001 | <0.001 |
| TyG index | 3.0 (2.1, 4.4) | 3.4 (2.3, 5.0) | 2.8 (1.7, 4.7) |
| Quartiles of HOMA-IR | | | |
| Q1 | 1 (Reference) | 1 (Reference) | 1 (Reference) |
| Q2 | 1.6 (0.6, 4.1) | 1.7 (0.6, 4.3) | 1.7 (0.6, 4.3) |
| Q3 | 1.4 (0.6, 3.8) | 1.6 (0.6, 4.0) | 1.3 (0.5, 3.5) |
| Q4 | 5.3 (2.4, 11.9) | 4.4 (2.0, 10.0) | 3.2 (1.3, 7.9) |
| P trend | <0.001 | <0.001 | <0.001 |
| HOMA-IR | 1.2 (1.1, 1.2) | 1.2 (1.1, 1.2) | 1.2(1.1, 1.3) |
| Model 1 does not adjust covariates; | | | |
| Model 2: adjusted for age, sex and race; | | | |
| Model 3: model 1 + adjusted for education, obesity, smoking status, hypertension, diabetes mellitus, hypercholesteremia, CKD, LDL-C and HDL-C. | | | |
| Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TyG, Triglyceride-glucose; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance; CHF, chronic heart failure. | | | |

# Subgroup analyses

Data outcomes from subgroup evaluations are illustrated in Fig. 3. No significant interactions by sub-groups were observed for the association between sex and race, education level, obesity, smoking status, hypertension, diabetes mellitus, hypercholesteremia or CKD status.

# ROC Analysis of TyG and HOMA-IR to predict CHF incidence

The AUCs of TyG index and HOMA-IR to predict CHF incidence were 0.675 (95% CI, 0.604-0.746) and 0.67 (95% CI,0.6-0.742), respectively. However, such data outcomes did not exhibit significant variations (P =

0.986) (Fig. 4, Table 3).

Table 3
AUC of TyG index and HOMA-IR to predict CHF incidence

| Variables | AUC(95%CI) | P value* |
|---|---|---|
| HOMA-IR | 0.670 (0.600-0.742) | Reference |
| TyG index | 0.675 (0.604-0.746) | 0.986 |
| Asterisk compared with HOMA-IR | | |
| Abbreviations: TyG, Triglyceride-glucose; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance; CHF, chronic heart failure. | | |

# Discussion

To the best of our knowledge, this study pioneered the role of the TyG index in predicting the occurrence of CHF events in patients. The main results of this prospective observational cohort study of 4992 young Americans revealed that the TyG index in young adulthood is positively correlated with the incidence of CHF, both pre-and post-adjustments for confounders, and this correlation remained stable even on subgroup analyses, rendering the TyG index to be a potential independent risk factor for CHF. This investigation also validated HOMA-IR as a separate independent risk factor for CHF, in agreement with results previously described in scientific literature. Finally, the study analyzed the AUC of CHF incidence, based on TyG index and HOMA-IR. Through comparative analyses, TyG index shares the same predicative value as HOMA- IR in predicting CHF incidence. TyG index can be employed as a surrogate marker for insulin resistance to predict CHF incidence. The results of this extended, prospective, observational investigation have substantial weight in aiding CHF prophylaxis.

It is well acknowledged that IR is intimately linked to the development of heart failure. Insulin resistance was first identified to be separately linked with the risk of heart failure following the Uppsala longitudinal study of adult males over the age of 70 [11]. In addition, it was reported that IR was capable of predicting the occurrence risk of ventricular systolic and diastolic dysfunction within 20 years among males in their 50s [30, 31] .The analyses of insulin resistance require complex methods that are challenging to obtain during routine clinical practice [32]. HOMA-IR is commonly used for testing IR [15]. However, there is no routine measurement of insulin concentration in clinical practice, which leads to HOMA- IR being unsuitable for large-scale clinical implementation. The triglyceride-glucose index is indicative of the metabolic level of triglycerides and glucose, which was first proposed by Luis E Simental-Mendía and colleagues, stating that the TyG index can replace the euglycemic-hyper-insulinemic clamp test and HOMA-IR to evaluate IR in healthy participants [23, 33]. Increased TyG index is associated with the occurrence of CHF, possibly since IR is recognized as a pivotal player in abnormal glucolipid metabolism [34]. Under IR, insulin-mediated glucose uptake in myocytes and adipocytes is impaired, the inhibition against liver glucose production and lipolysis is weakened, while the levels of plasma glucose and

triglycerides are increased [35]. The increase in blood glucose levels can cause myocardial fibrosis, stiffness increased and myocardial remodeling, typically leading to the occurrence and development of heart failure [1, 6, 36]. Previous studies have also confirmed a positive correlation between the increase in triglycerides and the development of heart failure [37].

Meanwhile, TyG index is correlated with various risk factors for heart failure. In a 9-year follow-up cohort study on hypertension in China, the TyG index predicted the incidence of hypertension [38]. The TyG index can also predict the risk of diabetes mellitus [39]. Many studies demonstrated that the TyG index is closely related to the prognosis of acute coronary syndrome [40–42]. Acute coronary syndrome, hypertension, diabetes mellitus and other factors can cause cardiac function and structural disorders, leading to heart failure [43]. A recent investigation on 546 patients with CHF and type II diabetes mellitus discovered a higher rate of heart failure re-hospitalization and cardiovascular mortality with an TyG index of 9.06, when compared to an TyG index of 8.55 [44]. In a study of patients undergoing echocardiography at a hospital in southern Taiwan Province, China, Tai-Hua Chiu and colleagues highlighted a high TyG index to be associated with elevated left atrial diameter and a reduced left ventricular ejection fraction [45]. Furthermore, this investigation revealed the predictive value of HOMA-IR on CHF. The increased risk of CHF in the high HOMA-IR population has already been demonstrated in previous studies on patients with diabetes mellitus combined with chronic renal disease, though without coronary heart disease [46]. However, this study demonstrated that if individuals are presented with high HOMA-IR despite being young and healthy, their risks of CHF in the future are also increased. The same finding was discovered in the long-term follow-up study of 15,792 cases (age - 45 to 64 years) by Orly Vardeny and colleagues, stating that HOMA-IR is an independent predictor of heart failure [10]. According to Satoru Kishi and colleagues, elevated IR in young people is an important life-long risk of left ventricular re-modeling and dysfunction in adulthood [47]. HOMA-IR is related to CHF, and its potential pathophysiological mechanism can be that long-term cumulative exposure to hyperglycemia and hyperinsulinemia could directly affect the contractility of myocardial cells and myocardium, leading to reactive interstitial fibrosis and extracellular collagen deposition, ultimately resulting in dysfunction of heart structure and function and consequent heart failure [48, 49].

This study also demonstrated that TyG index and HOMA-IR had similar predictive powers for CHF events, with AUC values (0.675 [95% CI, 0.604-0.746] vs 0.67 [95% CI, 0.6-0.742], P = 0.986). HOMA-IR was employed to assess the relationship between IR and disease [50–52]. However, TyG index in clinical practice is simpler to perform, rather than HOMA-IR detection, and are cheaper and easier to obtain. Therefore, the TyG index has added advantages in comparison to HOMA-IR regarding the clinical evaluation and prediction of CHF. TyG index can be used as an alternative index to predict heart failure events.

We are aware of several limitations in our study. The CARDIA study recruited only young people at the beginning of the research and did not consider people of differing ages and constitutions. Moreover, CARDIA data analysis by ethnicity was limited to African-American and caucasian-American adult individuals, and therefore, such results cannot be cautious to other ethnic groups. Future studies are

needed to assess the prevalence of CHF in other ethnicities as well as in children, athletes, and in individuals with specific diseases. Finally, the study did not compare the euglycemic-hyperinsulinemic clamp test (the gold standard for measuring IR) with the TyG index.

# Conclusions

This study suggests that TyG index and HOMA-IR in young adulthood are independent risk factors for the development of CHF. However, the TyG index can be easily popularized in clinical practice by low-cost experimental analyses. Heart failure is a major cause of global mortality, resulting in serious economic and social burden. Early identification and intervention of people with elevated TyG index can reduce the incidence of CHF. In view of the increasing prevalence of abnormal glucose and lipid metabolism and high IR, these findings are of great significance to public health.

# Abbreviations

| | |
|---|---|
| CARDIA | Coronary Artery Risk Development in Young Adults |
| TyG | Triglyceride-glucose |
| HOMA-IR | Homeostasis model assessment-insulin resistance |
| CHF | Congestive heart failure |
| ROC | Receiver operating characteristic |
| HR | Hazard ratio |
| CI | Confidence interval |
| AUC | Area under the curve |
| IR | Insulin resistance |
| BMI | Body mass index |
| eGFR | Estimate the glomerular filtration rate |
| CKD | Chronic kidney disease |
| LDL-C | Low-density lipoprotein cholesterol |
| HDL-C | High-density lipoprotein cholesterol |
| TC | Total cholesterol |

# Declarations

### Ethics approval and consent to participate

CARDIA was approved by institutional review boards of each field center; Each study participant provided informed written consent.

### Consent for publication

The consent to publish was obtained from all participants in this study.

### Availability of data and materials

The datasets used and / or analyzed during the current study are available from the corresponding author on reasonable requests.

### Competing interests

The authors declare that they have no competing interests.


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### Authors'contributions

Xianghui Zeng and Haobin Zhou performed data analysis and wrote the manuscript. Xiao Wang and Yuting Xue contributed to the analysis plan and reviewed and edited the manuscript. Qiong Zhan, Yujia Bai, Xingfu Huang, Hao Zhang, Zhuang Ma and Qingchun Zeng contributed to the discussion. Dingli Xu and Hao Ren had full access to all of the data in the study, reviewed, edited the manuscript, and took responsibility for the integrity of the data and the accuracy of the data analysis.

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# Figures

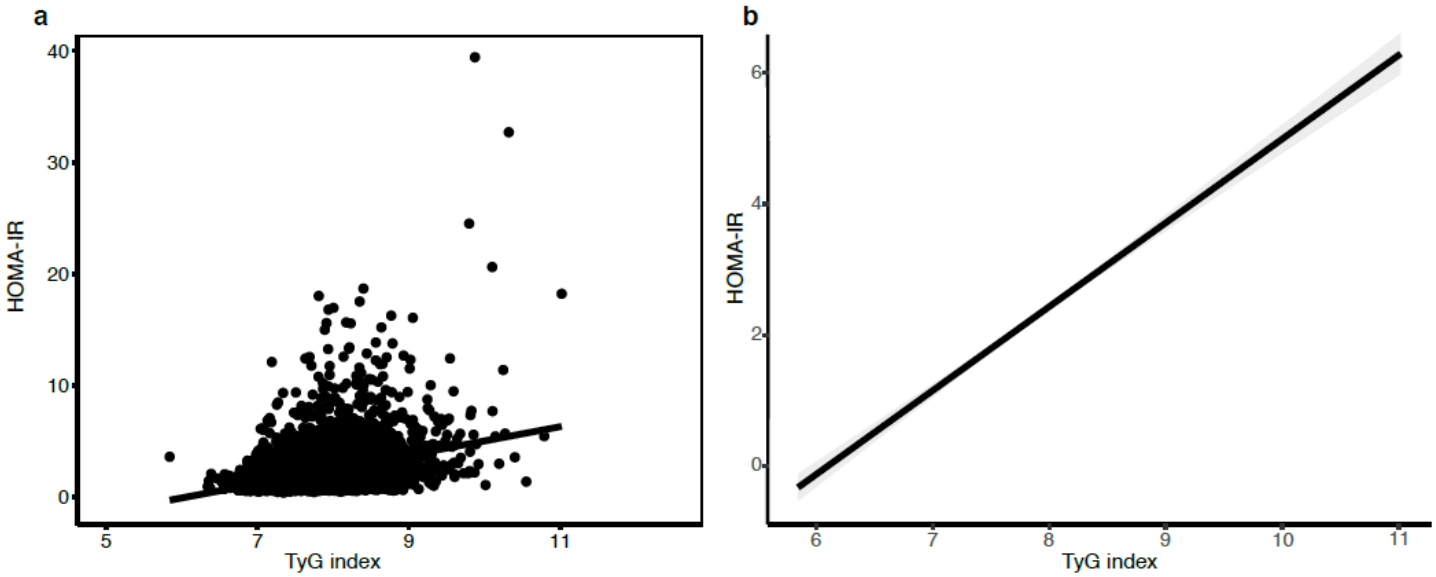



**Figure 1**

The association between TyG index andHOMA-IR. The association between TyG index and HOMA-IR. (a) Each black point represents a sample. (b) Solid black line represents the smooth curve fit between variables. Gray area represent the 95% of confidence interval from the fit. TyG, Triglyceride-glucose; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance.

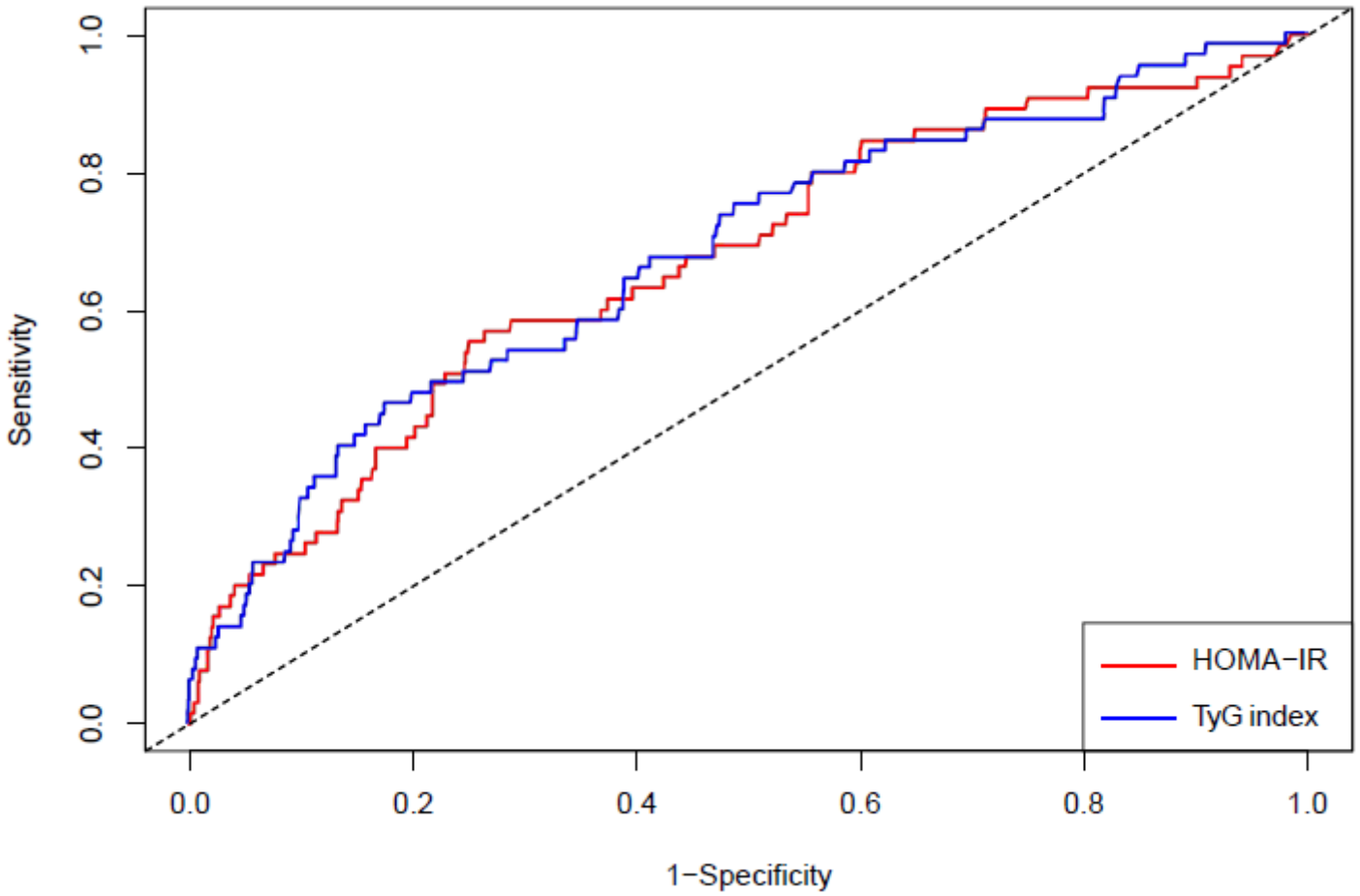
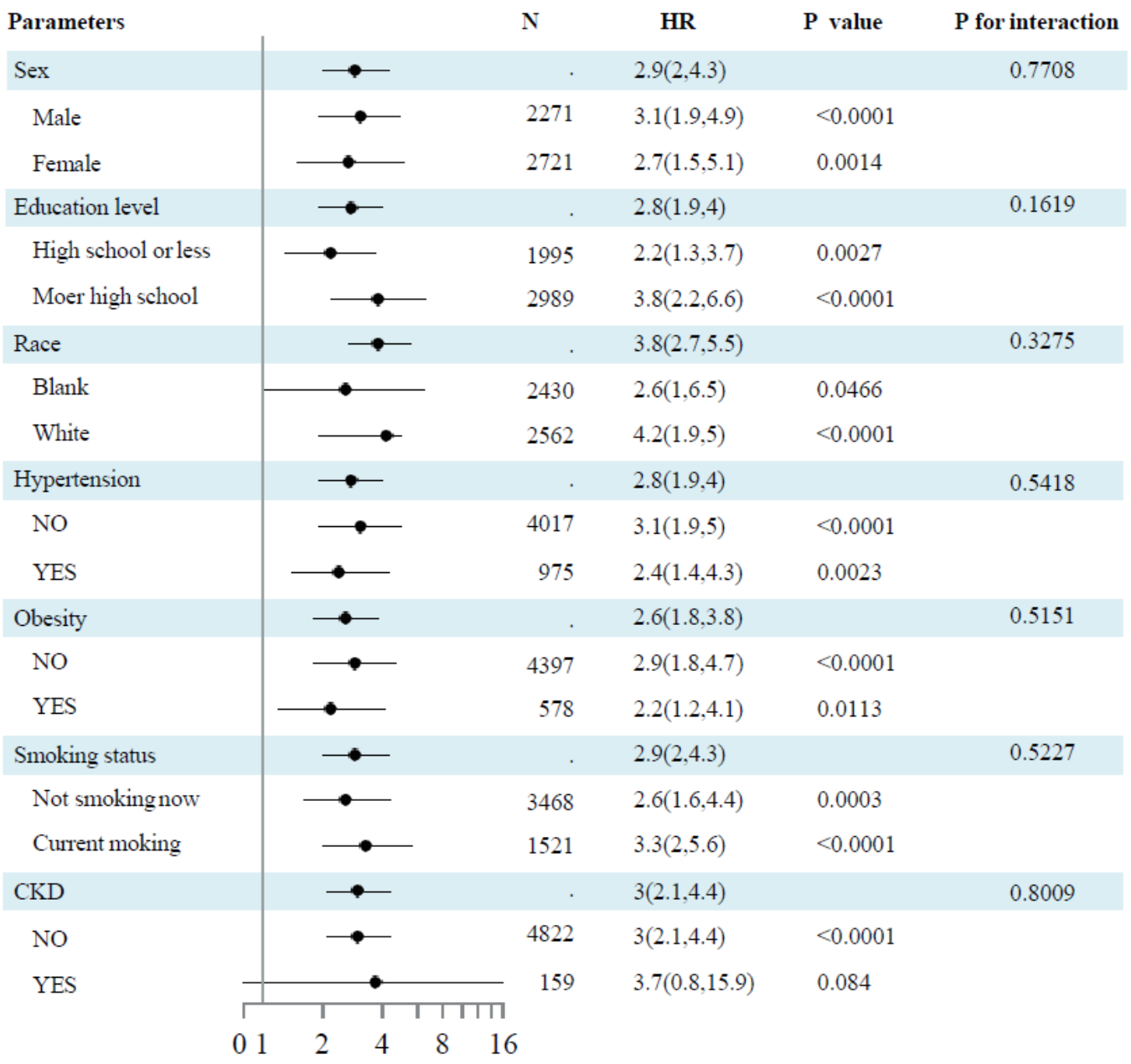



**Figure 2**

Kaplan- Meier curves for incidence of CHF stratified by quartiles of TyG index and HOMA-IR. Kaplan-Meier estimates were used to compute cumulative incidence of incident CHF by TyG index quartiles and HOMA-IR quartiles, and the differences in estimates were compared using the log-rank procedure. TyG, Triglyceride-glucose; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance; CHF, chronic heart failure.




## Figure 3

Association of CHF and TyG index by Subgroup analysis. Association of CHF and TyG index by Sub-group analysis.Data are hazard ratios (HRs) and 95% confidence limits (95% CLs). The participants were divided into subgroups according to sex, race, education, obesity, smoking status, hypertension, CKD. The results was evaluated after adjusted for age, sex, race, education, obesity, smoking status, hypertension, diabetes mellitus, hypercholesteremia, CKD, LDL-C, HDL-C except for the sub-group variable. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TyG, Triglyceride-glucose; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance; CHF, chronic heart failure.

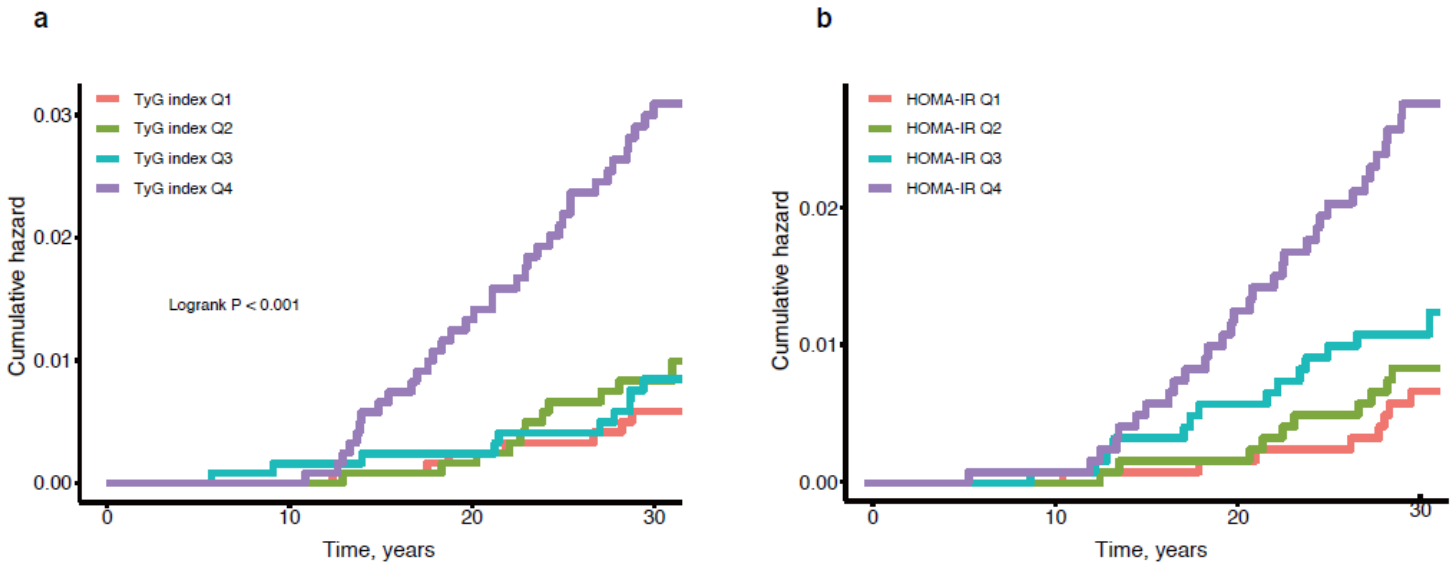



**Figure 4**

ROC Analysis of TyG index and HOMA-IR to predict the incident risk of CHF. Solid blue line was TyG index; solid red line was HOMA-IR. ROC, receiver operating characteristic; AUC, area under the curve; TyG, Triglyceride-glucose; CKD, chronic kidney diseases; HOMA-IR, homeostasis model assessment-insulin resistance; CHF, chronic heart failure.

# Supplementary Files

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