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Relationships among fibrosis-4, triglyceride-glucose index, and cardiovascular disease: Evidence from the NHANES 2003-2018

Ziliang Ye, Manyun Long, Lang Li *

Department of Cardiology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, PR China

HIGHLIGHTS

- The role of the triglyceride-glucose index (TyG) in the relationship between fibrosis-4 (FIB-4) and cardiovascular diseases (CVD) remains unclear.
- Individuals with FIB-4 levels above the median and elevated TyG levels (above the median) exhibited the highest risk of CVD (odds ratio = 6.02; 95 % CI: 3.60–10.06).
- Among CVD patients, those with elevated FIB-4 and TyG levels faced a substantially higher risk of all-cause mortality (HR = 2.98; 95 % CI: 1.75–5.09).
- Mediation analysis revealed that TyG partially mediated the effect of FIB-4 on CVD incidence (mediation proportion: 31.82 %, $P_{indir} < 0.001$), whereas TyG did not mediate the association between FIB-4 and ACM (mediation proportion: 1.28 %, $P_{indir} = 0.91$).

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ABSTRACT

Objective: The Fibrosis-4 (FIB-4) index is linked to cardiovascular diseases (CVD), but the role of the triglyceride-glucose (TyG) index in this relationship remains unclear. This study evaluates the associations among FIB-4, TyG, and CVD-related outcomes, and explores whether TyG mediates these effects.
Methods: This cross-sectional and cohort study analyzed data from NHANES (2003–2018). Logistic regression and Cox proportional hazards models assessed the associations between FIB-4, TyG, CVD, and all-cause mortality (ACM). Restricted cubic spline (RCS) curves examined potential non-linear relationships, and mediation analysis tested TyG's role in mediating the effect of FIB-4 on CVD and ACM.
Results: Among 19,119 participants, 2229 (9.28 %) were diagnosed with CVD. Individuals with FIB-4 levels above the median and elevated TyG levels (above the median) exhibited the highest risk of CVD (odds ratio = 6.02; 95 % CI: 3.60–10.06). Among CVD patients, those with elevated FIB-4 and TyG levels faced a substantially higher risk of ACM (HR = 2.98; 95 % CI: 1.75–5.09). RCS curves revealed a strong positive correlation between FIB-4, TyG, and both CVD and the risk of ACM. Mediation analysis revealed that TyG partially mediated the effect of FIB-4 on CVD incidence (mediation proportion: 31.82 %, $P_{indir} < 0.001$), whereas TyG did not mediate the association between FIB-4 and ACM (mediation proportion: 1.28 %, $P_{indir} = 0.91$).
Conclusion: Elevated FIB-4 levels indirectly increase CVD risk via TyG, and combining both indices improve CVD and mortality prediction. These findings suggest that managing both liver fibrosis and insulin resistance could reduce CVD and mortality risk.

1. Introduction

Cardiovascular diseases (CVD) [1–3] persist as a leading global health burden, contributing substantially to morbidity and mortality. From 1990 to 2019, the worldwide prevalence of CVD almost doubled, growing from 271 million to 523 million people, while the number of deaths attributable to CVD increased from 12.1 million to 18.6 million [4]. These trends emphasize the urgent need to identify novel risk factors and mechanistic pathways to enhance preventive strategies and clinical management. Among the emerging markers, the Fibrosis-4 (FIB-4) [5,6] index, a non-invasive tool initially developed to assess

* Correspondence author at. Department of Cardiology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, PR China.
E-mail address: drlilang@gxmu.edu.cn (L. Li).

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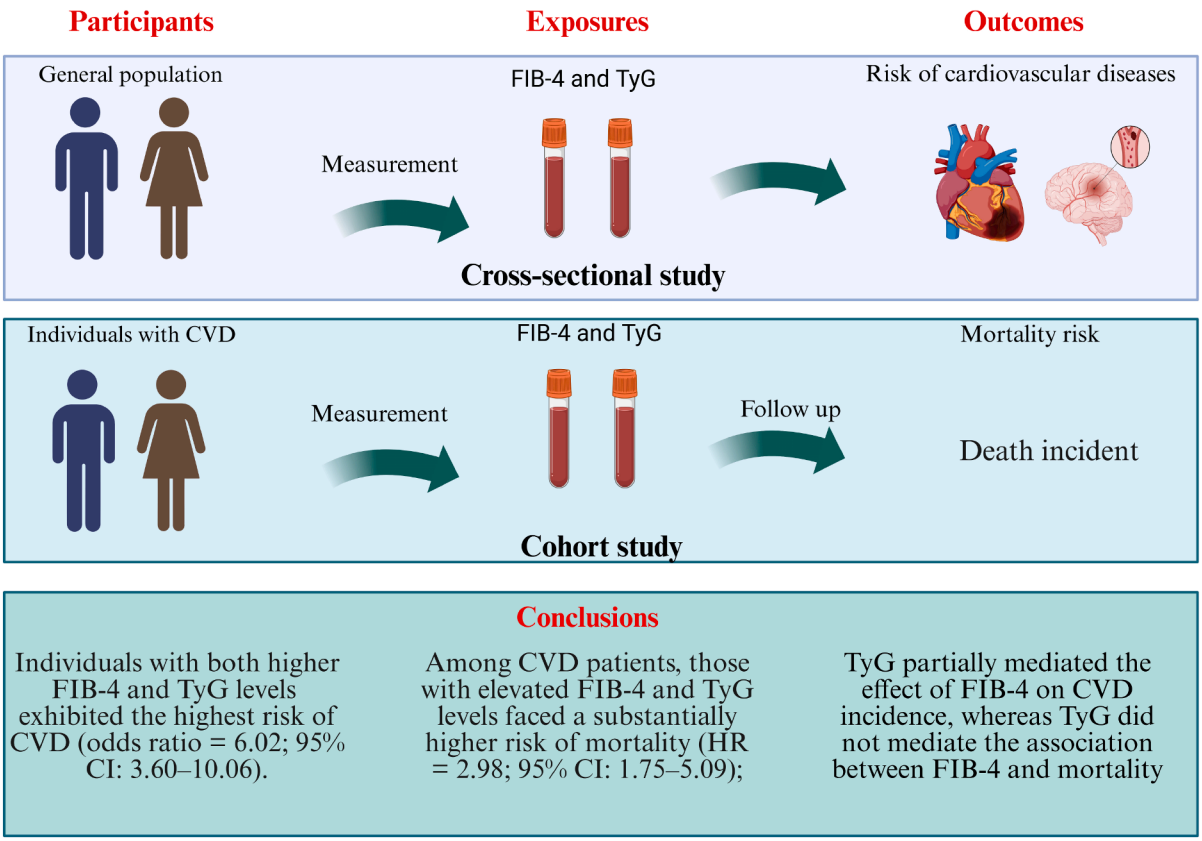

Central Illustration: Relationships Among Fibrosis-4, Triglyceride-Glucose Index, and Cardiovascular Disease: Evidence from the NHANES 2003-2018.

liver fibrosis, has garnered attention for its potential association with CVD [7,8]. Previous studies suggest that liver fibrosis, as indicated by elevated FIB-4 levels, may play a critical role in enhancing cardiovascular risk, which could be potentially through pathways related to metabolic disturbances [9–11]. However, the precise pathways linking FIB-4 to CVD remain incompletely understood.

The triglyceride-glucose index (TyG), a surrogate marker of insulin resistance [12,13], has been widely recognized as a strong predictor of

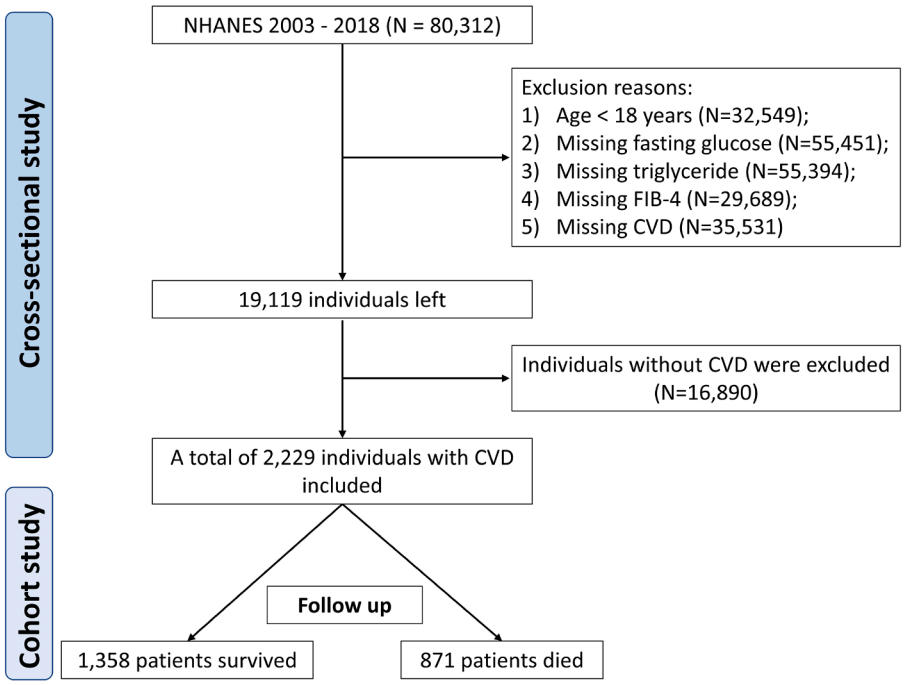

Fig. 1. The flow chart of this study.
NHANES: National Health and Nutrition Examination Survey; FIB-4: fibrosis-4; CVD: cardiovascular disease.

Table 1
Baseline characteristics of study population stratified by the median fibrosis-4 levels.

Variables	Total population	FIB-4 ≤ median	FIB-4 > median	P value
N	19,119	9558	9561	
FIB-4	1.10(0.01)	0.64(0.00)	1.65(0.02)	< 0.001
Age (years)	47.66(0.23)	37.12 (0.19)	60.24 (0.22)	< 0.001
Female	9868(51.60)	5317 (53.80)	4551 (48.97)	< 0.001
Body mass index (kg/m^2)	28.94(0.09)	29.19 (0.13)	28.65 (0.11)	< 0.001
BMI status				< 0.001
Normal weight	5550(30.14)	2850 (31.33)	2700 (29.39)	
Obesity	6999(35.94)	3702 (37.86)	3297 (34.47)	
Overweight	6317(32.89)	2908 (30.81)	3409 (36.13)	
Race/ethnicity, N (%)				< 0.001
Mexican American	3130(8.46)	1785 (10.85)	1345 (5.60)	
Non-Hispanic Black	3857(10.64)	1982 (11.73)	1875 (9.33)	
Non-Hispanic White	8359(68.08)	3780 (62.77)	4579 (74.41)	
Other Race	3773(12.83)	2011 (14.65)	1762 (10.65)	
Marital status, N (%)				< 0.001
Married	10,006 (56.36)	4519 (50.70)	5487 (63.21)	
Never married	3311(17.06)	2573 (25.52)	738(7.01)	
Others	5793(26.50)	2460 (23.79)	3333 (29.78)	
Education, N (%)				< 0.001
Below high school	2167(5.93)	764(4.86)	1403 (7.20)	
High school	7160(34.25)	3589 (34.39)	3571 (34.14)	
Over high school	9769(59.76)	5197 (60.75)	4572 (58.66)	
Smoke, N (%)				< 0.001
Active	3900(20.63)	2333 (24.54)	1567 (15.99)	
Former	4780(25.42)	1639 (19.17)	3141 (32.91)	
Never	10,423 (53.91)	5581 (56.29)	4842 (51.11)	
Alcohol user, N (%)				< 0.001
Active	6446(38.51)	3875 (69.57)	2571 (54.42)	
Former	2953(12.86)	1043 (16.04)	1910 (26.97)	
Never	2434(9.99)	1073 (14.39)	1361 (18.60)	
Hemoglobin (g/dl)	14.35(0.02)	14.35 (0.02)	14.36 (0.03)	0.830
Albumin (g/dl)	4.22(0.01)	4.23(0.01)	4.21(0.01)	0.010
Total bilirubin (mg/dl)	0.71(0.00)	0.68(0.01)	0.74(0.01)	< 0.001
Creatinine (mg/dl)	0.88(0.00)	0.84(0.00)	0.94(0.01)	< 0.001
Uric acid (mg/dl)	5.46(0.01)	5.34(0.02)	5.60(0.02)	< 0.001
Total cholesterol (mg/dl)	194.00(0.49)	191.84 (0.63)	196.57 (0.69)	< 0.001
HDL cholesterol (mg/dl)	54.45(0.21)	52.76 (0.26)	56.46 (0.29)	< 0.001

CVD [14–16]. Insulin resistance, characterized by impaired glucose and lipid metabolism, is a key driver of atherosclerosis and cardiovascular events. Prior studies [17,18] have shown that insulin resistance notably contributes to the progression of liver fibrosis, highlighting a strong association between the two. Additionally, Tutunchi et al. [19] have demonstrated a direct relationship between TyG and liver fibrosis, as measured by FIB-4, with higher TyG levels being associated with elevated FIB-4 levels. Given the substantial interplay between liver fibrosis and insulin resistance, it is possible that TyG could be involved in mediating the connection between FIB-4 and CVD. Yet, the extent to which TyG mediates this association, and whether it influences CVD-related outcomes such as mortality, remains unexplored.

Thus, this study seeks to investigate the associations among FIB-4, TyG, and CVD-related outcomes, including mortality, using data from the National Health and Nutrition Examination Survey (NHANES) spanning 2003 to 2018. Specifically, we seek to (1) evaluate the independent and combined effects of FIB-4 and TyG on CVD risk, (2) assess their impact on mortality among individuals with CVD, and (3) determine whether TyG mediates the relationship between FIB-4 and CVD incidence or mortality.

2. Methods

2.1. Study population

This cross-sectional and cohort study utilized data from the NHANES (https://wwwn.cdc.gov/nchs/nhanes/) spanning 2003 to 2018. NHANES survey collects comprehensive data through interviews, physical examinations, and laboratory tests. Ethical approval for NHANES was granted by the National Center for Health Statistics Ethics Review Board (**Supplementary figure 1**), and all participants provided written informed consent. Participants aged 18 years or older with complete data on FIB-4, TyG, and CVD diagnosis were included, and the detailed flow chart is shown in Fig. 1.

2.2. Exposure variables and outcomes

The primary exposure variables were the FIB-4 and TyG index. The FIB-4 index was calculated using the formula: (age × aspartate aminotransferase [AST]) / (platelet count × $\sqrt{}$alanine aminotransferase [ALT]) [5,20]. The TyG index was computed as ln(fasting triglyceride [mg/dL] × fasting blood glucose [mg/dL] / 2) [21,22]. The primary outcomes were CVD incidence and all-cause mortality (ACM). CVD was defined as a self-reported diagnosis of coronary heart disease, congestive heart failure, stroke, heart attack or angina. Mortality data were obtained through linkage with the National Death Index, with follow-up through December 31, 2019.

2.3. Covariates

Demographic and clinical data were systematically collected, encompassing a range of variables. These included age, sex (female and male), race/ethnicity (Mexican American, Non-Hispanic Black, Non-Hispanic White, and other racial/ethnic groups), education level (categorized as below high school, high school, and beyond high school), marital status (married, never married, and other marital statuses), smoking status (active smoker, former smoker, and non-smoker), and alcohol use (active drinker, former drinker, and non-drinker). Anthropometric measurements, including body mass index (BMI). BMI was classified into three categories: under 25.0 kg/m^2 as normal weight, between 25.0–30.0 kg/m^2 as overweight, and greater than or equal to 30.0 kg/m^2 as obese. Laboratory measurements were also conducted, including platelet count, AST, ALT, hemoglobin, albumin, total bilirubin, creatinine, uric acid, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, C-reactive protein, fasting triglycerides, and fasting glucose levels. Diabetes status

Table 1 (*continued*)

Variables	Total population	FIB-4 ≤ median	FIB-4 > median	P value
LDL cholesterol (mg/dl)	114.33(0.39)	114.19 (0.50)	114.49 (0.61)	0.700
C-reactive protein (mg/dl)	0.42(0.01)	0.45(0.01)	0.39(0.02)	0.004
Triglyceride (mg/dl)	128.60(1.18)	126.78 (1.53)	130.78 (1.60)	0.050
Fasting glucose (mg/dL)	106.12(0.32)	102.24 (0.34)	110.74 (0.54)	< 0.001
TyG	8.61(0.01)	8.56(0.01)	8.68(0.01)	< 0.001
Cardiovascular disease, N (%)	2229(9.28)	358(3.25)	1871 (16.47)	< 0.001
Hypertension, N (%)	8123(37.88)	2486 (25.04)	5637 (53.23)	< 0.001
Diabetes, N (%)	7030(31.61)	2350 (22.79)	4680 (42.82)	< 0.001
Antidiabetic treatment, N (%)	2241(8.85)	613(5.12)	1628 (13.32)	< 0.001
Antihyperlipidemic treatment, N (%)	3843(18.49)	686(7.13)	3157 (32.11)	< 0.001
Antihypertensive treatment, N (%)	6129(28.05)	1395 (14.23)	4734 (44.64)	< 0.001

HDL cholesterol: high-density lipoprotein cholesterol; LDL cholesterol: low-density lipoprotein cholesterol; TyG: triglyceride-glucose.
Median value of fibrosis-4: 0.98.

was determined by at least one of the following criteria: an HbA1c ≥ 6.5 %, a fasting blood glucose ≥ 126 mg/dL, a medical diagnosis of diabetes, or self-reported use of antidiabetic medications. Hypertension diagnosis was defined by either self-reported use of antihypertensive medications, physician diagnosis, or by having a systolic blood pressure (SBP) of 140 mmHg or higher, or a diastolic blood pressure (DBP) of 90 mmHg or higher. The use of antidiabetic treatment, antihyperlipidemic treatment, and antihypertensive treatment were also recorded.

2.4. Statistical analysis

To assess the associations of FIB-4, TyG, and their combined effects with CVD and mortality, participants were categorized into subgroups using median cutoffs for FIB-4 (≤ median vs. > median) and TyG (≤ median vs. > median). Additionally, four groups were created based on combined median thresholds: (1) FIB-4 ≤ median & TyG ≤ median, (2) FIB-4 ≤ median & TyG > median, (3) FIB-4 > median & TyG ≤ median, and (4) FIB-4 > median & TyG > median. The baseline characteristics were assessed by *t*-tests for continuous variables and chi-square tests for categorical variables. Continuous data are presented as mean ± standard error (SE), and categorical data are shown as frequencies (percentages).

Multivariable logistic regression analyses, adjusted for potential confounders, were conducted to calculate the odds ratios (ORs) and 95 % confidence intervals (CIs) to examine the association between FIB-4, TyG, and the incidence of CVD. Survival probabilities were visualized using Kaplan-Meier curves and compared via log-rank tests. Cox proportional hazards regression models estimated hazard ratios (HRs) for ACM. Three models were constructed: Model 1 (unadjusted), Model 2 (adjusted for sex, race/ethnicity, BMI, marital status, education, smoking, and alcohol use), and Model 3 (further adjusted for hemoglobin, total bilirubin, albumin, C-reactive protein, creatinine, lipid profiles, and medication use). Restricted cubic spline (RCS) analyses examined non-linear or linear associations between FIB-4, TyG, CVD and mortality risk.

Subgroup analyses stratified by sex, BMI, race/ethnicity, marital status, education, smoking, alcohol use, hypertension, and diabetes were conducted. Multivariable logistic and Cox regressions assessed associations within each subgroup. Mediation analyses were conducted to assess the role of TyG in mediating the relationship between FIB-4 and CVD incidence and mortality. In this framework, FIB-4 was treated as the exposure variable (X), TyG as the mediator (M), and CVD/mortality as the outcome (Y). The mediation process followed a four-step procedure: (1) Total effect (β_{total}): The total association between the exposure (X) and the outcome (Y) was established; (2) Effect of X on M ($\beta1$): The effect of the exposure (X) on the mediator (M) was quantified; (3) Direct effect (β_{dir}) and indirect effect ($\beta2$): The direct effect (β_{dir}) represents the association between the exposure (X) and the outcome (Y), adjusting for the mediator (M). The indirect effect ($\beta2$) refers to the portion of the effect of X on Y that is mediated through M; and (4) calculating mediation proportion as ($\beta1 \times \beta2 / \beta_{total}$) × 100 %, a validated approach in epidemiological studies [23,24]. All analyses incorporated NHANES sampling weights to address complex survey design. Statistical significance was considered at a two-tailed P value of <0.05. All analyses were conducted using RStudio (R version 4.4.1).

3. Results

3.1. Baseline characteristics of the study population

A total of 19,119 participants (9868 females [51.60 %] and 9251 males [48.4 %]), with a mean age of 47.66 (SE: 0.23) years, were enrolled in the study. The baseline characteristics, stratified by the median FIB-4 levels, are summarized in Table 1. Participants with FIB-4 levels above the median (n = 9561) were significantly older (60.24 vs.

Table 2
Odds ratios (95 % confidence intervals) for cardiovascular disease according to FIB-4 and TyG.

	Model 1		Model 2		Model 3	
Variables	OR (95 % CI)	P value	OR (95 % CI)	P value	OR (95 % CI)	P value
FIB-4						
FIB-4 ≤ median	Reference		Reference		Reference	
FIB-4 > median	5.87(5.02,6.86)	<0.001	4.54(3.62,5.69)	<0.001	3.77(2.66,5.34)	<0.001
TyG						
TyG ≤ median	Reference		Reference		Reference	
TyG > median	1.97(1.73,2.24)	<0.001	1.55(1.30,1.86)	<0.001	2.01(1.47,2.76)	<0.001
FIB-4 & TyG						
FIB-4 ≤ median & TyG ≤ median	Reference		Reference		Reference	
FIB.4 ≤median & TyG > median	2.38(1.74, 3.25)	<0.001	1.45(0.98,2.13)	0.060	1.63(0.99, 2.69)	0.060
FIB.4 > median & TyG ≤ median	7.03(5.33, 9.27)	<0.001	4.51(3.27,6.22)	<0.001	3.45(2.15, 5.53)	<0.001
FIB.4 > median & TyG > median	11.90(9.22,15.37)	<0.001	6.31(4.51,8.84)	<0.001	6.02(3.60,10.06)	<0.001

None was adjusted in model 1; Sex, race/ethnicity, body mass index, marital status, education, smoke and alcohol user were adjusted in model 2; Sex, race/ethnicity, body mass index, marital status, education, smoke and alcohol user, hemoglobin, total bilirubin, albumin, C-reactive protein, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, antidiabetic treatment, antihyperlipidemic treatment and antihypertensive treatment were adjusted in model 3.
FIB-4: fibrosis-4; TyG: triglyceride-glucose: OR: odds ratio; CI: confidence interval.
Median value of fibrosis-4: 0.98; Median value of TyG: 8.60.

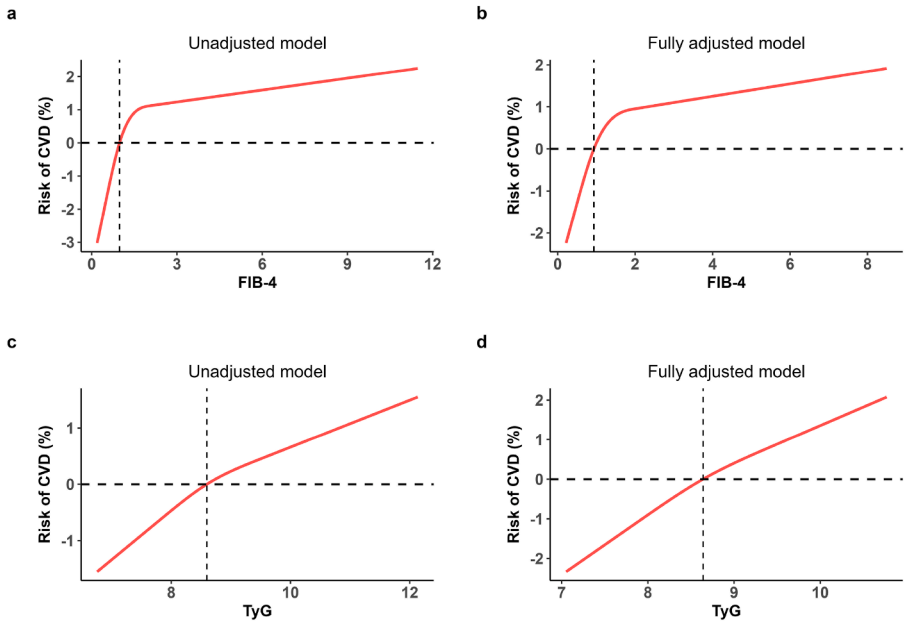

Fig. 2. Relationships between FIB-4, TyG, and CVD risk were demonstrated by restricted cubic spline curves.
Unadjusted model: none was adjusted; Fully adjusted model: sex, race/ethnicity, body mass index, marital status, education, smoke and alcohol user, hemoglobin, total bilirubin, albumin, C-reactive protein, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, antidiabetic treatment, antihyperlipidemic treatment and antihypertensive treatment were adjusted. FIB-4: Fibrosis-4; TyG: triglyceride-glucose; CVD: cardiovascular disease.

37.12 years), more likely to be male (51.03 % vs. 46.20 %), and had higher proportions of Non-Hispanic White ethnicity, lower education levels, and greater histories of smoking and alcohol use (all $P < 0.001$). Furthermore, these participants exhibited a higher metabolic risk profile, including elevated TyG index, fasting glucose, triglycerides, creatinine and uric acid (all $P < 0.001$). This group also showed a higher prevalence of hypertension (53.23 % vs. 25.04 %), diabetes (42.82 % vs. 22.79 %), and CVD (16.47 % vs. 3.25 %), in addition to increased use of antihypertensive, antidiabetic, and lipid-lowering medications (all $P < 0.001$).

3.2. Associations between FIB-4, TyG, and CVD risk

After adjusting for potential confounders, participants with FIB-4 levels above the median (0.98) presented a significantly higher risk of CVD (adjusted OR = 3.77; 95 % CI: 2.66–5.34) compared to those with FIB-4 levels below the median (Table 2). A similar trend was observed for TyG, where individuals with values above the median (8.60) had a higher likelihood of developing CVD (adjusted OR = 2.01; 95 % CI: 1.47–2.76) compared to those with lower TyG levels. Notably, the combined effect of elevated FIB-4 and TyG levels (> median for both indices) was associated with the highest CVD risk (adjusted OR = 6.02; 95 % CI: 3.60–10.06), suggesting an additive interaction between liver fibrosis and insulin resistance. RCS analyses revealed a distinct pattern: FIB-4 showed a significant non-linear relationship with CVD risk (P for non-linearity < 0.001), while the association between TyG and CVD risk followed a linear trend (P for non-linearity = 0.137; Fig. 2).

3.3. Subgroup analysis for CVD risk

We further performed a subgroup analysis to assess whether FIB-4, TyG, and their combination influence CVD risk across different groups. The subgroup analysis revealed that FIB-4 was significantly associated with an increased CVD risk in various groups, including males, females, and individuals with normal weight, overweight, and obesity (left panel of Fig. 3). For TyG, a higher CVD risk was observed in males, females, and those who were overweight or obese, whereas no significant association was found in the normal weight group (right panel of Fig. 3). When both FIB-4 and TyG were elevated, individuals with high levels of both markers had the highest CVD risk, and this trend remained consistent across multiple subgroups (**Supplementary Table 1**).

3.4. Associations between FIB-4, TyG, and mortality in CVD patients

Among the 2229 patients with CVD, 871 (33.39 %) died. Survival analysis (Fig. 4) revealed that patients who died had higher FIB-4 levels than those who survived ($p < 0.001$), while no difference in TyG levels was detected between the two groups ($p = 0.691$). Furthermore, patients with both FIB-4 (median: 1.59) and TyG (median: 8.81) levels below the median had the lowest mortality risk. After adjusting for confounders, participants with FIB-4 > median had a substantially higher risk of mortality (adjusted HR = 2.30; 95 % CI: 1.70–3.11) compared to those with FIB-4 < median (Table 3). In contrast, TyG > median was not associated with increased mortality risk (adjusted HR = 1.38; 95 % CI: 0.92–2.06). Interestingly, when combining FIB-4 and TyG, individuals with both FIB-4 > median & TyG > median had the highest mortality risk (adjusted HR = 2.98; 95 % CI: 1.75–5.09). Furthermore, RCS analysis (Fig. 5) revealed a substantial non-linear relationship between FIB-4 and mortality risk (P for non-linearity < 0.001), while the relationship between TyG and CVD risk was linear (P for non-linearity = 0.067).

3.5. Subgroup analysis for mortality

To evaluate the reliability of these findings, a subgroup analysis was performed on CVD patients across various categories. As illustrated in Fig. 6, the results from the stratified analysis were consistent with those presented in Table 3, demonstrating that higher levels of FIB-4 were related to an increased risk of ACM in multiple subgroups (left panel of Fig. 6). In contrast, no substantial relationship was detected between TyG and mortality risk in any subgroup (right panel of Fig. 6). Furthermore, patients with both FIB-4 and TyG levels above the median consistently displayed the highest mortality risk across all subgroups (**Supplementary Table 2**).

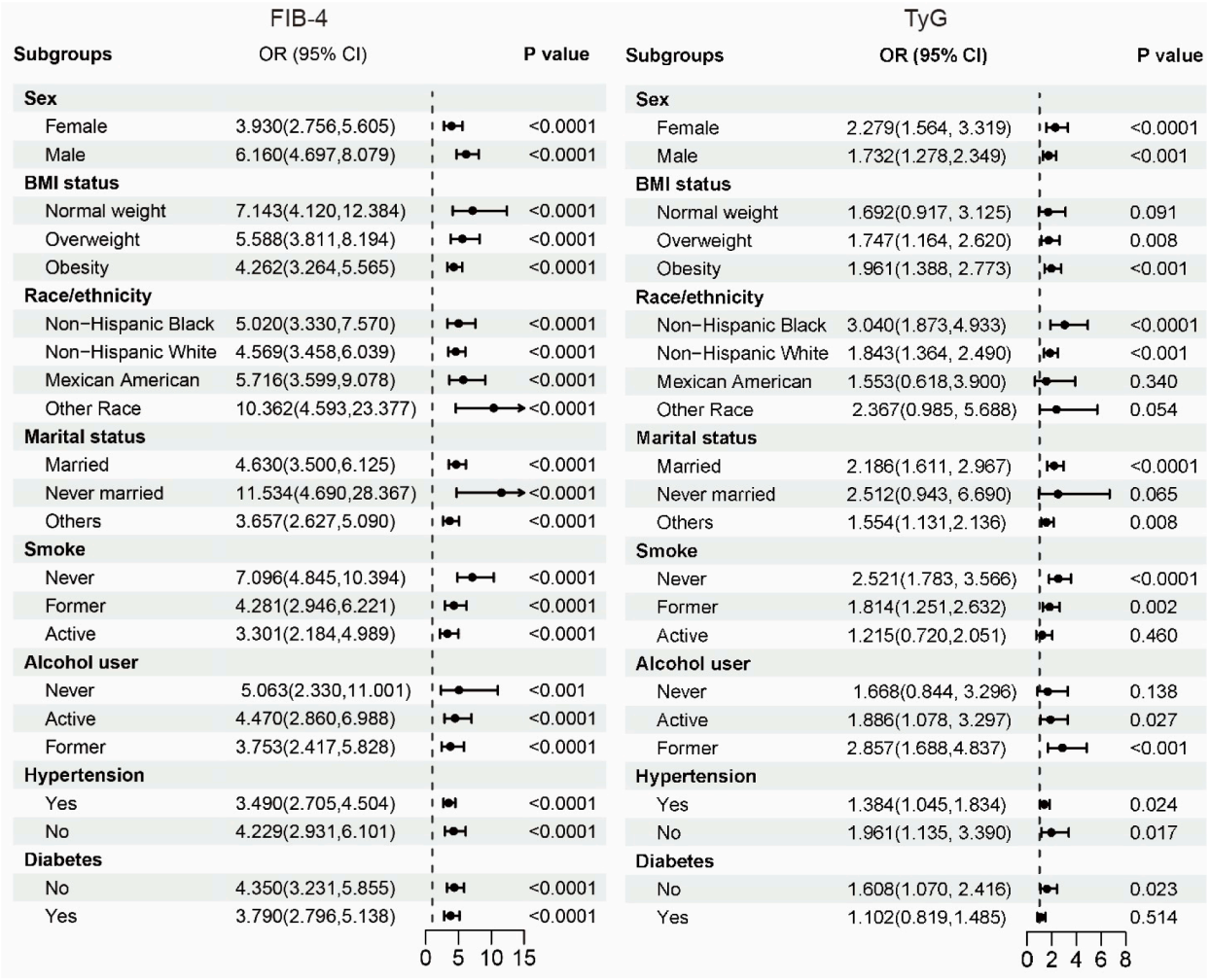

Fig. 3. Subgroup analysis of the association between FIB-4, TyG, and CVD risk.
OR: odds ratio; CI: confidence interval; BMI: body mass index; FIB-4: Fibrosis-4; TyG: triglyceride-glucose; CVD: cardiovascular disease.

3.6. Sensitivity analysis

Considering that no significant relationship between TyG and mortality risk was found in Table 3, while Fig. 5 illustrates a positive correlation between TyG and mortality risk, we further stratified CVD patients into five groups (Q1 to Q5) based on TyG levels to explore the relationship between TyG and mortality risk. Compared with the Q1 group, the risk of ACM in the Q4 and Q5 groups was significantly higher (p for trend = 0.04; **Supplementary Table 3**), suggesting that an increase in TyG levels is associated with a higher risk of mortality. Furthermore, we performed sensitivity analyses based on the FIB-4 risk categories: low (<1.30), indeterminate (1.30–2.67), and high (>2.67), as defined in a prior study [25]. Our results showed that participants in the highest FIB-4 category had the greatest risk of CVD and mortality compared to those in the lowest category (**Supplementary Tables 4 and 5**), and individuals in the higher TyG group also had a higher risk of CVD (**Supplementary Table 6**). We also evaluated whether there was an interaction between FIB-4 and TyG in relation to increased risks of CVD and mortality. The interaction analysis indicated that there was no significant interaction between FIB-4 and TyG for CVD (p for interaction = 0.184) or mortality risk (p for interaction = 0.631).

3.7. Mediation analysis of TyG in the relationship between FIB-4, CVD risk, and mortality

The potential mediating effects of FIB-4 and TyG on CVD incidence and mortality were further examined. The results suggest that FIB-4 directly influenced CVD occurrence (β_{dir} = 0.45, P_{dir} < 0.001), and this effect was partially mediated by TyG (mediation proportion: 31.82 %, P_{indir} < 0.001, left panel of Fig. 7). However, FIB-4 did not have a direct effect on mortality risk (β_{dir} = 0.44, P_{dir} = 0.09), and the influence of FIB-4 on mortality was not mediated by TyG (mediation proportion: 1.28 %, P_{indir} = 0.91, left panel of Fig. 7).

4. Discussion

This study provides novel insights into the interplay between liver fibrosis, assessed using the FIB-4 index, and insulin resistance, measured by the TyG index, in relation to CVD risk and mortality. Our findings demonstrate that elevated FIB-4 and TyG levels independently and synergistically predict CVD incidence, with TyG partially mediating the association between hepatic fibrosis and CVD. Furthermore, while FIB-4 and TyG were strongly associated with mortality in CVD patients, TyG did not mediate the relationship between FIB-4 and mortality. These results highlight the complex, pathway-specific roles of liver fibrosis and insulin resistance in cardiovascular pathogenesis and outcomes.

Our observation that elevated FIB-4 levels are associated with

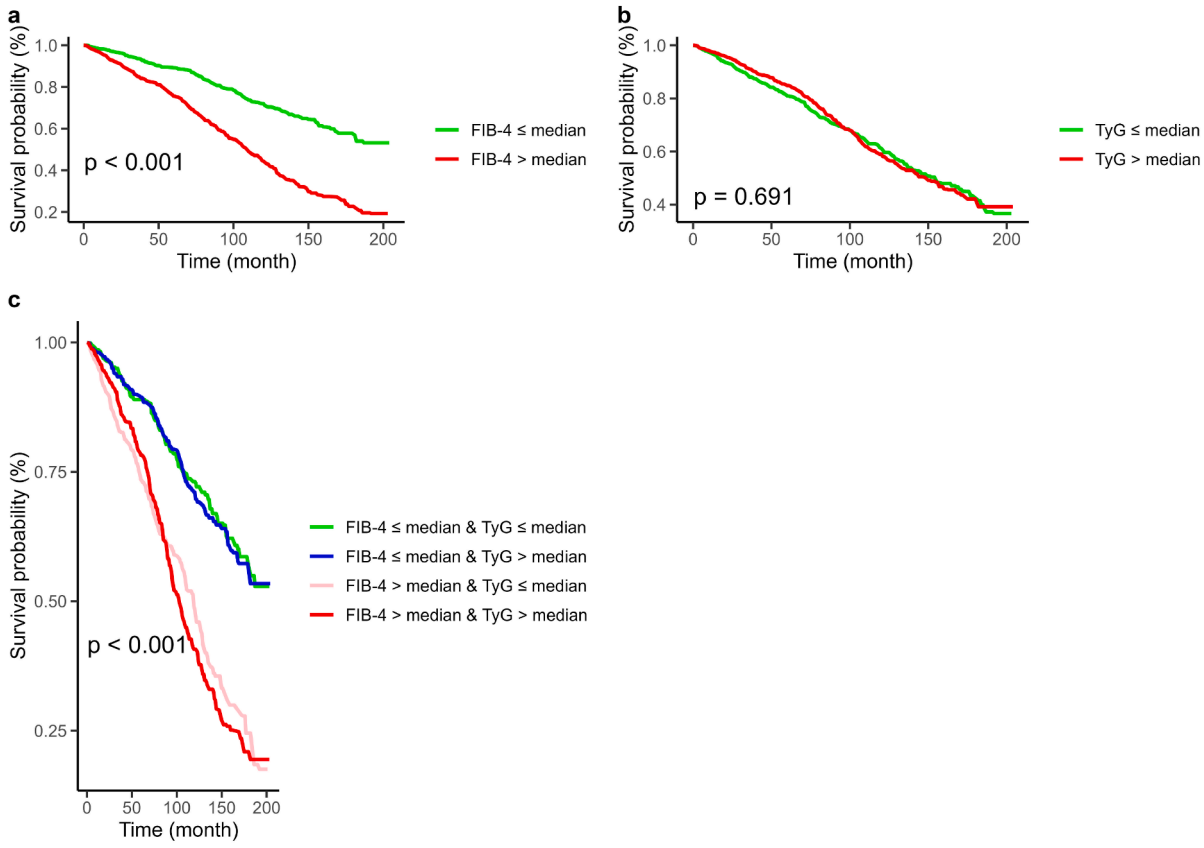

Fig. 4. Kaplan–Meier survival curves for FIB-4 (**a**), TyG (**b**), and their combination (**c**) in relation to all-cause mortality among individuals with cardiovascular disease.
Median value of fibrosis-4: 1.59; Median value of TyG: 8.81. FIB-4: Fibrosis-4; TyG: triglyceride-glucose.

Table 3
Hazard ratio (95 % confidence interval) for all-cause mortality according to the FIB-4 and TyG.

	Model 1		Model 2		Model 3	
Variables	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value
FIB-4						
FIB-4 ≤ median	Reference		Reference		Reference	
FIB-4 > median	2.50(2.05,3.03)	<0.0001	2.23(1.76,2.83)	<0.0001	2.30(1.70,3.11)	<0.0001
TyG						
TyG ≤ median	Reference		Reference		Reference	
TyG > median	0.97(0.82,1.14)	0.69	1.04(0.83,1.31)	0.74	1.38(0.92,2.06)	0.120
FIB-4 & TyG						
FIB-4 ≤ median & TyG ≤ median	Reference		Reference		Reference	
FIB.4 ≤median & TyG > median	1.02(0.77,1.36)	0.87	0.97(0.65,1.43)	0.86	1.36(0.83,2.24)	0.220
FIB.4 > median & TyG ≤ median	2.47(1.89,3.23)	<0.0001	2.03(1.45,2.85)	<0.0001	2.37(1.56,3.62)	<0.0001
FIB.4 > median & TyG > median	2.59(1.94,3.46)	<0.0001	2.36(1.62,3.43)	<0.0001	2.98(1.75,5.09)	<0.0001

None was adjusted in model 1; Sex, race/ethnicity, body mass index, marital status, education, smoke and alcohol user were adjusted in model 2; Sex, race/ethnicity, body mass index, marital status, education, smoke and alcohol user, hemoglobin, total bilirubin, albumin, C-reactive protein, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, antidiabetic treatment, antihyperlipidemic treatment and antihypertensive treatment were adjusted in model 3.
TyG: triglyceride-glucose: HR: Hazard ratio; CI: confidence interval.
Median value of fibrosis-4: 1.59; Median value of TyG: 8.81.

increased CVD risk aligns with prior studies [26–28] linking liver fibrosis to cardiovascular morbidity. For instance, a meta-analysis [29] has reported that non-alcoholic fatty liver disease (NAFLD) severity, often proxied by FIB-4, correlates with incident CVD (OR=2.58; 95 % CI: 1.78–3.75), likely due to shared pathways such as systemic inflammation [26,30], oxidative stress [31,32], and endothelial dysfunction [33,34]. Our study extends this knowledge by demonstrating that the FIB-4–CVD relationship is partially mediated by insulin resistance, as quantified by TyG. This finding contrasts with previous work [26,28,35] focusing solely on direct associations between liver fibrosis and CVD, neglecting intermediary metabolic mechanisms. Similarly, the synergistic amplification of CVD risk when FIB-4 and TyG are both elevated emphasizes the importance of considering both hepatic fibrosis and insulin resistance in risk stratification.

The TyG index, a validated surrogate for insulin resistance, independently predicted CVD risk in our cohort, consistent with meta-analyses linking TyG to subclinical atherosclerosis [36] and cardiovascular events [14]. However, our subgroup analyses revealed that TyG's

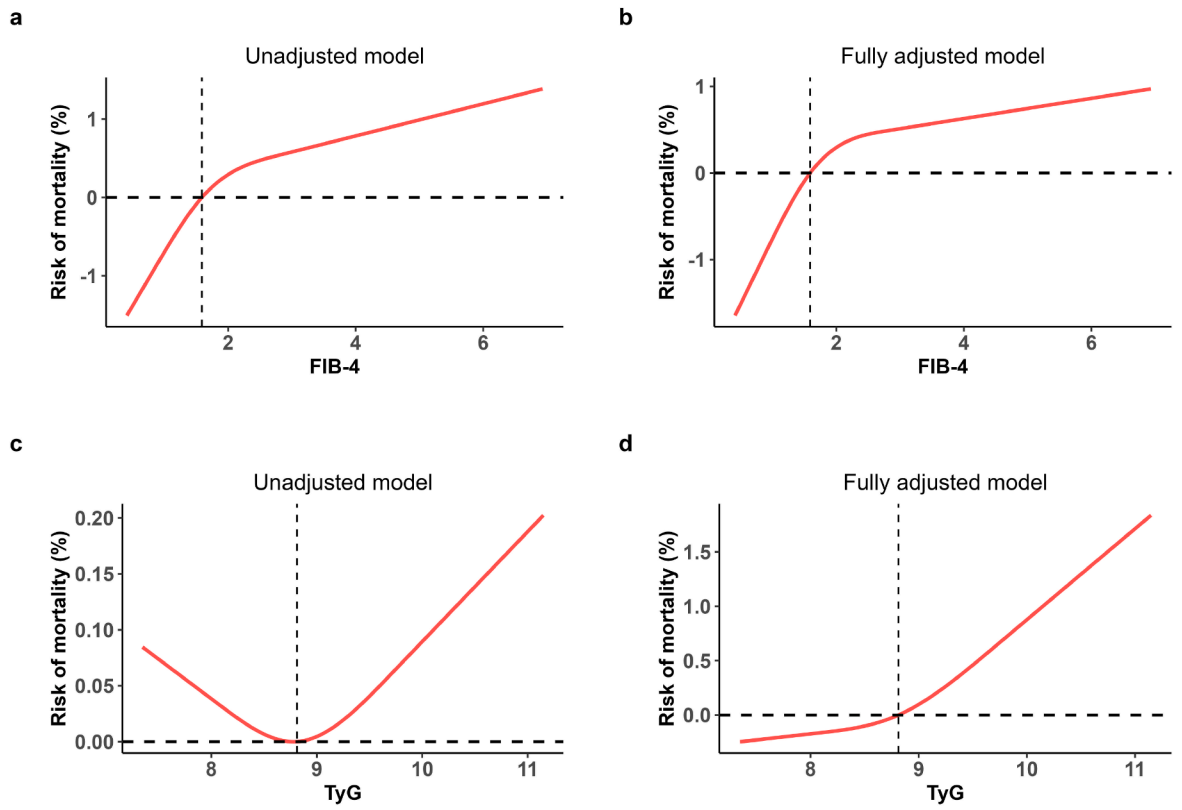

Fig. 5. Relationships between FIB-4, TyG, and all-cause mortality risk among individuals with cardiovascular disease were demonstrated by restricted cubic spline curves.

Unadjusted model: none was adjusted; Fully adjusted model: sex, race/ethnicity, body mass index, marital status, education, smoke and alcohol user, hemoglobin, total bilirubin, albumin, C-reactive protein, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, antidiabetic treatment, antihyperlipidemic treatment and antihypertensive treatment were adjusted. FIB-4: Fibrosis-4; TyG: triglyceride-glucose.

association with CVD was absent in individuals with normal BMI, suggesting that insulin resistance may predominantly drive cardiovascular risk in overweight/obese populations. Notably, our mediation analysis revealed that 31.8 % of FIB-4′s effect on CVD incidence operates through TyG, implicating insulin resistance as a key mechanistic bridge between liver fibrosis and cardiovascular pathology. The underlying mechanism may involve hepatic fibrosis disrupting the secretion of adipokines, hormones produced by adipose tissue that are crucial for regulating metabolism and inflammation [37]. This disruption could contribute to the development of systemic insulin resistance. Additionally, hepatic fibrosis impairs normal liver function, which affects gluconeogenesis [38] and potentially promotes the onset of insulin resistance. However, the absence of mediation for mortality outcomes suggests that liver fibrosis may influence survival through pathways independent of insulin resistance.

These findings have several clinical implications. First, the synergistic risk observed with combined FIB-4 and TyG elevation highlights the need for integrated risk assessment tools that incorporate both hepatic fibrosis and insulin resistance. Current CVD risk calculators [39,40] do not account for liver fibrosis, potentially underestimating risk in individuals with subclinical hepatic dysfunction. We propose that clinical strategies should not only focus on improving insulin sensitivity but also consider interventions that target liver health. This may include managing hepatic inflammation and fibrosis more aggressively, potentially via weight loss, dietary interventions, and pharmacologic treatments. Second, the partial mediation by TyG suggests that interventions targeting insulin resistance—such as lifestyle modifications [41], GLP-1 agonists [42], or SGLT2 inhibitors [43]—may attenuate the cardiovascular consequences of liver fibrosis. This is particularly relevant given the rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) [44,45], where concurrent insulin resistance and hepatic injury are common. Thirdly, the lack of TyG's mediation in mortality underscores the need for multidisciplinary management of CVD patients with elevated FIB-4, addressing both metabolic and non-metabolic pathways. Finally, while LDL- cholesterol is a well-established risk factor for CVD in the general population, lipid metabolism can be significantly altered in individuals with liver dysfunction, including those with liver fibrosis. Hepatic impairment may lead to abnormal lipid synthesis and clearance, potentially resulting in lower circulating LDL-C levels that do not accurately reflect the true atherogenic burden. In this study, we found that the FIB-4 index was significantly associated with both CVD risk and mortality. This suggests that FIB-4 may serve as a valuable tool for cardiovascular risk stratification in this population, potentially capturing risk not fully explained by traditional lipid parameters.

Several limitations warrant consideration. First, the cross-sectional design of the NHANES component limits causal inference for baseline associations. Second, CVD diagnoses were self-reported, potentially introducing misclassification bias. Third, despite adjusting for major confounders, residual confounding (e.g., unmeasured genetic or environmental factors) may persist. Fourth, the use of a single cross-sectional measure of FIB-4 and TyG limits our ability to examine the temporal relationship between these markers and CVD risk. Future prospective studies are warranted to explore whether reductions in FIB-4 and TyG over time are associated with corresponding decreases in CVD risk. If such relationships are confirmed, dynamic monitoring of FIB-4 and TyG could inform clinical decision-making and guide interventions aimed at improving liver health, insulin resistance, and cardiovascular outcomes. Additionally, repeated measurements of FIB-4 and TyG may offer further prognostic value over the course of treatment.

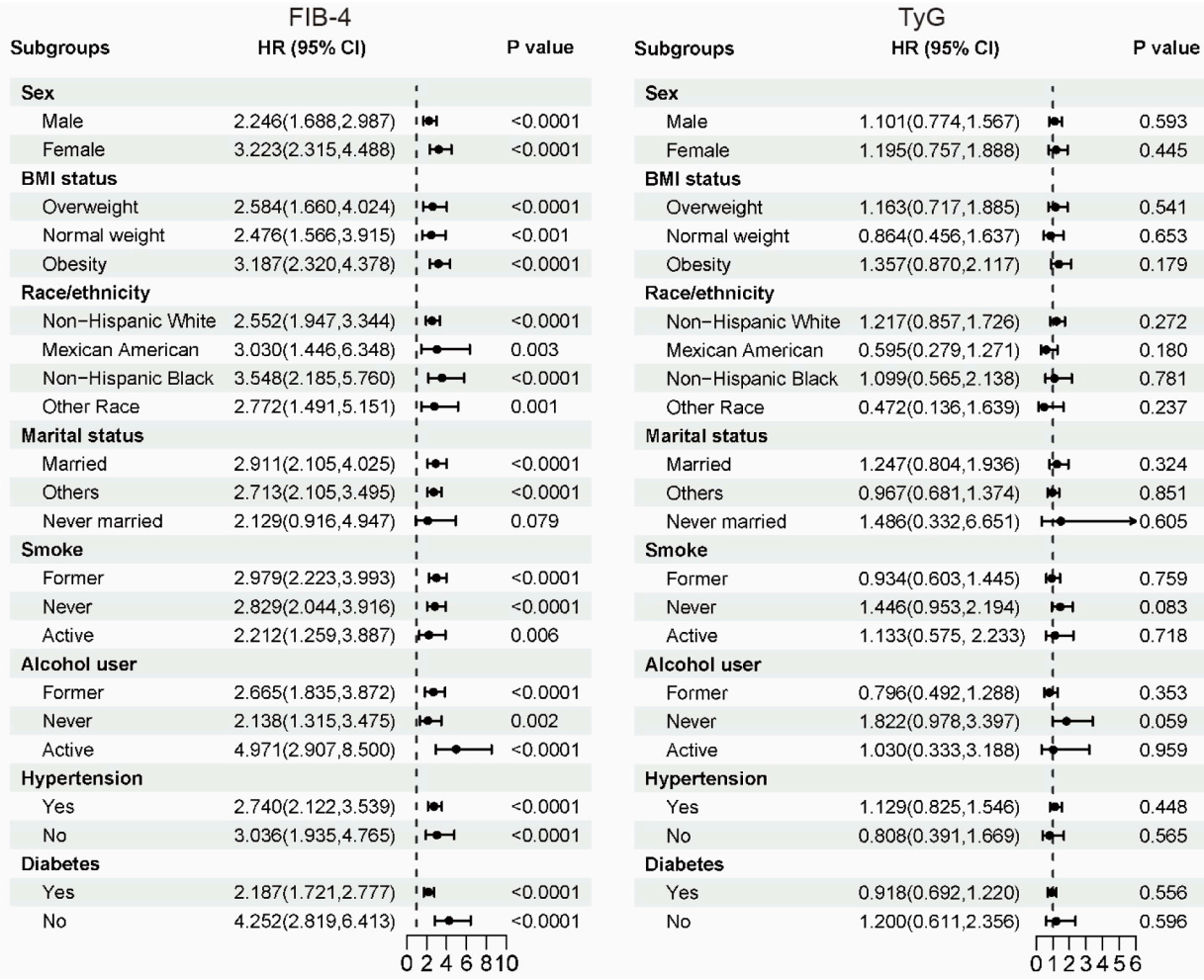

Fig. 6. Subgroup analysis of the association between FIB-4, TyG, and all-cause mortality among individuals with cardiovascular disease.
HR: Hazard ratio; CI: confidence interval; BMI: body mass index; FIB-4: Fibrosis-4; TyG: triglyceride-glucose.

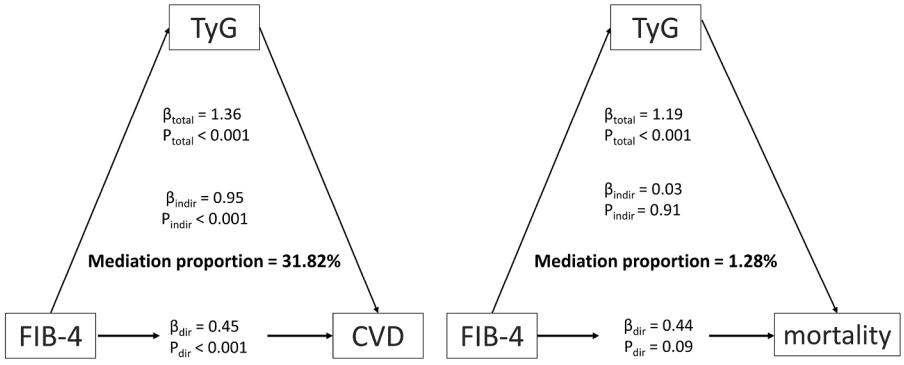

Fig. 7. Mediation analysis.
FIB-4: Fibrosis-4; TyG: triglyceride-glucose; CVD: cardiovascular disease.

5. Conclusion

In conclusion, this study elucidates the interaction role of FIB-4 and TyG in CVD risk and mortality. Elevated FIB-4 levels indirectly contribute to CVD incidence through insulin resistance, while their combined elevation identifies individuals at the highest risk. In contrast, FIB-4′s association with mortality in CVD patients operates independently of TyG, suggesting distinct mechanistic pathways. These findings advocate for the integration of hepatic fibrosis and insulin resistance in CVD risk prediction and highlight the potential benefits of targeting insulin resistance in patients with hepatic fibrosis. Future research should validate these associations and explore targeted interventions to mitigate the cardiovascular burden of hepatic dysfunction.

Ethical approval and consent to participate

The NHANES has received ethical approval from the National Center for Health Statistics Ethics Review Board (**Supplementary Figure 1**),

and all participants provided written informed consent.

Availability of data and material

All data can be found here: https://www.cdc.gov/nchs/nhanes.

Disclosures

None.

Disclosure statement

The authors have nothing to disclose.

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CRediT authorship contribution statement

Ziliang Ye: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Manyun Long:** Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization. **Lang Li:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2025.101014.

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