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Is insulin resistance the Eminence Grise of aging and non-communicable chronic diseases?

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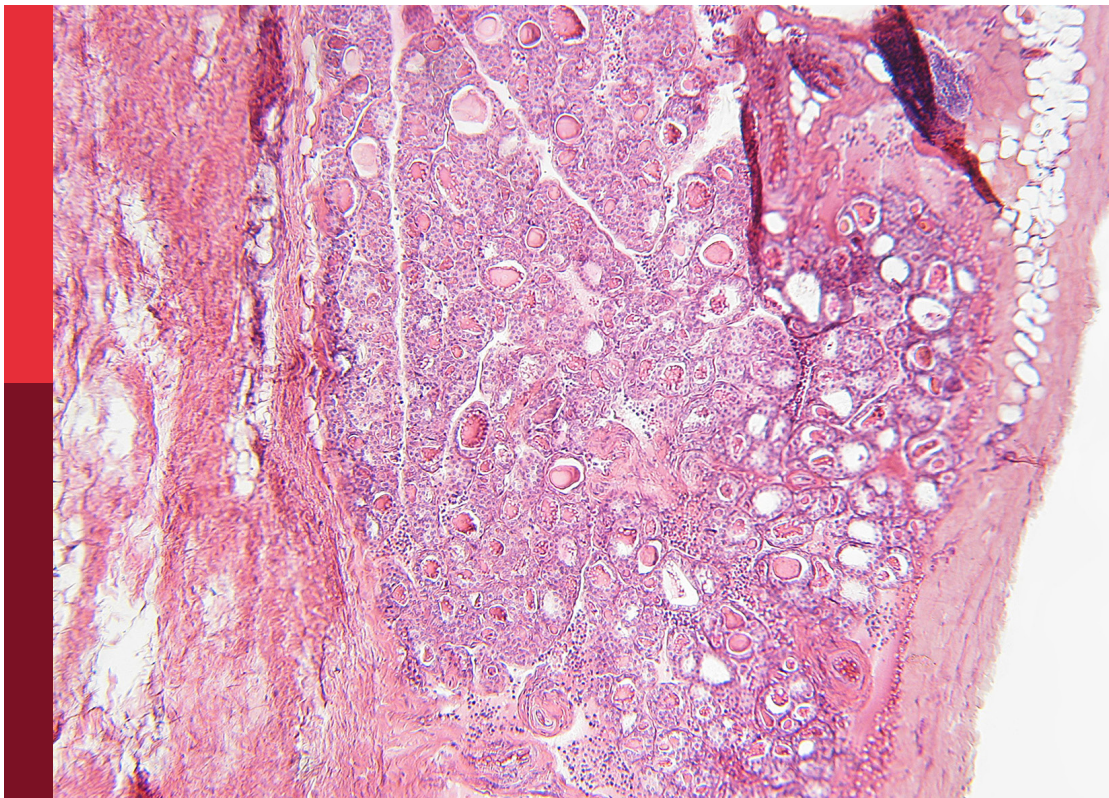

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Is insulin resistance the Eminence Grise of aging and non-communicable chronic diseases?

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Editorial: Is insulin resistance the Eminence Grise of aging and non-communicable chronic diseases?

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KEYWORDS

insulin resistance, non-communicable chronic diseases, aging, cardiovascular diseases, non-insulin-based surrogate indices for insulin resistance

Editorial on the Research Topic
Is insulin resistance the Eminence Grise of aging and non-communicable chronic diseases?

Insulin resistance (IR) is recognized as a central mechanism in metabolic dysfunction, with its influence extending far beyond glucose regulation. Increasingly, IR is recognized as the Eminence Grise — the unseen but powerful driver — behind many non-communicable chronic diseases (NCDs) and the biological processes of aging. The Research Topic "Is insulin resistance the Eminence Grise of aging and NCDs?" brings together 12 original investigations and reviews that collectively expand our understanding of IR as a systemic, multi-organ phenomenon. These studies explore IR not only as a metabolic hallmark but as a unifying pathophysiological thread linking cardiovascular, renal, hepatic, respiratory, neurological, and psychological disorders across the lifespan. The reviewed studies explored various accessible, non–insulin-based surrogate indices [Triglyceride-Glucose (TyG), Estimated Glucose Disposal Rate (eGDR)] across aging-related diseases. Although the hyperinsulinemic–euglycemic clamp remains the most accurate method for assessing IR, its application is often limited by the complexity and constraints of clinical settings.

Current knowledge and gaps

Decades of research have established that IR contributes to a wide range of metabolic and degenerative diseases. It plays a fundamental role in the development of type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and atherosclerosis (1, 2). Mechanistically, IR arises from the interplay between genetic susceptibility, ectopic lipid accumulation, mitochondrial dysfunction, chronic inflammation, and altered adipokine signaling (3). Beyond classical metabolic organs, impaired insulin signaling affects endothelial cells, neurons, and immune responses, contributing to vascular stiffness, neurodegeneration, and systemic low-grade inflammation — hallmarks of aging (1–5).

However, despite this well-established framework, several aspects remain underexplored. While the molecular basis of IR has been elucidated in skeletal muscle, liver, and adipose tissue, much less is known about its role in non-traditional target organs such as the lungs, kidneys, or brain. Moreover, there remains a gap in understanding the predictive and diagnostic value of emerging non–insulin-based IR indices, their relevance in acute settings, and their relationship with mental health and cognitive decline. Gaps also persist regarding pharmacological modulation, adipose–immune crosstalk, and longitudinal mechanistic studies integrating omics and imaging biomarkers.

The papers in this Topic address several of these gaps, validate surrogate markers, and deepen our understanding of IR.

IR and cardiovascular diseases

The interplay between IR and cardiovascular disease (CVD) remains a subject of persistent inquiry. Zhang et al. studied patients with T2DM suffering acute myocardial infarction and identified a strong correlation between the TyG index — a surrogate of IR — and major CVD. Their findings underscore TyG's potential as a valuable prognostic tool in this vulnerable population, highlighting how metabolic derangements aggravate cardiovascular risk even when left ventricular systolic function is preserved.

Complementing these findings, Wang et al. assessed hyperuricemia risk through eGDR, another non–insulin-based IR measure. Their results reinforce the notion that systemic metabolic inefficiency, reflected by lower eGDR, predisposes to urate accumulation — further linking IR to vascular and renal injury pathways.

IR role in acute and chronic renal disorders

Using the MIMIC-IV database, Wang et al. demonstrated that elevated TyG–body mass index is associated with both acute kidney injury and the need for renal replacement therapy in critically ill septic patients. These results extend the clinical significance of IR markers into acute care settings, showing their utility in identifying patients at higher risk of renal deterioration.

Zhang et al. analyzed associations between non–insulin-based IR indices and chronic diabetic nephropathy in U.S. adults (NHANES data). They confirmed that higher IR indices correspond to a greater prevalence of nephropathy, supporting their use for early detection of renal complications in diabetes care.

IR and liver diseases

Cao et al. revealed a U-shaped association between the TyG index and incident diabetes among adults with metabolic dysfunction–associated steatotic liver disease. This relationship suggests that both excessively low and high TyG values may be deleterious, reflecting the delicate balance between metabolic flexibility and dysfunction in the liver and underscoring the need for risk stratification in this population. In parallel, Zhao et al. explored the relationship between the single-point insulin sensitivity estimator (SPISE) and NAFLD in individuals with T2DM, demonstrating an inverse correlation and supporting SPISE as a non-invasive marker for hepatic insulin sensitivity in clinical practice.

IR, metabolic syndrome and population health

The manifestation of IR in clinical populations is strongly mediated by environmental and lifestyle interactions, emphasizing its multifactorial etiology. In a nested case–control study Rong et al. identified demographic, lifestyle, biochemical factors associated with metabolic syndrome among adult, reaffirming the multifactorial roots of IR that intertwine genetic susceptibility, environmental exposure, and behavioral risk.

Expanding to the adolescent population, Villasis-Keever et al. investigated the relationship between anxiety and cardiometabolic risk factors in obese youth using propensity score methods. Their findings highlight that psychological distress and metabolic dysregulation may reinforce each other early in life — positioning IR as a critical link between mental and metabolic health.

IR and pulmonary structural changes

Emerging evidence suggests that IR manifests in diverse organ systems through complex cellular mechanisms. Lin et al. examined the association between eGDR and preserved ratio impaired spirometry (PRISm), a condition reflecting early restrictive lung dysfunction. Their study revealed that reduced eGDR — a marker of heightened IR — correlates with PRISm, suggesting that systemic metabolic impairment may contribute to pulmonary structural or microvascular changes.

IR and cognition, brain structure, aging

The influence of IR on the brain is gaining prominence in aging research. Two articles here provide evidence of IR's role in cognitive decline. Wang et al. evaluated the link between IR and cognitive impairment using the eGDR in a non-diabetic aging population (CHARLS data), demonstrating that IR is an independent risk factor for reduced cognitive function of adults. This finding underscores the systemic impact of IR on neural function, even in the absence of overt diabetes.

Adding a genetic and neuroimaging dimension, Huang et al. used a Mendelian randomization approach to reveal that genetically predicted brain cortical structure mediates the causality between IR and cognitive impairment, providing compelling genetic evidence for a structural link between IR and neurological health.

Collectively, these studies reinforce the hypothesis that IR serves as a shared etiological substrate for both metabolic and neurodegenerative diseases — a defining feature of aging biology.

Reversing the tide: exercise and insulin sensitivity

Lifestyle interventions remain the cornerstone of IR management (5). In their systematic review and network meta-analysis, Pan et al. compared nine distinct exercise modalities and found heterogeneous effects on insulin sensitivity among individuals with diabetes. Aerobic, resistance, and combined training showed the most consistent benefits, but emerging modalities such as high-intensity interval training and mind–body exercises also demonstrated promise. This comprehensive synthesis not only supports personalized exercise prescriptions but also reaffirms the modifiability of IR — even in advanced disease stages.

In conclusion, this Research Topic decisively confirms that IR is the fundamental, hidden mechanism underlying the widespread convergence of aging and NCDs. The utility of validated, accessible indices allows for early and precise risk stratification across varies systems. The collective evidence strongly supports a paradigm shift where future therapeutic research focuses not just on downstream disease management, but on personalized strategies to restore insulin sensitivity and interrupt the devastating cascade initiated by the Eminence Grise. Bringing the hidden influence of IR into the light is the first critical step toward mitigating the global burden of NCDs.

Author contributions

DV: Visualization, Formal Analysis, Funding acquisition, Data curation, Validation, Resources, Writing – review & editing, Project administration, Methodology, Supervision, Software, Writing – original draft, Conceptualization, Investigation. IS-P: Writing – review & editing. AR: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Associations between non-insulin-based insulin resistance indices and diabetic nephropathy in patients with diabetes mellitus in US adults: a cross-sectional study of NHANES 1999–2018

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Objective: This study investigated the associations between non-insulin-based insulin resistance indices (METS-IR, TyG, TG/HDL, and TyG-BMI) and the risk of diabetic nephropathy (DN) in US adults with diabetes mellitus (DM).

Methods: This study was based on the 1999-2018 National Health and Nutrition Examination Survey (NHANES) database and included 6,891 patients with DM for cross-sectional analysis. Multivariate adjusted models and restricted cubic spline (RCS) models were employed to assess the association between the insulin resistance index and the risk of DN. Subgroup analyses were conducted to explore the impact of different population characteristics.

Results: The results indicated that higher quartiles of METS-IR, TyG, TG/HDL, and TyG-BMI were associated with a significantly increased risk of DN. After adjusting for multiple covariates, including gender, age, and race, the associations between these indices and the risk of DN remained significant, with corresponding odds ratios (ORs) of 1.51 (95% confidence interval [CI]: 1.29-1.76), 2.06 (95% CI: 1.77-2.40), 1.61 (95% CI: 1.38-1.88), and 1.57 (95% CI: 1.35-1.84), with all P-values less than 0.001. RCS analysis indicated a nonlinear relationship between these indices and the risk of DN. The TyG index exhibited a highly consistent association with the risk of DN in all models.

Conclusion: Non-insulin-based insulin resistance indices are significantly associated with the risk of DN. The TyG index is a superior tool for assessing the risk of DN. These indices can assist in identifying patients at risk of DN, thereby enabling the implementation of more effective preventive and therapeutic strategies.

KEYWORDS

insulin resistance, non-insulin-based, diabetic nephropathy, diabetes mellitus, NHANES

1 Introduction

Diabetes mellitus (DM), a prevalent metabolic disease with a worrisome global epidemic, is a significant public health concern (1). It is projected that the total number of individuals with diabetes worldwide will reach 780 million by 2045, a figure that represents a substantial threat to human health and well-being. Concurrently, the global prevalence of kidney disease is considerable, affecting approximately 850 million individuals. Chronic kidney disease (CKD) represents the predominant form of kidney disease, with a global prevalence of 9.1% (2). Although the onset and progression of CKD are influenced by various factors, including impaired fasting glucose, hypertension, high body mass index (BMI), a high-sodium diet, and a high-lead diet, DM is undoubtedly one of the most significant contributing factors (2). It is noteworthy that approximately 40% of patients with DM develop diabetic nephropathy (DN), which represents the most common and severe complication of DM (3–6). The principal clinical manifestations of DN include a significant reduction in glomerular filtration rate (GFR), abnormally elevated urinary albumin levels, and symptoms of hypertension. These pathophysiologic changes may eventually lead to end-stage renal disease (ESRD) (3, 7–9). Statistical analysis indicates that patients with DN exhibit a markedly elevated risk of all-cause mortality, reaching up to approximately 30 times that of diabetic patients without DN (10). This underscores the significant role of DN as a contributor to diabetes-related mortality (11). Consequently, it is paramount to identify and clarify the risk factors associated with DN to prevent its occurrence, delay its progression, and improve the quality of life of those affected.

Insulin resistance (IR) is defined as a reduction in cellular sensitivity to insulin, which results in a decline in the effectiveness of insulin in facilitating glucose uptake and utilization. Further research has demonstrated that insulin resistance plays a central role in the pathogenesis of diabetes and that its association with DN is also receiving increasing attention (12–14). Specifically, insulin resistance contributes to DN's progression through various biological mechanisms, including exacerbating renal hemodynamic disturbances, impairing podocyte function, inhibiting normal tubular function, and promoting glomerular hypertrophy and tubulointerstitial fibrosis (15, 16). Furthermore, several clinical studies have demonstrated that the severity of insulin resistance is strongly associated with increased microalbuminuria and significantly reduced glomerular filtration rate (eGFR) in diabetic patients (17–19). These findings collectively indicate that insulin resistance plays a pivotal role in the pathogenesis of DN and represents a critical link in the complex chain of this disease.

The hyperinsulin-normoglycemic clamp method (HEC) is the gold standard for assessing IR. However, despite its status as the gold standard, the HEC has not gained widespread acceptance in practical applications due to its high cost and complex procedure (20, 21). Furthermore, the homeostasis model assessment of insulin resistance (HOMA-IR) index, another frequently utilized method for assessing IR, presents similar challenges (20, 22). The high cost of plasma insulin or C-peptide measurements, coupled with the need for more standardization in clinical practice, has constrained the adoption of the HOMA-IR index. This is particularly the case for diabetic patients, as most of them are treated with insulin, making accurate measurement of insulin difficult, thus compromising the accuracy of the HOMA-IR index (22). Moreover, the HOMA-IR cannot reflect the intricate dynamic relationship between glucose and insulin metabolism. This is because it is based on a single point in time and is therefore unable to capture the dynamic changes in the glucose-insulin feedback system fully (23). Consequently, developing more efficient, economical, and accurate IR assessment methods is significant for clinical practice and scientific research.

To more accurately assess and manage IR in diabetic patients, researchers have developed a series of non-insulin-based IR indices, such as the metabolic insulin resistance score (METS-IR), the triglyceride-glucose (TyG), triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C), and the triglyceride-glucose body mass index (TyG-BMI), etc. METS-IR is an emerging method for assessing IR with the added benefit of evaluating an individual's cardiometabolic risk (24, 25). It is calculated based on a series of standardized measurements, including fasting plasma glucose (FPG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and BMI. Studies have demonstrated that METS-IR is as effective as the classic HOMA-IR index in assessing IR levels, and in some cases, it outperforms it (26). The TyG index, another innovative index for IR assessment, combines triglyceride and FBG levels and has the potential to serve as a reliable biomarker for IR (27). Notably, the TyG index not only possesses higher sensitivity than traditional homeostasis models but has also been confirmed by several studies to be independently and significantly associated with the risk of DN in individuals with decreased renal function (28), especially in individuals with type 2 diabetes mellitus (T2DM) (29, 30). Furthermore, the ability of the TyG index to predict DN is even better than that of the HOMA-IR index (29, 31). Moreover, a high TyG index has been demonstrated to be positively correlated with the risk of ESRD, further underscoring its pivotal role in predicting renal complications in diabetes (14). TG/HDL-C has garnered considerable attention as a straightforward predictor of IR. Previous studies have demonstrated that this ratio is not only strongly associated with IR status but also positively correlated with diabetes risk (32, 33). The ability of the TG/HDL-C ratio to predict the onset of diabetes is particularly significant when the ratio exceeds 0.35 (34). Finally, TyG-BMI, as a complement and extension of TyG, also demonstrated a high degree of correlation with IR, providing an additional reliable option for IR assessment (35).

In the current field of research on non-insulin-based IR indices and the risk of DN in patients with DM, although there is a wealth of research on the association between the TyG index and DN, there is a lack of in-depth exploration of the relationship between the METS-IR, TG/HDL, and TyG-BMI and DN. Furthermore, the majority of these studies have focused on Asian populations. In light of the limitations above, the primary objective of this study was to investigate the potential association between non-insulin-based insulin resistance indices and the development of DN among diabetic patients in the context of the U.S. population. This study aims to employ a big data-driven analytic strategy to clearly define and validate the efficacy and value of different IR indices in

predicting and assessing the risk of DN. Furthermore, to construct a more comprehensive understanding framework, this study will examine the intricate interactions between these IR indices and potential influencing factors, including age, gender, demographic characteristics, lifestyle habits, and coexisting chronic diseases. This will facilitate the elucidation of the multidimensional mechanisms of IR in developing DN.

2 Materials and methods

2.1 Research participants

All data for this study were obtained from the 1999-2018 National Health and Nutrition Examination Survey (NHANES) database. This database contains the results of cross-sectional surveys conducted every two years by the Centers for Disease Control and Prevention (CDC). The research protocol of the NHANES project strictly followed the guidelines of the Ethics Review Committee of the National Center for Health Statistics (NCHS). It ensured that all participants signed an informed consent form. Furthermore, during the data analysis phase, NIH policy regulations were followed. Given the anonymity and non-direct contact nature of the data, it was used directly in the study without needing additional ethical review. The study adhered rigorously to the standards set forth by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative, ensuring the highest quality in study design and reporting.

At the study's outset, a sample population was drawn from ten consecutive survey cycles, resulting in 101,316 participants. To ensure the accuracy and relevance of the study results, we implemented a rigorous data cleaning and exclusion process to exclude ineligible participants. These exclusions included individuals under the age of 20, non-diabetic patients, pregnant females, and those with missing data, particularly on demographic characteristics, chronic disease status, biomarkers related to IR, and diagnostic indicators of DN. Following the implementation of a rigorous screening process, 6,891 eligible participants were identified for analysis in this study (Figure 1).

2.2 Definition of disease

The following criteria were employed to define DM in this study: (1) a precise diagnosis by a healthcare professional, (2) FPG at or above the threshold of 126 mg/dl, (3) glycosylated hemoglobin (HbA1c) level of not less than 6.5%, and (4) the individual was receiving diabetic medication or insulin therapy. We employed two core indicators to assess renal function: the urine albumin-to-creatinine ratio (UACR) and the eGFR. The eGFR was calculated according to the recommended formula by the Collaborative Group on Epidemiology of Chronic Kidney Disease (CKD-EPI). To diagnose DN, we employed the internationally recognized criteria, which stipulate that a UACR value of not less than 30 mg/g or an eGFR value of less than 60 mL/min/1.73 m^2 must be met.

2.3 Assessment of the non-insulin-based IR indices

To ensure the accuracy and reliability of the results, we employ the following scientifically validated formulas in the assessment of IR:

METS-IR is calculated by the formula Ln[2 × FPG(mg/dl) + TG (mg/dl)] × BMI(kg/m^2)/Ln[HDL-C(mg/dl)] (24). TyG is calculated by the formula Ln[TG(mg/dl) × FPG(mg/dl)/2] (27). TG/HDL-C is calculated by dividing the TG (mg/dL) by the HDL-C (mg/dL) (36). TyG-BMI is calculated by the formula TyG ×BMI(kg/m^2) (35).

All biochemical measurements were conducted after a minimum of 8.5 hours of fasting, utilizing an automated biochemical analyzer to guarantee the precision of the data. FPG, TG, and HDL-C concentrations were measured in strict accordance with standard operating procedures. Meanwhile, BMI was calculated as a standardized body mass indicator by dividing weight (kg) by the square of height (m).

2.4 Covariate assessment

To ascertain the association between the IR Index and DN, we constructed multivariate adjustment models to resolve the potential impact of confounding variables on this relationship. The covariates included in this study were gender, age, race, education, marital status, household economic status, alcohol intake, smoking behavior, physical activity level, and a history of a range of important chronic diseases, including hypertension, coronary heart disease (CHD), stroke, and cancer. Race was classified as Mexican American, Non-Hispanic White, Non-Hispanic Black, and Other Race. The sample was divided into three educational attainment categories based on the years of education completed: less than 9th grade, 9th through 12th grade, and more than 12th grade. Marital status was simplified into two categories: cohabitation and solitude. This was done to explore the role of family structure factors. To categorize household economic status, income was carefully divided into three intervals based on the Poverty-to-Income Ratio (PIR) criterion, as officially defined by the U.S. government. These intervals were designated as low (PIR ≤1.3), medium (PIR > 1.3 to ≤3.5), and high (PIR > 3.5). This study assessed smoking and drinking habits using standardized assessment methods. Smoking status was defined based on whether the participant had smoked more than 100 cigarettes in their lifetime and whether they were a current smoker. Alcohol consumption was assessed by asking whether the participant had consumed at least 12 alcoholic beverages of any type in the past year. Physical activity was classified into three categories: vigorous, moderate, and inactive. A comprehensive medical history was obtained for each participant, encompassing hypertension, CHD, stroke, and cancer. For hypertension, participants were queried as to whether they had ever been informed by a medical professional that they had hypertension or were currently taking medication for it. For CHD, participants were asked whether they had ever been diagnosed with the condition, whether they had experienced angina or a heart attack, or whether they were currently undergoing treatment for it. Similarly, participants were asked whether they had ever been informed by a medical

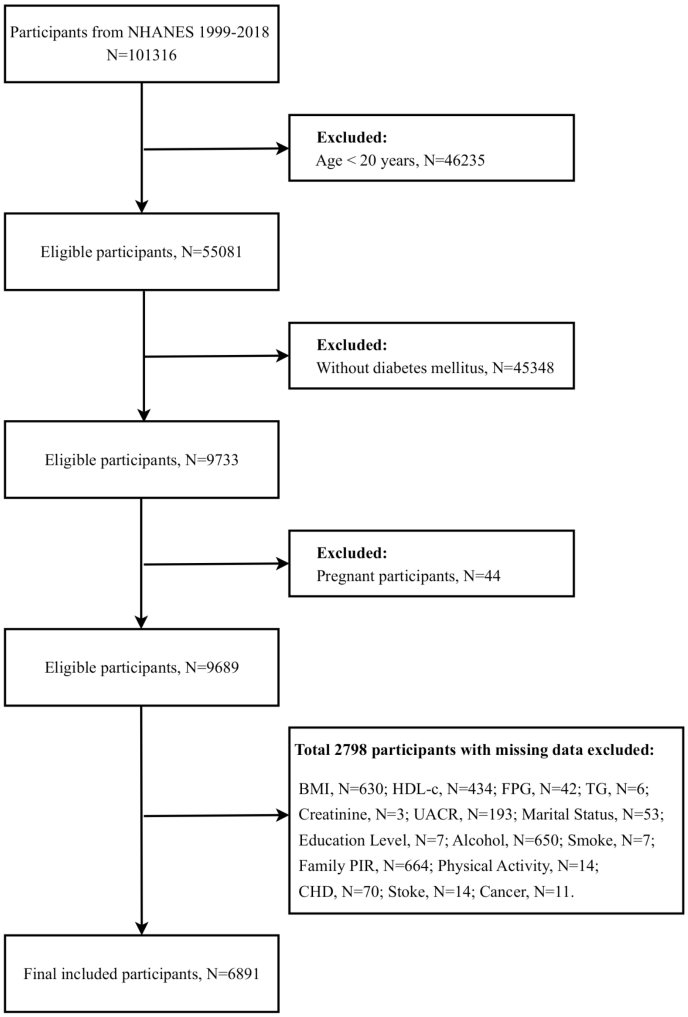

FIGURE 1
Participant screening flowchart. BMI, Body mass index; HDL-c, High density lipoprotein cholesterol; FPG, Fasting plasma-glucose; TG, Triglyceride; UACR, Urinary albumin/creatinine ratio; PIR, Poverty-to-income ratio; CHD, Coronary heart disease.

professional that they had experienced a stroke. Finally, participants were queried as to whether they had ever been diagnosed with cancer.

2.5 Statistical analysis

For continuous variables, the Shapiro-Wilk test was employed to verify the normality of the data. Based on the test results, the mean ± standard deviation or median (25th and 75th percentile) was selected to characterize the variables according to their normal distribution. One-way analysis of variance (ANOVA) or Kruskal-Wallis nonparametric tests were employed to assess the existence of statistically significant differences between groups concerning the distribution characteristics of the variables in question. Categorical variables were presented as frequencies and percentages, and the chi-square test was employed to analyze differences between groups.

To gain insight into the intricate relationship between IR indices and DN, we constructed logistic regression models to assess the impact of each index and its quartiles on the risk of DN. This was accomplished by estimating the ratio of ratios (ORs) and their 95% confidence intervals (CIs). Three levels of multivariate-adjusted models were gradually built to eliminate the potential interference of confounding variables. Model 1 served as the baseline without any adjustment. Model 2 incorporated essential demographic characteristics such as age, gender, and race. Model 3 further introduced educational attainment, marital status, family PIR, smoking and drinking habits, level of physical activity, and history of chronic diseases such as hypertension, CHD, stroke, and cancer as adjustment variables to enhance the explanatory power and predictive accuracy of the model.

To ascertain the existence of a potential nonlinear dose-response relationship between the IR indices and DN, a restricted cubic spline (RCS) model was employed. In this model, the IR indices were considered a continuous variable. Based on their distributional properties, the 5th, 35th, 65th, and 95th percentiles were selected as critical points for analysis. Should a nonlinear association be observed, a likelihood ratio test was employed to ascertain the critical point or threshold effect between the indices and the risk of DN with greater precision.

Furthermore, subgroup analyses were conducted to stratify the participants based on variables such as gender, education, marital status, family PIR, smoking and drinking habits, and the presence of hypertension, CHD, stroke, and cancer. This was done to explore the heterogeneity of the pattern of the association between IR index and DN among subgroups with different characteristics. Through interaction analysis, we evaluated the stability and consistency of the association between IR index and DN risk within each subgroup.

Throughout the statistical analysis, the principle of a two-sided test was followed, and a p-value of less than 0.05 was considered statistically significant. All data analysis was conducted using the R 4.4.0 software (provided by the R Foundation at http://www.R-project.org) in conjunction with the SPSS version 23.0 (IBM Corporation, Armonk, New York, USA) statistical package. Graphical presentations were generated using GraphPad Prism version 9.0 (GraphPad Software, USA).

3 Results

3.1 Baseline characteristics

In this study, the baseline characteristics of 6,891 patients with DM were analyzed. Of these, 2,660 were diagnosed with DN, and 4,231 were not. The results of the statistical analysis indicated that, although there was no significant difference in the distribution of gender between the two groups ($p = 0.183$), there were statistically significant differences in the age structure, ethnic composition, education level, marital status, and family economic status (all $p < 0.05$). In particular, the DN patient population exhibited a higher mean age, reaching 67 years, compared to a mean age of 60 for non-DN patients. Non-Hispanic white and black individuals comprised a significantly higher percentage of DN patients compared to other racial groups. Regarding educational attainment, a more significant proportion of patients with DN had lower levels of education. The analysis of marital status revealed a significantly higher proportion of patients with DN living alone. In contrast, analysis of family economic status, as measured by the PIR, showed that low income was more concentrated among individuals with DN. Further analysis of lifestyle and health status revealed significant differences between DN and non-DN patients in terms of smoking, drinking habits, physical activity participation, and the prevalence of multiple chronic diseases. The proportion of smokers was higher in the group of DN patients, whereas the proportion of alcohol consumers and those with a high level of physical activity were relatively lower. Moreover, the prevalence of hypertension, CHD, stroke, and cancer was significantly higher in patients with DN, underscoring the complexity of the association between these diseases. At the biochemical level, significant differences were observed in FPG, HbA1c, total cholesterol (TC), TG, UACR, and eGFR between patients with and without DN. These differences directly reflected the impaired renal function and metabolic abnormalities observed in patients with DN. Notably, BMI, HDL-C, and specific IR indices such as METS-IR and TyG-BMI did not show significant differences between the two groups (Table 1).

3.2 Relationships between IR indices and DN

To investigate the relationships between METS-IR, TyG, TG/HDL, TyG-BMI, and DN among diabetic patients, three analytic models were constructed to assess potential confounding effects comprehensively. The specific model setup was as follows: Model 1 did not include any adjustments. Model 2 incorporated gender, age, and race as adjustment variables based on Model 1. Model 3 further extended the adjustment to include educational attainment, marital

TABLE 1 Baseline characteristics of participants with diabetes mellitus.

Variables	Total (n = 6891)	Non-DN (n = 4231)	DN (n = 2660)	*P*
Gender, n (%)				0.183
Male	3679 (53.39)	2232 (52.75)	1447 (54.40)	
Female	3212 (46.61)	1999 (47.25)	1213 (45.60)	
Age (years)	62.00 (51.00, 71.00)	60.00 (48.00, 67.00)	67.00 (58.00, 76.00)	<0.001
Race, n (%)				<0.001
Mexican American	1386 (20.11)	874 (20.66)	512 (19.25)	
Non-Hispanic White	2665 (38.67)	1547 (36.56)	1118 (42.03)	
Non-Hispanic Black	1633 (23.70)	998 (23.59)	635 (23.87)	
Other Race	1207 (17.52)	812 (19.19)	395 (14.85)	
Education Level, n (%)				<0.001
Less than 9th grade	1245 (18.07)	684 (16.17)	561 (21.09)	
9–12th grade	1170 (16.98)	675 (15.95)	495 (18.61)	
More than 12th grade	4476 (64.95)	2872 (67.88)	1604 (60.30)	

(Continued)

TABLE 1 Continued

Variables	Total (n = 6891)	Non-DN (n = 4231)	DN (n = 2660)	*P*
Marital Status, n (%)				<0.001
Cohabitation	4170 (60.51)	2694 (63.67)	1476 (55.49)	
Solitude	2721 (39.49)	1537 (36.33)	1184 (44.51)	
Family PIR, n (%)				<0.001
Low (≤1.3)	2407 (34.93)	1407 (33.25)	1000 (37.59)	
Medium (1.3–3.5)	2785 (40.42)	1654 (39.09)	1131 (42.52)	
High (>3.5)	1699 (24.66)	1170 (27.65)	529 (19.89)	
Smoke, n (%)				0.001
Yes	3532 (51.26)	2104 (49.73)	1428 (53.68)	
No	3359 (48.74)	2127 (50.27)	1232 (46.32)	
Alcohol, n (%)				<0.001
Yes	4170 (60.51)	2635 (62.28)	1535 (57.71)	
No	2721 (39.49)	1596 (37.72)	1125 (42.29)	
Physical Activity, n (%)				<0.001
Inactive	3266 (47.40)	1814 (42.87)	1452 (54.59)	
Moderate	2233 (32.40)	1426 (33.70)	807 (30.34)	
Vigorous	1392 (20.20)	991 (23.42)	401 (15.08)	
Hypertension, n (%)				<0.001
Yes	4302 (62.44)	2374 (56.11)	1928 (72.51)	
No	2588 (37.56)	1857 (43.89)	731 (27.49)	
Coronary heart disease, n (%)				<0.001
Yes	675 (9.80)	292 (6.90)	383 (14.40)	
No	6216 (90.20)	3939 (93.10)	2277 (85.60)	
Stroke, n (%)				<0.001
Yes	522 (7.58)	217 (5.13)	305 (11.47)	
No	6369 (92.42)	4014 (94.87)	2355 (88.53)	
Cancer, n (%)				<0.001
Yes	953 (13.83)	512 (12.10)	441 (16.58)	
No	5938 (86.17)	3719 (87.90)	2219 (83.42)	
BMI (kg/m^2)	30.82 (26.97, 35.97)	30.90 (27.10, 36.03)	30.70 (26.83, 35.87)	0.168
FPG (mg/dL)	131.00 (108.00, 168.00)	129.00 (107.00, 158.00)	136.00 (110.00, 188.00)	<0.001
HbA1c (%)	6.70 (6.00, 7.80)	6.60 (5.90, 7.50)	6.90 (6.20, 8.20)	<0.001
TC (mg/dL)	185.00 (157.00, 217.00)	187.00 (159.00, 217.00)	181.50 (153.00, 218.00)	0.002
TG (mg/dL)	155.00 (105.00, 233.00)	151.00 (103.00, 225.00)	163.00 (108.00, 246.00)	<0.001
HDL-c (mg/dL)	45.00 (38.00, 55.00)	45.00 (39.00, 55.00)	45.00 (38.00, 55.00)	0.215
Creatinine (mg/dL)	0.90 (0.72, 1.10)	0.82 (0.70, 0.97)	1.09 (0.82, 1.36)	<0.001
UACR (mg/g)	12.40 (6.50, 37.53)	8.26 (5.42, 13.73)	59.55 (27.54, 176.01)	<0.001
eGFR (ml/min/1.73m^2)	85.83 (66.53, 100.84)	92.09 (79.05, 104.17)	62.20 (48.87, 91.47)	<0.001
METS-IR	49.98 (42.10, 59.52)	49.97 (42.04, 59.46)	49.99 (42.28, 59.75)	0.519

(Continued)

TABLE 1 Continued

Variables	Total (n = 6891)	Non-DN (n = 4231)	DN (n = 2660)	*P*
TyG	9.24 (8.76, 9.80)	9.18 (8.72, 9.72)	9.33 (8.82, 9.91)	<0.001
TG/HDL	3.37 (2.04, 5.78)	3.24 (1.97, 5.55)	3.64 (2.15, 6.09)	<0.001
TyG-BMI	288.55 (247.46, 339.98)	288.62 (246.88, 337.89)	288.50 (248.42, 343.01)	0.296

Data are shown as median (25th, 75th percentiles) or percentages, p <0.05 considered statistically significant.
DN, Diabetic nephropathy; PIR, Poverty-to-income ratio; BMI, Body mass index; FPG, Fasting plasma-glucose; HbA1c, Hemoglobin A1c; TC, Total cholesterol; TG, Triglyceride; HDL-c, High-density lipoprotein cholesterol; UACR, Urinary albumin/creatinine ratio; eGFR, Estimated glomerular filtration rate; METS-IR, Metabolic Score for Insulin Resistance; TyG, Triglyceride-glucose; TG/HDL, Triglyceride/High-density lipoprotein; TyG-BMI, Triglyceride glucose - body mass index.

status, family PIR, smoking habits, alcohol consumption status, physical activity level, and history of chronic diseases such as hypertension, CHD, stroke, and cancer. The analysis results indicated that METS-IR, TyG, TG/HDL, and TyG-BMI were significantly associated with the risk of DN. In particular, the unadjusted model demonstrated no significant association between METS-IR and DN. However, in Models 2 and 3, METS-IR demonstrated a positive correlation with the risk of DN, with the adjusted ORs remaining stable at 1.02 (95% CI: 1.01-1.02), with a p-value of <0.001. This indicates that the gender, age, and race factors significantly affect the relationship. In contrast, the TyG and TG/HDL indices demonstrated a significant association with an increased risk of DN in all models. Furthermore, the risk of DN exhibited a notable increase with increasing levels of these indices. TyG-BMI index did not demonstrate a significant association with DN in the unadjusted model; the positive association with DN risk became significant in both Model 2 and Model 3.

Further refinement of these associations through quartile analyses revealed that the high quartile groups of METS-IR, TyG, TG/HDL, and TyG-BMI were all at significantly elevated risk of DN, corresponding to ORs of 1.51 (95% CI: 1.29-1.76), 2.06 (95% CI: 1.77-2.40), 1.61 (95% CI: 1.38-1.88) and 1.57 (95% CI: 1.35-1.84), with all p-values less than 0.001. These findings strongly support the role of these IR indices as potential predictors of the development of DN in diabetic patients (Table 2).

To investigate the nonlinear relationship between the non-insulin-based IR indices and the risk of DN in diabetic patients, we employed RCS modeling. After adjusting for several potential confounding variables, including gender, age, race, education, marital status, family PIR, smoking habits, drinking status,

TABLE 2 Relationship between METS-IR, TyG, TG/HDL, TyG-BMI, and DN in patients with diabetes mellitus in different models.

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
METS-IR	1.00 (1.00 ~ 1.01)	0.344	1.02 (1.01 ~ 1.02)	**<0.001**	1.01 (1.01 ~ 1.02)	**<0.001**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.02 (0.89 ~ 1.17)	0.769	1.07 (0.92 ~ 1.23)	0.386	1.03 (0.89 ~ 1.20)	0.672
Quartile 3	0.99 (0.86 ~ 1.14)	0.888	1.22 (1.05 ~ 1.41)	**0.008**	1.12 (0.96 ~ 1.30)	0.136
Quartile 4	1.04 (0.91 ~ 1.19)	0.576	1.72 (1.48 ~ 2.01)	**<0.001**	1.51 (1.29 ~ 1.76)	**<0.001**
TyG	1.28 (1.20 ~ 1.36)	**<0.001**	1.50 (1.40 ~ 1.60)	**<0.001**	1.47 (1.37 ~ 1.58)	**<0.001**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.03 (0.89 ~ 1.18)	0.685	1.06 (0.92 ~ 1.23)	0.432	1.06 (0.91 ~ 1.23)	0.475
Quartile 3	1.19 (1.03 ~ 1.36)	**0.016**	1.30 (1.12 ~ 1.50)	**<0.001**	1.25 (1.07 ~ 1.45)	**0.004**
Quartile 4	1.60 (1.39 ~ 1.83)	**<0.001**	2.13 (1.83 ~ 2.48)	**<0.001**	2.06 (1.77 ~ 2.40)	**<0.001**
TG/HDL	1.01 (1.01 ~ 1.02)	**0.027**	1.02 (1.02 ~ 1.03)	**<0.001**	1.02 (1.01 ~ 1.03)	**<0.001**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.10 (0.95 ~ 1.26)	0.194	1.13 (0.98 ~ 1.31)	0.092	1.10 (0.95 ~ 1.28)	0.200
Quartile 3	1.23 (1.07 ~ 1.41)	**0.004**	1.38 (1.19 ~ 1.60)	**<0.001**	1.27 (1.09 ~ 1.48)	**0.002**

(Continued)

TABLE 2 Continued

Variables	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Quartile 4	1.34 (1.17 ~ 1.54)	**<0.001**	1.75 (1.51 ~ 2.04)	**<0.001**	1.61 (1.38 ~ 1.88)	**<0.001**
TyG-BMI	1.00 (1.00 ~ 1.00)	0.177	1.01 (1.01 ~ 1.01)	**<0.001**	1.01 (1.01 ~ 1.01)	**<0.001**
Categories						
Quartile 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Quartile 2	1.05 (0.92 ~ 1.21)	0.454	1.08 (0.93 ~ 1.24)	0.322	1.04 (0.90 ~ 1.21)	0.592
Quartile 3	0.95 (0.82 ~ 1.09)	0.439	1.16 (1.01 ~ 1.35)	**0.042**	1.08 (0.93 ~ 1.26)	0.294
Quartile 4	1.11 (0.96 ~ 1.27)	0.153	1.79 (1.54 ~ 2.09)	**<0.001**	1.57 (1.35 ~ 1.84)	**<0.001**

The bold values indicated statistically significant.
Model 1: crude.
Model 2: adjusted for Gender, Age, Race.
Model 3: adjusted for Gender, Age, Race, Education Level, Marital Status, Family PIR, Smoke, Alcohol, Physical Activity, Hypertension, Coronary heart disease, Stroke, Cancer.
DN, Diabetic nephropathy; METS-IR, Metabolic Score for Insulin Resistance; TyG, Triglyceride-glucose; TG/HDL, Triglyceride/High-density lipoprotein; TyG-BMI, Triglyceride glucose - body mass index; OR, Odds ratio; CI, Confidence interval.

physical activity level, hypertension, CHD, stroke, and cancer, The analyses revealed that the four IR indices (METS-IR, TyG, TG/HDL, and TyG-BMI) were not only highly significant overall correlations with DN risk (all *p*-values for overall < 0.001) but also exhibited an evident nonlinear character (*p*-values for nonlinear 0.038, < 0.001, 0.001, 0.039, respectively). Further threshold analyses were conducted to define inflection point values for each IR indices. The following values were identified: 49.98 for METS-IR, 9.24 for TyG, 3.37 for TG/HDL, and 288.55 for TyG-BMI. This finding is of particular significance, as it indicates

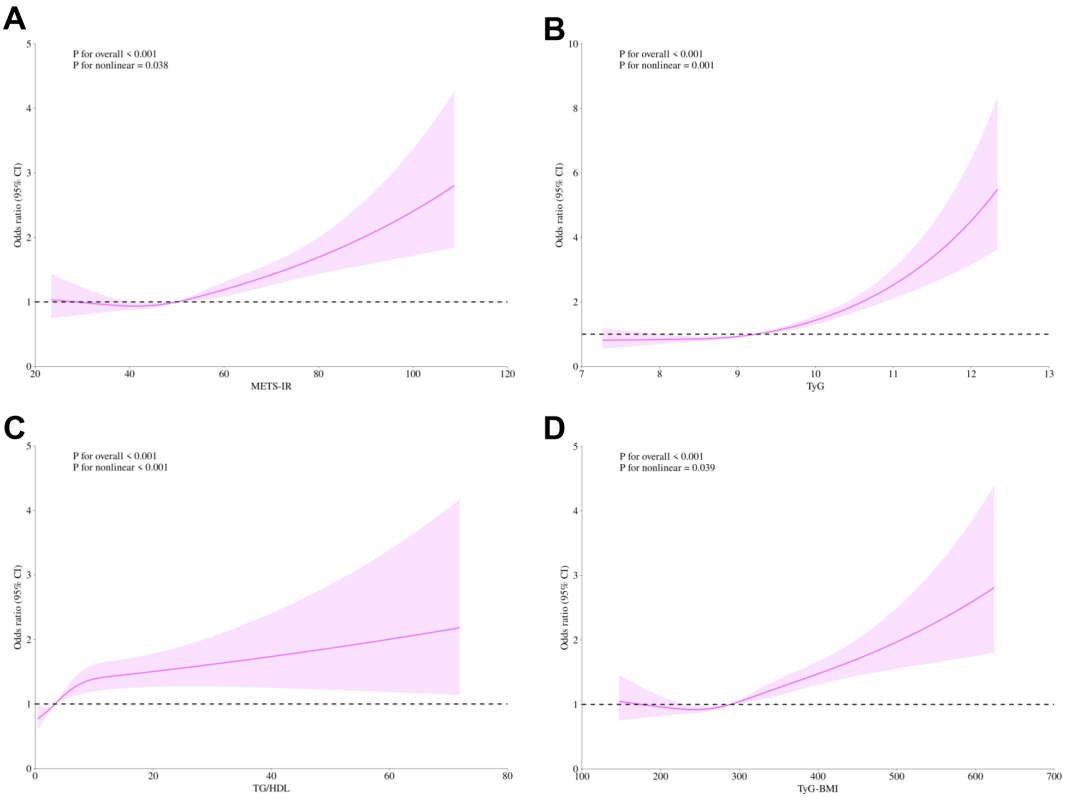

FIGURE 2
Non-linear relationship of METS-IR **(A)**, TyG **(B)**, TG/HDL **(C)**, TyG-BMI **(D)**, and diabetic nephropathy. The solid purple line displays the odds ratio, with the 95% confidence intervals represented by purple shading. They were adjusted for gender, age, race, education level, marital status, family PIR, smoking, alcohol, physical activity, hypertension, coronary heart disease, stroke, and cancer. METS-IR, Metabolic Score for Insulin Resistance; TyG, Triglyceride-glucose; TG/HDL, Triglyceride/High-density lipoprotein; TyG-BMI, Triglyceride glucose - body mass index; CI, Confidence interval; PIR, Poverty-to-income ratio.

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that when IR indices exceed these critical thresholds, the risk of DN increases significantly as the index levels are further elevated (Figure 2).

3.3 Subgroup analysis

To investigate the relationship between individual indices of IR and DN in different subgroups, the analysis was stratified by gender, education, marital status, family PIR, smoking, alcohol consumption, hypertension, CHD, stroke, and cancer. The results demonstrated that, when stratified using a cut-off value of 49.98, no significant differences were observed between METS-IR levels and the incidence of DN (all $p > 0.05$). Additionally, no significant interactions were detected (all interaction $p > 0.05$), either when comparing within subgroups or examining the interaction effect across subgroups (Figure 3). The TyG index demonstrated a higher prevalence of DN in individuals with TyG ≥ 9.24 compared to those with TyG < 9.24 in most subgroups, except subgroups with less than 9th-grade education, confirmed CHD, and confirmed cancer. Of particular note, in the subgroup analysis of gender and smoking habits, the correlation between TyG levels and DN risk was more significant within the female subgroup and the nonsmoking subgroup. Nevertheless, no significant interaction between TyG and DN risk was observed in the other subgroups (all interaction $p > 0.05$), as illustrated in Figure 4. For the TG/HDL ratio, individuals with TG/HDL ≥ 3.37 exhibited a heightened risk of DN across a diverse range of subgroups, except males, individuals below the 9th grade, those belonging to different PIR subgroups, smokers, alcohol drinkers, those without hypertension, individuals with confirmed coronary artery disease, individuals with confirmed stroke, and individuals with confirmed cancer. Further analysis revealed that within the specific subgroups of education and smoking habits, the TG/HDL ratio was more strongly correlated with the risk of DN in the highly educated subgroup and the nonsmoking subgroup. No significant interaction effects were observed within the remaining subgroups (all interaction $p > 0.05$), as illustrated in Figure 5. Finally, in terms of the TyG-BMI index, individuals with a TyG-BMI ≥288.55 exhibited a lower prevalence of DN in the female subgroup and the subgroup up to the 9th grade compared to participants with a TyG-BMI <288.55 (all $p < 0.05$). In contrast, no significant differences were observed

Subgroup	n (%)	< 49.98	≥ 49.98	OR (95%CI)	P	P for interaction
All patients	6891 (100.00)	1328/3445	1332/3446	0.96 (0.87 ~ 1.06)	0.453	
Gender						0.700
Male	3679 (53.39)	731/1881	716/1798	0.99 (0.86 ~ 1.14)	0.906	
Female	3212 (46.61)	597/1564	616/1648	0.92 (0.79 ~ 1.07)	0.272	
Education Level						0.273
Less than 9th grade	1245 (18.07)	321/690	240/555	0.84 (0.66 ~ 1.06)	0.145	
9–12th grade	1170 (16.98)	236/566	259/604	1.05 (0.82 ~ 1.34)	0.686	
More than 12th grade	4476 (64.95)	771/2189	833/2287	0.97 (0.86 ~ 1.11)	0.697	
Marital Status						0.225
Cohabitation	4170 (60.51)	714/2072	762/2098	1.00 (0.88 ~ 1.15)	0.953	
Solitude	2721 (39.49)	614/1373	570/1348	0.89 (0.76 ~ 1.04)	0.149	
Family PIR						0.157
Low (≤1.3)	2407 (34.93)	480/1132	520/1275	0.91 (0.77 ~ 1.08)	0.267	
Medium (1.3–3.5)	2785 (40.42)	591/1422	540/1363	0.90 (0.77 ~ 1.06)	0.212	
High (>3.5)	1699 (24.66)	257/891	272/808	1.16 (0.93 ~ 1.44)	0.181	
Smoke						0.857
Yes	3532 (51.26)	693/1724	735/1808	0.97 (0.84 ~ 1.11)	0.651	
No	3359 (48.74)	635/1721	597/1638	0.95 (0.82 ~ 1.10)	0.485	
Alcohol						0.370
Yes	4170 (60.51)	748/2066	787/2104	1.00 (0.87 ~ 1.14)	0.974	
No	2721 (39.49)	580/1379	545/1342	0.92 (0.78 ~ 1.08)	0.298	
Hypertension						0.386
Yes	4302 (62.44)	918/2036	1010/2266	0.99 (0.87 ~ 1.12)	0.861	
No	2588 (37.56)	409/1408	322/1180	0.91 (0.76 ~ 1.09)	0.321	
Coronary heart disease						0.778
Yes	675 (9.80)	179/318	204/357	1.04 (0.75 ~ 1.44)	0.820	
No	6216 (90.20)	1149/3127	1128/3089	0.96 (0.86 ~ 1.07)	0.428	
Stroke						0.818
Yes	522 (7.58)	154/259	151/263	0.90 (0.62 ~ 1.30)	0.580	
No	6369 (92.42)	1174/3186	1181/3183	0.97 (0.87 ~ 1.08)	0.551	
Cancer						0.871
Yes	953 (13.83)	241/526	200/427	1.00 (0.76 ~ 1.31)	0.991	
No	5938 (86.17)	1087/2919	1132/3019	0.96 (0.86 ~ 1.07)	0.466	

FIGURE 3
Subgroup analysis of the relationship between METS-IR and diabetic nephropathy. Adjusted variables: gender, age, race, education level, marital status, family PIR, smoking, alcohol, physical activity, hypertension, coronary heart disease, stroke, and cancer. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis. METS-IR, Metabolic Score for Insulin Resistance; PIR, Poverty-to-income ratio; OR, odds ratio; CI, confidence interval.

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Subgroup	n (%)	< 9.24	≥ 9.24	OR (95%CI)	P	P for interaction
All patients	6891 (100.00)	1205/3445	1455/3446	1.39 (1.25 ~ 1.54)	<.001	
Gender						0.039
Male	3679 (53.39)	659/1786	788/1893	1.24 (1.08 ~ 1.43)	0.002	
Female	3212 (46.61)	546/1659	667/1553	1.60 (1.37 ~ 1.87)	<.001	
Education Level						0.186
Less than 9th grade	1245 (18.07)	242/554	319/691	1.18 (0.93 ~ 1.49)	0.175	
9–12th grade	1170 (16.98)	215/565	280/605	1.49 (1.17 ~ 1.91)	0.001	
More than 12th grade	4476 (64.95)	748/2326	856/2150	1.43 (1.26 ~ 1.64)	<.001	
Marital Status						0.938
Cohabitation	4170 (60.51)	651/2052	825/2118	1.39 (1.21 ~ 1.59)	<.001	
Solitude	2721 (39.49)	554/1393	630/1328	1.40 (1.19 ~ 1.65)	<.001	
Family PIR						0.825
Low (≤1.3)	2407 (34.93)	412/1106	588/1301	1.41 (1.18 ~ 1.67)	<.001	
Medium (1.3–3.5)	2785 (40.42)	533/1422	598/1363	1.42 (1.21 ~ 1.67)	<.001	
High (>3.5)	1699 (24.66)	260/917	269/782	1.27 (1.02 ~ 1.58)	0.032	
Smoke						0.009
Yes	3532 (51.26)	648/1699	780/1833	1.21 (1.05 ~ 1.40)	0.008	
No	3359 (48.74)	557/1746	675/1613	1.63 (1.40 ~ 1.90)	<.001	
Alcohol						0.843
Yes	4170 (60.51)	689/2078	846/2092	1.35 (1.18 ~ 1.55)	<.001	
No	2721 (39.49)	516/1367	609/1354	1.43 (1.22 ~ 1.69)	<.001	
Hypertension						0.225
Yes	4302 (62.44)	882/2189	1046/2113	1.45 (1.27 ~ 1.64)	<.001	
No	2588 (37.56)	322/1255	409/1333	1.28 (1.07 ~ 1.53)	0.007	
Coronary heart disease						0.161
Yes	675 (9.80)	185/333	198/342	1.16 (0.84 ~ 1.60)	0.382	
No	6216 (90.20)	1020/3112	1257/3104	1.42 (1.28 ~ 1.59)	<.001	
Stroke						0.672
Yes	522 (7.58)	145/269	160/253	1.52 (1.05 ~ 2.21)	0.028	
No	6369 (92.42)	1060/3176	1295/3193	1.38 (1.24 ~ 1.54)	<.001	
Cancer						0.142
Yes	953 (13.83)	226/511	215/442	1.15 (0.88 ~ 1.51)	0.311	
No	5938 (86.17)	979/2934	1240/3004	1.44 (1.29 ~ 1.61)	<.001	

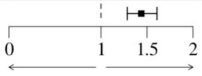

FIGURE 4
Subgroup analysis of the relationship between TyG and diabetic nephropathy. Adjusted variables: gender, age, race, education level, marital status, family PIR, smoking, alcohol, physical activity, hypertension, coronary heart disease, stroke, and cancer. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis. TyG, Triglyceride-glucose; PIR, Poverty-to-income ratio; OR, odds ratio; CI, confidence interval.

between TyG-BMI levels and DN prevalence in any of the remaining subgroups (all $p > 0.05$). Notably, in the subgroup analysis stratified by education, the low-education subgroup exhibited a higher correlation between TyG-BMI and DN risk. Similarly, no significant interactions were found within the remaining subgroups (all interactions $p > 0.05$), as shown in Figure 6.

4 Discussion

The objective of this study was to investigate the association between non-insulin-based IR indices (METS-IR, TyG, TG/HDL, and TyG-BMI) and DN through a cross-sectional analysis of 6,891 U.S. adults with DM from the NHANES 1999-2018 database. The findings indicated that individuals in the highest quartiles of METS-IR, TyG, TG/HDL, and TyG-BMI exhibited a markedly elevated risk of developing DN. After adjusting for multiple covariates, including gender, age, and race, this association remained significant and demonstrated a nonlinear relationship. These findings further confirm the importance of IR in the pathogenesis of DN and provide a potential assessment tool for the non-insulin-based IR indices in the prevention and management of DN.

IR is not only a core pathophysiologic feature of diabetes, but it also plays a pivotal role in the development and progression of DN (19, 37). IR contributes to the development of DN through a variety of biological pathways, including increased inflammatory response (38, 39), oxidative stress (40, 41), endothelial dysfunction (42, 43), and the promotion of accumulation of extracellular matrix (44), which collectively leads to alterations in renal structure and function. In the progression of DN, IR may contribute to glomerulosclerosis by increasing the filtration pressure in the kidney, leading to glomerular hyperfiltration (18, 45). Furthermore, IR has been linked to the dysfunction of podocytes, a crucial component of the glomerular filtration membrane (46, 47). Podocyte injury can result in the development and progression of proteinuria. Concurrently, hyperinsulinemia in the IR state may facilitate the proliferation and fibrosis of renal cells through the

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Subgroup	n (%)	< 3.37	≥ 3.37	OR (95%CI)	P	P for interaction
All patients	6891 (100.00)	1247/3445	1413/3446	1.19 (1.07 ~ 1.32)	0.001	
Gender						0.581
Male	3679 (53.39)	611/1646	836/2033	1.15 (0.99 ~ 1.32)	0.060	
Female	3212 (46.61)	636/1799	577/1413	1.24 (1.06 ~ 1.44)	0.007	
Education Level						0.010
Less than 9th grade	1245 (18.07)	266/573	295/672	0.89 (0.70 ~ 1.13)	0.342	
9–12th grade	1170 (16.98)	219/571	276/599	1.45 (1.13 ~ 1.87)	0.004	
More than 12th grade	4476 (64.95)	762/2301	842/2175	1.22 (1.07 ~ 1.39)	0.004	
Marital Status						0.919
Cohabitation	4170 (60.51)	658/2011	818/2159	1.17 (1.02 ~ 1.34)	0.027	
Solitude	2721 (39.49)	589/1434	595/1287	1.21 (1.02 ~ 1.42)	0.025	
Family PIR						0.767
Low (≤1.3)	2407 (34.93)	434/1107	566/1300	1.17 (0.98 ~ 1.40)	0.079	
Medium (1.3–3.5)	2785 (40.42)	549/1411	582/1374	1.16 (0.99 ~ 1.37)	0.068	
High (>3.5)	1699 (24.66)	264/927	265/772	1.22 (0.98 ~ 1.52)	0.081	
Smoke						0.030
Yes	3532 (51.26)	641/1632	787/1900	1.07 (0.93 ~ 1.23)	0.356	
No	3359 (48.74)	606/1813	626/1546	1.34 (1.15 ~ 1.56)	<.001	
Alcohol						0.380
Yes	4170 (60.51)	711/2046	824/2124	1.12 (0.98 ~ 1.29)	0.096	
No	2721 (39.49)	536/1399	589/1322	1.28 (1.08 ~ 1.51)	0.004	
Hypertension						0.253
Yes	4302 (62.44)	903/2175	1025/2127	1.24 (1.09 ~ 1.41)	0.001	
No	2588 (37.56)	343/1269	388/1319	1.09 (0.91 ~ 1.30)	0.363	
Coronary heart disease						0.472
Yes	675 (9.80)	168/306	215/369	1.12 (0.81 ~ 1.55)	0.505	
No	6216 (90.20)	1079/3139	1198/3077	1.20 (1.07 ~ 1.34)	0.002	
Stroke						0.539
Yes	522 (7.58)	129/237	176/285	1.30 (0.89 ~ 1.88)	0.174	
No	6369 (92.42)	1118/3208	1237/3161	1.17 (1.05 ~ 1.31)	0.004	
Cancer						0.443
Yes	953 (13.83)	221/497	220/456	1.10 (0.84 ~ 1.45)	0.481	
No	5938 (86.17)	1026/2948	1193/2990	1.21 (1.08 ~ 1.35)	0.001	

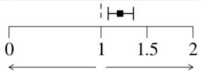

FIGURE 5
Subgroup analysis of the relationship between TG/HDL and diabetic nephropathy. Adjusted variables: gender, age, race, education level, marital status, family PIR, smoking, alcohol, physical activity, hypertension, coronary heart disease, stroke, and cancer. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis. TG/HDL, Triglyceride/High-density lipoprotein; PIR, Poverty-to-income ratio; OR, odds ratio; CI, confidence interval.

activation of signaling pathways, including JAK/STAT, MAPK, and PI3K/Akt (48–51).

This study revealed significant associations between all four non-insulin-based IR indices (METS-IR, TyG, TG/HDL, and TyG-BMI) and the risk of DN. This finding supports the notion that IR is a critical factor in the pathogenesis of DN. Of particular interest is that the TyG index demonstrated a highly consistent association with DN risk across all analyzed models. This result echoes several previous studies and further solidifies the utility and validity of the TyG index as a DN risk assessment tool. Several studies have confirmed the strong association between the TyG index and albuminuria (30, 52). In patients with T2DM, the TyG index was associated with DN independently of other factors, demonstrating a superior ability to identify DN compared with the traditional HOMA-IR index (29, 30). Furthermore, the METS-IR, TG/HDL, and TyG-BMI indices showed significant correlations with DN risk in the adjusted model. Notably, while all these indices of IR demonstrated potential in predicting the risk of DN, the evaluation of their predictive value varied somewhat across studies. For instance, one study in a rural Chinese population observed that a high METS-IR score was associated with an increased risk of mild decline and rapid deterioration of renal function (13). In contrast, in patients with a primary diagnosis of T2DM, the risk of DN increased with elevated TyG index and TyG-BMI. However, the efficacy in diagnosing DN was relatively low (53). Furthermore, a retrospective analysis of 521 patients with T2DM showed that among the four metrics for assessing IR, the TyG index, in conjunction with the TG/HDL ratio, exhibited the most significant predictive effect, followed by the METS-IR. In contrast, the TyG-BMI exhibited a relatively weak effect (54). The TyG index demonstrated the strongest association with DN risk in the present study, followed by the TG/HDL ratio. In contrast, the METS-IR and TyG-BMI indices exhibited relatively inferior performance. These findings reflect the differential performance of different IR indices in specific populations and emphasize the need to comprehensively consider multiple factors in clinical applications and research to develop more accurate risk assessment and intervention strategies.

Furthermore, it is essential to acknowledge that many factors, including genetic predisposition (55, 56), environmental exposures (57), lifestyle, and comorbidities (58), influence the relationship between IR and DN. The subgroup analyses conducted in this study

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Subgroup	n (%)	< 288.55	≥ 288.55	OR (95%CI)	P	P for interaction
All patients	6891 (100.00)	1331/3445	1329/3446	0.96 (0.87 ~ 1.07)	0.463	
Gender						0.106
Male	3679 (53.39)	768/1999	679/1680	1.05 (0.92 ~ 1.21)	0.469	
Female	3212 (46.61)	563/1446	650/1766	0.86 (0.74 ~ 1.00)	0.046	
Education Level						0.031
Less than 9th grade	1245 (18.07)	332/696	229/549	0.75 (0.59 ~ 0.95)	0.016	
9–12th grade	1170 (16.98)	238/570	257/600	1.03 (0.81 ~ 1.32)	0.792	
More than 12th grade	4476 (64.95)	761/2179	843/2297	1.01 (0.89 ~ 1.15)	0.861	
Marital Status						0.094
Cohabitation	4170 (60.51)	722/2093	754/2077	1.03 (0.90 ~ 1.18)	0.663	
Solitude	2721 (39.49)	609/1352	575/1369	0.86 (0.73 ~ 1.01)	0.060	
Family PIR						0.093
Low (≤1.3)	2407 (34.93)	488/1158	512/1249	0.91 (0.77 ~ 1.08)	0.288	
Medium (1.3–3.5)	2785 (40.42)	587/1400	544/1385	0.89 (0.76 ~ 1.04)	0.136	
High (>3.5)	1699 (24.66)	256/887	273/812	1.20 (0.96 ~ 1.49)	0.105	
Smoke						0.857
Yes	3532 (51.26)	715/1774	713/1758	0.96 (0.84 ~ 1.11)	0.605	
No	3359 (48.74)	616/1671	616/1688	0.95 (0.82 ~ 1.11)	0.532	
Alcohol						0.060
Yes	4170 (60.51)	751/2091	784/2079	1.04 (0.91 ~ 1.19)	0.524	
No	2721 (39.49)	580/1354	545/1367	0.86 (0.73 ~ 1.01)	0.066	
Hypertension						0.204
Yes	4302 (62.44)	907/2011	1021/2291	1.00 (0.88 ~ 1.14)	0.973	
No	2588 (37.56)	423/1433	308/1155	0.89 (0.74 ~ 1.07)	0.214	
Coronary heart disease						0.624
Yes	675 (9.80)	187/334	196/341	1.07 (0.77 ~ 1.48)	0.695	
No	6216 (90.20)	1144/3111	1133/3105	0.96 (0.86 ~ 1.07)	0.417	
Stroke						0.349
Yes	522 (7.58)	158/260	147/262	0.79 (0.54 ~ 1.14)	0.208	
No	6369 (92.42)	1173/3185	1182/3184	0.98 (0.88 ~ 1.09)	0.717	
Cancer						0.856
Yes	953 (13.83)	241/518	200/435	0.95 (0.72 ~ 1.25)	0.705	
No	5938 (86.17)	1090/2927	1129/3011	0.97 (0.87 ~ 1.08)	0.575	

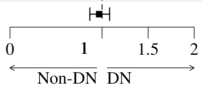

FIGURE 6
Subgroup analysis of the relationship between TyG-BMI and diabetic nephropathy. Adjusted variables: gender, age, race, education level, marital status, family PIR, smoking, alcohol, physical activity, hypertension, coronary heart disease, stroke, and cancer. The model was not adjusted for the stratification variables themselves in the corresponding stratification analysis. TyG-BMI, Triglyceride glucose - body mass index; PIR, Poverty-to-income ratio; OR, odds ratio; CI, confidence interval.

demonstrated the impact of various demographic characteristics, lifestyle habits, and chronic disease histories on the relationship between IR and DN. For instance, the correlation between the TyG index and the risk of DN was more pronounced in the female and nonsmoking subgroups. This may be attributed to disparate patterns of insulin sensitivity or insulin secretion in women and nonsmokers (59, 60). Furthermore, the association between TyG-BMI and DN risk was more pronounced in the less educated subgroup. This may be attributed to lower socioeconomic status and health literacy, influencing patients' lifestyle and healthcare access (61). These findings indicate that socioeconomic status, lifestyle, and personal behavior may affect the relationship between IR and DN. It is crucial to consider the specificity of different population subgroups when developing prevention and management strategies for DN.

Non-insulin-based IR indices (METS-IR, TyG, TG/HDL, and TyG-BMI) offer significant advantages over traditional methods of assessing IR (HEC and HOMA-IR) (26, 31, 33, 53). Firstly, these novel indices do not necessitate the direct measurement of insulin levels, which confers them an advantage in cost and operational complexity. The high cost of insulin or C-peptide measurements, the necessity for specific laboratory equipment and specialized personnel, and the availability of these resources in resource-limited settings limit the widespread use of these measurements in such settings. Second, non-insulin-based indices are straightforward to calculate and rely solely on routine biochemical markers, such as FPG, TG, HDL-C, and BMI, which can typically be measured in a standard clinical laboratory (62). This simplicity renders these indices more suitable for large-scale epidemiological studies and routine clinical practice. Moreover, as these indices are not dependent on insulin measurements, they are instrumental in patients with diabetes, especially those on insulin therapy. In patients receiving exogenous insulin, elevated insulin levels may not accurately reflect IR status, as the use of insulin may confound insulin sensitivity (22). Furthermore, the non-insulin-based indices' capacity to reflect many dimensions of IR, including the severity of IR and its correlation with cardiovascular disease risk, contributes to a more comprehensive evaluation of the overall health status of diabetic patients (63–68). Finally, the practical value of these indices in predicting and assessing the risk of DN has been confirmed by previous studies and the present study. They may

be advantageous in the early identification of high-risk patients, facilitating timely preventive and interventional measures.

The principal strength of this study lies in the utilization of a comprehensive, nationally representative database, NHANES, which encompasses a diverse array of population characteristics, thereby ensuring the generalizability and reliability of the findings. Second, we adjusted for confounding variables to obtain more plausible results. Furthermore, multiple indices of non-insulin-based IR were employed in this study, and detailed subgroup analyses were conducted to assess these indices' association with DN comprehensively. Nevertheless, it should be noted that this study has limitations. First, as this was a cross-sectional study, it was impossible to determine whether the observed associations were causal. Second, although we considered several potential confounding variables, there may still be unconsidered variables, such as genetic factors and polymorphisms, which may impact the results. Future studies could further explore the impact of these factors on the association between IR and DN. Furthermore, the study was conducted primarily on a U.S. population, and the results may not be generalizable to other racial or regional groups.

5 Conclusion

In conclusion, the present study investigated the complex associations between non-insulin-based IR indices (METS-IR, TyG, TG/HDL, and TyG-BMI) and the risk of DN. The results demonstrated that all of these indices were significantly correlated with the risk of DN, with the most significant correlation being that of the TyG index. This finding highlights the potential application of these IR indices in the prevention and management of DN. It provides clinicians with a more accurate risk identification and management tool, which is expected to optimize the individualized treatment plan for DN patients. Future studies should further explore the application of these indices in different populations and evaluate their role in the early diagnosis and treatment of DN. In the meantime, further longitudinal studies are required to ascertain the causal relationship between these indices and DN.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Centers for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm).

Ethics statement

The studies involving humans were approved by National Center for Health Statistics Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. YH: Data curation, Investigation, Project administration, Writing – original draft. YM: Data curation, Investigation, Project administration, Writing – original draft. WL: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Genetically predicted brain cortical structure mediates the causality between insulin resistance and cognitive impairment

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Background: Insulin resistance is tightly related to cognition; however, the causal association between them remains a matter of debate. Our investigation aims to establish the causal relationship and direction between insulin resistance and cognition, while also quantifying the mediating role of brain cortical structure in this association.

Methods: The publicly available data sources for insulin resistance (fasting insulin, homeostasis model assessment beta-cell function and homeostasis model assessment insulin resistance, proinsulin), brain cortical structure, and cognitive phenotypes (visual memory, reaction time) were obtained from the MAGIC, ENIGMA, and UK Biobank datasets, respectively. We first conducted a bidirectional two-sample Mendelian randomization (MR) analysis to examine the susceptibility of insulin resistance on cognitive phenotypes. Additionally, we applied a two-step MR to assess the mediating role of cortical surficial area and thickness in the pathway from insulin resistance to cognitive impairment. The primary Inverse-variance weighted, accompanied by robust sensitivity analysis, was implemented to explore and verify our findings. The reverse MR analysis was also performed to evaluate the causal effect of cognition on insulin resistance and brain cortical structure.

Results: This study identified genetically determined elevated level of proinsulin increased reaction time (beta=0.03, 95% confidence interval [95%CI]=0.01 to 0.05, p=0.005), while decreasing the surface area of rostral middle frontal (beta=-49.28, 95%CI=-86.30 to -12.27, p=0.009). The surface area of the rostral middle frontal mediated 20.97% (95%CI=1.44% to 40.49%) of the total effect of proinsulin on reaction time. No evidence of heterogeneity, pleiotropy, or reverse causality was observed.

Conclusions: Briefly, our study noticed that elevated level of insulin resistance adversely affected cognition, with a partial mediation effect through alterations in brain cortical structure.

KEYWORDS

brain cortical structure, cognition, insulin resistance, mediation, Mendelian randomization

1 Introduction

Epidemiological studies indicate that over 55 million people were affected by dementia in 2019. The World Health Organization projects this number to increase to 139 million by 2050. The economic impact of dementia is expected to escalate from US$1.3 trillion in 2019 to US$2.8 trillion by 2030, presenting significant social and economic challenges (1). The causes of dementia are multifactorial, with Alzheimer's disease (AD) identified as the primary contributor, accounting for nearly 70% of cases. The cognitive dysfunction associated with dementia is often overlooked in its early stages but progressively worsens, eventually leading to irreversible and incurable conditions in advanced stages. Therefore, this underscores the critical importance of early detection and intervention in managing dementia.

Insulin resistance (IR) is a pathological state characterized by impaired insulin responsiveness, requiring elevated level of insulin to maintain glucose homeostasis in both peripheral tissues and the brain (2), a key feature of Type 2 diabetes mellitus (T2DM) and metabolic syndrome. Additionally, it has been primarily associated with coronary heart disease (3), stroke (4), and AD (5). The hyperinsulinemic-euglycemic clamp, considered the gold standard for measuring insulin resistance, is limited in clinical application owing to its invasiveness, high cost, time-consuming nature, and laborious procedure (6). By comparison, fasting insulin, homeostasis model assessment beta-cell function (HOMA-B), homeostasis model assessment insulin resistance (HOMA-IR), and proinsulin serve as more accessible markers for reflecting insulin resistance (7).

The literature has suggested an association between insulin resistance and cognition. In a previous observational study involving older patients with hypertension, elevated HOMA-IR was related to cognitive impairment (8). Smith et al.'s investigation (9) supported the close relationship between increased HOMA-IR and decreased executive function in patients with vascular cognitive impairment. However, conflicting results from other studies reported no relationship between insulin resistance and AD (10). In a longitudinal study involving older participants without dementia, a higher baseline HOMA-IR was found to predict cognitive degeneration seven years later (11). Despite robust epidemiological evidence, the potential pathogenesis and causal direction between insulin resistance and cognition remain poorly established. Challenges such as selection bias, confounding factors, reverse causality, and relatively small sample size in the observation studies obscure a conclusive resolution to the bidirectional chicken-and-egg question.

Furthermore, limited studies have delved into the underlying mechanisms or mediating pathways connecting insulin resistance and cognition. Previous research has demonstrated alterations in brain cortical structure associated with both insulin resistance (12) and cognitive dysfunction (13). Insulin receptors are extensively expressed in the brain, with predominant distribution in the cerebellum, frontal cortex, and hippocampus, as proved by studies in animal models and post-mortem human brains (14, 15). Thus, insulin may play a crucial role in multiple brain regions. A previous study utilized 18F-fludeoxyglucose - positron emission tomography to measure cerebral glucose metabolism and revealed that blood fasting insulin was linked to glucose metabolism of the inferior parietal, hippocampus, and parahippocampus region (16). Insulin in the peripheral blood might traverse the blood-brain barrier and participate in specific regions' synaptic and neuronal activity. Various cortical structures serve distinct physiological functions, and cortical atrophy is a recognized pathophysiological process contributing to cognitive impairment. Accordingly, brain cortical structure might be a latent mediator between insulin resistance and cognition.

Mediation analysis (MR) applies single nucleotide polymorphisms (SNPs) closely relevant to the exposure factors as instrumental variables (IVs) to deduce the causality between exposure and outcome (17). Owing to the random assignment of SNPs during meiosis, MR can yield robust causal evidence that is less influenced by confounders and reverse causality. Therefore, MR stands as a well-established statistical method, overcoming limitations inherent in traditional observational studies. Leveraging and extending MR, mediation MR analysis offers an opportunity to assess the complex interlocking causality among insulin resistance, brain cortical structure, and cognition. Moreover, the identified intermediate factors contribute to the exploration of the potential etiology and pathogenesis of cognitive impairment. As far as we know, the causal exploration of mediating pathways from insulin resistance to cognition is lacking. To fill the knowledge gap, our investigation attempted to (i) ascertain whether insulin resistance is causally associated with cognition and (ii) quantify

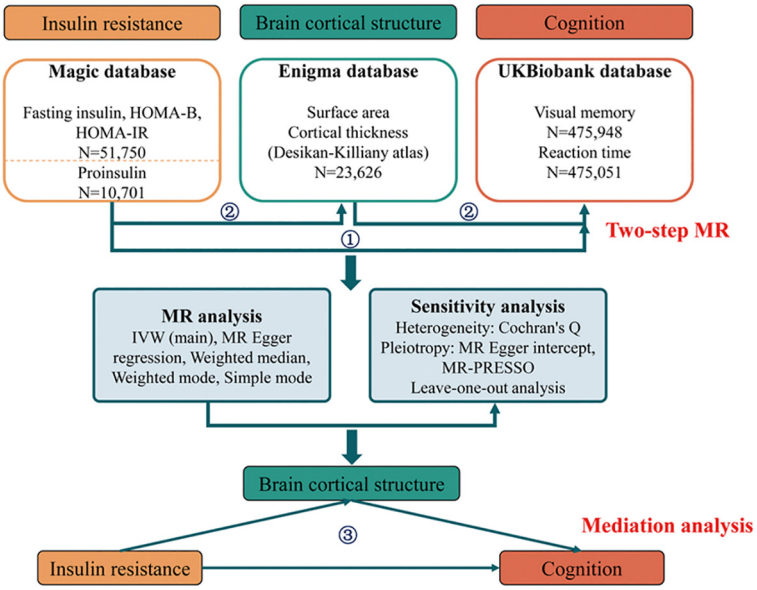

FIGURE 1
Flowchart of the two-step mediation MR study. MR, Mendelian randomization; HOMA-B, homeostasis model assessment beta-cell function; HOMA-IR, homeostasis model assessment insulin resistance; IVW, inverse-variance weighted; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

the extent to which brain cortical structure mediates the effects of insulin resistance on cognition.

2 Materials and methods

2.1 Study design

The flowchart in Figure 1 demonstrates the comprehensive procedure of our exploration. In stage 1, we performed a two-sample bidirectional univariable MR analysis to establish the causality between insulin resistance and cognition. In stage 2, we used a two-step bidirectional univariable MR to select candidate mediators in the causality between insulin resistance and cognition. In stage 3, we constructed a mediation model and quantified the proportion of insulin resistance's effect on cognition mediated by brain cortical structure. Our study adheres to the STROBE-MR guidelines (Supplementary Table S1).

2.2 Data sources

2.2.1 Insulin resistance

We used fasting insulin, HOMA-B, HOMA-IR, and proinsulin as established proxies for insulin resistance (1). Towards fasting insulin, HOMA-B, and HOMA-IR (18), we chose genetic IVs from the publicly available meta-analyses of glucose and insulin-related traits consortium (MAGIC), with 51750 participants without diabetes from 26 European cohorts. The three surrogate markers of insulin resistance were log-transformed. The regression analyses were adjusted for age and sex, together with BMI (2). Regarding proinsulin, genome-wide association studies (GWAS) summary statistics were attained from MAGIC either (19). The meta-analysis consisted of 10701 European individuals without diabetes from four cohorts. The regression analyses were adjusted for fasting insulin in addition to age and sex. More detailed characteristics of cohorts have been provided in Supplementary Table S2.

2.2.2 Brain cortical structure

Summary statistics for brain cortical structure were derived from the enhancing neuro imaging genetics through meta analysis (ENIGMA) database (20), encompassing 51665 participants across 60 cohorts worldwide. Specifically, 33709 individuals were of European ancestry. Among them, 10803 participants were from the UK Biobank consortium. The imaging phenotype was measured using the T1 structural Magnetic Resonance Imaging sequence combined with the Desikan-Killiany atlas, which contained surficial area (SA) and thickness (TH) for both global and 34 functionally specialized cortical regions. The mean value of global SA was 169647.43 mm^2, and the mean value of global TH was 2.45 mm. The SA and TH of 34 cortical regions were adjusted based on global measurements to mitigate the impact of individual differences on results. To avoid sample overlap between traits, we employed meta-results involving exclusively European and non-UKB individuals. Consequently, the ultimate sample size used in our study for brain cortical structure was 23626. The detailed cohort information is available in Supplementary Table S3.

2.2.3 Cognition

Following existing literature, summary-level statistics for cognition were achieved from the UK Biobank (21), gathering up to 502649 population-based individuals. After excluding patients

with neurological disorders, 480416 participants completed the five cognitive assessments through the computerized touchscreen. To magnify statistical power, we chose visual memory and reaction time as proxies for cognition (22). The visual memory was evaluated via a "6 pairs matching" test, requiring individuals to recall and match the position of 6 pairs of cards based on their memory. The number of errors was counted, with higher counts represented poorer cognitive performance. The reaction time was measured through a symbol matching test, akin to a "snap" card game. The completion time (in milliseconds) was recorded, with a longer time symbolized poorer cognitive performance. The scores of visual memory and reaction time were transformed with [ln(x + 1)] and [ln(x)], respectively, to achieve normal distribution.

The GWAS data utilized in our research originated from distinct cohorts or consortia, ensuring the absence of sample overlap.

2.3 Instrumental variable selection

Strictly quality control procedures were implemented to guarantee the robustness and precision of the causality among insulin resistance, brain cortical structure, and cognition. (1) SNPs strongly linked to insulin resistance phenotype ($p < 5\times10^{-8}$) were selected as IVs. Nevertheless, for SA and TH, the locus-wide significance level threshold was set to a relatively relaxed 1×10^{-6} to retain more IVs; (2) clumping procedure: removing IVs in linkage disequilibrium with $r^2<0.001$, and clumping window=10000kb; (3) the minor allele frequency (MAF) > 0.01; (4) the F-statistic > 10, with the detailed calculation formula provided elsewhere (17); (5) harmonizing procedure: excluding palindromic and inconsistent IVs; (6) steiger filtering: the IVs were determined to be more predictive of exposure than outcome; (7) PhenoScanner V2 scanning: discarding the IVs correlated ($p < 1\times10^{-5}$) with confounding factors (23).

2.4 Statistical analysis

All analyses were conducted in the R version 4.1.2 environment using "TwoSampleMR" and "MRPRESSO" packages. The figures were drawn through FreeSurfer (version 7.2.0, https://surfer.nmr.mgh.harvard.edu) and Figdraw (https://www.figdraw.com).

2.4.1 Primary analysis

Five complementary MR approaches with accommodated assumptions were conducted, including inverse variance weighted (IVW) (primary), MR Egger, weighted median, weighted mode, and simple mode. (1) The IVW is the optimal statistical approach assuming the validity of all IVs (24). However, the precision of IVW is susceptible to directional pleiotropy. (2) The MR Egger is a less efficient analytical method capable of providing unbiased estimations even if all IVs are pleiotropic, but it is substantially influenced by outliers (25). (3) The weighted median method is applicable when there are <50% invalid IVs and is robust to outliers (24). (4) The weighted mode persists steady even though IVs are disqualified or violate the pleiotropy hypothesis (26). (5) The simple mode is an unweighted empirical density function mode with relatively low statistical efficiency (27). As for multiple comparison correction, the statistically significant threshold was set at 0.025 (0.05/2) for the MR analysis between insulin resistance and cognition, and 0.0015 (0.05/34) for the MR analysis between insulin resistance and brain cortical structure. P-values between 0.05 and the specified threshold were considered nominally significant.

2.4.2 Mediation analysis

The two-step univariable mediation MR analysis was implemented to investigate whether brain cortical structure mediates the causal pathway from insulin resistance to cognition outcome. The total effect of insulin resistance on cognition (c) can be decomposed into two components: (1) the direct effects of insulin resistance on cognition (without mediators, c') and (2) the indirect effects mediated by brain cortical structure (a×b, where a represents the influence of insulin resistance on brain cortical structure and b represents the influence of brain cortical structure on cognition) (28). The mediation percentage was calculated using the equation (a×b)/c. Subsequently, we applied the delta method to calculate 95% confidence intervals (CI).

2.4.3 Sensitivity analysis

Several sensitivity analyses were carried out to validate the reliability of the identified causal relationship. The Cochran's Q statistics of MR Egger and IVW approaches were conducted to determine latent heterogeneity. A p-value larger than 0.05 indicated the absence of heterogeneity. The MR Egger intercept and Mendelian Randomised Multi-Effects Residuals and Heteroscedasticity (MR-PRESSO) approaches were concurrently employed to determine the latent horizontal pleiotropy. The intercept of MR Egger was nearly zero, and the p-value was greater than 0.05, demonstrating no pleiotropy. The leave-one-out analysis investigated whether the removal of a single SNP substantially influenced the total effect.

2.4.4 Reverse MR analysis

For causality found to be significant or nominally significant in the forward MR analysis, we carried out the reverse MR analysis to verify the bidirectional relationship in the pathway. The threshold for IVs strongly correlated to cognition traits was set at 5×10^{-8}, and the other procedures were similar to the forward MR analysis.

3 Results

3.1 Causality of insulin resistance on cognition

Following the rigorous screening steps mentioned above, 9 SNPs with fasting insulin, 12 SNPs with HOMA-B, 8 SNPs with HOMA-IR, and 8 SNPs with proinsulin were selected as IVs, respectively. The comprehensive information for IVs of insulin resistance is listed in Supplementary Table S4. The IVs strongly linked to fasting insulin substantially overlapped with those in

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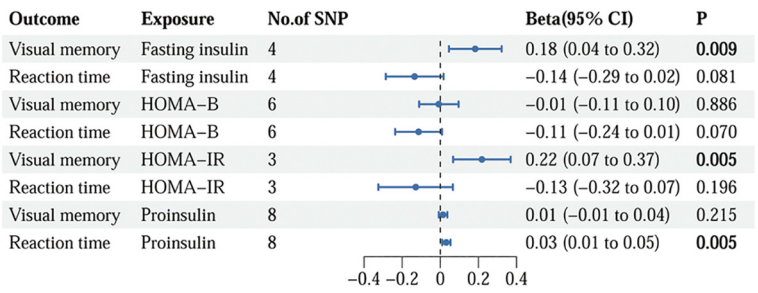

FIGURE 2
The causality of genetically predicted insulin resistance on cognition using IVW methods. IVW, inverse variance weighted; SNP, single nucleotide polymorphism; CI, confidence interval; HOMA-B, homeostasis model assessment beta-cell function; HOMA-IR, homeostasis model assessment insulin resistance.

HOMA-IR. The relationships between insulin resistance phenotypes and cognition phenotypes are illustrated in Figure 2. The IVW method demonstrated that fasting insulin (beta=0.18, 95%CI=0.04 to 0.32, p=0.009) and HOMA-IR (beta=0.22, 95% CI=0.07 to 0.37, p=0.005) were causally correlated with visual memory. Additionally, a significant detrimental effect of proinsulin on reaction time was discovered using the IVW method (beta=0.03, 95%CI=0.01 to 0.05, p=0.005). However, no association was observed for HOMA-B.

3.2 Causality of insulin resistance on brain cortical structure

As illustrated in Figures 3, 4, the influence of insulin resistance on brain cortical structure, both protective and adverse, were determined. No significant causality was discovered for altering global SA and TH with insulin resistance. Concerning SA of specific regions, a higher level of proinsulin was nominally associated with a decreased SA of the rostral middle frontal (IVW: beta=-49.28, 95%CI=-86.30 to -12.27, p=0.009). The causal effects of HOMA-IR on SA of both precentral (IVW: beta=-161.91, 95%CI=-272.50 to -51.32, p=0.004) and insula (IVW: beta=84.15, 95% CI=26.30 to 142.00, p=0.004) turned borderline significant after Bonferroni adjustment. The fasting insulin and HOMA-IR determined both adverse impacts on the SA of the precentral and protective effects on the SA of the insula simultaneously. Respecting TH of specific regions, genetically predicted HOMA-IR was inversely related to TH of rostral anterior cingulate (IVW: beta=-0.09, 95% CI=-0.15 to -0.03, p=0.003). The proinsulin susceptibility was negatively linked to TH of the caudal anterior cingulate (IVW: beta=-0.03, 95%CI=-0.04 to -0.01, p=0.003). Nevertheless, limited evidence was noticed for the causality of HOMA-B on SA and TH. The detailed causality between each insulin resistance phenotype and brain cortical structure is presented in Supplementary Tables S5, S6.

3.3 Causality of brain cortical structure on cognition

Building upon the established causality between insulin resistance and brain cortical structure of specific regions. The SA

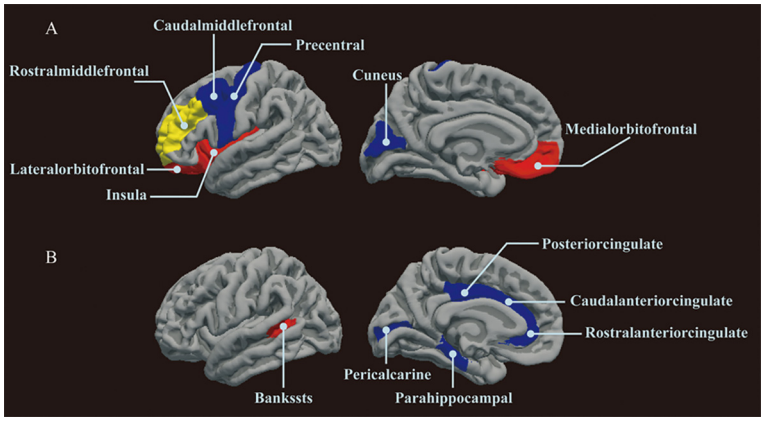

FIGURE 3
The results of MR analysis showed that insulin resistance potentially influenced the brain cortical structure of specific regions. **(A)** MR analysis results of insulin resistance on cortical surface area. **(B)** MR analysis results of insulin resistance on cortical thickness. Brain regions with positive and negative IVW-derived β values are shown in red and blue, respectively, brain region with negative IVW-derived β value and mediates the association between insulin resistance and cognition is shown in yellow. MR, Mendelian randomization; IVW, inverse variance weighting.

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and TH of specific regions were chosen as candidate mediators. Subsequently, we performed MR analysis on SA and TH of specific regions concerning cognition phenotypes. We observed that genetically determined SA of cuneus had a positive causal direction with reaction time (IVW: beta=2.79×10^{-4}, 95% CI=5.99×10^{-5} to 4.98×10^{-4}, p=0.013). The SA of the rostral middle frontal exhibited protective effects against longer reaction time (beta=-1.32×10^{-4}, 95%CI=-2.04×10^{-4} to -5.91×10^{-5}, p=0.0004), as indicated by robust IVW estimation. Consistent directional results were observed across all MR estimations.

3.4 Cortical structure mediates the causality of insulin resistance on cognition

We analyzed the rostral middle frontal and cuneus's SA as candidate mediators of the pathway from proinsulin to reaction time. Our study indicated that a higher level of proinsulin might result in lower SA of the rostral middle frontal, which in turn was related to a longer reaction time. However, the mediation model was invalid using the SA of cuneus as a mediator. As shown in Figure 5, the SA of the rostral middle frontal partially mediated the pathway from proinsulin to reaction time, accounting for 20.97% (95%CI=1.44% to 40.49%, p<0.05).

3.5 Sensitivity analysis

Estimation for Cochran's Q statistic MR Egger and IVW tests indicated no significant heterogeneity in the causality. The MR-PRESSO global test showed a considerable p value and the MR-Egger intercept was nearly zero, emphasizing no significant horizontal pleiotropy (Supplementary Table S7). None underlying outliers were confirmed in the MR-PRESSO analysis. Furthermore, the observed causal estimate was not substantially affected by any strong driven SNP, as indicated by the leave-one-out test. The MR steiger filtering was determined to be more predictive of exposure than the outcome. Consequently, there was sufficient evidence supporting the robustness of our uncovering.

3.6 Reverse MR analysis

We further employed reverse MR analysis to evaluate the existence of bidirectional causality in the identified results from the forward analysis. We included up to 23 SNPs for visual memory and 58 for reaction time. Comprehensive information on the IVs is displayed in Supplementary Table S8. Results in Supplementary Table S9 indicated no significant causality for genetically predicted reaction time on proinsulin, reaction time on SA of rostral middle frontal, and SA of rostral middle frontal on proinsulin. No evidence of heterogeneity and pleiotropy was found in the reverse MR analysis (Supplementary Tables S10).

4 Discussion

Through MR analysis, we investigated the causal influence of insulin resistance-related traits on cognition and evaluated the mediating effects of brain cortical structure in the pathway. Specifically, we identified that an elevated level of proinsulin, a marker of insulin resistance, led to increased reaction time, with the SA of rostral middle frontal mediated 20.97% of this effect. This study added suggestive evidence that brain cortical structure was crucial in the pathogenesis linking insulin resistance to the advancement of cognitive impairment.

Insulin resistance, a complicated phenotype, is typically assessed through various proxy indexes, with the euglycemic hyperinsulinemic glucose clamp technique considered the gold standard. Owing to the deficiency of updated large-scale GWAS on this gold standard measurement, we utilized four commonly employed surrogate markers in our MR analysis (29). Our study demonstrated a significant detrimental effect of insulin resistance traits on cognitive performance, specifically fasting insulin, HOMA-IR, and proinsulin, with no such effect observed for HOMA-B. It has been reported that compared to HOMA-B, higher HOMA-IR presented a closer connection with incident T2DM in Chinese adults (30). Given that diabetes is a well-established risk factor for cognitive impairment, this discrepancy could explain the lack of effect observed for HOMA-B. Furthermore, HOMA-IR, rather than

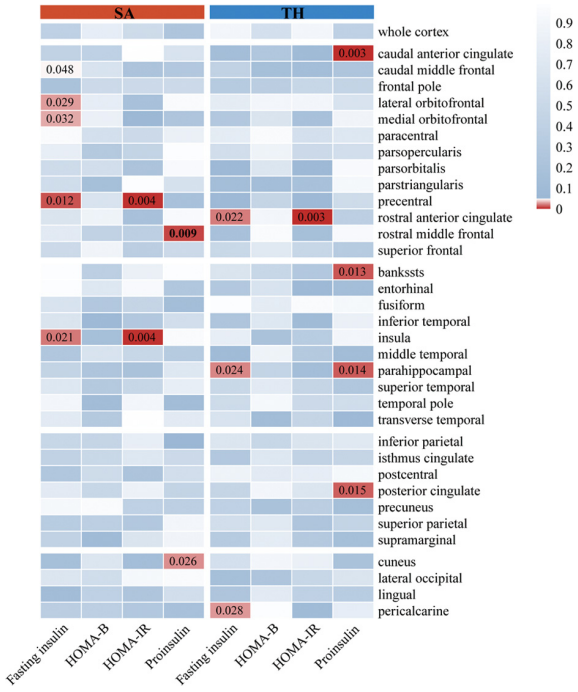

FIGURE 4
The results of MR analysis showed that insulin resistance potentially influenced the brain cortical structure of specific regions. The color of each block described the IVW-derived P-values of each MR analysis. P-values of <0.05 were shown in red, and P-values of >0.05 were shown in blue. MR, Mendelian randomization; IVW, inverse variance weighted; SA, surficial area; TH, thickness; HOMA-B, homeostasis model assessment beta-cell function; HOMA-IR, homeostasis model assessment insulin resistance.

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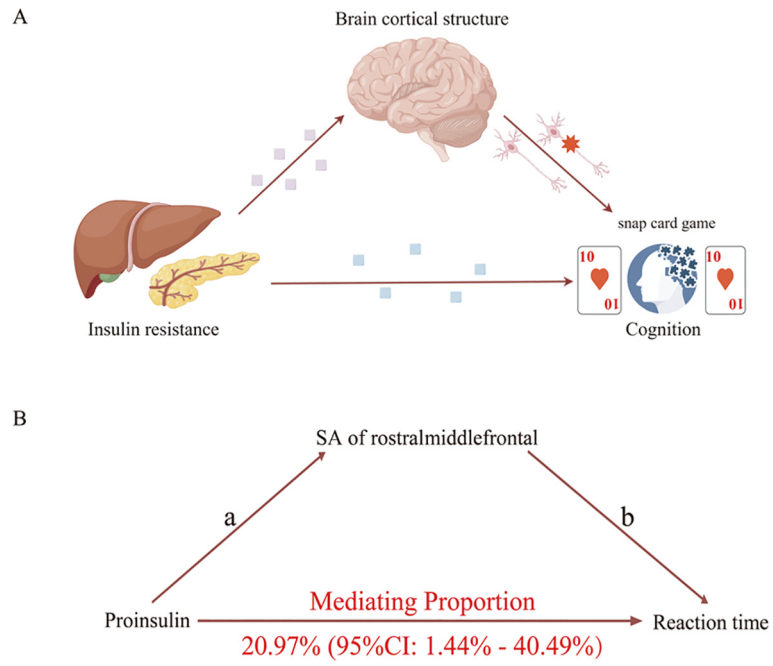

FIGURE 5
Schematic diagram of the mediation model. **(A)** Schematic diagram of the brain cortical structure's effect on the pathway from insulin resistance to cognition. **(B)** Schematic diagram of the rostral middle frontal surficial area's effect on the pathway from proinsulin to reaction time.

HOMA-B, revealed a significant elevation in AD and a strong correlation with T-tau and P-tau in Cerebrospinal fluid (31). Collectively, these studies suggest that HOMA-IR is a more valuable indicator than HOMA-B. Considering the substantial overlap in IVs between fasting insulin and HOMA-IR, it is plausible that both are causally correlated with visual memory.

The adverse effect of higher insulin resistance on cognition aligned with several cross-sectional (32) and longitudinal studies (33). Contrary to the results mentioned above, one previous study conducted by Thankappan S et al. reported a null relationship between insulin resistance and AD with a relatively lower sample size (10). Surprisingly, Hooshmand B (11) followed 269 adults without dementia for 7 years, discovering the linkage between HOMA-IR and cognition in longitudinal analysis instead of at baseline. These discrepancies may reflect limitations inherent in observational research, such as confounding factors, reverse causality, and selection bias. Evidence from MR studies also showed a potential causal link between insulin resistance (34) and related traits (obesity) (35) with cognition. However, controversial MR analyses simultaneously existed, indicating no causality between HOMA-IR and cognition after controlling socioeconomic position and educational attainment (36). Additionally, prior MR analyses, using two large-scale population samples to explore causal associations (37), revealed genetic evidence of an association of HOMA-IR with verbal intelligence in the Generation Scotland: Scottish Family Health sample, whereas this correlation was not validated in the UK Biobank sample. Consequently, the inconsistent results across MR studies may attributed mainly to heterogeneity in the selection of participants, cohorts, sample size, and different phenotypes of insulin resistance and cognition. Further replication through randomized controlled trials is warranted.

Our study uncovered the latent causal influence of insulin resistance on brain cortical SA and TH. Post-mortem human brain studies have established the presence of insulin receptors in the brain, especially in the cortical regions (14). Consistent with our findings, the Rhineland Study, encompassing 973 participants, reported a similar inverse association between insulin resistance and the structure of the precentral cortex, temporal cortex, and cuneus (12). Our findings suggested that the specific brain cortical regions susceptible to insulin resistance are mainly distributed in the frontal, temporal, and limbic lobes. The underlying mechanisms for insulin resistance affecting brain cortical structure may be as follows. First, studies have shown that the increased cerebrospinal fluid Aβ42 (38), t-tau, and p-tau levels (31) were related to insulin resistance, which are pathological hallmarks of cognitive impairment disorder. Second, brain cortical glucose metabolism might be impacted by insulin resistance, which reflects the activity of neuronal and synaptic (16). Finally, insulin resistance may induce atherosclerosis, vascular endothelial dysfunction, oxidative stress, and chronic inflammation (39), contributing to cortical thinning and subsequent clinical events, including cognitive impairment. However, specific mechanisms remain unclear, necessitating further research in the future. Notably, the protective effects of genetically determined insulin resistance on the structure of orbitofrontal, insula, and bankssts are varied from logical expectation. Increased cortical SA or TH was generally considered a protective indicator against cognitive impairment. One plausible explanation is that compensatory hypertrophy or neural adaptation mitigates the adverse influence of higher insulin resistance on brain functional

regions. Altogether, our study emphasizes the intricate and heterogeneous essence of insulin pathways within the brain.

Our research provided suggestive evidence that the SA of the rostral middle frontal mediates the effect of proinsulin on reaction time. It has been indicated that the structure of the rostral middle frontal was vulnerable in patients with T2DM, and the altered structure of this brain region held high diagnostic value for T2DM patients with mild cognitive impairment (40). The rostral middle frontal is a crucial component of the dorsolateral prefrontal cortex, playing a vital role in executive function. Additionally, the rostral middle frontal, along with the parietal lobe, constitutes a segment the dorsal attentional network (41). We employed the symbol matching test to evaluate reaction time, serving as an indicator of attention and executive function. However, another MR estimation did not support the causality among glycemia, brain structure and cognition (42). This study utilized T2DM and glycosylated hemoglobin as exposure, with hippocampal and white matter hyperintensity volumes as brain structural outcomes, which is largely different from ours. Consequently, we deduce that insulin resistance, rather than T2DM, exerts a direct influence on the brain structure. The SA of the rostral middle frontal may represent a latent pathophysiological process in the correlation between insulin resistance and cognition.

In the current survey, we primarily target the possible mediating role of phenotypes related to brain cortical structure, with approximately 80% of the mediation influence on cognition yet to be elucidated. The multi-model neuroimaging methods offer opportunities to unravel insulin resistance-related cognitive impairment (43). Unexplored mediating pathways may involve the macrostructures and microstructures, metabolism, perfusion, neural function, and brain network. Given that previous studies have established the causal effect of obesity (44) and blood lipids (45) on brain cortical structure, it is possible that these are essential candidate mediators as well. Future research is warranted to identify additional mediation factors along the pathway from insulin resistance to cognition.

This MR analysis exhibits multiple strengths. Firstly, the advantages of the MR statistic framework enable causality inference comparable to randomized controlled trials. Secondly, we incorporated comprehensive phenotypes related to insulin resistance, enhancing the integrity and rigor of the estimation. Thirdly, UK Biobank samples were excluded from the MR analysis of brain cortical structure. Thus, there was no sample overlap with the GWAS data used in our research, significantly reducing potential bias (46). Fourthly, sensitivity analyses and Bonferroni corrections were conducted sequentially to check the credibility of the discovered causality. Lastly, we implemented rigorous screening steps for mediators to guarantee the reliability and rationality of the mediation model. Nevertheless, certain limitations need to be considered. Firstly, the temporary measurement of insulin resistance is disposed to change over time without lifelong representation. Secondly, despite the absence of heterogeneity and pleiotropy in our findings, we cannot eliminate all potential biases and confounders. Thirdly, our research was restricted to individuals of European and American ancestry, minimizing population admixture confounding while limiting generalizability to other ethnic groups. Finally, the driven causality of insulin resistance on brain cortical structure did not withstand the Bonferroni correction, which just indicated suggestive causality. Caution explanations with additional validation in distinct cohorts are warranted.

Our research provided conceivable genetic evidence that elevated level of insulin resistance increased the susceptibility to cognitive impairment, with a partial mediation effect observed through the SA of the rostral middle frontal. Broader efforts are necessary to probe additional mediators. Our findings promote a better recognizing of the biological mechanisms underlying cognitive impairment induced by insulin resistance. Interventions to improve insulin sensitivity may serve as precautions against brain cortical atrophy and subsequent cognitive impairment. Nevertheless, further confirmation through randomized controlled trials is necessary.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the institutional review boards granted ethical permission for each cohort involved in the GWAS analysis (meta-analyses of glucose and insulin-related traits consortium (MAGIC), enhancing neuro imaging genetics through meta-analysis (ENIGMA), and UK Biobank). We then extracted the summary-level data for conducting secondary MR analysis. Therefore, we did not acquire additional ethical approval. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CH: Data curation, Formal Analysis, Funding acquisition, Investigation, Visualization, Writing – original draft, Writing – review & editing. YZ: Data curation, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. ML: Data curation, Investigation, Visualization, Writing – original draft. QG: Investigation, Visualization, Writing – original draft. SY: Investigation, Writing – original draft. ZL: Investigation, Writing – original draft. MR: Investigation, Writing – original draft. XZ: Conceptualization, Funding acquisition, Writing – review & editing. XQZ: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. ZS: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2024.1443301/full#supplementary-material

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Association between SPISE and NAFLD in patients with type 2 diabetes

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Aims: Non-alcoholic fatty liver disease (NAFLD) is closely related to type 2 diabetes (T2D), with reduced insulin sensitivity being a key factor in their disrupted metabolic processes. The single point insulin sensitivity estimator (SPISE) is a novel index. This study aims to explore the association between SPISE and NAFLD in T2D population.

Methods: This study included a total of 2,459 patients with T2D. SPISE was calculated based on high density lipoprotein-cholesterol (HDL-c), triglycerides (TG), and body mass index (BMI). Participants were categorized into NAFLD and non-NAFLD groups based on the results of ultrasonographic diagnosis. The relationship between SPISE and NAFLD was analyzed separately for each gender.

Results: The overall prevalence of NAFLD is 38.5%. In females and males, the SPISE was significantly reduced in the NAFLD group compared to the non-NAFLD group (both $P < 0.05$). The prevalence of NAFLD showed a significant reduction across quartiles of the SPISE in both genders (both $P < 0.05$).

Additionally, univariate correlation analysis showed a negative correlation between SPISE and NAFLD (both $P < 0.05$). In multivariate regression analysis, a reduced SPISE was identified as an independent risk factor for NAFLD (odds ratios of 0.572 and 0.737, 95% CI of 0.477–0.687 and 0.587–0.926, respectively).

Moreover, the area under the receiver operating characteristic (ROC) curve for SPISE was 0.209 in females and 0.268 in males (95% CI of 0.175–0.244 and 0.216–0.320, respectively). These results are more meaningful than those of other variables.

Conclusion: SPISE is significantly reduced in NAFLD patients with T2D. Compared to other indicators, SPISE demonstrates superior predictive value in diagnosing NAFLD, and it is independent of gender.

KEYWORDS

type 2 diabetes, SPISE, NAFLD, insulin sensitivity, insulin resistance

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is a widespread health issue, with a worldwide prevalence of 25% (1). It has become the primary cause of chronic liver disease under the influence of type 2 diabetes (T2D) and obesity (2). Reports indicate that NAFLD has become the fastest-growing cause of liver-related deaths globally (3). Moreover, it is closely associated with the progression of chronic kidney disease (CKD) and cardiovascular disease (CVD) (4, 5). Many metabolic disorders not only affect the incidence of NAFLD but also increase the risk of its progression to non-alcoholic steatohepatitis (NASH), cirrhosis, hepatocellular carcinoma, and even death (6). And the link between T2D and NAFLD is thoroughly documented (7). Research indicates that T2D is associated with more than double the risk of advanced hepatopathy (8). Furthermore, a meta-analysis reported that the prevalence of NASH with T2D patients was approximately 37.3%, significantly higher than the prevalence of progressive NAFLD in the general population (9). Therefore, in clinical practice, it would be valuable to have a simple and inexpensive index that could screen for NAFLD among T2D patients.

Numerous studies indicate that reduced insulin sensitivity (Si) or insulin resistance (IR) is one of the key pathophysiological factors in NAFLD (10–12). The gold standard for measuring insulin sensitivity is the hyperinsulinemic-euglycemic clamp (13); however, due to its cost, time consumption, and invasiveness, it is not widely used in clinical practice. The single point insulin sensitivity estimator (SPISE) is an alternative index of IR calculated from high density lipoprotein-cholesterol (HDL-c), triglycerides (TG), and body mass index (BMI) (14). Research indicates a strong correlation between SPISE and the hyperinsulinemic-euglycemic clamp (15). Additionally, the SPISE index is closely related to metabolic syndrome (MetS), cardiovascular metabolic risk in adolescents, and the cardiovascular prognosis of patients with T2D (16–18). It is also worth mentioning that SPISE is not only considered an effective indicator for predicting diabetes development in obese children (19), but SPISE-5.4 has also been proven to be a good predictor of diabetes development (20). Recent studies have reported a significant reduction in the SPISE among adolescents with obesity-related NAFLD (21). Additionally, research from Japan indicates that a reduction in SPISE is associated with an increased risk of NAFLD (22). Research also suggested an association between SPISE and pediatric NAFLD; however, after adjusting for confounding factors, this association is no longer significant (23). Currently, there is scarce research on the relationship between SPISE and NAFLD among T2D patients. This study aims to clarify the link between SPISE and NAFLD in T2D patients and assess SPISE's predictive potential for NAFLD in this population.

2 Materials and methods

2.1 Study participants

During the period from February 2020 to March 2023, we collected clinical data from patients with T2D who were treated at the Department of Endocrinology of the Linyi People's Hospital, Shandong Province, China. Exclusion criteria included: (1) patients under the age of 18; (2) patients with liver or kidney dysfunction; (3) evidence of autoimmune hepatitis, viral hepatitis, drug-induced fatty liver, or other chronic liver diseases; (4) habitual drinkers who consume alcohol more than 5 days per week, equivalent to an average daily intake of 38 grams for males and 26 grams for females (24); (5) patients with incomplete clinical data. Ultimately, 2,459 eligible patients were included in the study.

2.2 Anthropometric and Biochemical measurements

Participant demographic information and clinical baseline data were collected, such as age, gender, duration of diabetes, and smoking and drinking habits. Height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured and recorded. Morning fasting venous blood samples were collected to determine levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), serum creatinine (Scr), uric acid (UA), fasting plasma glucose (FBG); glycated hemoglobin (HbA1c, high performance liquid chromatography) and hemoglobin (Hb), were measured using a biochemical analyzer (Cobas c 702, Roche, Germany). Urinary albumin to creatinine ratio (UACR) was tested by an autoanalyzer (Beckman Coulter AU5821). Fasting insulin (FINS, direct chemiluminescence method) was measured by the fully automated sample processing system (Aptio Automation, SIEMENS, USA).

Bioelectrical impedance analysis (Omron DUALSCAN HDS-2000, Kyoto, Japan) was employed to assess visceral fat area (VFA) and subcutaneous fat area (SFA).

2.3 Definition of NAFLD

Fatty liver diagnosis begins with ultrasound imaging and is supplemented by clinical evaluation, including medical history and physical examination, with specific attention to alcohol intake. Additional factors such as viral hepatitis and medication use are assessed. Laboratory tests, particularly liver function tests, help rule out other fatty liver conditions, culminating in a definitive diagnosis of NAFLD.

Parameter calculations

1. Body mass index (BMI) = weight (kg) / height $(m)^2$;
2. TG/HDL-c = TG (mmol/l) / HDL-c (mmol/l);
3. SPISE index = $(600 \times \text{HDL-c } [\text{mg/dL}]^{0.185})$ / $(\text{TG } [\text{mg/dL}]^{0.2} \times \text{BMI } [\text{kg/m}^2]^{1.338})$ (14);
4. HOMA-IR = FPG (mmol/L) × FINS (IU/mL)/22.5 (25).

2.4 Statistical analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL, USA). Normally distributed variables were

TABLE 1 Clinical and biochemical characteristics stratified by gender.

Variables	All	Female	Male	*P*
Number	2459	1441	1018	
Age (years)	57.10 ± 13.4	58.3 ± 13.3	55.4 ± 13.3	<0.001
diabetes duration (years)	7.0 (2.0 ~ 13.0)	7.0 (2.0 ~ 13.0)	8.0 (2.0 ~ 13.0)	0.548
Smoking (*n*, %)	385 (15.7%)	9 (0.6%)	376 (37.0%)	<0.001
BMI (kg/m^2)	25.40 ± 3.89	25.21 ± 3.99	25.68 ± 3.71	0.003
VFA (cm^2)	89.00 (64.00 ~ 119.00)	79.00 (58.00 ~ 104.00)	106.00 (80.00 ~ 133.00)	<0.001
SFA (cm^2)	180.00 (138 ~ 229.00)	176.50 (131.25 ~ 228.00)	186.00 (148.00 ~ 230.00)	0.001
SBP (mmHg)	129.7 ± 19.2	130.3 ± 19.8	128.8 ± 18.2	0.043
DBP (mmHg)	80.3 ± 11.9	79.0 ± 11.8	82.2 ± 11.8	<0.001
TC (mmol/L)	4.85 ± 1.33	4.99 ± 1.30	4.65 ± 1.33	<0.001
LDL-c (mmol/L)	3.08 ± 1.50	3.18 ± 1.72	2.94 ± 1.12	<0.001
TG (mmol/L)	1.41 (0.99 ~ 2.09)	1.41 (0.99 ~ 2.03)	1.41 (0.99 ~ 2.20)	0.212
HDL-c (mmol/L)	1.18 ± 0.35	1.25 ± 0.37	1.08 ± 0.30	<0.001
TG / HDL-c ratio	1.25 (0.78 ~ 2.05)	1.17 (0.74 ~ 1.90)	1.39 (0.83 ~ 2.34)	<0.001
HbA1c (%)	9.43 ± 2.28	9.40 ± 2.25	9.48 ± 2.32	0.383
FPG (mmol/L)	9.24 ± 4.03	9.24 ± 4.12	9.24 ± 3.91	0.969
ALT (U/L)	17.40 (12.80 ~ 26.40)	16.15 (11.90 ~ 24.50)	19.40 (14.10 ~ 31.10)	<0.001
AST (U/L)	17.30 (14.00 ~ 22.70)	16.90 (13.60 ~ 22.30)	18.00 (14.60 ~ 23.40)	<0.001
GGT (U/L)	21.00 (15.00 ~ 32.00)	19.00 (14.00 ~ 27.00)	26.00 (18.00 ~ 41.00)	<0.001
UA (μmolL)	290.87 ± 101.22	269.75 ± 97.45	320.92 ± 98.91	<0.001
Scr (μmol/L)	66.80 ± 28.45	60.15 ± 27.89	76.32 ± 26.49	<0.001
UACR (mg/g)	12.10 (6.20 ~ 47.50)	12.20 (6.60 ~ 42.80)	11.70 (5.60 ~ 54.00)	0.167
Hb (g/L)	138.82 ± 18.96	131.85 ± 16.17	148.66 ± 18.24	<0.001
FINS (μIU/mL)	16.70 (10.40 ~ 22.94)	17.17 (10.71 ~ 23.44)	15.77 (10.21 ~ 21.55)	0.054
SPISE	6.10 (5.04 ~ 7.39)	6.25 (5.22 ~ 7.57)	5.87 (4.81 ~ 7.08)	<0.001
HOMA-IR	6.40 (3.46 ~ 9.78)	6.40 (3.52 ~ 9.71)	6.37 (3.40 ~ 10.19)	0.905
NAFLD (*n*, %)	946 (38.5%)	520 (36.1%)	426 (41.8%)	0.004

BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ - glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; UACR, urinary albumin to creatinine ratio; Hb, hemoglobin; FINS, fasting insulin; SPISE, the single point insulin sensitivity estimator; HOMA-IR, homeostatic model assessment for insulin resistance; NAFLD, non-alcoholic fatty liver disease. Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. Independent-Samples T test and Mann-Whitney U test were used for comparisons of normally and abnormally distributed continuous variables between male and female groups, respectively. Categorical variables were presented as percentage (%), and were compared by chi-square test. Statistical differences were defined by *P* (two-tailed) less than 0.05.

described using mean ± SD and analyzed with independent samples T-tests. Non-normally distributed variables were described using medians (interquartile ranges) and analyzed with Mann-Whitney U tests. Analysis of variance (ANOVA) and Student–Newman–Keuls tests were performed for multiple and pairwise comparisons of normally distributed data, and Kruskal-Wallis 1-way ANOVA test for abnormal distributions. Categorical variables were presented as percentage (%) and assessed using chi-square tests. Independent factors influencing NAFLD were identified using Spearman's correlation and logistic regression analyses. Significance was set at $P < 0.05$ (two-tailed). The SPISE index's ability to predict NAFLD was evaluated via the receiver operating characteristic (ROC) curve analysis.

3 Results

3.1 Clinical and biochemical characteristics

As shown in Table 1, this study included 2459 patients with T2D, with a mean age of 57.10 ± 13.4 years. The overall incidence of NAFLD was 38.5%, with rates of 36.1% in females and 41.8% in males. Compared to males, females had higher levels of age, SBP, TC, LDL-c, HDL-c and SPISE, but lower proportion of smokers, BMI, VFA, SFA, DBP, TG/HDL-c ratio, ALT, AST, GGT, UA, Scr, and Hb (all $P < 0.05$). There were no significant differences in diabetes duration, TG, HbA1c, FPG, UACR, HOMA-IR and FINS between the two groups (all $P > 0.05$).

TABLE 2 Comparison of clinical and biochemical characteristics between non-NAFLD and NAFLD groups.

Variables	Female			Male		
	Non-NAFLD group	NAFLD group	*P*	Non-NAFLD group	NAFLD group	*P*
Number	921	520		592	426	
Age (years)	59.38 ± 12.91	56.38 ± 13.83	<0.001	58.33 ± 12.90	51.37 ± 12.89	<0.001
Diabetes duration (years)	8.0 (3.0 ~ 15.0)	5.0 (1.0 ~ 10.0)	<0.001	10.0 (4.0 ~ 15.0)	5.0 (2.0 ~ 10.0)	<0.001
Smoking (%)	5 (0.5%)	8 (0.8%)	0.730	203 (34.3%)	173 (40.6%)	0.048
BMI (kg/m^2)	24.07 ± 3.64	27.23 ± 3.80	<0.001	24.45 ± 3.42	27.37 ± 3.43	<0.001
VFA (cm^2)	67.00 (48.00 ~ 90.00)	97.00 (77.00 ~ 120.50)	<0.001	92.00 (64.75 ~ 121.00)	124.00 (101.00 ~ 151.00)	<0.001
SFA (cm^2)	155.00(116.00 ~ 200.00)	214.00 (171.00 ~ 261.00)	<0.001	168.00 (129.00 ~ 202.00)	211.00 (175.00 ~ 255.50)	<0.001
SBP (mmHg)	128.84 ± 20.30	132.97 ± 18.59	<0.001	127.79 ± 19.45	130.10 ± 16.26	0.040
DBP (mmHg)	77.32 ± 11.65	82.02 ± 11.52	<0.001	80.06 ± 11.66	85.11 ± 11.35	<0.001
TC (mmol/L)	4.87 ± 1.32	5.20 ± 1.26	<0.001	4.48 ± 1.26	4.89 ± 1.39	<0.001
LDL-c (mmol/L)	3.06 ± 1.35	3.39 ± 2.21	<0.001	2.89 ± 1.14	3.05 ± 1.08	0.006
TG (mmol/L)	1.25 (0.88 ~ 1.74)	1.72 (1.28 ~ 2.55)	<0.001	1.21 (0.85 ~ 1.79)	1.79 (1.26 ~ 2.80)	<0.001
HDL-c (mmol/L)	1.29 ± 0.38	1.17 ± 0.33	<0.001	1.12 ± 0.28	1.03 ± 0.31	<0.001
TG / HDL-c ratio	1.01 (0.64 ~ 1.59)	1.55 (1.04 ~ 2.37)	<0.001	1.11 (0.70 ~ 1.80)	1.83 (1.20 ~ 3.07)	<0.001
HbA1c (%)	9.33 ± 2.36	9.52 ± 2.03	0.118	9.52 ± 2.48	9.42 ± 2.08	0.531
FPG (mmol/L)	8.91 ± 4.22	9.83 ± 3.87	<0.001	9.02 ± 4.28	9.56 ± 3.30	0.026
ALT (U/L)	14.60 (10.90 ~ 22.00)	19.15 (14.20 ~ 29.75)	<0.001	17.40 (13.20 ~ 25.10)	23.70 (16.20 ~ 38.30)	<0.001
AST (U/L)	16.40 (13.18 ~ 21.33)	17.70 (14.23 ~ 24.68)	<0.001	17.30 (14.00 ~ 21.43)	19.00 (15.20 ~ 26.45)	<0.001
GGT (U/L)	16.95 (12.00 ~ 23.00)	24.00 (17.00 ~ 33.00)	<0.001	21.00 (16.00 ~ 31.00)	33.00 (24.00 ~ 53.00)	<0.001
UA (μmolL)	257.23 ± 94.17	291.77 ± 99.30	<0.001	310.61 ± 102.19	335.26 ± 92.40	<0.001
Scr (μmol/L)	62.20 ± 32.20	56.54 ± 17.39	<0.001	78.64 ± 30.54	73.12 ± 19.18	<0.001
UACR (mg/g)	12.85 (6.70 ~ 58.13)	11.40 (6.40 ~ 30.20)	0.010	13.90 (5.80 ~ 83.40)	9.30 (5.10 ~ 36.60)	0.002
Hb (g/L)	129.29 ± 16.77	136.36 ± 13.98	<0.001	144.36 ± 20.26	154.71 ± 12.72	<0.001
FINS (μIU/mL)	16.57 (8.44 ~ 23.18)	18.41 (13.27 ~ 24.47)	0.002	15.00 (9.14 ~ 22.33)	16.44 (11.29 ~ 21.27)	0.263
SPISE	6.87 (5.79 ~ 8.20)	5.35 (4.57 ~ 6.21)	<0.001	6.48 (5.50 ~ 7.91)	5.12 (4.33 ~ 5.95)	<0.001
HOMA-IR	5.71 (2.91 ~ 9.12)	7.57 (4.81 ~ 10.53)	<0.001	5.53 (2.90 ~ 10.21)	6.92 (3.94 ~ 10.13)	0.009

BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ - glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; UACR, urinary albumin to creatinine ratio; Hb, hemoglobin; FINS, fasting insulin; SPISE, the single point insulin sensitivity estimator; HOMA-IR, homeostatic model assessment for insulin resistance; NAFLD, non-alcoholic fatty liver disease; Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. Independent-Samples T test and Mann-Whitney U test were used for comparisons of normally and abnormally distributed continuous variables between non-NAFLD and NAFLD groups, respectively. Categorical variables were presented as percentage (%), and were compared by chi-square test. Statistical differences were defined by *P* (two-tailed) less than 0.05.

As shown in Table 2, for each gender, subjects were divided into two groups, including non-NAFLD and NAFLD groups, and the levels of each variable were compared. For females, compared to the non-NAFLD group, the NAFLD group showed significantly increased BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c ratio, FPG, ALT, AST, GGT, UA, Hb, FINS and HOMA-IR (all $P < 0.05$), while age, diabetes duration, HDL-c, Scr, UACR and SPISE were significantly decreased (all $P < 0.05$). For males, the proportion of smokers and the levels of BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c ratio, FBG, ALT, AST, GGT, UA, Hb and HOMA-IR were higher in the NAFLD group compared to the non-NAFLD group (all $P < 0.05$), while age, diabetes duration, HDL-c, Scr, UACR and SPISE were lower (all $P < 0.05$).

As shown in Table 3, male and female patients were separately divided into four groups according to the quartiles of the SPISE: Q1 group (female: 2.58–5.22; male: 2.25–4.81), Q2 group (female: 5.22–6.25; male: 4.81–5.87), Q3 group (female: 6.25–7.57; male: 5.87–7.08), and Q4 group (female: 7.57–14.52; male: 7.08–15.05). For the females, as the quartiles of SPISE increased, the duration of diabetes, HDL-c showed a gradual increased, while the age, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c, FPG, ALT, AST, GGT, UA, Hb, FINS, HOMA-IR and the incidence of NAFLD exhibited a gradual decreased (all $P < 0.05$). There was

TABLE 3 Comparison of variables according to the categories of the SPISE.

Variables	Female					Male				
	Q1	Q2	Q3	Q4	P	Q1	Q2	Q3	Q4	P
Age (years)	56.32 ± 15.30	59.80 ± 12.30[a]	59.37 ± 11.92[a]	57.72 ± 13.25[b]	0.001	48.30 ± 13.22	55.44 ± 12.82[a]	59.14 ± 11.24[ab]	58.81 ± 13.14[ab]	<0.001
Diabetes duration (years)	6.0 (2.0∼10.0)	8.0(3.0∼13.0)[a]	8.0(3.0∼15.0)[a]	8.0(2.0∼13.0)	0.020	5.0(2.0∼10.0)	8.0(3.0∼13.0)[a]	10.0(3.0∼15.0)[a]	8.0(3.0∼15.0)[ab]	<0.001
Smoking (n, %)	1(0.3%)	4(1.1%)	0(0%)	4(1.1%)	0.123	110(43.5%)	100(38.9%)	91(35.8%)	75(29.6%)	0.012
BMI (kg/m^2)	29.81 ± 3.63	25.94 ± 1.85[a]	23.95 ± 1.79[ab]	21.09 ± 1.90[abc]	<0.001	29.66 ± 3.19	26.65 ± 1.71[a]	24.74 ± 1.69[ab]	21.62 ± 2.28[abc]	<0.001
VFA (cm^2)	114.50 (91.00∼138.00)	88.00[a] (74.00∼104.00)	71.00[ab] (59.00∼90.00)	46.50[abc] (30.00∼64.00)	<0.001	140.00 (118.75∼166.25)	119.00[a] (97.00∼139.00)	97.50[ab] (79.00∼117.25)	63.50[abc] (38.00∼83.00)	<0.001
SFA (cm^2)	246.50 (206.75∼294.25)	195.00[a] (160.50∼228.50)	162.00[ab] (134.00∼188.00)	113.50[abc] (80.00∼144.00)	<0.001	242.00 (206.00∼287.75)	196.00[a] (170.00∼232.00)	179.00[ab] (148.00∼200.00)	124.50[abc] (99.75∼162.00)	<0.001
SBP (mmHg)	133.96 ± 19.42	132.17 ± 18.62	129.97 ± 19.70[a]	125.22 ± 20.38[abc]	<0.001	133.31 ± 18.03	128.48 ± 17.30[a]	129.05 ± 18.49[a]	124.18 ± 17.95[abc]	<0.001
DBP (mmHg)	82.36 ± 12.00	79.82 ± 11.27[a]	78.18 ± 11.89[a]	75.68 ± 11.10[abc]	<0.001	86.85 ± 12.01	81.80 ± 10.51[a]	81.90 ± 11.72 [a]	78.15 ± 11.30 [abc]	<0.001
TC (mmol/L)	5.20 ± 1.36	4.98 ± 1.28 [a]	4.85 ± 1.30 [a]	4.91 ± 1.25 [a]	0.002	5.02 ± 1.53	4.69 ± 1.29 [a]	4.47 ± 1.16 [ab]	4.42 ± 1.25 [ab]	<0.001
LDL-c (mmol/L)	3.26 ± 1.67	3.35 ± 2.58	3.05 ± 1.05 [b]	3.04 ± 1.10 [b]	0.035	2.93 ± 1.10	3.11 ± 1.32 [a]	2.95 ± 0.99 [b]	2.77 ± 1.02 [b]	0.009
TG (mmol/L)	2.23 (1.58∼3.14)	1.62 [a] (1.25∼2.09)	1.26 [ab] (0.98∼1.60)	0.87 [abc] (0.68∼1.14)	<0.001	2.90 (2.02∼4.56)	1.65 [a] (1.28∼2.14)	1.22 [ab] (0.99∼1.54)	0.83 [abc] (0.66∼1.07)	<0.001
HDL-c (mmol/L)	1.05 ± 0.25	1.16 ± 0.25 [a]	1.30 ± 0.36 [ab]	1.49 ± 0.43 [abc]	<0.001	0.89 ± 0.23	1.01 ± 0.18 [a]	1.11 ± 0.22 [ab]	1.32 ± 0.35 [abc]	<0.001
TG / HDL-c ratio	2.19 (1.46∼3.22)	1.42 [a] (1.06∼1.92)	1.01 [ab] (0.74∼1.42)	0.62 [abc] (0.43∼0.87)	<0.001	3.24 (2.18∼5.59)	1.68 [a] (1.25∼2.23)	1.15 [ab] (0.85∼1.48)	0.66 [abc] (0.50∼0.90)	<0.001
HbA1c, n (%)	9.43 ± 1.98	9.24 ± 2.06 [a]	9.42 ± 2.46 [a]	9.48 ± 2.45 [bc]	0.532	9.70 ± 2.24	9.20 ± 2.10	9.16 ± 2.13	9.86 ± 2.71	0.001
FPG (mmol/L)	10.00 ± 3.78	9.11 ± 4.09 [a]	9.00 ± 4.24 [a]	8.83 ± 4.27 [a]	0.001	10.12 ± 3.36	9.31 ± 3.59	8.61 ± 3.46 [ab]	8.94 ± 4.88 [a]	<0.001
ALT (U/L)	19.10 (13.33∼30.90)	15.80 [a] (12.15∼24.35)	15.20 [a] (11.20∼21.93)	15.20 [a] (11.00∼23.00)	<0.001	24.10 (16.70∼40.05)	20.00 [a] (14.90∼31.00)	18.35 [a] (13.70∼26.55)	17.00 [a] (12.60∼24.50)	<0.001
AST (U/L)	17.40 (14.30∼25.65)	16.60 [a] (13.53∼21.20)	16.20 [a] (13.10∼21.10)	17.10 [a] (13.70∼22.33)	0.003	19.30 (15.50∼28.70)	17.50 [a] (14.10∼22.95)	17.40 [a] (14.13∼21.78)	17.80 [a] (14.10∼22.58)	<0.001
GGT (U/L)	25.00 (17.00∼36.05)	19.00 [a] (14.00∼27.00)	17.80 [a] (13.00∼24.00)	15.00 [abc] (12.00∼21.00)	<0.001	35.80 (26.00∼56.75)	27.00 [a] (20.55∼41.00)	24.00 [a] (18.00∼35.00)	19.00 [abc] (14.00∼28.00)	<0.001
UA (μmol/L)	309.19 ± 99.23	270.56 ± 92.10 [a]	252.96 ± 86.42 [ab]	245.67 ± 99.05 [ab]	<0.001	364.28 ± 100.97	325.67 ± 90.46 [a]	304.37 ± 87.60 [ab]	289.40 ± 100.36 [ab]	<0.001
Scr (μmol/L)	60.23 ± 21.89	60.26 ± 31.84	61.38 ± 32.56	58.75 ± 23.83	0.659	76.27 ± 27.85	76.84 ± 28.34	77.83 ± 26.61	74.29 ± 22.79	0.500

(Continued)

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no statistically significant difference in the proportion of smokers, HbA1c, Scr and UACR among the four groups (all $P > 0.05$). For the males, as the quartiles of SPISE increased, the age, duration of diabetes, HDL-c showed a gradual increased, while the proportion of smokers, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c, HbA1c, FPG, ALT, AST, GGT, UA, UACR, Hb, HOMA-IR and the incidence of NAFLD exhibited a gradual decreased (all $P < 0.05$). There was no statistically significant difference in Scr and FINS among the four groups (all $P > 0.05$).

3.2 Univariate analysis

As shown in Table 4, the relationship between NAFLD and each variable was analyzed using Spearman's correlation analysis. In females, the results indicated that NAFLD was positively correlated with BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c, HbA1c, FBG, ALT, AST, GGT, UA, Hb, FINS and HOMA-IR (all $P < 0.05$), and negatively correlated with age, duration of diabetes, HDL-c, Scr, UACR, and SPISE (all $P < 0.05$). In males, the proportion of smokers, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c, FBG, ALT, AST, GGT, UA, Hb and HOMA-IR were positively correlated with NAFLD, while age, duration of diabetes, HDL-c, UACR and SPISE were negatively correlated (all $P < 0.05$). In females, there was no significant relationship between NAFLD and the proportion of smokers (all $P > 0.05$), and in males, there was no apparent relationship between NAFLD and HbA1c, Scr and FINS (all $P > 0.05$).

3.3 Logistic regression analysis

Using NAFLD as the dependent variable, based on the results of Spearman's correlation analysis, the independent variables included age, diabetes duration, HDL-c, Scr, UACR, SPISE, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c, HbA1c, FBG, ALT, AST, GGT, UA, Hb, FINS and HOMA-IR for females, and the proportion of smokers, age, diabetes duration, HDL-c, UACR, SPISE, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, TG/HDL-c, FBG, ALT, AST, GGT, UA, Hb and HOMA-IR for males. A binary logistic regression analysis was conducted to identify the independent correlates of NAFLD (Table 5). The results indicated that in females, SPISE (OR: 0.572, 95% CI 0.477–0.687), VFA (OR: 1.009, 95% CI 1.001–1.017), FPG (OR: 1.059, 95% CI 1.002–1.120), DBP (OR: 1.026, 95% CI 1.006–1.046), UA (OR: 1.005, 95% CI 1.002–1.008), TC (OR: 1.236, 95% CI 1.036–1.475), and Scr (OR: 0.973, 95% CI 0.958–0.988) were independently associated with NAFLD, while in males, SPISE (OR: 0.737, 95% CI 0.587–0.926), VFA (OR: 1.013, 95% CI 1.005–1.021), diabetes duration (OR: 0.940, 95% CI 0.903–0.978), Hb (OR: 1.030, 95% CI 1.013–1.047), and GGT (OR: 1.009, 95% CI 1.002–1.016) were independently related to NAFLD.

3.4 Areas under the ROC curve analysis

Finally, based on the variables that entered the model last, the formula used to calculate SPISE and the insulin resistance-related indicators, the predictive capabilities of SPISE, HDL-c, diabetes

TABLE 3 (Continued)

Variables	Female					Male				
	Q1	Q2	Q3	Q4	P	Q1	Q2	Q3	Q4	P
UACR (mg/g)	13.60 (6.90~42.90)	11.30 (6.20~33.45)	11.70 (6.88~42.33)	12.05 (6.45~53.65)	0.318	15.10 (6.40~94.70)	9.15 (4.93~33.23)	8.60 (4.65~44.35)	14.00 (6.20~73.10)	0.001
Hb (g/L)	134.96 ± 14.93	133.09 ± 15.95	130.54 ± 16.79 [ab]	128.85 ± 16.34[ab]	<0.001	153.85 ± 15.99	151.78 ± 16.87	148.85 ± 17.59 [a]	140.21 ± 19.40 [abc]	<0.001
FINS (μIU/mL)	19.34 (14.75~25.47)	17.23 (10.96~23.51)	16.84 [a] (9.90~23.18)	15.02 [a] (6.12~21.76)	<0.001	17.81 (12.02~22.09)	15.49 (10.64~19.98)	14.89 (9.10~20.64)	14.85 (9.33~21.61)	0.071
HOMA-IR	8.48 (5.30~11.94)	6.58 [a] (3.58~9.46)	5.76 [a] (3.50~9.39)	5.03 [ab] (2.02~8.22)	<0.001	7.70 (4.33~10.69)	6.96 [a] (3.62~10.22)	5.24 [a] (3.24~8.43)	5.14 [a] (2.75~8.61)	0.001
NAFLD, n (%)	241(66.2%)	156(43.6%)	88(24.4%)	35(9.7%)	<0.001	176(69.3%)	138(53.7%)	81(31.9%)	31(12.3%)	<0.001

BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ - glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; UACR, urinary albumin to creatinine ratio; Hb, hemoglobin; FINS, fasting insulin; SPISE, the single point insulin sensitivity estimator; HOMA-IR, homeostatic model assessment for insulin resistance; NAFLD, non-alcoholic fatty liver disease. Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. Analysis of variance (ANOVA) and Student–Newman–Keuls tests were performed for multiple and pairwise comparisons of normally distributed data, and Kruskal-Wallis 1-way ANOVA test for abnormal distributions. Categorical variables were presented as percentage (%) and were compared by chi-square test. Statistical differences were defined by P (two-tailed) less than 0.05. [a]$P < 0.05$ versus Q1; [b]$P < 0.05$ Q3 versus Q2; [c]$P < 0.05$ Q4 versus Q3.

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TABLE 4 The correlation between NAFLD and different variables by univariate analysis.

Variables	Female		Male	
	For NAFLD		For NAFLD	
	Correlation coefficient	*p*	Correlation coefficient	*p*
Age	−0.096	<0.001	−0.267	<0.001
Diabetes duration	−0.177	<0.001	−0.244	<0.001
Smoking	0.014	0.602	0.064	0.041
BMI	0.396	<0.001	0.405	<0.001
VFA	0.414	<0.001	0.414	<0.001
SFA	0.403	<0.001	0.395	<0.001
SBP	0.110	<0.001	0.085	0.007
DBP	0.205	<0.001	0.223	<0.001
TC	0.137	<0.001	0.155	<0.001
LDL-c	0.135	<0.001	0.110	<0.001
TG	0.323	<0.001	0.336	<0.001
HDL-c	−0.191	<0.001	−0.198	<0.001
TG / HDL-c ratio	0.314	<0.001	0.331	<0.001
HbA1c	0.070	0.010	−0.004	0.891
FPG	0.148	<0.001	0.131	<0.001
ALT	0.248	<0.001	0.270	<0.001
AST	0.123	<0.001	0.150	<0.001
GGT	0.329	<0.001	0.379	<0.001
UA	0.194	<0.001	0.154	<0.001
Scr	−0.058	0.028	−0.059	0.061
UACR	−0.069	0.010	−0.099	0.002
Hb	0.214	<0.001	0.269	<0.001
FINS	0.108	0.002	0.048	0.263
SPISE	−0.450	<0.001	−0.441	<0.001
HOMA-IR	0.176	<0.001	0.113	0.009

BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ - glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; UACR, urinary albumin to creatinine ratio; Hb, hemoglobin; FINS, fasting insulin; SPISE, the single point insulin sensitivity estimator; HOMA-IR, homeostatic model assessment for insulin resistance; NAFLD, non-alcoholic fatty liver disease; Correlation coefficients between NAFLD and different variables were determined by Spearman's correlation analysis.

duration, Scr, VFA, BMI, GGT, ALT, TG, TG/HDL-c ratio, HOMA-IR, Hb, UA, and TC for NAFLD were evaluated separately for different genders (Table 6). The results showed that in females, the area under the ROC curve for SPISE was 0.209 (95% CI 0.175–0.244, $P < 0.001$), and in males, it was 0.268 (95% CI 0.216–0.320, $P < 0.001$), both of which were superior to the other variables.

4 Discussion

This study found that SPISE was independently associated with NAFLD in T2D population, with no gender differences observed. Additionally, SPISE demonstrated a clear advantage in predicting NAFLD within this population.

NAFLD as the most prevalent liver disease, exhibits an increasing trend in incidence (26). Reports indicated a strong correlation between T2D and NAFLD: the incidence of NAFLD and NASH was particularly pronounced in individuals diagnosed with T2D (9); the existence of NAFLD raised the risk of T2D development by five times (27). In this study, the overall incidence of NAFLD was 38.5%, which is higher than the global incidence rate, further validating the aforementioned perspective (1). Therefore, the high prevalence of NAFLD in T2D population warrants attention. Currently, the routine method for diagnosing NAFLD in clinical practice is through ultrasound. However, due to its time-consuming and labor-intensive nature, it is not suitable for large-scale epidemiological studies. SPISE is an insulin sensitivity index based on lipids and BMI, our study found that it is closely related to traditional IR indicators, including HOMA-IR and the TG/HDL-c ratio. As the SPISE quartiles increased, both HOMA-IR and the TG/HDL-c ratio were gradually decreased. Additionally, some studies had found that the SPISE demonstrated higher

TABLE 5 The relative risk for NAFLD by logistic regression analysis.

Variables	B	SE	Wald	*P*	OR	95.0 % CI for OR
Female						
SPISE	−0.558	0.093	36.165	<0.001	0.572	0.477–0.687
VFA	0.009	0.004	5.252	0.022	1.009	1.001–1.017
FPG	0.057	0.028	4.087	0.043	1.059	1.002–1.120
DBP	0.025	0.01	6.672	0.01	1.026	1.006–1.046
UA	0.005	0.001	13.628	<0.001	1.005	1.002–1.008
TC	0.212	0.09	5.535	0.019	1.236	1.036–1.475
Scr	−0.027	0.008	11.79	0.001	0.973	0.958–0.988
Male						
SPISE	−0.305	0.116	6.856	0.009	0.737	0.587–0.926
VFA	0.013	0.004	9.581	0.002	1.013	1.005–1.021
Diabetes duration	−0.062	0.02	9.214	0.002	0.94	0.903–0.978
Hb	0.03	0.008	12.353	<0.001	1.03	1.013–1.047
GGT	0.009	0.004	5.743	0.017	1.009	1.002–1.016

NAFLD, non-alcoholic fatty liver disease; SPISE, the single point insulin sensitivity estimator; VFA, visceral fat area; FPG, fasting plasma glucose; DBP, diastolic blood pressure; UA, uric acid; TC, total cholesterol; Scr, serum creatinine; Hb, hemoglobin; GGT,γ- glutamyl transpeptidase; SE, standard error; CI, confidence interval; OR, odd ratio.

TABLE 6 Analysis of areas under the ROC curves for predicting NAFLD.

	Female			Male		
Variables	Area	SE	95.0 % CI	Area	SE	95.0 % CI
SPISE	0.209	0.017	0.175–0.244	0.268	0.027	0.216–0.320
HDL-c	0.364	0.022	0.570–0.654	0.390	0.030	0.331–0.449
Diabetes duration	0.421	0.023	0.376–0.466	0.369	0.029	0.312–0.427
Scr	0.458	0.023	0.412–0.503	0.432	0.030	0.373–0.492
VFA	0.756	0.018	0.720–0.792	0.723	0.027	0.671–0.775
BMI	0.762	0.018	0.726–0.799	0.713	0.027	0.659–0.766
GGT	0.724	0.020	0.686–0.763	0.744	0.026	0.693–0.795
ALT	0.612	0.022	0.569–0.655	0.656	0.029	0.599–0.713
TG	0.697	0.021	0.657–0.738	0.681	0.028	0.626–0.736
TG / HDL-c ratio	0.694	0.021	0.653–0.734	0.675	0.028	0.619–0.731
HOMA-IR	0.612	0.022	0.570–0.654	0.555	0.031	0.495–0.615
Hb	0.618	0.022	0.575–0.662	0.684	0.028	0.628–0.739
UA	0.629	0.022	0.587–0.672	0.570	0.030	0.511–0.630
TC	0.599	0.022	0.555–0.644	0.608	0.030	0.549–0.666

NAFLD, non-alcoholic fatty liver disease; SPISE, the single point insulin sensitivity estimator; HDL-c, high-density lipoprotein cholesterol; Scr, serum creatinine; VFA, visceral fat area; BMI, body mass index; GGT, γ- glutamyl transpeptidase; ALT, alanine aminotransferase; TG, triglyceride; HOMA-IR, homeostatic model assessment for insulin resistance; Hb, hemoglobin; UA, uric acid; TC, total cholesterol; SE, standard error; CI, confidence interval.

accuracy in predicting MetS and IR compared to other measures such as the TG/HDL-c ratio and HOMA-IR (14, 28). Extensive research had confirmed that NAFLD was closely associated with insulin resistance and metabolic syndrome (10, 11, 29, 30). Recent studies have reported that SPISE was closely associated with NAFLD related to adolescent obesity and NAFLD in healthy screening participants (21, 22). However, there is currently a lack of evidence for SPISE as a predictor of NAFLD in T2D population.

Our study corroborated the capability of SPISE to predict NAFLD among T2D population. HOMA-IR and the TG/HDL-c ratio were also closely related to NAFLD (31, 32), and therefore we included these IR-related indicators in our study. The results showed that they did not enter the regression model, and compared to SPISE, their area under the ROC curve was significantly smaller. A Japanese study similarly found that a 1.8-fold increased risk of concurrent NAFLD and T2D was associated with SPISE, aligning with our findings (22). However, that study included only 58 patients with both NAFLD and T2D, whereas our study involved 2,459 T2D patients with NAFLD. Additionally, we conducted gender-stratified analyses, which yielded consistent results, further

substantiating the predictive power of SPISE in this group. Beyond IR, dyslipidemia and obesity are also significant factors related to NAFLD (33). SPISE, as a comprehensive indicator that includes metrics related to lipids and obesity, is convenient, accessible and low-cost, making it highly suitable for large-scale clinical application.

In addition, the results of this study indicated that NAFLD was closely associated with VFA in both males and females. This is generally consistent with previous research findings (34). GGT, ALT and AST are liver enzymes closely associated with NAFLD and NASH (35–37). In our analysis of female samples using Spearman's correlation, AST, GGT, and ALT all showed positive correlations with NAFLD, yet these variables were not included in the final binary logistic regression model. In contrast, in male samples, GGT was incorporated into the regression model. However, the predictive power of the liver enzyme included in the final regression model, as indicated by the area under the ROC curve, remained inferior to that of the SPISE index. This gender discrepancy may stem from differences in research methodologies and sample selection criteria.

5 Limitations

This study faces several limitations. Firstly, due to its cross-sectional design, we cannot establish a causal relationship between the SPISE index and NAFLD. Secondly, the diagnosis of NAFLD was not made using the gold standard of liver biopsy, which may lead to diagnostic bias. Lastly, as this study was conducted at a single center, future research should be multi-center in order to further validate our findings and the replication of the study.

6 Conclusion

This study demonstrated that SPISE may have potential advantages over other commonly used biomarkers in identifying NAFLD among T2D patients. As a simple insulin sensitivity index, the specific utility of SPISE in predicting NAFLD among T2D patients remains to be further investigated.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of Linyi People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HZ: Conceptualization, Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review and editing. BJ: Methodology, Software, Visualization, Writing – original draft, Writing – review and editing. XW: Investigation, Writing – review and editing. SS: Writing – review and editing. JS: Writing – review and editing. XM: Data curation, Writing – review and editing. GG: Funding acquisition, Visualization, Writing – review and editing. BB: Funding acquisition, Visualization, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The relationship between anxiety and cardiometabolic risk factors in adolescents with obesity: propensity scores

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Background: It has been described that there is a relationship between metabolic health and anxiety.

Objective: To determine the relationship between anxiety and metabolic syndrome, as well as cardiometabolic risk factors, in adolescents with obesity.

Methods: We conducted a comparative cross-sectional study of adolescents with obesity between January 2019 and December 2022. In each patient, we recorded somatometric measurements, lipid profiles, and serum insulin levels. Anxiety was measured using the Spence Children's Anxiety Scale. Participants were divided into those with and without anxiety. Patients with anxiety were matched to patients without anxiety using propensity scores based on z-score body mass index (zBMI). Mann–Whitney U tests and χ^2 tests were used.

Results: Of the 564 adolescents, 32.6% (n = 184) suffered from anxiety. In the overall study population, no differences in biochemical and cardiometabolic parameters were observed between the adolescents with and without anxiety prior to adjusting the groups based on zBMI. After matching using their zBMI, we found that the adolescents with anxiety had higher serum uric acid levels (5.9 mg/dl vs. 5.4 mg/dl, p = 0.041), an increased incidence of metabolic syndrome (39.1% vs. 15.9%, p = 0.002), hyperglycemia (21.7% vs. 8.6%, p = 0.020), and lower HDLc (67.3% vs. 34.7%, p < 0.001), than those without anxiety. Girls with anxiety had a higher proportion of cardiometabolic risk factors compared to those without anxiety.

Conclusions: Adolescents with obesity and anxiety had higher cardiometabolic risk factors than those without anxiety.

KEYWORDS

obesity, anxiety, metabolic syndrome, insulin resistance, cardiometabolic factors

Introduction

Anxiety disorders are the most common mental health problems among adolescents, with a worldwide prevalence of 6.5% (1). Anxiety disorders typically have their onset during adolescence (2) and are characterized by excessive worry, fear, and apprehension, as well as physical symptoms, such as fatigue, palpitations, and tension (3).

Unlike the many studies that have established a strong association between depression in pediatric patients and being overweight and obese, studies on anxiety are more limited, but research has found an increase in the frequency of anxiety disorders and low self-esteem among children and adolescents with obesity; all of which lead to a deterioration in the quality of life (4, 5). However, it must be considered that it is not clear if being overweight or obese causes anxiety or vice versa. The relationship between anxiety and obesity appears to involve a complex interaction of biological, psychological, and social factors. Biologically, imbalances in appetite-regulating hormones and cortisol have been noted. Psychologically, low self-esteem, negative self-image, and reduced life satisfaction resulting from obesity can contribute to the development of anxiety. Socially, the easy availability of high-calorie fast foods, increased consumption of sugary drinks, extended screen time on electronic devices, and limited opportunities for physical activity are possible contributing factors (6–9).

Moreover, a connection has also been established between anxiety, depression, and a higher risk of cardiovascular disease (CVD). Several pathophysiological factors, including inflammation, oxidative stress, and autonomic dysfunction, have been proposed as systemic processes contributing to this link (10–13). The combined effect of these changes in patients with both obesity and anxiety may accelerate the progression of CVD. In adults with obesity, the metabolic profile tends to be more unfavorable when anxiety is also present (11–14), though similar studies in children and adolescents are limited (15).

The objective of the study was to determine the relationship between anxiety and metabolic syndrome, as well as cardiometabolic risk factors, in adolescents with obesity.

Methods

Subjects

This cross-sectional study was conducted in Mexico between January 2019 and May 2022 with a sample of patients from three tertiary care pediatric centers (Hospital Infantil de Mexico Federico Gómez, Pediatric Hospital Centro Médico Nacional Siglo XXI, and High Specialty South Central Hospital of Petroleos Mexicanos). Patients aged 10–18 years with a diagnosis of obesity, defined as a body mass index (BMI) of >95th percentile on the 2000 Center for Disease Control and Prevention (CDC) Growth Charts (16), were included. Exclusion criteria were the presence of genetic syndromes, the use of medications that can influence weight or appetite (e.g., steroids, selective serotonin reuptake inhibitors such as fluoxetine or sertraline, insulin sensitizers, anorexigenics, and intestinal fat absorption inhibitors), the use of hepatotoxic medications, chronic liver disease, and declining the invitation to participate.

Demographic and clinical information

Demographic information, including age, sex, medical history, and medication use, was collected with the objective of describing the population and identifying whether they met the selection criteria. Anthropometric data, fasting plasma glucose, insulin, and lipid concentrations [high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), and triglycerides (TGLs)] were collected. Levels of physical sexual maturation were determined by a pediatric endocrinologist based on the Tanner scale, which comprises five stages of pubertal development (17). Children in Tanner stage 1 were classified as prepubertal, Tanner stages 2–4 as pubertal, and Tanner 5 as post-pubescent.

Anthropometry

A certified nutritionist measured and recorded the anthropometric indicators of each patient. Height was measured using a Seca model 769 stadiometer (Seca GmbH & Co. KG, Hamburg, Germany). Weight measurements were performed using the bioimpedance method (Tanita BC-568 Segmental Body Composition Monitor, Tokyo, Japan). The participants were weighed barefoot in their underwear.

Anxiety measurement

The presence of elevated levels of anxiety was determined using the Mexican version of the Spence Children's Anxiety Scale (SCAS) (18). The questionnaire is used as a screening to identify the presence of anxiety. It comprises 38 questions about the respondent's experience of anxiety symptoms, to which responses are given on a four-point Likert scale with the options never (0), sometimes (1), often (2), or always (3) (19). The SCAS includes six subscales that measure specific anxiety disorders. These are panic attacks and agoraphobia, separation anxiety, social phobia, specific fears, obsessive-compulsive disorder, and generalized anxiety disorder. The Child Report version of the SCAS was used. Elevated anxiety was deemed present when a participant's total score was ≥60 and a specific anxiety disorder when the score on the relevant subscale was ≥ the 84th percentile. The cut-off scores refer to T-scores to identify children within a subclinical range vs. a clinical range (18).

The global validity and reliability of the SCAS were 0.95 and 0.88, respectively; and in Mexican samples, the validity and reliability were 0.92 and 0.61, respectively (19, 20). The subclinical T-score cut-off (≥60) was used to define the 'with anxiety' and 'without anxiety' subgroups (18–20).

Cardiometabolic profile measurement

After a minimum of 12 hours of fasting, blood samples from participants were obtained from the forearm antecubital vein between 7:00 and 8:00 a.m. Serum samples were frozen at −20°C until analysis. Levels of glucose, TGL, HDLc, LDLc, and uric acid were determined using colorimetric enzymatic methods (Bayer Diagnostics, Puteaux, France). Insulin levels were measured by chemiluminescence (Roche/Hitachi Modular P and D Chemistry Analyzer, Roche Diagnostics Corp., Indianapolis, USA; Hitachi Ltd., Tokyo, Japan). Intra- and inter-assay coefficients of variation <7% were considered acceptable. A standard curve was generated for each assay.

Identification of cardiometabolic health risks

Insulin resistance

Each participant's insulin resistance (IR) index (Homeostatic Model Assessment: HOMA-IR) was calculated using the following formula: HOMA-IR = fasting glucose (mg/dl) X fasting insulin (μU/ml)/405. The HOMA-IR cutoff point for a diagnosis of IR was 2.5 (21).

Hypertriglyceridemia

In children <10 years old, hypertriglyceridemia was diagnosed when plasma TGL levels were ≥90th percentile for a child of the participant's age and sex. In children >10 years old, it was diagnosed when plasma TGL levels were ≥150 mg/dl (22).

Altered HDLc and altered LDLc

Low HDLc for children <10 years was judged as that <10th percentile for the participant's age and sex. In children >10 years, low HDLc was defined as <40 mg/dl in

boys and <50 mg/dl in girls (21). High LDLc was defined as >130 mg/dl (22).

Impaired fasting glucose

Elevated fasting plasma glucose was considered a fasting glucose level ≥100 mg/dl (22).

Arterial hypertension

Children with hypertension were considered to have diastolic or systolic blood pressure ≥ the 90th percentile for age and sex, according to the National Blood Pressure Education Program Working Group (23).

Metabolic syndrome

Metabolic syndrome was defined when at least three of the following cardiometabolic abnormalities were present, according to the definitions already mentioned above: hypertension, obesity, hypertriglyceridemia, reduced HDLc, or elevated fasting plasma glucose (22, 24).

Statistical analysis

Kolmogorov–Smirnov tests revealed that the quantitative variables had a non-parametric distribution. These were described as the median, minimum, and maximum and the qualitative variables were presented as proportions and frequencies. Comparisons of quantitative variables between groups were performed using the Mann–Whitney U test. For qualitative variables, χ^2 tests were applied. A p-value of <0.05 was considered statistically significant. STATA v.14.0 (Stata Corp. 2015. College Station, TX, USA) was used for the statistical analyses.

Participant matching

To minimize the impact of any bias introduced by BMI z-scores (zBMI), patients with anxiety were matched to patients without anxiety using propensity scoring. The propensity scores were based on the zBMI. The propensity score technique used was nearest-neighbor matching at a 1:1 ratio without replacement. The caliper was set at 0.01. The pymatch library for Python v.3.7 was used. Subsequently, this analysis was stratified by sex.

Ethics

This study was conducted in accordance with the tenets of the 2013 version of the Declaration of Helsinki. The protocol was approved by the National Research and Health Ethics Committee of the Mexican Social Security Institute (R-2014-785-024). Both the participants and their parents/caregivers gave written informed consent for participation and publication.

Results

Participant characteristics

A total of 589 adolescents with obesity participated in this study. Of these, 25 were excluded due to incomplete questionnaires.

A total of 564 adolescents were analyzed. The sample had a median age of 12 years, with a minimum and maximum of 10 and 18 years, respectively, and there was a predominance of boys (53.6%). The median BMI was 30.1 kg/m^2 and the median zBMI was 2.4. Of the participants, 92.6% (n = 522) were in Tanner stages 2–4 (pubertal) (Table 1).

It was noteworthy that the median HDLc was 38.0 mg/dl, which falls below the normal range. The rest of the biochemical parameters had medians that were not significantly different from normal levels for adolescents (Table 2). The cardiometabolic parameter that showed the greatest frequency (63.6%, n = 359) of divergence from normal levels was HDLc. Hypertriglyceridemia was found in 41.7% (n = 235) of the sample. IR and metabolic syndrome were identified in 223 patients (39.5%) (Table 3).

TABLE 1 General characteristics of the adolescents with obesity with and without anxiety.

Characteristic	Participants, n (%)			*p*
	Total n = 564	No anxiety n = 380	Anxiety n = 184	
Sex, n (%)				0.249
Female	262 (46.4)	187 (49.2)	76 (41.3)	
Male	302 (53.6)	193 (50.8)	108 (58.7)	
Age, years; median (min-max)	12.0 (10.0–18.0)	12.0 (10.0–18.0)	12 (10–18)	0.700
BMI, kg/m^2; median (min-max)	30.1 (18.5–58.0)	29.5 (10.7–43.2)	30.81 (21.3–58.0)	0.269
BMI z-score, median (min-max)	2.4 (0.8–4.6)	2.43 (1.3–3.6)	2.56 (1.2–4.6)	0.125
Waist circumference, cm, median (min-max)	92.5 (72.0, 117.5)	92.0 (72.0, 116.0)	93.5 (74, 143.4)	0.441
Tanner pubertal stage, n (%)				0.974
1	42 (7.3)	28 (7.3)	14 (7.5)	
2	85 (15.0)	60 (15.7)	25 (13.7)	
3	168 (29.8)	108 (28.5)	60 (32.5)	
4	212 (37.5)	145 (38.2)	67 (36.3)	
5	58 (10.2)	39 (10.3)	18 (10.0)	

min, minimum; max, maximum.

Anxiety-related symptoms

Anxiety-related symptoms were found in 32.6% (n = 184) of the adolescents in this study. Of the six specific disorders identified by the SCAS subscales, separation anxiety disorder occurred most frequently among those with overall anxiety (92.5%, n = 170), followed by panic attacks and agoraphobia (81.0%, n = 149).

In comparing the demographic, biochemical, and cardiometabolic characteristics of adolescents with and without anxiety-related symptoms, we observed non-significant trends indicating higher zBMI (2.6 vs. 2.4, p = 0.125), serum glucose levels (92.0 mg/dl vs. 91.4 mg/dl, p = 0.138) (see Table 2), and hyperglycemia (28.8% vs. 20.0%, p = 0.126) among those with anxiety. However, no significant trends were noted for any of the other parameters (Table 3).

In view of the tendency toward higher zBMI in adolescents with anxiety, we matched participants from the anxiety and non-anxiety groups based on zBMI. We then compared the lipid profiles and cardiometabolic factors between the groups. This analysis showed that the adolescents with obesity and anxiety had higher serum uric acid levels (5.9 mg/dl vs. 5.4 mg/dl, $p = 0.041$) and lower HDLc levels (37.0 mg/dl vs. 40.0 mg/dl, $p = 0.019$) than those without anxiety. A comparison of cardiometabolic factors found that the adolescents in our sample with anxiety had a significantly higher incidence of hyperglycemia (21.7% vs. 8.6%, $p = 0.020$) and metabolic syndrome (39.1% vs. 15.9%, $p = 0.002$), and significantly lower HDLc (67.3% vs. 34.7%, $p < 0.001$) than those without anxiety (Table 4).

Finally, as shown in Table 5, when analyzing the data by sex, girls with anxiety exhibited a higher proportion of cardiometabolic risk factors (elevated fasting glucose, decreased HDLc, IR, and metabolic syndrome), compared to their counterparts without anxiety. In contrast, among boys, the only significant finding was a higher proportion of decreased HDLc in those with anxiety compared to those without.

Discussion

The primary finding of this study was that 32.5% of the adolescents with obesity also experienced anxiety-related symptoms, with separation anxiety (92.5%) being the most prevalent type of anxiety disorder. Furthermore, adolescents with anxiety demonstrated an increase in cardiometabolic risk factors. Specifically, we observed that these adolescents had higher serum levels of uric acid and glucose, along with lower HDLc, compared to their non-anxious peers. Notably, girls with anxiety exhibited a more adverse cardiometabolic profile. Consistent with our findings, Cheuiche et al. reported a significant association between the severity of anxiety and cardiovascular risk factors, such as larger waist circumference and higher body fat percentage (25).

These findings are novel, especially as pediatric studies on this topic remain limited. For instance, Ji et al. reported that adults with anxiety have a greater risk of metabolic syndrome compared to those without anxiety (15), while van Reedt Dortland et al. found that anxiety and depression are associated with decreased HDLc and increased abdominal obesity (26). Several studies have identified inflammation as a key factor in the development of cardiovascular disease, with a bidirectional relationship to mental health. Anxiety, obesity, and cardiovascular disease are thought to be linked by a complex interaction of biopsychosocial factors and neurobiological mechanisms, such as hormonal imbalances in the

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TABLE 2 Comparison of the biochemical characteristics of adolescents with obesity and with or without anxiety.

Characteristic	Participants, median (min-max)			p
	Total n = 564	No anxiety n = 380	Anxiety n = 184	
Biochemical profile, median (min-max)				
Glucose, mg/dl	92.0 (70.0–189.0)	91.4 (70.4–117.0)	92.0 (73.0–124.2)	0.138
HDL cholesterol, mg/dl	38.0 (12.0–65.0)	38.0 (20.0–63.0)	38.0 (12.0–60.0)	0.265
LDL cholesterol, mg/dl	96.0 (56.0–194.0)	96.0 (16.0–194.0)	96.1 (37.4–167.0)	0.717
Triglycerides, mg/dl	140.0 (109.0–533.0)	143.0 (54.0–533.0)	139.5 (40.0–328.0)	0.666
Uric acid, mg/dl	5.8 (0.7–10.0)	5.8 (2.3–10.0)	5.9 (2.0–10.5)	0.302
Insulin, mu/ml	10.9 (2.2–75.2)	10.7 (2.4–79.6)	11.5 (2.2–75.2)	0.481
HOMA-IR	2.4 (0.4–19.2)	2.3 (0.4–19.2)	2.5 (0.4–17.8)	0.377
Systemic blood pressure, median (min-max)				
Systolic, mmHg	114.0 (83.0–146.0)	113.0 (90.0–135.0)	115.0 (88.0–140.0)	0.473
Diastolic, mmHg	71.0 (50.0–100.0)	71.0 (51.0–90.0)	71.0 (50.0–95.0)	0.499

min, minimum; max, maximum.

TABLE 3 Comparison of the cardiometabolic factors of adolescents with obesity and with or without anxiety.

Characteristic	Participants, n (%)			p
	Total n =564	No anxiety n = 380	Anxiety n = 184	
Cardiometabolic factors, n (%)				
Impaired fasting glucose	129 (22.9)	76 (20.0)	53 (28.8)	0.126
Altered HDL cholesterol	359 (63.6)	233 (61.3)	127 (69.0)	0.250
Altered LDL cholesterol	51 (9.0)	37 (9.7)	14 (7.6)	0.573
Hypertriglyceridemia	235 (41.7)	161 (42.4)	74 (40.2)	0.712
Arterial hypertension	35 (6.2)	25 (6.58)	9 (4.9)	0.610
Insulin resistance	223 (39.5)	147 (38.7)	76 (41.3)	0.712
Metabolic syndrome	223 (39.5)	145 (38.2)	78 (42.4)	0.517

min, minimum; max, maximum.

hypothalamic-pituitary-adrenal axis and increased cortisol levels (12, 27).

The relationship between fasting hyperglycemia and elevated cortisol is largely attributed to glucocorticoid-induced hepatic gluconeogenesis and impaired insulin secretion, contributing to

TABLE 4 Comparison of the biochemical and cardiometabolic characteristics of adolescents with obesity and with or without anxiety.

Characteristic	Participants		
	No anxiety	Anxiety	
	n = 92	n = 92	p
General characteristics, median (min-max)			
BMI z-score	2.6 (1.5–3.3)	2.54 (1.5–3.6)	0.896
Waist circumference, cm	92.5 (74.0-112.5)	93.0 (73.0-121.0)	0.416
Biochemical profile, median (min-max)			
Glucose, mg/dl	90.0 (70.0–108.0)	92.0 (73.0–124.0)	0.059
HDL cholesterol, mg/dl	40.0 (24.0–55.0)	37.0 (16.0–51.0)	**0.019**
LDL cholesterol, mg/dl	91.2 (62.0–145.0)	96 (55.9–155.0)	0.251
Triglycerides, mg/dl	138.0 (64.0–236.0)	128.0 (40.0–328.0)	0.883
Uric acid, mg/dl	5.4 (3.0–8.5)	5.9 (3.7–8.4)	**0.041**
Insulin, mu/ml	12.3 (2.5–79.6)	13.5 (2.2–75.2)	0.394
HOMA-IR	2.7 (0.6–19.2)	2.9 (0.4–17.8)	0.274
Systemic blood pressure, median (min-max)			
Systolic, mmHg	113.0 (90.0–131.0)	115.0 (89.0–139.0)	0.447
Diastolic, mmHg	70.0 (50.0–90.0)	71.0 (50.0–94.0)	0.572
Cardiometabolic factors, n (%)			
Elevated fasting glucose	8 (8.6)	20 (21.7)	**0.020**
Decreased HDL cholesterol	32 (34.7)	62 (67.3)	**<0.001**
Increased LDL cholesterol	2 (2.1)	6 (6.5)	0.404
Hypertriglyceridemia	32 (34.7)	34 (36.9)	0.922
Arterial hypertension	6 (6.5)	6 (6.5)	1.000
Insulin resistance	34 (36.9)	42 (45.6)	0.301
Metabolic syndrome	14 (15.9)	36 (39.1)	**0.002**

min, minimum; max, maximum.
Propensity scoring.
Bold values are statistically significant.

features of metabolic syndrome (28–30). Impaired insulin function, higher fasting glucose, and increased diabetes risk have also been observed in individuals with anxiety and depression (31). Likewise, in adolescents with obesity, it has been reported that fasting insulin and HOMA-IR levels are 40% higher in those with depression (32).

Another cardiometabolic alteration identified was elevated serum uric acid levels in adolescents with anxiety compared to those without anxiety. This finding is associated with the higher prevalence of metabolic syndrome in adolescents with anxiety. Recent studies have shown that elevated uric acid levels independently predict the development of diabetes and contribute to IR, fatty liver, and dyslipidemia in the context of metabolic syndrome (33). These effects may be driven by mitochondrial

TABLE 5 Comparison of the biochemical and cardiometabolic characteristics of adolescents with obesity and with or without anxiety.

Characteristic	Female, n=101			Male, n=83.		
	No anxiety	Anxiety		No anxiety	Anxiety	*p*
	n = 62	n = 39	*p*	n = 29	n = 54	
General characteristics, median (min-max)						
BMI z-score	2.6 (1.3–3.3)	2.4 (1.2–4.6)	0.301	2.6 (1.6–2.9)	2.6 (1.5–4.1)	0.272
Waist circumference, cm	89.0 (76.6-112.5)	91.5 (73.3-121.0)	0.333	98.0 (85.9-108.9)	94.5 (73.0-117.5)	0.434
Biochemical profile, median (min-max)						
Glucose, mg/dl	88.0 (76.0–97.0)	91.0 (86.0–124.0)	0.069	96.0 (70.0–108.0)	93.0 (74.0–115.0)	0.142
HDL cholesterol, mg/dl	40.0 (24.0–55.0)	37.0 (16.0–59.0)	0.342	42.0 (25.0–54.0)	38.0 (21.0–57.0)	**0.010**
LDL cholesterol, mg/dl	91.2 (62.0–145.0)	99.0 (40.0–146.0)	0.316	90.2 (55.9–122.0)	93.9 (37.4–155.0)	0.175
Triglycerides, mg/dl	134.0 (64.0–236.0)	148.0 (53.0–323.0)	0.294	148.0 (77.0–235.0)	119.0 (40.0–328.0)	0.127
Uric acid, mg/dl	4.8 (3.9–7.1)	5.4 (3.0–8.0)	0.084	5.5 (3.7–8.5)	6.3 (3.3–9.7)	0.590
Insulin, mu/ml	11.4 (4.8–31.5)	16.5 (5.3–40.4)	**0.010**	14.5 (2.5–79.6)	10.5 (2.2–75.2)	0.309
HOMA-IR	2.3 (1.0–7.3)	3.5 (1.3–11.2)	**0.006**	3.5 (0.6–19.2)	2.4 (0.4–17.8)	0.302
Systemic blood pressure, median (min-max)						
Systolic, mmHg	113.0 (90.0–131.0)	115.0 (89.0–139.0)	0.447	112.0 (91.0–130.0)	111.0 (88.0–138.0)	0.347
Diastolic, mmHg	70.0 (50.0–90.0)	71.0 (50.0–94.0)	0.572	71.0 (50.0–92.0)	72.0 (50.0–93.0)	0.572
Cardiometabolic factors, n (%)						
Elevated fasting glucose	0 (0.0)	8 (20.5)	**0.001**	8 (27.6)	13 (24.0)	0.845
Decreased HDL cholesterol	26 (41.9)	28 (71.8)	**0.011**	6 (20.7)	35 (64.8)	**0.001**
Increased LDL cholesterol	3 (4.8)	4 (10.2)	0.298	0 (0.0)	2 (3.7)	0.455
Hypertriglyceridemia	18 (29.0)	19 (48.7)	0.105	13 (44.8)	16 (29.6)	0.224
Arterial hypertension	3 (4.8)	4 (10.2)	0.298	2 (3.7)	1 (1.8)	0.247
Insulin resistance	17 (27.4)	23 (58.9)	**0.007**	17 (58.6)	20 (37.0)	0.102
Metabolic syndrome	4 (6.4)	19 (48.7)	**<0.001**	10 (34.4)	18 (33.3)	0.758

min, minimum; max, maximum.
Propensity scoring, stratified by sex.
Bold values are statistically significant.

oxidative stress and impaired insulin-stimulated nitric oxide production in endothelial cells. Some researchers have also suggested that a high intake of purine- and fructose-rich foods may contribute to elevated uric acid levels, obesity, and the development of metabolic syndrome (34, 35).

Our study indicates that adolescent girls with anxiety are more likely to experience cardiometabolic risk factors compared to their non-anxious peers. Recent research suggests that psychosocial stress might be a more significant risk factor for cardiometabolic disease in women than in men, possibly due to greater exposure to stress or increased susceptibility to its effects (36). Evidence highlights stronger associations between depression, anxiety, and type 2 diabetes in women compared to men (37, 38). Additionally, sex differences have been observed in the relationship between early adversity and obesity, with girls showing a higher risk of developing obesity linked to early-life stress (39). However, recent reviews have pointed out that few studies have explicitly explored sex-related differences in cardiometabolic outcomes (40).

Despite the significant findings, several limitations must be acknowledged. First, the study's cross-sectional design limits our ability to establish causality between anxiety and cardiometabolic risk factors. Further research is needed to explore the cardiometabolic changes in adolescents with both obesity and anxiety (5). Additionally, it is important to note that we used the SCAS, which is a valid self-report questionnaire that assesses DSM-IV-defined anxiety symptoms in children. Compared to similar tools such as the Screen for Child Anxiety Related Emotional Disorders (SCARED), which correlates well with the SCAS (r = 0.89), the SCAS is shorter and has a simpler factor structure (41, 42). Other widely used instruments, such as the Revised Children's Manifest Anxiety Scale (43) and the Fear Survey Schedule for Children-Revised (44), are more general measures of anxiety and do not specifically address DSM-IV anxiety disorders.

During patient recruitment, the COVID-19 pandemic and associated lockdowns occurred. Most of the sample (76.0%) was collected prior to the pandemic, with patient recruitment temporarily halted during this period and resuming in January 2022 (14.0%, n=137). A sub-analysis comparing patients recruited before and after the pandemic found no significant differences in the proportion of anxiety. This may be attributed to the fact that the latter group of patients was no longer experiencing social isolation at the time of their inclusion in the study.

As a final reflection, we would like to discuss how to incorporate the study findings into the management of obesity in adolescents. Latin America and Mexico are experiencing an epidemiological transition, with rising rates of childhood obesity and chronic diseases that increase morbidity and mortality (45). Furthermore, psychological changes during adolescence may exacerbate the negative emotions associated with obesity, creating a vicious cycle. Based on the above, it seems important that weight reduction interventions should incorporate mental health strategies (such as relaxation techniques, meditation, and cognitive-behavioral therapy) to enhance adherence to weight reduction programs and improve both short- and long-term health outcomes (46, 47).

Conclusions

We found that adolescents with obesity and anxiety had higher serum uric acid levels, lower HDLc levels, and higher incidences of hyperglycemia and metabolic syndrome than adolescents with obesity but without anxiety. It is of the utmost importance to develop a multidisciplinary treatment for this population that considers nutritional advice support, teaches coping skills, encourages meditation, and provides cognitive-behavioral therapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The protocol was approved by the National Research and Health Ethics Committee of the Mexican Social Security Institute (R-2014-785-024). Both the participants and their parents/caregivers gave written informed consent to participation and publication. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

MV-K: Project administration, Supervision, Validation, Writing – review & editing. JZ-C: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. AP-E: Investigation, Writing – review & editing. WM-A: Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Association between estimated glucose disposal rate and preserved ratio impaired spirometry in adults

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Background: Preserved ratio impaired spirometry (PRISm) is a newly defined phenotype of lung function impairment, characterized by a normal FEV1/FVC ratio alongside an FEV1/0.8 < FEV1 predicted value. Previous studies have linked PRISm to various adverse clinical outcomes, but its association with insulin resistance, as indicated by estimated glucose disposal rate (eGDR), remains underexplored.

Methods: A total of 13,661 participants were included in this analysis after excluding individuals with missing data on PRISm (n = 10,954) and eGDR (n = 5,827). The median eGDR for the overall sample was calculated, and differences in baseline characteristics between the PRISm and non-PRISm groups were assessed. Logistic regression models were employed to analyze the relationship between eGDR and PRISm, adjusting for various confounders. Subgroup analyses were conducted based on gender and age. Additionally, the restricted cubic spline analysis was used to evaluate the non-linear relationship between eGDR and PRISm, and ROC analysis was performed to determine the predictive accuracy of eGDR for identifying PRISm.

Results: Participants in the PRISm group exhibited significantly lower median eGDR values compared to the non-PRISm group (9.92 vs. 12.01 mg/kg/min; $P < 0.001$), indicating greater insulin resistance. The weighted multivariable logistic regression analysis revealed that each unit increase in eGDR was associated with a 15.1% reduction in the odds of PRISm in unadjusted models, and 7.3% in fully adjusted models (OR = 0.927, 95% CI: 0.880–0.976; $P = 0.005$). Subgroup analyses demonstrated a stronger association between eGDR and PRISm in females and individuals over 40 years of age. The restricted cubic spline analysis indicated a significant non-linear relationship, with an optimal eGDR cutoff of 11.423 mg/kg/min identified via ROC analysis (AUC = 0.626), demonstrating modest predictive accuracy.

Conclusion: Our study demonstrates a significant inverse association between estimated glucose disposal rate (eGDR) and preserved ratio impaired spirometry (PRISm) among a diverse population of US adults. Participants with lower eGDR values exhibited a higher prevalence of PRISm, indicating greater insulin resistance and potential metabolic dysfunction. The findings suggest that eGDR may serve as a valuable marker for assessing the risk of PRISm, particularly among women and older adults.

KEYWORDS

estimated glucose disposal rate, eDGR, insulin resistance, preserved ratio impaired lung function, PRISM, lung function, lung injury

Introduction

Chronic lung disease affects hundreds of millions of people worldwide and ranks as the third leading cause of death globally, following cardiovascular disease and cancer (1). Common lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and bronchiectasis, often lead to significant changes in lung function, particularly resulting in airflow obstruction (2, 3). This obstruction is typically identified through lung function testing conducted after administering a bronchodilator, characterized by a reduced ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC). In contrast, non-obstructive lung function abnormalities, commonly referred to as restrictive lung disease, are marked by a symmetric reduction in both FEV1 and FVC (4).

However, preserved ratio impaired lung function (PRISm) is a relatively underexplored lung disease that is characterized by a decrease in FVC while the ratio of forced expiratory volume in one second to forced vital capacity FEV1/FVC remains within the normal range, with the global prevalence of PRISm estimated to be between 6.6% and 17.6% (5). Although PRISm has historically been viewed as a transitional state between normal lung function and COPD, retrospective studies have shown that only approximately 23% of individuals with PRISm progress to COPD (6). Some studies have shown that PRISm is significantly associated with increased risks of mortality, as well as adverse cardiovascular and respiratory outcomes (4), and is linked to a higher prevalence of diabetes, heart disease, and hypertension among individuals with chronic diseases (7, 8). In contrast, PRISm has been independently linked to higher cardiovascular risk and increased mortality (9). It may represent a distinct clinical phenotype with unique pathophysiological and prognostic implications, rather than merely an early stage of obstructive lung disease (10).

Insulin resistance is a condition characterized by a diminished response to insulin, which results in decreased efficiency of glucose uptake and utilization, ultimately leading to metabolic abnormalities and serving as a significant risk factor for various metabolic disorders such as type 2 diabetes, hypertension, dyslipidemia, and obesity (11, 12). Recent research has highlighted the correlation between insulin resistance and pulmonary diseases, including impaired lung function and asthma, indicating that individuals with insulin resistance often experience compromised respiratory health, which suggests that metabolic dysregulation may exert both direct and indirect effects on lung function (13–15).

The concept of estimated glucose disposal rate (eGDR) has emerged as a valuable tool for assessing insulin sensitivity, particularly in individuals with diabetes. eGDR is derived from clinical parameters such as body mass index (BMI) and blood pressure, making it a useful surrogate marker for insulin resistance (16). Compared to other insulin resistance markers such as TyG, TyG-BMI, and METS-IR, recent studies have shown that eGDR has superior predictive ability for adverse cardiometabolic outcomes, including stroke and cardiovascular disease (17, 18). While the relationship between insulin resistance and various metabolic disorders has been extensively studied, research exploring the connection between insulin resistance and PRISm remains relatively scarce. These findings suggest that eGDR may also be a more effective indicator for identifying individuals at risk of PRISm, particularly in populations with metabolic disturbances. Therefore, we utilized the national health and nutrition examination surveys (NHANES) database to explore the association between eGDR and PRISm, aiming to further elucidate their potential link in metabolic health and lung function. We hypothesized that decreased insulin sensitivity, as reflected by lower eGDR, would be negatively associated with lung function and increase the likelihood of PRISm, thereby linking metabolic and respiratory health.

Abbreviations: PRISm, Preserved ratio impaired spirometry; eGDR, Estimated glucose disposal rate; FEV1, First second forced expiratory volume; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; PIR, poverty income ratio; BMI, Body Mass Index; eGFR, estimated glomerular filtration rate; ROC, Receiver operating characteristic; RCS, Restricted cubic spline.

Methods

Study and data

The National Health and Nutrition Examination Survey (NHANES), conducted by the National Center for Health

Statistics (NCHS) at the U.S. Centers for Disease Control and Prevention (CDC), is a cross-sectional survey employing a complex, multistage sampling design to gather data representative of the non-institutionalized U.S. population. NHANES operates in two-year cycles, collecting data through in-home interviews and standardized physical examinations. For this study, data from three NHANES cycles (2007–2008, 2009–2010 and 2011–2012) were utilized, based on the availability of lung function measurements. The dataset can be accessed at (https://www.cdc.gov/nchs/nhanes/index.htm). The study population included U.S. adults aged 20–79 who met the criteria for valid spirometry testing. Participants with missing lung function data or essential variables required to estimate predicted forced expiratory volume in one second (FEV1) or to calculate estimated glucose disposal rate (eGDR) were excluded. The participant selection flowchart is illustrated in Figure 1.

Definitions of eGDR and PRISm

The insulin resistance index, estimated glucose disposal rate (eGDR), was calculated using the following equation: eGDR = 21.158 - (0.09 × waist circumference [cm]) - (3.407 × hypertension [yes = 1, no = 0]) - (0.551 × glycated hemoglobin A1c [HbA1c] [%]) (16). Hypertension was defined as (1) systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, (2) self-reported physician diagnosis of hypertension, or (3) use of antihypertensive medication. Preserved Ratio Impaired Spirometry (PRISm) was defined as a forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC) ≥0.7 with an abnormal spirometry result (FEV1 <80% of the predicted value) (4). Predicted FEV1 values were calculated using the Global Lung Function Initiative (GLI-2012) reference equations, implemented via specialized software available at (https://gli-calculator.ersnet.org/index.html) (19).

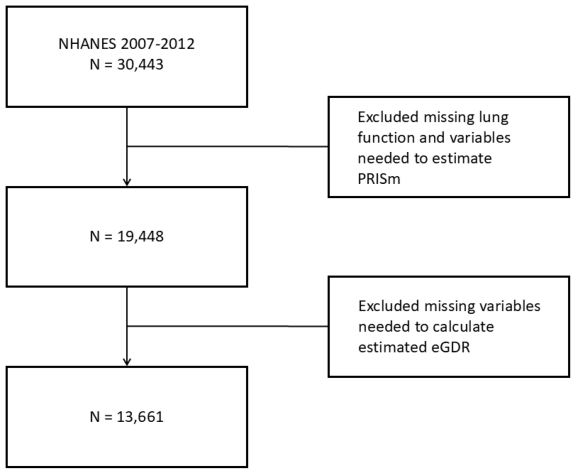

FIGURE 1
Flowchart depicting the screening process for selecting the study population.

Covariates

Demographic data (age, gender, race/ethnicity, and poverty income ratio), health-related behaviors (smoking status and alcohol consumption), medical history (cardiovascular disease and stroke) were collected from NHANES through standardized questionnaires. Ethnicity was categorized as Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other races. The poverty income ratio (PIR) was calculated as the ratio of monthly family income to the federal poverty level, following the Department of Health and Human Services guidelines, and categorized into low income (≤1.30), middle income (1.31–3.50), and high income (>3.50) (20). Body mass index (BMI) was categorized into normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2), and included as a categorical variable in multivariable regression analyses. Cardiovascular disease and stroke were identified based on affirmative responses to the following question: "Has a doctor or other health professional ever told you that you had congestive heart failure, coronary heart disease, angina, heart attack, or stroke?" Alcohol consumption was determined by asking, "Have you had at least 12 alcoholic drinks in the past year?" Smoking status was defined as a binary variable (yes/no), based on responses to the questions: "Have you smoked at least 100 cigarettes in your lifetime?" and "Do you currently smoke?" Additionally, laboratory data included cotinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the CKD-EPI equation (21), and eGFR was included as a continuous covariate in the models.

Statistical analysis

We conducted weighted analyses according to NHANES guidelines. Continuous variables that did not follow a normal distribution were expressed as medians with interquartile ranges, and group comparisons were performed using the Mann-Whitney U test. Categorical data were presented as proportions, with group comparisons using the chi-square test. Ordinal data were also expressed as proportions, with group comparisons performed using the Mann-Whitney U test. To examine the association between eGDR and PRISm, we employed weighted multivariable logistic regression, constructing three models: Model 1: Unadjusted; Model 2: Adjusted for gender, age, ethnicity, and PIR; Model 3: Adjusted for all covariates (gender, age, ethnicity, PIR, BMI, cotinine, AST, ALT, GFR creatinine clearance, cardiovascular disease, stroke, alcohol consumption, and smoking status). We also conducted subgroup and interaction analyses to explore the relationship between eGDR and PRISm across different populations. To assess potential nonlinear associations, we used restricted cubic spline analysis. Finally, we performed a receiver operating characteristic (ROC) analysis to evaluate the predictive ability of eGDR for PRISm. All statistical analyses were performed

using R software (version 4.0.0) and SPSS (version 25.0), with statistical significance set at $P < 0.05$.

Results

Baseline characteristics

In Table 1, a total of 13,661 participants were included in the final analysis after excluding those with missing data on PRISm (n = 10,954) and eGDR (n = 5,827). The median eGDR for the overall sample was 11.89 (IQR: 9.08–13.33). Participants in the PRISm group had significantly lower median eGDR values compared to the non-PRISm group [9.92 (IQR: 8.04–12.49) vs. 12.01 (IQR: 9.22–13.38); $P < 0.001$], indicating greater insulin resistance in the PRISm group. The PRISm group was older, with a median age of 48 (IQR: 34–61) compared to 44 (IQR: 30–59) in the non-PRISm group ($P < 0.001$). Cotinine levels were also higher in the PRISm group [0.09 (IQR: 0.02–30.55) vs. 0.05 (IQR: 0.02–12.70); $P < 0.001$] and median eGFR was significantly lower in the PRISm group [85.47 (IQR: 64.70–103.07) vs. 89.84 (IQR: 69.66–108.48); $P < 0.001$]. No significant differences were observed in ALT ($P = 0.332$) and AST ($P = 0.167$) levels between the two groups.

Ethnicity was significantly associated with PRISm status ($P < 0.001$). PRISm was most prevalent in non-Hispanic Black participants (53.94%), and least common in Mexican American (7.11%). BMI was also significantly associated with PRISm ($P < 0.001$), with a higher proportion of obese individuals in the PRISm group (50.30%) compared to the non-PRISm group (33.51%). Smoking status did not differ significantly between the two groups ($P = 0.978$). However, alcohol consumption was significantly lower in the PRISm group, with only 63.93% reporting alcohol consumption compared to 75.64% in the non-PRISm group ($P < 0.001$). Cardiovascular disease and stroke were more common in the PRISm group, with heart disease present in 11.00% of PRISm cases compared to 5.09% in the non-PRISm group ($P < 0.001$), and stroke present in 4.12% of PRISm cases compared to 1.95% in the non-PRISm group ($P < 0.001$).

Logistic regression models

Weighted multivariable logistic regression analysis demonstrated a significant negative association between eGDR and PRISm (Table 2). In the unadjusted model (Model 1), each unit increase in eGDR was associated with a 15.1% reduction in the odds of PRISm (OR = 0.849, 95% CI: 0.820–0.880; $P < 0.001$). After adjusting for gender, age, race/ethnicity, and poverty income ratio (Model 2), the association remained significant (OR = 0.849, 95% CI: 0.818–0.881; $P < 0.001$). In the fully adjusted model (Model 3), which included additional covariates such as BMI, cotinine, ALT, AST, GFR, cardiovascular disease, stroke, alcohol consumption, and smoking, each unit increase in eGDR was associated with a 7.3% reduction in the odds of PRISm (OR = 0.927, 95% CI: 0.880–0.976; $P = 0.005$). When eGDR was categorized into quartiles, the highest quartile (Q4) was associated with a 41.7% lower risk of PRISm compared to the lowest quartile (Q1) in the fully adjusted model (OR = 0.583, 95% CI: 0.393–0.867; $P = 0.009$). A significant trend was observed across quartiles (P for trend = 0.002), further supporting a negative relationship between eGDR and PRISm.

Subgroup and interaction analysis

Subgroup analyses revealed significant differences in the relationship between eGDR and PRISm across gender and age groups (Table 3). Among women, eGDR was significantly associated with lower odds of PRISm (OR = 0.874, 95% CI: 0.821–0.929; $P < 0.001$), while no significant association was observed in men ($P = 0.702$). The interaction between gender and eGDR was significant ($P = 0.012$), indicating that the association was stronger in women. Similarly, a significant association was found in participants over 40 years of age (OR = 0.913, 95% CI: 0.848–0.982; $P = 0.016$), but not in those aged 40 or younger ($P = 0.146$), with a significant interaction effect for age ($P = 0.016$). No significant interactions were observed between eGDR and race ($P = 0.408$) or poverty income ratio ($P = 0.984$), although significant associations between eGDR and PRISm were found in Mexican American, Non-Hispanic Black racial groups.

Nonlinear and ROC analysis

The restricted cubic spline (RCS) analysis revealed a significant nonlinear relationship between eGDR and PRISm (P-nonlinear < 0.001). As shown in Figure 2, the OR for PRISm decreases as eGDR increases, with the most pronounced reduction occurring at lower eGDR levels. Beyond an eGDR value of approximately 12 mg/kg/min, the association stabilizes, with the OR approaching 1. This indicates that higher eGDR levels are associated with a lower likelihood of PRISm, but the effect diminishes as eGDR increases. ROC analysis revealed that the area under the curve (AUC) for eGDR predicting PRISm was 0.626, indicating modest predictive accuracy (Figure 3). The optimal cutoff value for eGDR was 11.423 mg/kg/min, with a sensitivity of 63.9% and specificity of 57.2%.

Discussion

Preserved ratio impaired spirometry (PRISm) is a newly defined phenotype of lung function impairment, characterized by individuals exhibiting a normal FEV1/FVC ratio, while having an FEV1 less than 0.8 times the predicted value (5). Although PRISm shares some features with both obstructive and restrictive lung patterns, it is distinct in that it does not follow the typical patterns of either (10). PRISm is associated with various adverse clinical outcomes, such as increased respiratory symptoms, elevated comorbidity rates of hypertension and diabetes, and higher mortality rates (4, 7, 8). Furthermore, PRISm is a heterogeneous condition, with only a subset of individuals progressing to COPD,

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TABLE 1 Baseline characteristics of the study population.

Variables	Total (n = 13661)	Non-PRISm (n = 12493)	PRISm (n = 1168)	Statistic	*P*
eGDR (mg/kg/min), M (Q_1, Q_3)	11.89 (9.08, 13.33)	12.01 (9.22, 13.38)	9.92 (8.04, 12.49)	-14.29	<0.001
Quantile, n (%)				**-14.24**	**<0.001**
Q1	3412 (24.98)	2928 (23.44)	484 (41.44)		
Q2	3418 (25.02)	3108 (24.88)	310 (26.54)		
Q3	3415 (25.00)	3215 (25.73)	200 (17.12)		
Q4	3416 (25.01)	3242 (25.95)	174 (14.90)		
Age, M (Q_1, Q_3)	44.00 (30.00, 59.00)	44.00 (30.00, 59.00)	48.00 (34.00, 61.00)	-5.20	<0.001
Sex, n (%)				**0.00**	**0.965**
Male	6991 (51.17)	6394 (51.18)	597 (51.11)		
Female	6670 (48.83)	6099 (48.82)	571 (48.89)		
Ethnicity, n (%)				**853.73**	**<0.001**
Mexican American	2289 (16.76)	2206 (17.66)	83 (7.11)		
Other Hispanic	1491 (10.91)	1413 (11.31)	78 (6.68)		
Non-Hispanic White	5713 (41.82)	5471 (43.79)	242 (20.72)		
Non-Hispanic Black	2957 (21.65)	2327 (18.63)	630 (53.94)		
Other Race	1211 (8.86)	1076 (8.61)	135 (11.56)		
PIR, n (%)				**-3.38**	**<0.001**
≤1.3	4144 (33.08)	3772 (32.86)	372 (35.50)		
>1.3 and ≤3.5	4510 (36.01)	4099 (35.71)	411 (39.22)		
>3.5	3872 (30.91)	3607 (31.43)	265 (25.29)		
BMI (kg/m^2), n (%)				-10.39	<0.001
<25	4439 (32.53)	4159 (33.32)	280 (24.08)		
≥25 and < 30	4438 (32.52)	4140 (33.17)	298 (25.62)		
<30	4768 (34.94)	4183 (33.51)	585 (50.30)		
Cotinine (ng/mL), M (Q_1, Q_3)	0.05 (0.02, 13.25)	0.05 (0.02, 12.70)	0.09 (0.02, 30.55)	-5.08	<0.001
eGFR ($mL/min/1.73\ m^2$), M (Q_1, Q_3)	89.41 (69.17, 108.08)	89.84 (69.66, 108.48)	85.47 (64.70, 103.07)	-6.06	<0.001
ALT (U/L), M (Q_1, Q_3)	21.00 (16.00, 28.00)	21.00 (16.00, 28.00)	21.00 (16.00, 28.00)	-0.97	0.332
AST (U/L), M (Q_1, Q_3)	23.00 (20.00, 28.00)	23.00 (20.00, 28.00)	23.00 (19.00, 28.00)	-1.38	0.167
Smoke, n (%)				**0.00**	**0.978**
Yes	5525 (45.36)	5031 (45.37)	494 (45.32)		
No	6655 (54.64)	6059 (54.63)	596 (54.68)		
Alcohol, n (%)				**68.28**	**<0.001**
Yes	8725 (74.60)	8062 (75.64)	663 (63.93)		
No	2971 (25.40)	2597 (24.36)	374 (36.07)		
Heart Disease, n (%)				**65.31**	**<0.001**
Yes	685 (5.62)	565 (5.09)	120 (11.00)		
No	11500 (94.38)	10529 (94.91)	971 (89.00)		

(Continued)

TABLE 1 Continued

Variables	Total (n = 13661)	Non-PRISm (n = 12493)	PRISm (n = 1168)	Statistic	*P*
Stroke, n (%)				22.41	<0.001
Yes	261 (2.14)	216 (1.95)	45 (4.12)		
No	11913 (97.86)	10867 (98.05)	1046 (95.88)		

eGDR, Estimated Glucose Disposal Rate; PRISm, Preserved Ratio Impaired Spirometry; BMI: Body Mass Index; eGFR, Estimated Glomerular Filtration Rate; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase.

TABLE 2 Multivariate logistic regression analysis of the association between eGDR and PRISm across different models.

Variables	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	*OR* (95% CI)	*P*	*OR* (95% CI)	*P*
eGDR	0.849 (0.820, 0.880)	<0.001	0.849 (0.818, 0.881)	<0.001	0.927 (0.880, 0.976)	0.005
Categories						
Q 1	Reference	/	Reference	/	Reference	/
Q 2	0.611 (0.484, 0.772)	<0.001	0.620 (0.470, 0.817)	0.001	0.785 (0.585, 1.055)	0.106
Q 3	0.405 (0.316, 0.520)	<0.001	0.441 (0.350, 0.556)	<0.001	0.660 (0.501, 0.869)	0.004
Q 4	0.362 (0.281, 0.467)	<0.001	0.310 (0.232, 0.415)	<0.001	0.583 (0.393, 0.867)	0.009
P for trend	/	<0.001	/	<0.001	/	0.002

Model 1: Unadjusted; Model 2: Adjusted for gender, age, ethnicity, poverty income ratio; Model 3: Adjusted for all covariates (gender, age, ethnicity, PIR, BMI, cotinine, AST, ALT, GFR creatinine clearance, cardiovascular disease, stroke, alcohol consumption, and smoking status); eGDR, Estimated Glucose Disposal Rate; PRISm, Preserved Ratio Impaired Spirometry; OR, Odds ratio; CI, Confidence Interval.

suggesting that PRISm may represent a unique clinical phenotype with its own pathophysiological and prognostic implications (6, 9). This study investigates the relationship between estimated glucose disposal rate (eGDR), an indicator of insulin resistance, and PRISm. Our results show that lower eGDR is significantly associated with an increased risk of PRISm, suggesting a negative relationship between insulin resistance and PRISm.

The baseline characteristics of participants further clarified the differences between the PRISm and non-PRISm groups. Notably, the PRISm group was older, had higher cotinine levels, lower eGFR, and a higher prevalence of cardiovascular diseases and obesity. While it is widely acknowledged that smoking impairs lung function, cotinine is specifically associated with reduced lung function and airflow obstruction (22). Additionally, Obesity, a recognized risk factor for both insulin resistance and respiratory diseases, increases airway resistance while simultaneously altering breathing patterns, thereby affecting ventilation and oxygenation (23); at the same time, the accumulation of visceral adipose tissue due to obesity is closely associated with a higher incidence of respiratory diseases (24). However, in the multivariable logistic regression analysis, eGDR remained significantly negatively correlated with PRISm even after fully adjusting for confounding factors such as sex, age, race, BMI, cotinine levels, liver and kidney function, cardiovascular disease, smoking, and alcohol consumption. This suggests that higher insulin sensitivity, as reflected by higher eGDR, is associated with a lower risk of developing PRISm, independent of these potential confounders.

In the multivariable logistic regression analysis, all models demonstrated a significant negative association between eGDR and

TABLE 3 Subgroup and interaction analysis of eGDR and PRISm by gender, age, ethnicity, and poverty ratio.

Subgroup	*OR* (95% CI)	*P*	*P* for interaction
Overall	0.927 (0.880, 0.976)	0.005	
Gender			0.012
Male	0.938 (0.669, 1.315)	0.702	
Female	0.874 (0.821, 0.929)	<0.001	
Age			0.016
≤40	0.949 (0.883, 1.019)	0.146	
>40	0.913 (0.848, 0.982)	0.016	
Ethnicity			0.408
Mexican American	0.732 (0.646, 0.83)	<0.001	
Other Hispanic	0.860 (0.715, 1.033)	0.104	
Non-Hispanic White	0.927 (0.857, 1.002)	0.055	
Non-Hispanic Black	0.908 (0.858, 0.961)	0.002	
Other Race	1.073 (0.896, 1.285)	0.433	
PIR			0.984
≤1.3	0.941 (0.873, 1.014)	0.109	
>1.3 and ≤3.5	0.912 (0.846, 0.983)	0.017	
>3.5	0.939 (0.854, 1.034)	0.193	

eGDR, Estimated Glucose Disposal Rate; PRISm, Preserved Ratio Impaired Spirometry; OR, Odds ratio; CI, Confidence Interval.

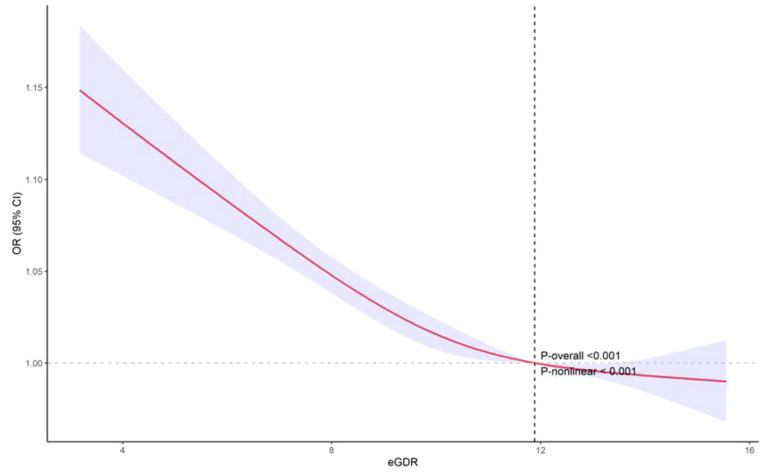

FIGURE 2
Nonlinear relationship between eGDR and PRISm: restricted cubic spline analysis. eGDR, Estimated Glucose Disposal Rate; PRISm, Preserved Ratio Impaired Spirometry.

PRISm. In both unadjusted and adjusted models, each unit increase in eGDR was associated with a 15.1% reduction in the likelihood of PRISm. This relationship persisted in the fully adjusted model, where even after accounting for potential confounders such as sex, age, ethnicity, BMI, cotinine levels, renal and hepatic function, cardiovascular disease, smoking, and alcohol consumption, each unit increase in eGDR was still linked to a 7.3% decrease in the likelihood of PRISm.

These findings suggest that higher eGDR levels, indicative of better insulin sensitivity, are associated with a lower risk of PRISm. This relationship may be partly explained by the characteristics of participants with moderate or severe insulin resistance, who often present with systemic inflammation—marked by elevated levels of white blood cells, neutrophils, and plasma interleukin-6—and dyslipidemia, characterized by high triglycerides and low HDL cholesterol. Insulin resistance is typically accompanied by chronic low-grade inflammation, which promotes the release of inflammatory mediators such as tumor necrosis factor-α and interleukin-6 (25, 26). These factors not only impair systemic metabolism but also directly affect lung tissue, leading to airway inflammation and structural remodeling, which contribute to airflow limitation and reduced lung function (27–29). Additionally, insulin resistance increases oxidative stress in the body, which refers to an imbalance between the production of free radicals and antioxidant defenses. Elevated levels of free radicals can damage cells, including lung cells, causing dysfunction and structural damage (30). This damage not only compromises airway patency but may also trigger an inflammatory response in the lungs, further exacerbating lung function impairment (31). Beyond systemic effects, insulin resistance may impair lung function via adipose tissue dysfunction, which promotes pro-inflammatory adipokines like resistin and reduces anti-inflammatory adiponectin (32, 33). Resistin is linked to asthma, COPD, fibrosis, and acute lung injury, while adiponectin suppresses pulmonary inflammation by inhibiting TNF-α, IL-6, and chemokine production (34, 35). These adipokine shifts may mediate the adverse impact of insulin resistance on lung health. Moreover, chronic hyperinsulinemia may also interfere with cellular repair and regeneration pathways in the lung, limiting the ability to recover from environmental or inflammatory insults (36).

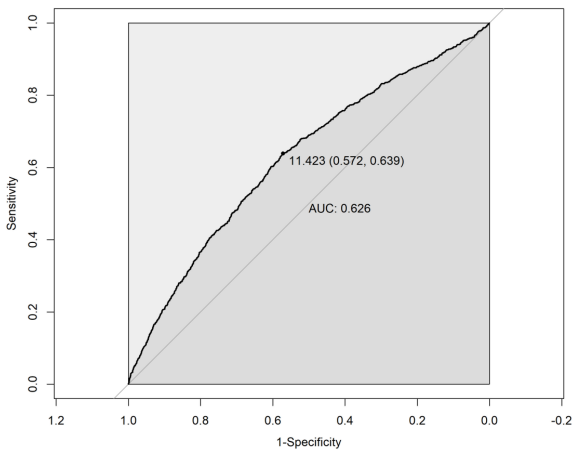

FIGURE 3
Receiver operating characteristic (ROC) curve for eGDR in predicting PRISm. eGDR, Estimated Glucose Disposal Rate; PRISm, Preserved Ratio Impaired Spirometry.

Subgroup analyses in our study revealed that this association was more pronounced among females and individuals aged over 40 years. The stronger association in women may be attributable to differences in body fat distribution and hormonal regulation (37, 38). Sex-specific patterns in insulin resistance, influenced by sex steroid hormones, may partly explain this finding. Estrogens play a protective role in metabolic regulation, and their decline after menopause contributes to increased insulin resistance and diabetes risk (39). A Evidence from both human genetics and animal models has shown that disruption of estrogen signaling—such as through aromatase or estrogen receptor α deficiency—can lead to marked metabolic dysfunction (38). Moreover, estrogen,

which has anti-inflammatory effects, may play a protective role in premenopausal women; with age-related hormonal changes, metabolic dysregulation may have a more deleterious impact on lung function (40). These findings suggest that insulin resistance may have a more pronounced impact on lung function in women due to hormone-related differences in insulin sensitivity and inflammation. In older adults, age-related skeletal muscle dysfunction—characterized by mitochondrial impairment, metabolic dysregulation, inflammation, and sarcopenia—leads to reduced insulin sensitivity and is a key mechanism underlying insulin resistance in the elderly (41). The synergistic effects of sarcopenia and insulin resistance can exacerbate systemic inflammation and oxidative stress, both of which are known to impair lung function (14, 42). Additionally, age-related declines in lung elasticity, respiratory muscle strength, and ventilatory responsiveness may render older adults more vulnerable to the adverse effects of metabolic abnormalities on pulmonary function (43). In contrast, no significant interaction was observed between eGDR and race or poverty-to-income ratio; however, notable associations were found within specific racial groups. Notably, significant associations between eGDR and PRISm were observed in Non-Hispanic Black and Mexican American participants. This finding aligns with prior studies indicating that both racial groups exhibit higher levels of insulin resistance and insulin secretion compared to non-Hispanic Whites. For instance, Haffner et al. reported that both Non-Hispanic Black and Mexican American individuals showed significantly higher levels of insulin resistance than their non-Hispanic White counterparts (44). Similarly, Hasson et al. highlighted the heightened insulin resistance and upregulated beta-cell function in African Americans, potentially contributing to their elevated risk of metabolic diseases (45). These metabolic characteristics may also influence pulmonary outcomes, thereby partially explaining the higher prevalence of PRISm in these populations.

The non-linear relationship observed in the restricted cubic spline analysis indicates that while higher levels of eGDR are associated with a decreased likelihood of PRISm, this association tends to plateau once eGDR exceeds approximately 12 mg/kg/min. This suggests a potential threshold effect, beyond which further improvements in insulin sensitivity confer minimal additional benefit in reducing PRISm risk. Such a plateau is biologically plausible, as metabolic improvements may only translate to clinical benefits up to a certain point, after which risk stabilizes. Interventions targeting insulin resistance may therefore be particularly beneficial for individuals with lower baseline eGDR. Additionally, ROC curve analysis demonstrated that eGDR has a certain predictive accuracy in identifying PRISm, with an AUC of 0.626. Although the AUC indicates only limited discriminatory power, this result suggests that eGDR may be more suitable as a metabolic health risk indicator rather than a standalone diagnostic tool for PRISm. In future research or clinical practice, eGDR could be combined with other biomarkers—such as inflammatory markers, lung imaging parameters, or genetic risk scores—to enhance predictive performance and facilitate early identification of high-risk individuals.

Overall, our findings demonstrate that lower eGDR, indicating higher insulin resistance, is significantly associated with increased PRISm risk, independent of common confounders. This association is stronger in women and older adults, likely due to hormonal and age-related physiological changes. The observed threshold effect suggests that improving insulin sensitivity may be most beneficial in individuals with lower baseline eGDR. While eGDR alone has limited predictive power, it may serve as a useful metabolic marker when combined with other indicators to better identify individuals at risk for PRISm.

Limitations

This study has several limitations that should be acknowledged. First, the cross-sectional design restricts our ability to establish causal relationships between eGDR and PRISm, as we can only infer associations rather than direct causation. Additionally, the reliance on self-reported data for lifestyle factors, such as smoking and alcohol consumption, may introduce bias or inaccuracies. The use of eGDR as a surrogate measure of insulin sensitivity, while clinically relevant, may not capture all aspects of metabolic health, potentially leading to residual confounding. Furthermore, although we adjusted for numerous known confounders, residual confounding from unmeasured or unknown variables—such as environmental exposures, detailed dietary patterns, genetic predispositions, and undiagnosed comorbidities—cannot be completely ruled out. Moreover, the generalizability of our findings may be limited, as the study population primarily consisted of adults from specific demographic groups, which may not fully represent the broader population. Finally, while we adjusted for several potential confounders, residual or unrecognized confounders may still influence the observed associations. Future research should aim to address these limitations through longitudinal designs and more comprehensive assessments of metabolic health and environmental factors.

Conclusion

In conclusion, our study demonstrates a significant inverse association between estimated eGDR and PRISm among a diverse population of US adults. Participants with lower eGDR values exhibited a higher prevalence of PRISm, indicating greater insulin resistance and potential metabolic dysfunction. The findings suggest that eGDR may serve as a valuable marker for assessing the risk of PRISm, particularly among women and older adults. Given the growing recognition of the interplay between metabolic health and respiratory function, further research is warranted to elucidate the underlying mechanisms linking insulin resistance and pulmonary impairment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The National Health and Nutrition Examination Surveys (NHANES) program received approval from the National Center for Health Statistics Research (NCHS) Ethics Review Board, and all survey participants consented by signing a consent form. The NCHS permits researchers to utilize the data they provide for research purposes. Prior to public release, the NCHS anonymizes NHANES data, ensuring anonymity throughout analysis. Hence, no additional ethical approval or informed consent was necessary for our secondary data analysis in this study. Further information regarding the NCHS Research Ethics Review Board Approval is available on the NHANES website (https://www.cdc.gov/nchs/nhanes/irba98.htm). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

TL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. SJ: Data curation, Resources, Visualization, Writing – review & editing. XS: Data curation, Funding acquisition, Software, Validation, Writing – review & editing. SH: Conceptualization, Formal analysis, Validation, Writing – review & editing. HM: Conceptualization, Data curation, Formal analysis, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1525573/full#supplementary-material

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Evaluating the link between insulin resistance and cognitive impairment using estimated glucose disposal rate in a non-diabetic aging population: results from the CHARLS

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Background: Emerging evidence suggests insulin resistance may contribute to neurodegeneration, yet its role in non-diabetic populations remains unclear. This study explores the relationship between estimated glucose disposal rate (eGDR), a measure of insulin sensitivity, and incident cognitive dysfunction in non-diabetic adults.

Methods: Our longitudinal analysis utilized data from 5,178 CHARLS participants (age $\geq$ 45 years). Insulin sensitivity was quantified using eGDR, calculated from waist circumference, hypertension status, and hemoglobin A1c levels. Participants were stratified by eGDR quartiles for comparative analysis. We employed multivariable Cox models, survival curves, restricted cubic splines, and sensitivity testing to evaluate associations with cognitive outcomes.

Results: Over an 8.7-year follow-up, cognitive dysfunction developed in 36.9% of participants. Analyses revealed significant metabolic-cognitive associations, with each standard deviation increase in eGDR linked to a 15.8% reduction in risk (adjusted hazard ratio [HR] = 0.792, 95% confidence interval [CI]: 0.793–0.881). Restricted cubic spline analysis identified non-linear threshold effects, with risk accelerating below certain eGDR levels ($P < 0.05$). Kaplan-Meier survival analysis demonstrated significant differences in cognitive impairment incidence across eGDR quartiles ($P = 0.003$). Additionally, both eGDR and metabolic score for insulin resistance (METS-IR) showed comparable predictive value for cognitive impairment risk, outperforming other metabolic indices, including the atherogenic index of plasma (AIP), and the triglyceride glucose index (TyG).

Conclusion: These findings position eGDR as a promising biomarker for cognitive risk stratification in non-diabetic adults. However, further multi-database studies should validate these associations and explore the underlying mechanisms.

KEYWORDS

cognitive impairment, estimated glucose disposal rate, insulin resistance, diabetes mellitus, CHARLS

Introduction

The rising prevalence of cognitive impairment poses a significant public health burden, intensified by shifting age demographics worldwide. This complex condition arises from an interplay of hereditary factors, environmental influences, and lifestyle variables. Of particular interest is insulin resistance (IR), which has gained attention as a modifiable factor linked to progressive cognitive decline (1–3). Although traditionally viewed through the lens of metabolic disease and Type 2 diabetes mellitus (T2DM), contemporary research establishes IR as an independent predictor of cognitive dysfunction even in individuals with normal glucose regulation (3–6). These findings align with insulin's diverse neurological functions, including its involvement in brain energy homeostasis, synaptic maintenance, and neuroprotective mechanisms. Mounting evidence further implicates disrupted insulin pathways in the development of Alzheimer's pathology and other neurodegenerative disorders.

Current diagnostic approaches for IR evaluation, which primarily rely on fasting blood glucose (FBG) and hemoglobin A1c (HbA1c) measurements, demonstrate diminished reliability in non-diabetic populations (7–10). Such metrics often fail to detect early metabolic disturbances occurring outside pancreatic regulation. eGDR, a novel composite index combining abdominal obesity, hypertensive status, and glycemic control parameters, presents a more robust solution. Prior investigations have primarily concentrated on diabetic subjects, potentially obscuring IR's true effects through glucose-related confounding variables while also facing sample size limitations. Importantly, this innovative measure shows superior accuracy in detecting metabolic dysfunction among populations with preserved glucose tolerance (11, 12) and effectively forecasts cardiovascular-metabolic disease trajectories (13–15). Nevertheless, the connection between eGDR and cognitive performance remains unexplored. Clarifying this relationship may provide valuable tools for identifying high-risk subgroups and implementing timely preventive measures in metabolically vulnerable, non-diabetic individuals.

Utilizing the China Health and Retirement Longitudinal Study (CHARLS) dataset, this research examines how eGDR correlates with newly developed cognitive dysfunction in non-diabetic individuals. Additionally, the analysis compares the eGDR with three contemporary metabolic markers: the metabolic score for insulin resistance (METS-IR), the atherogenic index of plasma (AIP), and the triglyceride glucose index (TyG), in order to assess their respective prognostic capacities for predicting cognitive impairment. These investigations seek to clarify the role of insulin resistance and lipid metabolism in cognitive aging while establishing potential diagnostic applications for eGDR in metabolically at-risk, non-diabetic cohorts.

Materials and methods

Study population

This study draws upon data from the CHARLS, a nationally representative cohort study initiated in 2011, with subsequent follow-up waves in 2013, 2015, 2018, and 2020 (16). A total of 12,527 participants were excluded based on the following criteria: missing data on eGDR (n = 7,767); a diagnosis of DM in 2011 (n = 1,486); a history of brain injury, intellectual disability, stroke, or memory impairment, or incomplete information (n = 524); a diagnosis of cognitive impairment or missing cognitive impairment data in 2011 (n = 2,490); age under 45 years (n = 124); or loss to follow-up (n = 136). Following these exclusions, the final sample comprised 5,178 eligible participants (Figure 1). All study participants provided written informed consent before enrollment. This research project received ethical approval from Peking University's Biomedical Ethics Review Committee (IRB00001052-11015), with data collection strictly limited to consenting individuals for final analysis.

Calculation of eGDR and IR stratification

The estimated glucose disposal rate was derived from the equation: eGDR (mg/kg/min) = 21.158-(0.09 × waist circumference [cm])-(3.407 × hypertension [1 = yes, 0 = no])-(0.551 × hemoglobin A1c) [%]). Participants were then stratified by eGDR quartiles for insulin resistance level comparisons.

Cognitive function assessment in CHARLS

The CHARLS employed the Mini-Mental State Examination (MMSE) to measure cognitive performance, utilizing this standardized tool's capacity to evaluate both global functioning and specific domains including memory retention and cognitive processing. For memory assessment, researchers administered a ten-item verbal recall test, with participants required to repeat words both immediately following presentation and after a 5-min delay, where one point was allocated for each accurate response (potential score: 0–20). The evaluation of fundamental cognitive capacities incorporated three components: arithmetic tasks involving successive subtraction from 100, geometric figure replication to assess spatial reasoning, and temporal awareness questions regarding date identification. Performance on these measures contributed equally to a maximum of 11 points. By aggregating results from both domains (total possible: 31 points), investigators identified cognitive impairment using a validated cutoff of <11 points (17, 18).

Potential covariates

This investigation expanded upon existing literature by incorporating a multidimensional array of covariates spanning sociodemographic attributes, health behaviors, and clinical biomarkers. Participant profiles captured age, sex, residential classification (urban/rural), geographical location (northern/southern China), educational background (categorized as ≤9 years, 10–12 years, or ≥13 years of schooling), and partnership status (married/cohabiting versus single/divorced/widowed). Health behavior indicators documented tobacco use, alcohol consumption, and sensory impairments,

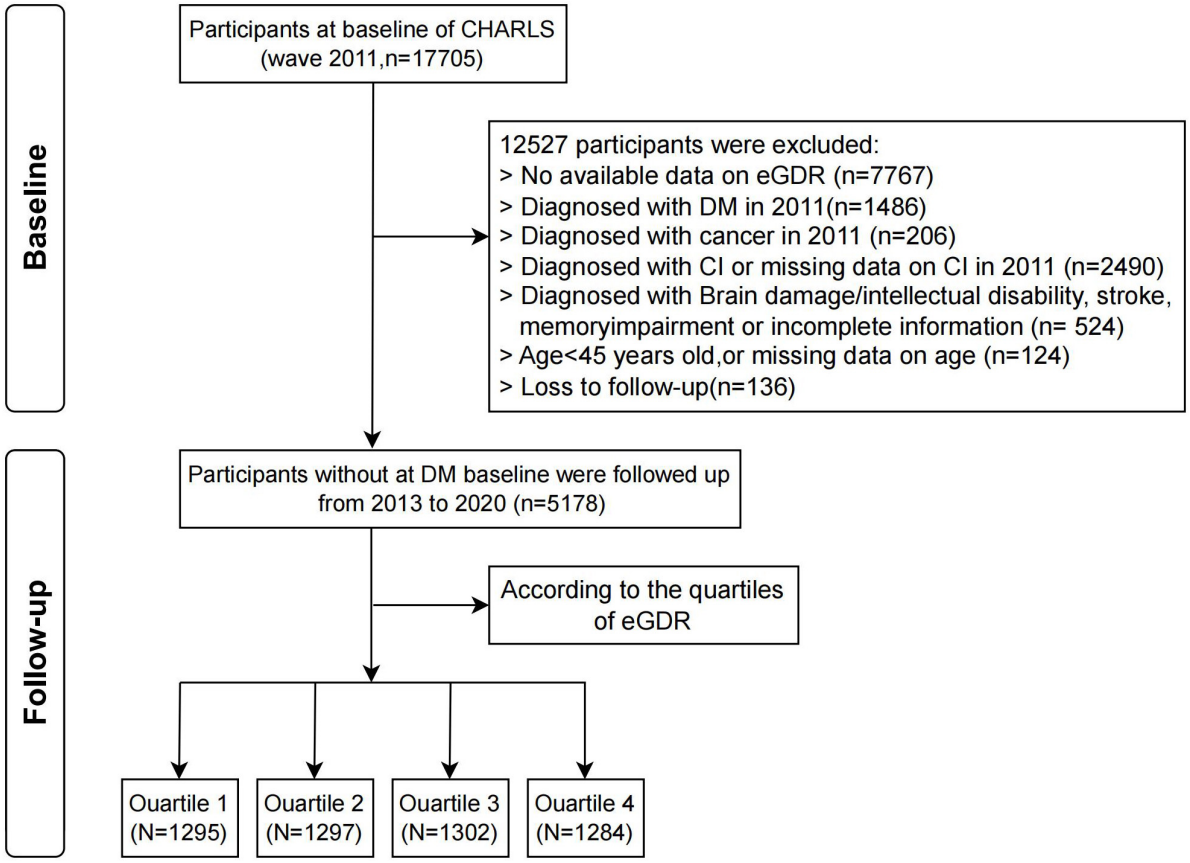

FIGURE 1
Participant selection process flowchart. eGDR, estimated glucose disposal rate; CI, cognitive impairment; CHARLS, China Health and Retirement Longitudinal Study; DM, diabetes mellitus.

alongside psychosocial factors (social engagement levels and depressive symptoms) and cardiometabolic risk markers (elevated blood pressure and adiposity). Biochemical analyses quantified glycemic control (HbA1c, fasting blood glucose [FBG]), hematologic parameters (hemoglobin), and lipid profiles (total cholesterol [TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol[LDL-C]). Adiposity was determined via body mass index (BMI) (weight[kg]/height[m]^2), classifying obesity at $\geq$28 kg/m^2. Hypertension criteria included: (1) clinical diagnosis, (2) antihypertensive medication use, or (3) systolic/diastolic pressures exceeding 140/90 mmHg. Diabetes mellitus was operationalized through: (1) self-reported diagnosis, (2) glucose-lowering drug use, (3) FPG $\geq$ 126 mg/dL (7.0 mmol/L), or 4) HbA1c $\geq$ 6.5%. Depressive symptomatology was evaluated using the CESD-10 instrument (score range: 0–30 points).

Statistical analysis

Comparisons across eGDR quartiles were conducted to examine variations in demographic, health, and metabolic characteristics, including age, sex, education, marital status, rural residence, geographic region, BMI, WC, systolic blood pressure (SBP), diastolic blood pressure (DBP), obesity, smoking, alcohol use, hemoglobin, FBG, vision impairment, HbA1c, TC, TG, HDL, LDL, diabetes, hearing loss, depressive symptoms, and social isolation. Continuous data following normal distributions were summarized as means with standard deviations (mean $\pm$ SD) and compared using parametric analysis of variance, while non-normally distributed measures were reported as medians with interquartile ranges [median (IQR)] and analyzed through non-parametric Kruskal-Wallis tests. Categorical data were expressed as frequency counts with percentages [n (%)], with group differences examined via χ^2 tests. The dose-response association between eGDR and cognitive impairment was investigated using restricted cubic splines (RCS), with Cox proportional hazards models applied to evaluate this relationship through both continuous and categorical parameterizations of eGDR. Three progressively adjusted models were constructed: a crude model (unadjusted), a partially adjusted model (controlling for demographic factors including age, sex, residence location, marital status, and education level, along with behavioral covariates of smoking and alcohol consumption), and a fully adjusted model (incorporating all potential confounders). Additional stratified analyses were performed using multivariable Cox regression to identify potential effect modifications across population subgroups. Kaplan-Meier survival analysis with log-rank tests compared cognitive impairment risk across eGDR quartiles. Sensitivity analyses were conducted under four conditions: (1) excluding

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TABLE 1 Baseline characteristics of participants stratified by quartiles of eGDR.

Characteristic	Quartiles of eGDR				*P*-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Participants	1295	1297	1302	1284	
eGDR	9.45 ± 2.07	6.50 ± 0.68	8.92 ± 0.91	10.70 ± 0.27	<0.001
TyG	4.64 ± 0.29	4.74 ± 0.29	4.68 ± 0.29	4.61 ± 0.28	
AIP	−0.02 ± 0.31	0.09 ± 0.30	0.02 ± 0.32	−0.05 ± 0.30	
METS-IR	35.31 ± 7.58	40.39 ± 7.23	36.75 ± 7.91	34.45 ± 5.46	
Age, years	59.01 (8.42)	58.34 (8.84)	55.95 (7.90)	56.34 (8.23)	<0.001
Gender					0.257
Male	645 (49.85%)	655 (50.54%)	689 (52.92%)	679 (52.96%)	
Female	649 (50.15%)	641 (49.46%)	613 (47.08%)	603 (47.04%)	
Rural residence					<0.001
Rural	700 (54.05%)	791 (60.99%)	847 (65.05%)	901 (70.17%)	
Urban	595 (45.95%)	506 (39.01%)	455 (34.95%)	383 (29.83%)	
Region					<0.001
South	574 (44.32%)	669 (51.58%)	678 (52.07%)	802 (62.46%)	
North	721 (55.68%)	628 (48.42%)	624 (47.93%)	482 (37.54%)	
Marital status					0.002
Married and living with spouse	1105 (85.33%)	1119 (86.28%)	1172 (90.02%)	1104 (85.98%)	
Others	190 (14.67%)	178 (13.72%)	130 (9.98%)	180 (14.02%)	
Education					0.216
Junior high school and below	1122 (86.64%)	1140 (87.90%)	1120 (86.02%)	1103 (85.90%)	
Senior high school	144 (11.12%)	135 (10.41%)	165 (12.67%)	151 (11.76%)	
Junior college or above	29 (2.24%)	22 (1.70%)	17 (1.31%)	30 (2.34%)	
Smoking status					0.036
Yes	511 (39.46%)	537 (41.40%)	553 (42.47%)	578 (45.02%)	
No	784 (60.54%)	760 (58.60%)	749 (57.53%)	706 (54.98%)	
Drinking status					0.959
Yes	561 (43.35%)	570 (43.95%)	562 (43.16%)	551 (42.91%)	
No	733 (56.65%)	727 (56.05%)	740 (56.84%)	733 (57.09%)	
Blind or partially blind					0.194
Yes	58 (4.48%)	60 (4.63%)	47 (3.61%)	69 (5.37%)	
No	1237 (95.52%)	1237 (95.37%)	1255 (96.39%)	1215 (94.63%)	
Deaf or partially deaf					0.151
Yes	90 (6.95%)	78 (6.02%)	63 (4.84%)	74 (5.76%)	
No	1205 (93.05%)	1218 (93.98%)	1239 (95.16%)	1210 (94.24%)	
Obesity					<0.001
Yes	338 (26.24%)	204 (15.81%)	33 (2.54%)	8 (0.63%)	
No	950 (73.76%)	1086 (84.19%)	1264 (97.46%)	1269 (99.37%)	
Depression					0.003
Yes	382 (30.25%)	368 (29.21%)	385 (30.20%)	444 (35.46%)	
No	881 (69.75%)	892 (70.79%)	890 (69.80%)	808 (64.54%)	
Social isolation					0.171
Yes	763 (58.92%)	775 (59.75%)	779 (59.83%)	808 (62.93%)	
No	532 (41.08%)	522 (40.25%)	523 (40.17%)	476 (37.07%)	

(Continued)

TABLE 1 (Continued)

Characteristic	Quartiles of eGDR				*P*-value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
SBP, mmHg	146.85 (19.48)	132.90 (20.39)	118.00 (11.20)	116.31 (11.58)	<0.001
DBP, mmHg	85.11 (11.67)	77.99 (11.58)	70.74 (8.70)	69.18 (8.77)	<0.001
BMI, Kg/m2	26.18 (3.39)	24.27 (3.82)	23.33 (2.51)	20.68 (2.43)	<0.001
WC, cm	93.55 (7.44)	87.41 (10.72)	84.89 (3.79)	74.95 (5.16)	<0.001
HbA1c, %	5.15 (0.41)	5.13 (0.41)	5.10 (0.36)	4.95 (0.38)	<0.001
FBG, mg/dL	103.49 (16.36)	102.47 (16.73)	100.08 (13.94)	97.67 (13.12)	<0.001
Hemoglobin, g/dL	14.78 (2.26)	14.59 (2.18)	14.43 (2.19)	14.17 (2.05)	<0.001
TC, mg/dL	199.07 (38.81)	192.80 (35.85)	191.22 (36.75)	185.21 (35.45)	<0.001
TG, mg/dL	125.67 (89.39–178.99)	109.74 (78.76–160.18)	99.12 (72.57–139.83)	85.85 (63.72–119.47)	<0.001
HDL-C, mg/dL	47.07 (13.02)	50.24 (14.66)	51.95 (14.74)	55.90 (15.18)	<0.001
LDL-C, mg/dL	122.57 (35.63)	115.98 (33.40)	116.66 (33.29)	110.91 (31.98)	<0.001

BMI, body mass index; SBP systolic blood pressure; DBP diastolic blood pressure; eGDR estimated glucose disposal rate; METS-IR, metabolic score for insulin resistance; AIP, atherogenic index of plasma; TyG, triglyceride glucose index; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; WC waist circumference; CI, cognitive impairment.

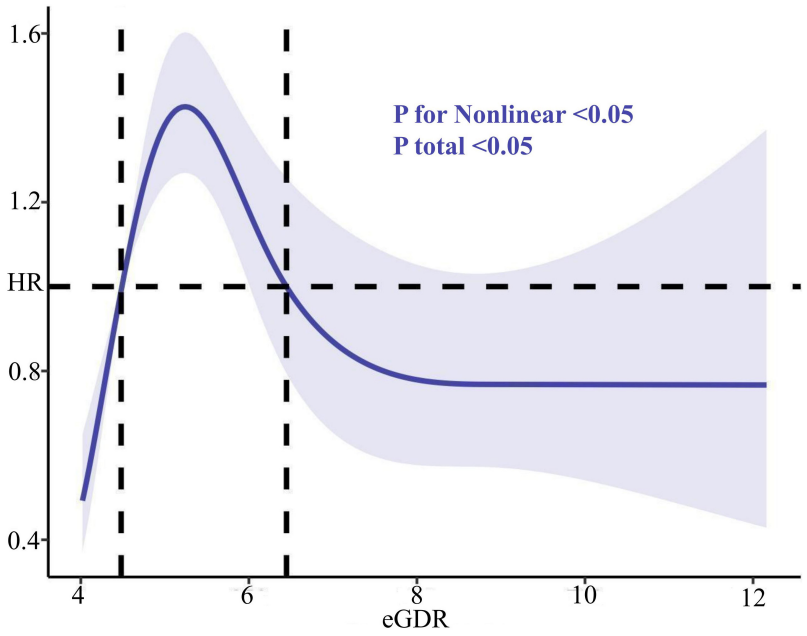

FIGURE 2
Association of eGDR and the risk of cognitive impairment using a multivariable-adjusted restricted cubic spines model. Restricted cubic spline analysis has four knots at the 5th, 35th, 65th, and 95th percentiles of eGDR. eGDR, estimated glucose disposal rate.

participants with cognitive impairment onset by 2013 and (2) redefining diabetes based solely on FBG and HbA1c levels.

Results

Baseline characteristics

Table 1 displays the baseline characteristics of participants stratified by quartiles of eGDR. Significant differences were observed across most demographic and health variables among the eGDR quartiles ($P < 0.05$). Participants in the lowest quartile of eGDR (Quartile 1, indicating higher insulin resistance) were generally older, had higher waist circumference, HbA1c, FBG, BMI, and blood pressure levels compared to those in higher eGDR quartiles. Conversely, HDL levels were lowest and triglyceride levels highest in Quartile 1, indicative of poorer metabolic health in this group. Notably, gender, vision and hearing impairment, educational level, alcohol consumption, and social isolation did not vary significantly across eGDR quartiles ($P > 0.05$).

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Association between baseline eGDR and cognitive impairment incidence

During the follow-up period, 1,913 participants (36.94%) developed cognitive impairment (Supplementary Table 1). The RCS analysis (Figure 2) revealed a significant non-linear association between eGDR and cognitive impairment incidence, with a higher risk of cognitive impairment observed as eGDR decreased (indicating increased insulin resistance) ($P < 0.05$). This association persisted across all adjusted models, suggesting a potential threshold effect in the link between eGDR and cognitive impairment risk.

Cox proportional hazards and Kaplan-Meier survival analysis of the association between eGDR and cognitive impairment

The Cox proportional hazards models demonstrated an inverse relationship between eGDR and cognitive impairment risk. Progressive multivariable adjustment revealed consistent associations: each unit reduction in eGDR corresponded to a 21.8% lower risk (HR = 0.792, 95%CI: 0.745–0.801, $P = 0.014$) in the unadjusted model, 19.5% (hazard ratio [HR] = 0.805, 95% confidence interval [CI]: 0.795–0.818, $P = 0.014$) after demographic adjustment, and 15.8% (HR = 0.842, 95%CI: 0.793–0.881, $P = 0.039$) in the fully-adjusted model (Table 2). When analyzed categorically, the highest three eGDR quartiles showed non-significant protective trends (all HR < 1, $P > 0.05$) in Model III (Table 2). Supporting these findings, Kaplan-Meier curves displayed significant divergence in cognitive impairment incidence by eGDR quartile (log-rank $P = 0.003$), with progressively shorter median survival times observed in lower quartiles (Figure 3).

Cox proportional hazards models comparing METS-IR, AIP, and TyG versus eGDR for CI risk

In the fully adjusted models, three metabolic indices demonstrated distinct associations with cognitive impairment. The metabolic score for insulin resistance (METS-IR) exhibited a significant inverse relationship, with each standard deviation increase corresponding to a reduced risk of cognitive impairment (HR = 0.99, 95%CI: 0.98–1.00, $P = 0.002$) (Supplementary Table 2). This protective effect was more pronounced in the quartile analyses, where participants in the highest METS-IR quartile had an 18% lower risk of cognitive impairment compared to those in the lowest quartile (HR = 0.82, 95%CI: 0.72–0.94, $P = 0.005$) (Supplementary Table 2). For the atherogenic index of plasma (AIP), linear regression analysis revealed a non-significant trend (HR = 0.90, 95%CI: 0.78–1.05, $P = 0.170$), although participants in the highest AIP quartile approached marginal significance (HR = 0.89, 95%CI = 0.78–1.02, $P = 0.100$) (Supplementary Table 3). In contrast, the triglyceride glucose index (TyG) demonstrated a near-significant linear association with cognitive impairment

TABLE 2 Multivariate-adjusted hazard ratios (95% confidence intervals) of estimated glucose disposal rate for cognitive impairment.

eGDR	Total N	No. of cognitive impairment	Model 1		Model 2		Model 3	
			HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Continues								
Per SD increase	5178	1913 (36.94)	0.792 (0.745, 0.801)	0.014	0.805 (0.795, 0.818)	0.018	0.842 (0.793, 0.881)	0.039
Quartiles								
Q1	1295	462 (35.68)	Reference		Reference		Reference	
Q2	1297	509 (39.24)	0.830 (0.797, 0.862)	0.057	0.835 (0.781, 0.866)	0.068	0.842 (0.823, 0.867)	0.114
Q3	1302	441 (33.87)	0.811 (0.779, 0.838)	0.163	0.823 (0.808, 0.841)	0.703	0.844 (0.824, 0.867)	0.486
Q4	1284	501 (39.02)	0.826 (0.791, 0.853)	0.097	0.803 (0.768, 0.839)	0.005	0.823 (0.795, 0.846)	0.051

HR, hazard ratio; CI, confidence interval; eGDR, estimated glucose disposal rate. Model1: unadjusted; Model 2: adjusted for age, sex, rural residence, marital status, education level, smoking status and drinking status; Model 3: adjusted all confounding factors(age, sex, rural residence, marital status, education level, region, smoking status, drinking status, deaf or partially deaf, blind or partially blind).

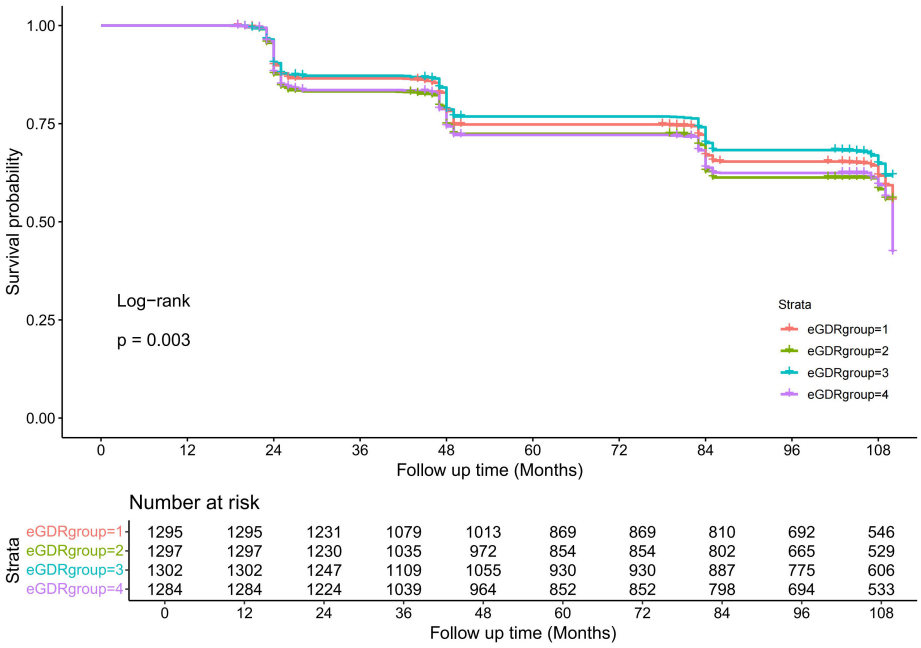

FIGURE 3
The Kaplan-Meier analysis for cognitive impairment was based on eGDR quartiles. eGDR, estimated glucose disposal rate.

risk (HR = 0.85, 95% CI: 0.72–1.00, P = 0.050), with participants in the highest TyG quartile showing robust protection against cognitive impairment (HR = 0.83, 95%CI: 0.73–0.95, P = 0.010) (Supplementary Table 4).

Subgroup analysis

The association between eGDR and cognitive impairment risk demonstrated significant heterogeneity by smoking status. Among never-smokers, each SD increment in eGDR corresponded to a 12.2% lower risk (HR = 0.822, 95%CI: 0.784–0.861, P = 0.038). Smokers showed a similar but non-significant inverse relationship (P = 0.216), with significant between-group heterogeneity (pinteraction = 0.023). No significant effect modification was observed for age, sex, or alcohol consumption (all pinteraction > 0.05, Table 3).

TABLE 3 Subgroup analysis of the association between eGDR (per 1 SD) and cognitive impairment.

Variables	HR (95%CI)	*P*-value	P interaction
Age, years			0.610
<60	0.983 (0.866, 1.117)	0.792	
≥60	0.082 (0.796, 0.844)	0.639	
Gender			0.070
Male	0.952 (0.842, 1.077)	0.433	
Female	1.113 (0.991, 1.250)	0.071	
Smoking status			0.023
Yes	0.919 (0.804, 1.051)	0.216	
No	0.822 (0.784, 0.861)	0.038	
Drinking status			0.081
Yes	0.951 (0.835, 1.082)	0.447	
No	1.107 (0.991, 1.237)	0.072	

HR, hazard ratio; CI, confidence interval; eGDR, estimated glucose disposal rate.

Sensitivity analysis

Sensitivity analyses using alternative modeling approaches consistently showed modest associations between continuous eGDR measurements and cognitive outcomes (Table 4). Both models produced comparable effect estimates, reinforcing the primary findings while demonstrating robustness to different analytical specifications.

Discussion

This investigation demonstrates that both the eGDR and METS-IR show similar predictive value for cognitive impairment risk, while outperforming other metabolic indices including the TyG and AIP. These results suggest that comprehensive measures of insulin sensitivity provide better prognostic capability than lipid-focused metrics for assessing cognitive risk. The comparable performance of these two insulin sensitivity markers emphasizes the fundamental role of insulin resistance in cognitive decline, consistent with their common physiological basis in glucose metabolism regulation (19–22). In contrast, the TyG displays only modest predictive ability, indicating its more limited capacity to reflect the complex metabolic dysfunction associated with neurodegeneration. Similarly, the AIP shows the weakest association, suggesting

TABLE 4 Sensitivity analysis of the association between eGDR (Q1–Q4) and cognitive impairment.

eGDR	Total N	No. of cognitive impairment	HR (95%CI)	*P*-value
FBG+HbA1c				
Continues				
Per SD increase	5228	1932 (36.95)	0.845 (0.832, 0.864)	0.041
Quartiles				
Q1	1308	467 (35.70)	Reference	
Q2	1306	512 (39.20)	0.842 (0.783, 0.905)	0.114
Q3	1307	445 (34.05)	0.877 (0.824, 0.927)	0.486
Q4	1307	508 (38.87)	0.833 (0.807, 0.864)	0.121
Excluded CI during or before wave 2				
Continues				
Per SD increase	3943	983 (24.93)	0.851 (0.804, 0.896)	0.033
Quartiles				
Q1	986	248 (25.15)	Reference	
Q2	985	251 (25.48)	0.883 (0.865, 0.901)	0.867
Q3	984	233 (23.68)	0.853 (0.748, 0.934)	0.697
Q4	988	251 (25.40)	0.868 (0.797, 0.906)	0.832

HR, hazard ratio; CI, confidence interval; eGDR, estimated glucose disposal rate; FBG, fasting blood glucose; HbA1c, hemoglobin A1c.

that lipid-centered evaluations offer comparatively less insight into cognitive trajectory modulation than measures of insulin-glucose homeostasis.

The role of insulin resistance in metabolic disorders is well-established, and it is now being more commonly linked to neurodegenerative processes. Studies have documented that insulin resistance adversely affects cognitive function, particularly in populations at risk for metabolic syndrome or diabetes (1, 4–6, 23–25). Reflecting the current literature, our research highlights the crucial role of insulin sensitivity in cognitive health, suggesting that eGDR may serve as a significant marker for assessing cognitive risk in individuals without diabetes. In contrast to studies that depend only on fasting glucose or HbA1c, eGDR includes extra factors such as waist size and blood pressure, giving a fuller picture of insulin resistance (26, 27). The analysis of subgroups uncovered a significant association between eGDR and cognitive impairment risk in non-smokers, whereas this was not the case for smokers, implying a potential interaction effect. Non-smokers with lower eGDR levels had a higher risk of cognitive impairment, while smokers did not exhibit this pattern. Smoking is known to exacerbate oxidative stress and vascular inflammation, which may interact with insulin resistance in complex ways, potentially diminishing the observable impact of eGDR on cognitive impairment in this subgroup (27). Future research could further elucidate the biological interactions between smoking and insulin resistance in relation to cognitive health. Significant differences in survival without cognitive impairment across eGDR quartiles were shown by the Kaplan-Meier survival analysis, with participants in higher quartiles (indicating lower insulin resistance) experiencing longer periods free from cognitive impairment. These findings underscore the cumulative impact of metabolic health on cognitive outcomes over time, reinforcing the notion that insulin sensitivity plays a protective role against cognitive decline. This aligns with studies suggesting that maintaining metabolic health can delay or prevent the onset of neurodegenerative diseases (28–31). The sensitivity analyses, which included models adjusting for various potential confounders, confirmed the robustness of our findings. The relationship between eGDR and cognitive impairment risk was stable across these models, even after redefining diabetes solely by FBG and HbA1c levels and excluding those with early cognitive decline. This research highlights eGDR's effectiveness as a predictor of cognitive impairment risk, especially among non-diabetic groups. However, additional longitudinal studies with more refined insulin resistance measures may further strengthen these findings.

This study has several limitations. First, while we controlled for multiple confounders, unmeasured factors may still influence the observed relationships. Second, eGDR was only measured at baseline, limiting our ability to observe changes in insulin resistance over time. Furthermore, using self-reported data on health behaviors, including smoking and alcohol use, could result in biases in reporting. Lastly, the generalizability of our findings may be limited to non-diabetic populations within a specific age range, underscoring the need for studies in diverse cohorts. Future research could focus on longitudinal changes in eGDR and their relationship with cognitive outcomes, particularly in populations at risk for both metabolic and cognitive disorders. Studying the biological pathways that associate insulin resistance with cognitive impairment may also offer valuable insights into targeted interventions. Moreover, examining the interaction effects of lifestyle factors, such as smoking and dietary habits, on the insulin resistance-cognitive impairment relationship could guide more personalized preventive strategies.

Conclusion

These findings suggest that elevated insulin resistance, as reflected by reduced eGDR levels, may represent a modifiable risk factor for cognitive decline in non-diabetic middle and older adults. The observed correlation underscores the potential of eGDR measurements in cognitive risk assessment, necessitating further research to clarify its role in predictive modeling and to inform strategies for maintaining cognitive health in aging populations.

Data availability statement

The original contributions presented in this study are included in this article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Biomedical Ethics Review Committee of Peking University (IRB00001052-11015). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. FX: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. MZ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1522028/full#supplementary-material

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The risk of hyperuricemia assessed by estimated glucose disposal rate

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Purpose: The estimated glucose disposal rate (eGDR) is a simple and noninvasive clinical measure used to assess insulin resistance (IR), yet its potential utility as a marker for hyperuricemia risk had not been systematically evaluated. This study aimed to investigate the relationship between eGDR and hyperuricemia risk among American adults.

Methods: Data for this cross-sectional study were obtained from the 2007–2018 National Health and Nutrition Examination Survey (NHANES). Hyperuricemia was identified as a serum urate (SU) concentration of ≥7 mg/dL in males and ≥6 mg/dL in females. The relationship between eGDR and hyperuricemia risk was assessed using multivariate logistic regression and restricted cubic spline (RCS) methods, with additional subgroup and interaction analyses performed.

Results: With increasing eGDR values, the prevalence of hyperuricemia decreased significantly (29.93% vs. 19.11% vs. 13.20% vs. 5.03%, ***P***<0.001). Multivariate logistic regression indicated that eGDR was independently associated with the risk of hyperuricemia after controlling for covariates including demographic, lifestyle, and clinical factors (OR=0.93, 95%CI: 0.90-0.96, ***P***<0.001). RCS analysis further revealed a nonlinear relationship, with a turning point at eGDR 7.96 mg/kg/min. Subgroup analysis revealed a stronger inverse association between eGDR and hyperuricemia risk in females.

Conclusions: The eGDR is inversely associated with hyperuricemia and appears to be a promising epidemiological tool for evaluating the impact of IR on the risk of hyperuricemia.

KEYWORDS

hyperuricemia, insulin resistance, estimated glucose disposal rate, NHANES, population-based study

1 Introduction

Hyperuricemia, characterized by abnormally high uric acid levels in the blood, is a common chronic metabolic condition (1). It serves as a key factor in the development of gout (a very painful long-term systemic inflammatory arthritis caused by the deposition of monosodium urate crystal) (2, 3) and has been increasingly associated with conditions such as diabetes, metabolic syndrome, cardiovascular diseases, and higher mortality rates (4–6). In recent years, the global rise in hyperuricemia cases has placed a considerable burden on healthcare systems and economies (7).

Insulin resistance (IR) is an important pathophysiological risk factor for hyperuricemia (8). IR, with consequent compensatory hyperinsulinemia, can disrupt uric acid homeostasis by altering renal urate excretion and potentially increasing *de novo* uric acid production (8, 9). The hyperinsulinemic-euglycemic clamp remains the most reliable method for measuring insulin resistance; however, its use in large-scale epidemiological studies is constrained by the complexity and time requirements of the procedure (10). The estimated glucose disposal rate (eGDR) is a clinical parameter-based index for evaluating insulin sensitivity (11). Initially developed for type 1 diabetes (T1DM) patients, it incorporates variables such as waist circumference (WC), glycated hemoglobin (HbA1c), and hypertension status (12, 13). Moreover, the recognition exists that these individual risk factors (including central obesity, hypertension, and inflammatory states), integral to the eGDR and often co-manifesting, are capable of mechanistically altering the intricate dynamics between glucose regulation and uric acid levels by exacerbating overall metabolic dysregulation. Lower eGDR values indicate poorer insulin sensitivity and greater IR. Compared with traditional methods such as the homeostasis model assessment of insulin resistance (HOMA-IR) and the triglyceride-glucose (TyG) index, eGDR demonstrates superior performance, is simpler to use, does not require fasting blood samples, and is particularly well-suited for large-scale studies (14, 15). Recently, research has shown that eGDR effectively reflects IR and is strongly linked to metabolic syndrome, cardiovascular diseases, and diabetes complications (11, 16–19).

Although IR is a well-established correlate of hyperuricemia with multiple established measurement indices, a notable research gap persists regarding the eGDR. The potential value of eGDR as a simple, non-fasting metric requiring only basic clinical parameters-which could serve as a robust insulin sensitivity marker particularly advantageous for large-scale epidemiological studies and hyperuricemia risk stratification in diverse populations-remains insufficiently investigated. Given the absence of studies on eGDR and hyperuricemia risk, our research, utilizing the National Health and Nutrition Examination Survey (NHANES) data, examine this relationship in the U.S. population. We predict that increased eGDR values are associated with a reduced risk of hyperuricemia.

2 Materials and methods

2.1 Study population

Data for this study were drawn from NHANES, a survey conducted by the National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC). The survey used a stratified, randomized, multi-stage sampling approach to ensure a nationally representative sample. Participants underwent physical examinations, completed health and nutrition surveys, and participated in laboratory tests. The NHANES protocol was reviewed and approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), and written informed consent was collected from all participants. Detailed methodologies and datasets are available at https://wwwn.cdc.gov/nchs/nhanes/. The NHANES cycles from 2007 to 2018, comprising 59842 participants, were utilized in this study, with exclusions applied to individuals under 20, pregnant women, and those lacking complete eGDR and uric acid data, resulting in 29328 participants.

2.2 Definition of eGDR and hyperuricemia

The eGDR (mg/kg/min) is estimated using the formula: eGDR = 21.158 − (0.09 × WC) − (3.407 × HTN) − (0.551 × HbA1c) (13, 20). In this equation, WC represents waist circumference in centimeters, HTN indicates hypertension status (1 = yes, 0 = no), and HbA1c refers to glycated hemoglobin (%). Hyperuricemia is determined by serum urate (SU) levels of 7 mg/dL or more in men and 6 mg/dL or more in women (21).

2.3 Assessment of covariates

In this study, covariates included demographic characteristics (age, gender, and race), socio-economic factors (marital status, income, and education), smoking history, alcohol consumption, diuretics use, health conditions (hypertension, diabetes, cardiovascular disease, chronic kidney disease, and gout), and other indicators such as body mass index (BMI), WC, HbA1c, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c). Smoking history encompasses both current and former smoking. Alcohol consumption was determined having consumed at least 12 alcoholic drinks in the past year. Use of diuretics was determined based on responses to the question: “During the past 30 days, have you used or taken any prescription medications?”. Diagnosis of chronic kidney disease was determined by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 and/or a urine

albumin-to-creatinine ratio (UACR) of 30 mg/g or more. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which incorporates age, gender, race, and serum creatinine (Scr) levels (22). Diabetes was diagnosed based on a self-reported history, fasting plasma glucose (FPG) levels of ≥7.0 mmol/L, HbA1c levels of ≥6.5%, or the use of antidiabetic drugs. Hypertension was defined as a self-reported history, systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or the use of antihypertensive medications. Cardiovascular diseases were identified through participants' self-reported histories of heart attacks, strokes, heart failure, coronary artery disease, or angina. The presence of gout was established through the question: "Has a doctor or other health professional ever told you that you have gout?". Full methodological details for each variable analyzed in this research are publicly accessible via the NHANES database (https://wwwn.cdc.gov/nchs/nhanes/).

2.4 Statistical analysis

In accordance with CDC guidelines, statistical analyses utilized a complex multistage cluster survey design and incorporated sampling weights. Continuous variables were presented as means with 95% confidence intervals (CIs), while categorical variables were summarized as percentages with 95% CIs. Weighted Student's t-tests and chi-squared tests were used to evaluate group differences in continuous and categorical variables, respectively. Logistic and linear regression models were applied to investigate the relationships between eGDR and hyperuricemia or SU levels. To assess potential nonlinear associations between eGDR and hyperuricemia risk, restricted cubic spline (RCS) regression with four knots was performed, with the median value as the reference point. A two-piecewise regression model was employed to identify intervals, and the Log-likelihood ratio test was used to evaluate the presence of a threshold effect. Subgroup analyses were carried out based on covariate stratification, with the other covariates being adjusted for. Receiver operating characteristic (ROC) curve analysis and decision curve analysis (DCA) were employed to compare the classification accuracy and clinical utility of eGDR with those of other alternative indicators. Statistical analyses in this research were performed using Empower software (http://www.empowerstats.com) and R software (http://www.R-project.org), with a two-sided P value < 0.05 considered statistically significant.

3 Results

3.1 Baseline characteristics of study population.

The study population consisted of 29328 participants with a mean age of 47.49 years. The racial composition included 8.64% Mexican Americans, 10.53% Non-Hispanic Blacks, 66.94% Non-Hispanic Whites, 5.90% Other Hispanics, and 7.98% from other racial groups. A weighted analysis was performed to evaluate the general and clinical characteristics of participants with and without hyperuricemia (Table 1). The results showed that individuals with hyperuricemia were generally older, predominantly male, more likely to smoke and consume alcohol, and more frequently used diuretics (P<0.01). They also had higher prevalence rates of diabetes, hypertension, chronic kidney disease, cardiovascular disease, gout, as well as elevated BMI, WC, HbA1c, TG, TC, and LDL-c levels (P<0.001). Additionally, they were found to have lower educational attainment and reduced HDL-c levels (P<0.01). Furthermore, eGDR levels were significantly reduced in the hyperuricemia group compared to the non-hyperuricemia group (P<0.001).

3.2 Baseline characteristics of four different quartiles (1-4) based on increasing eGDR values.

Participants were classified into four groups based on eGDR quartiles (Table 2). Compared to those in the lowest quartile, individuals in the higher quartiles were younger, more likely to be female and drinkers, and had lower rates of smoking, diuretic use, diabetes, hypertension, chronic kidney disease, cardiovascular disease, and gout (P<0.001). They also tended to have higher levels of education and a greater PIR (poverty income ratio) (P<0.001). Significant reductions were noted in BMI, WC, HbA1c, TG, TC, and LDL-c levels, while HDL-c levels were significantly higher (P<0.001). Race distribution also differed significantly (P<0.001). SU levels and hyperuricemia prevalence decreased with rising eGDR levels which is in agreement with the previous report (23) (P<0.001).

3.3 Analyzing the relationship between eGDR and hyperuricemia or SU levels using Logistic and Linear regression analysis.

Our findings demonstrate a significant negative association between elevated eGDR levels and hyperuricemia, which persists across models 1 (OR=0.78, 95%CI: 0.78-0.79, P<0.001), 2 (OR=0.79, 95%CI: 0.78-0.80, P<0.001), and 3 (OR=0.93, 95%CI: 0.90-0.96, P<0.001) (Table 3). Further stratification by eGDR quartiles, using the lowest quartile as a reference, shows that individuals in the highest quartile also have a lower risk of hyperuricemia in the fully adjusted model (OR=0.49, 95%CI: 0.38-0.63, P<0.001). The analysis of SU levels as the dependent variable and eGDR levels as the independent variable through linear regression also demonstrates a negative relationship between them (β=-1.19, 95%CI: -1.98–0.39, P=0.003) (Table 4).

3.3 RCS analysis

RCS analysis to assess non-linearity in the relationship between eGDR and hyperuricemia (Figure 1). The threshold effect analysis

TABLE 1 Baseline characteristics of study population, weighted.

Characteristics	Overall (n=29328)	Non-hyperuricemia (n=24359)	Hyperuricemia (n=4969)	*P* value
Age (years)	47.49 (47.04, 47.94)	46.93 (46.46, 47.41)	50.39 (49.75, 51.02)	<0.001
Gender				<0.001
Female	50.90 (50.28, 51.51)	54.65 (53.98, 55.33)	31.18 (29.56, 32.85)	
Male	49.10 (48.49, 49.72)	45.35 (44.67, 46.02)	68.82 (67.15, 70.44)	
Race (%)				<0.001
Mexican American	8.64 (7.25, 10.28)	9.00 (7.56, 10.68)	6.77 (5.45, 8.38)	
Non-Hispanic Black	10.53 (9.22, 12.01)	10.21 (8.96, 11.62)	12.21 (10.43, 14.25)	
Non-Hispanic White	66.94 (64.10, 69.66)	66.64 (63.77, 69.39)	68.51 (65.37, 71.48)	
Other Hispanic	5.90 (5.00, 6.96)	6.18 (5.22, 7.29)	4.48 (3.72, 5.38)	
Other Races	7.98 (7.15, 8.90)	7.97 (7.12, 8.91)	8.04 (6.95, 9.28)	
PIR (%)				0.193
<=1.3	21.62 (20.32, 22.96)	21.77 (20.41, 23.19)	20.81 (19.36, 22.33)	
>1.3, <=3.5	35.41 (34.11, 36.73)	35.14 (33.76, 36.55)	36.83 (34.87, 38.83)	
>3.5	42.98 (40.96, 45.02)	43.09 (41.00, 45.21)	42.36 (39.71, 45.06)	
Education level (above high school) (%)	61.45 (59.62, 63.24)	61.94 (60.06, 63.78)	58.88 (56.32, 61.39)	0.006
Smoking history (%)	44.47 (43.28, 45.67)	43.63 (42.30, 44.97)	48.88 (46.96, 50.80)	<0.001
Alcohol consumption (%)	80.56 (79.38, 81.68)	80.17 (78.92, 81.36)	82.59 (81.00, 84.07)	0.002
Diabetes (%)	12.79 (12.24, 13.36)	11.66 (11.08, 12.26)	18.72 (17.35, 20.18)	<0.001
Hypertension (%)	36.74 (35.71, 37.77)	33.07 (32.00, 34.16)	56.00 (54.12, 57.86)	<0.001
Chronic kidney disease (%)	13.81 (13.21, 14.43)	11.45 (10.89, 12.03)	26.29 (24.60, 28.04)	<0.001
Cardiovascular disease (%)	8.27 (7.81, 8.76)	7.30 (6.82, 7.81)	13.38 (11.98, 14.90)	<0.001
Gout (%)	3.95 (3.63, 4.31)	2.73 (2.45, 3.04)	10.38 (9.24, 11.65)	<0.001
Diuretics (%)	6.94 (6.52, 7.38)	5.12 (4.76, 5.50)	16.51 (15.23, 17.87)	<0.001
BMI (kg/m^2)	29.00 (28.84, 29.17)	28.38 (28.21, 28.55)	32.31 (31.99, 32.62)	<0.001
WC (cm)	99.34 (98.90, 99.78)	97.53 (97.08, 97.97)	108.85 (108.08, 109.62)	<0.001
HbA1c (%)	5.64 (5.62, 5.65)	5.61 (5.59, 5.63)	5.76 (5.72, 5.79)	<0.001
TG (mmol/L)	1.40 (1.37, 1.43)	1.32 (1.29, 1.35)	1.78 (1.71, 1.86)	<0.001
TC (mmol/L)	4.99 (4.97, 5.02)	4.97 (4.95, 5.00)	5.11 (5.06, 5.16)	<0.001
LDL-c (mmol/L)	2.94 (2.92, 2.97)	2.93 (2.91, 2.95)	3.02 (2.96, 3.07)	0.003
HDL-c (mmol/L)	1.38 (1.37, 1.39)	1.41 (1.39, 1.42)	1.24 (1.22, 1.25)	<0.001
eGDR (mg/kg/min)	7.86 (7.79, 7.93)	8.16 (8.09, 8.24)	6.28 (6.17, 6.40)	<0.001

Weighted analyses to evaluate the general and clinical characteristics of participants with and without hyperuricemia.
PIR, poverty income ratio; BMI, body mass index; WC, waist circumference; HbA1c, glycated hemoglobin; TG, triglycerides; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; eGDR, estimated glucose disposal rate.

shows that the inflection point for eGDR levels is 7.66 mg/kg/min, with a more pronounced relationship on the right side (OR=0.76, 95%CI: 0.71-0.82, ***P***<0.001) compared to the left side (OR=1.02, 95%CI: 0.98-1.06, ***P***=0.395) (Table 5).

3.4 Subgroup analyses

In analyses stratified by variables such as age (<60/≥60 years), gender (female/male), race (Mexican American/Non-Hispanic

TABLE 2 Baseline characteristics of four eGDR quartiles (increasing order, 1-4), weighted.

Characteristics	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* value
Age (years)	56.73 (56.25, 57.21)	53.20 (52.57, 53.83)	45.06 (44.51, 45.62)	37.70 (37.11, 38.28)	<0.001
Gender					<0.001
Female	44.88 (43.24, 46.53)	51.93 (50.47, 53.38)	44.39 (42.95, 45.84)	61.07 (59.59, 62.52)	
Male	55.12 (53.47, 56.76)	48.07 (46.62, 49.53)	55.61 (54.16, 57.05)	38.93 (37.48, 40.41)	
Race (%)					<0.001
Mexican American	7.13 (5.70, 8.89)	7.49 (6.12, 9.12)	11.87 (9.91, 14.15)	7.70 (6.54, 9.05)	
Non-Hispanic Black	14.01 (11.92, 16.39)	11.44 (9.96, 13.11)	8.35 (7.23, 9.64)	9.12 (7.99, 10.40)	
Non-Hispanic White	68.99 (65.55, 72.24)	68.15 (65.10, 71.06)	65.84 (62.68, 68.88)	65.35 (62.52, 68.07)	
Other Hispanic	4.56 (3.67, 5.65)	5.22 (4.38, 6.22)	6.82 (5.73, 8.09)	6.67 (5.56, 7.98)	
Other Races	5.32 (4.59, 6.15)	7.70 (6.64, 8.91)	7.12 (6.14, 8.24)	11.16 (9.82, 12.64)	
Married (%)	58.82 (56.92, 60.70)	56.96 (55.18, 58.73)	59.01 (57.03, 60.96)	48.60 (46.49, 50.72)	<0.001
PIR (%)					<0.001
<=1.3	22.34 (20.55, 24.25)	20.74 (19.30, 22.26)	21.61 (19.96, 23.37)	21.78 (19.93, 23.75)	
>1.3, <=3.5	37.55 (35.91, 39.23)	37.81 (35.84, 39.82)	34.45 (32.48, 36.48)	32.62 (30.71, 34.58)	
>3.5	40.10 (37.61, 42.65)	41.45 (38.97, 43.97)	43.94 (41.11, 46.80)	45.60 (42.87, 48.36)	
Education level (above high school) (%)	55.69 (53.67, 57.70)	59.29 (56.92, 61.62)	60.13 (57.67, 62.54)	69.10 (66.78, 71.32)	<0.001
Smoking history (%)	51.91 (50.27, 53.54)	47.27 (45.42, 49.13)	43.35 (41.80, 44.92)	37.31 (35.36, 39.29)	<0.001
Alcohol consumption (%)	78.22 (76.64, 79.72)	78.89 (77.45, 80.27)	82.36 (80.70, 83.90)	82.19 (80.59, 83.69)	<0.001
Diabetes (%)	37.17 (35.68, 38.70)	12.63 (11.58, 13.76)	5.20 (4.64, 5.81)	0.95 (0.70, 1.29)	<0.001
Hypertension (%)	95.13 (94.42, 95.76)	64.70 (63.08, 66.29)	2.48 (2.07, 2.97)	0.00 (0.00, 0.00)	<0.001
Chronic kidney disease (%)	27.47 (26.20, 28.79)	17.59 (16.45, 18.78)	7.33 (6.64, 8.10)	6.11 (5.46, 6.84)	<0.001
Cardiovascular disease (%)	18.70 (17.48, 19.99)	11.42 (10.45, 12.47)	3.67 (3.14, 4.30)	1.80 (1.45, 2.24)	<0.001
Gout (%)	9.74 (8.86, 10.70)	4.61 (3.95, 5.39)	2.22 (1.77, 2.78)	0.50 (0.36, 0.68)	<0.001
Diuretics (%)	19.79 (18.56, 21.09)	9.05 (8.14, 10.05)	1.19 (0.94,1.51)	0.53 (0.34, 0.84)	<0.001
BMI (kg/m^2)	35.43 (35.17, 35.69)	29.84 (29.62, 30.06)	29.05 (28.91, 29.19)	23.20 (23.10, 23.29)	<0.001
WC (cm)	117.09 (116.60, 117.57)	102.09 (101.58, 102.60)	99.94 (99.71, 100.18)	82.39 (82.14, 82.64)	<0.001
HbA1c (%)	6.32 (6.27, 6.36)	5.67 (5.65, 5.70)	5.47 (5.45, 5.48)	5.23 (5.22, 5.24)	<0.001
TG (mmol/L)	1.78 (1.71, 1.85)	1.47 (1.41, 1.52)	1.44 (1.39, 1.48)	0.98 (0.96, 1.00)	<0.001
TC (mmol/L)	4.95 (4.91, 5.00)	5.11 (5.07, 5.16)	5.14 (5.10, 5.18)	4.79 (4.76, 4.82)	<0.001
LDL-c (mmol/L)	2.88 (2.83, 2.92)	3.02 (2.97, 3.08)	3.11 (3.08, 3.15)	2.76 (2.73, 2.80)	<0.001
HDL-c (mmol/L)	1.22 (1.21, 1.23)	1.38 (1.37, 1.40)	1.32 (1.30, 1.33)	1.56 (1.54, 1.58)	<0.001
SU (mg/dL)	6.06 (6.01, 6.12)	5.59 (5.54, 5.64)	5.45 (5.40, 5.50)	4.76 (4.73, 4.80)	<0.001
Hyperuricemia (%)	29.93 (28.53, 31.36)	19.11 (17.81, 20.49)	13.20 (12.07, 14.42)	5.03 (4.41, 5.75)	<0.001

Participants were classified into four quartiles based on increasing eGDR from quartile 1 to quartile 4.

Black/Non-Hispanic White/Other Hispanic/Other Races), BMI (≤25/25-30/>30 kg/m^2), diabetes (yes/no), cardiovascular disease (yes/no), and chronic kidney disease (yes/no), the association between eGDR and hyperuricemia risk was significantly stronger in females (OR=0.87, 95%CI: 0.82-0.91) than in males (OR=0.97, 95%CI: 0.93-1.01) (***P*** for interaction=0.001)(Figure 2). Across other subgroups, the relationship showed no significant variation (***P*** for interaction > 0.05).

TABLE 3 Logistic regression analysis to assess relation between eGDR and hyperuricemia.

Hyperuricemia	OR (95%CI) *P* value		
	Model 1	Model 2	Model 3
Continuous			
eGDR	0.78 (0.78, 0.79) <0.001	0.79 (0.78, 0.80) <0.001	0.93 (0.90, 0.96) <0.001
Categories			
Q1	reference	reference	reference
Q2	0.53 (0.50, 0.58) <0.001	0.54 (0.50, 0.59) <0.001	1.02 (0.88, 1.18) 0.823
Q3	0.34 (0.31, 0.37) <0.001	0.34 (0.31, 0.38) <0.001	0.75 (0.63, 0.89) 0.001
Q4	0.13 (0.11, 0.14) <0.001	0.13 (0.11, 0.15) <0.001	0.49 (0.38, 0.63) <0.001
P for trend	<0.001	<0.001	<0.001

Logistic regression analyses in three different models of adjustment were performed to investigate the relationships between eGDR and hyperuricemia.
OR, odds ratio.
95% CI, 95% confidence interval.
Model 1: non-adjusted.
Model 2: adjusted for age, gender, race, marital status, PIR, education level, smoking, and alcohol consumption.
Model 3: adjusted for age, gender, race, marital status, PIR, education level, smoking, alcohol consumption, diabetes, chronic kidney disease, cardiovascular disease, gout, diuretics, BMI, TG, LDL-c, and HDL-c.

TABLE 4 Linear regression analysis to assess relation between eGDR and SU levels.

SU	β (95%CI) *P* value		
	Model 1	Model 2	Model 3
Continuous			
eGDR	-0.16 (-0.17, -0.16) <0.001	-9.06 (-9.44, -8.69) <0.001	-1.19 (-1.98, -0.39) 0.003
Categories			
Q1	reference	reference	reference
Q2	-0.50 (-0.54, -0.45) <0.001	-25.69 (-28.27, -23.11) <0.001	-1.35 (-5.35, 2.64) 0.506
Q3	-0.64 (-0.68, -0.59) <0.001	-37.50 (-40.21, -34.79) <0.001	-4.92 (-9.31, -0.53) 0.028
Q4	-1.28 (-1.32, -1.24) <0.001	-70.09 (-73.01, -67.17) <0.001	-14.02 (-19.62, -8.42) <0.001
P for trend	<0.001	<0.001	<0.001

Linear regression analyses in three different models of adjustment were performed to investigate the relationships between eGDR and SU levels.
95% CI, 95% confidence interval.
Model 1: non-adjusted.
Model 2: adjusted for age, gender, race, marital status, PIR, education level, smoking, and alcohol consumption.
Model 3: adjusted for age, gender, race, marital status, PIR, education level, smoking, alcohol consumption, diabetes, chronic kidney disease, cardiovascular disease, gout, diuretics, BMI, TG, LDL-c, and HDL-c.

3.5 ROC and DCA analyses

We evaluated eGDR in comparison with other IR surrogates, such as the Triglyceride-Glucose index (TyG) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). As illustrated in Figure 3, both ROC and DCA analyses were performed. The area under the curves (AUCs) for eGDR, TyG, and HOMA-IR were 69.5%, 65.0%, and 64.2%, respectively, highlighting eGDR as the most effective discriminator for hyperuricemia risk. Moreover, DCA indicated that the eGDR model offered increased net benefit across a broader range of threshold probabilities, reflecting its superior clinical usefulness.

TABLE 5 Threshold effect analysis of eGDR on hyperuricemia risk.

Model	OR (95% CI) *P* value
Total	0.93 (0.90, 0.96) <0.001
Breakpoint (K)	7.66
OR1 (<7.96)	1.02 (0.98, 1.06) 0.395
OR2 (>7.96)	0.76 (0.71, 0.82) <0.001
OR2/OR1	0.75 (0.69, 0.82) <0.001
P for logarithmic likelihood ratio	<0.001

OR, odds ratio.
95% CI, 95% confidence interval.
adjusted for age, gender, race, marital status, PIR, education level, smoking, alcohol consumption, diabetes, chronic kidney disease, cardiovascular disease, gout, diuretics, BMI, TG, LDL-c, and HDL-c.

4 Discussion

This study reports the results of our investigation about whether the eGDR, used to assess IR, can serve as a straightforward and noninvasive indicator of hyperuricemia. A cross-sectional analysis of 29328 participants revealed a negative and nonlinear correlation between the eGDR and the risk of hyperuricemia.

IR and SU levels were described bidirectionally interconnected because higher SU levels are known to adversely affect the insulin signaling pathway causing IR while IR is a known predictor for the

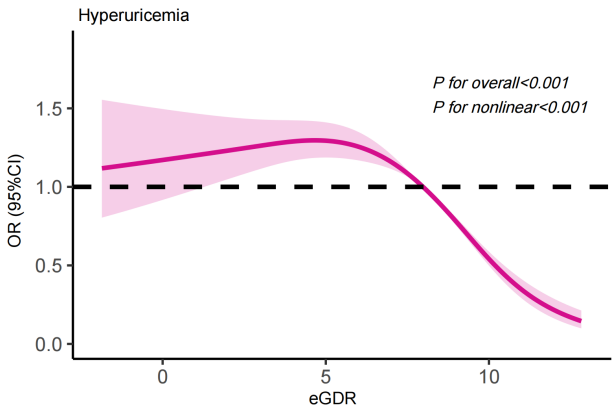

FIGURE 1
The results of RCS analysis.

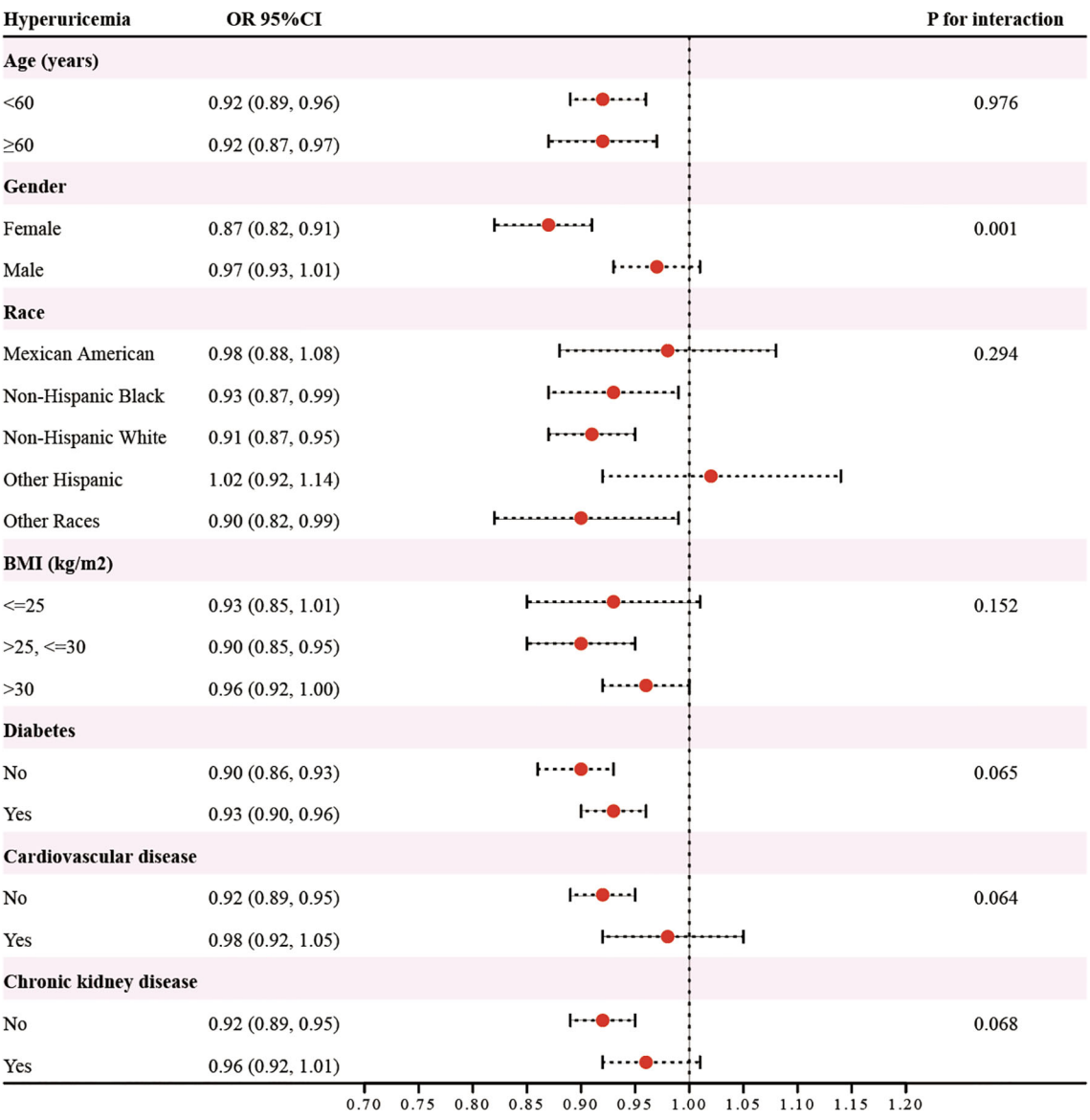

FIGURE 2
The results of subgroup analysis.

development of hyperuricemia (8, 24). Renal anti-uricosuric effect of insulin was also described preserved in states of IR in human. In compensatory hyperinsulinemia in the state of IR a chronic anti-uricosuric pressure on the kidney cause in hyperuricemia (25). In an *in vitro* experiment, insulin was shown to stimulate urate uptake in human proximal tubular cells (PTC-05) and HEK293T cells and in Xenopus oocyte expression system, where insulin was shown to stimulate urate uptake activity of urate reabsorption transporter, glucose transporter 9 (GLUT9) (26). The eGDR, which is based on clinical parameters, provides a practical and accurate assessment of insulin sensitivity and resistance (27). Specifically, the three components of eGDR reflect IR from different perspectives: Increased WC indicates visceral fat accumulation, which can promote the release of inflammatory factors, exacerbate IR, and reduce renal uric acid excretion, thereby leading to elevated SU levels (28). Hypertension is often associated with IR and may reduce uric acid clearance through renal hemodynamic alterations (29). Elevated HbA1c reflects chronic hyperglycemia and IR, both of which can also influence the renal tubular handling of uric acid (30). Our study found a nonlinear association between eGDR and the risk of hyperuricemia. When eGDR is below the threshold of 7.66, increases in eGDR have limited impact on hyperuricemia risk. However, once eGDR exceeds 7.66, further increases are significantly associated with a reduced risk of hyperuricemia. Therefore, eGDR may serve as a simple and practical screening tool for assessing hyperuricemia risk, especially in primary care settings where more complex measures of IR are unavailable. We propose 7.66 as a potential cutoff value for screening purposes. Our research also revealed that the relationship between eGDR and hyperuricemia risk was stronger in women, potentially reflecting their distinct physiological traits in metabolic regulation (31). Additionally, estrogen plays a role in reducing inflammation and

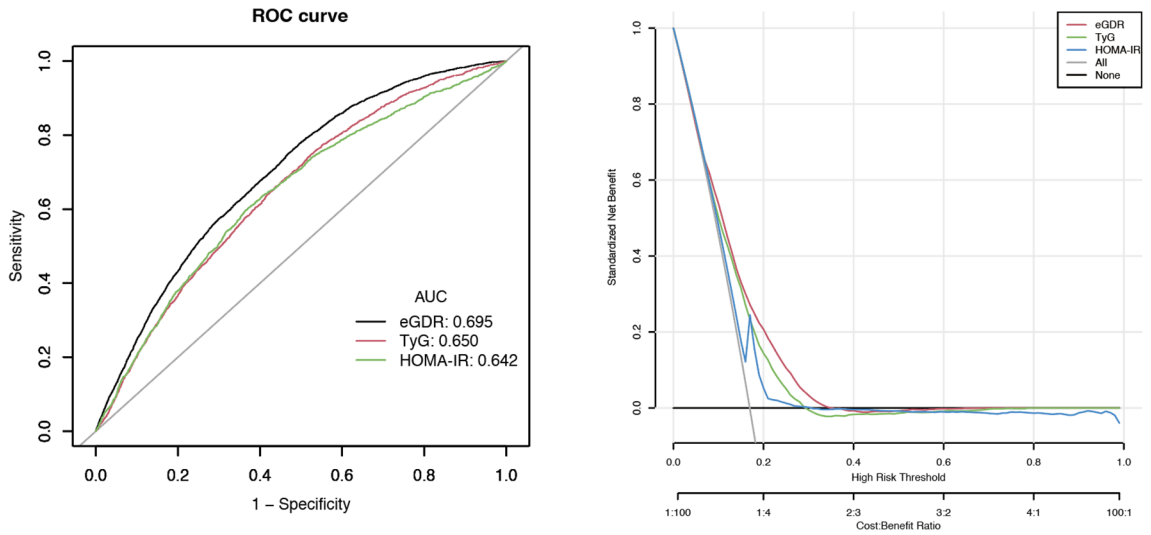

FIGURE 3
The results of ROC and DCA analyses.

enhancing insulin sensitivity, but its decline after menopause may worsen insulin resistance and disrupt uric acid metabolism (32–35). Estradiol reduces the expression of urate reabsorption transporters, including urate transporter 1 (URAT1) and GLUT9, as well as the efflux transporter ATP-binding cassette sub-family G member 2 (ABCG2), in ovariectomized mice, regardless of hormone replacement therapy (36). Additionally, 17-β-estradiol (E2) has been found to decrease GLUT9 protein levels in human renal tubular epithelial cells (HK2) through estrogen receptor β (ERβ) (37).

The interaction between IR and hyperuricemia is bidirectional, with both conditions sharing metabolic and pathological mechanisms that perpetuate a vicious cycle (4). Obesity, hyperglycemia, and lipid metabolism disorders are common factors linking IR and hyperuricemia, as they promote purine metabolism, oxidative stress, and inflammation, leading to increased uric acid production and decreased insulin sensitivity (38, 39). Clinical evidence showing that allopurinol combined with standard treatment in severe Covid-19 patients reduced oxidative and inflammatory disorders, suggesting that lowering serum urate levels can mitigate oxidative stress (40). In hyperuricemia, reactive oxygen species (ROS) are overproduced during uric acid formation by xanthine oxidases. Both ROS and intracellular uric acid can regulate multiple signaling pathways. For instance, studies demonstrate increased ROS production during 3T3-L1 cell differentiation into adipocytes, indicating that ROS generation correlates with fat accumulation. Interestingly, in fully differentiated 3T3-L1 adipocytes, ROS production was markedly inhibited by NADPH oxidase inhibitors, but not by oxypurinol, rotenone, or thenoyltrifluoroacetone (41).

Uric acid is recognized as an important antioxidant *in vivo*, capable of scavenging ROS such as hydroxyl radicals and peroxynitrite (42, 43). However, under severe oxidative stress, its antioxidant capacity may be overwhelmed, potentially disrupting metabolic homeostasis. Although xanthine oxidase is a key enzyme in uric acid production and a known source of ROS, the relationship between oxidative stress and xanthine oxidase activity remains complex. Some studies indicate that oxidative stress in hyperuricemia may occur independently of xanthine oxidase activity (44), and clinical trials with xanthine oxidase inhibitors (e.g., allopurinol, febuxostat) have yielded inconsistent effects on oxidative stress-related outcomes. Therefore, further research is needed to clarify whether oxidative stress directly disrupts uric acid metabolism or whether their interaction involves additional regulatory mechanisms.

However, this study has limitations. First, given the study's cross-sectional design, the direction of causality cannot be ascertained, and the role of hyperuricemia in amplifying IR cannot be ruled out. Second, although adjustments were made for several covariates, the effects of unaccounted confounders such as treatment with allopurinol and differences in diuretic use cannot be entirely ruled out. Third, subgroup analyses for factors such as diabetes types, nonalcoholic fatty liver disease (NAFLD) and metabolic syndrome were not performed. Finally, our results, derived from a US population sample, require further verification to ensure their applicability to other demographic groups.

5 Conclusion

A nationally representative study among adults aged 20 years or older identified a negative association between the eGDR and the risk of hyperuricemia.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://wwwn.cdc.gov/nchs/nhanes.

Ethics statement

The studies involving humans were approved by the Ethics Review Board of the National Center for Health Statistics (https://www.cdc.gov/nchs/nhanes/about/erb.html). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

ZW: Writing – original draft, Writing – review & editing. RL: Writing – original draft, Writing – review & editing. FT: Writing – original draft, Writing – review & editing. YS: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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Factors associated with metabolic syndrome among adult residents in Dalian: a nested case-control study

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Objective: This study aimed to investigate risk factors for metabolic syndrome (MS) among adult residents in Dalian, Liaoning Province, China, using a nested case-control design.

Methods: Adult participants from Dalian who took part in both baseline and follow-up phases of the Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal (REACTION) Study were evaluated through standardized questionnaires, physical examinations, and biochemical analyses. A total of 536 individuals diagnosed with MS were matched in a 1:4 ratio to 2,144 controls based on comparable demographic and clinical characteristics. Group differences were assessed via t-tests, rank sum tests, and χ^2 tests. Multivariate conditional logistic regression was applied to identify risk factors for MS.

Results: (1) The case group demonstrated significantly higher values for body weight(67.42 ± 9.77 vs. 62.39 ± 9.31, *P*<0.001), body mass index (BMI) (25.99 ± 3.36 vs 24.00 ± 3.14, *P*<0.001), hip circumference (HC) (100.72 ± 6.47 vs 97.84 ± 6.38, *P*<0.001), homeostatic model assessment for insulin resistance (HOMA–IR) (2.27 ± 1.19 vs 1.70 ± 0.92, *P*<0.001),total cholesterol (TC) (5.54 ± 1.08 vs 5.40 ± 0.97, *P*=0.003), low-density lipoprotein cholesterol (LDL-C) (3.38(2.79,3.96) vs 3.17(2.67,3.71), *P*<0.001), alanine aminotransferase (ALT) (16.00(13.00,21.00) vs 15.00(11.00,19.00), *P*<0.001), gamma-glutamyl transferase (GGT) (22.00 (17.00,33.00) vs 18.00(14.00,27.00), *P*<0.001), serum uric acid (UA) (303.50 (263.00,355.00) vs 281.00(245.00,325.00), *P*<0.001), glycosylated hemoglobin (HbA1c) (5.93 ± 0.88 vs 5.75 ± 0.68, *P*<0.001), and fasting insulin (FINS) (8.05 (5.90,10.70) vs 6.15(4.60,8.30), *P*<0.001) (2). Higher prevalence rates were also observed for coronary heart disease (4.86% vs 2.87%, *P*=0.020), habitual snoring (66.53% vs 54.96%, *P*<0.001), and consumption of fresh juice (17.99% vs 13.12%, *P*=0.004), beef and mutton (78.42% vs 74.07%, *P*=0.038), and soda the case group (20.15% vs 16.32%, *P*=0.049). Meanwhile, lower participation in aerobic activities(1.20% vs 2.92%, *P*=0.030) and shorter average daily sleep duration (7.55 ± 1.02 vs 7.69 ± 1.17, *P*=0.028) were noted in the case group (3). Regression analysis identified longer average daily sleep duration as a protective factor (OR=0.844, 95%CI: 0.761-0.936, *P*=0.001), while fresh juice intake(OR=1.846, 95%CI: 1.315-2.592, *P*<0.001), beef and mutton consumption(OR=1.282, 95% CI:1.007-1.632, *P*=0.044), LDL-C(OR=1.409, 95%CI: 1.245-1.595, *P*<0.001), GGT (OR=1.004, 95%CI: 1.001-1.008, *P*=0.017), UA(OR=1.005, 95%CI: 1.003-1.007, *P* < 0.001), HOMA-IR (OR=1.464, 95%CI: 1.313-1.633, *P* < 0.001), HC(OR=1.030,

95%CI: 1.007-1.053, P = 0.009), and BMI(OR=1.118, 95%CI: 1.064-1.174, P < 0.001)were significant risk factors.

Conclusion: LDL-C, GGT, UA, HOMA-IR, HC, BMI, daily sleep duration, and consumption of beef and mutton, and fresh juice were strongly associated with the incidence of MS among adult residents in Dalian.

KEYWORDS

metabolic syndrome, risk factors, nested case-control study, fresh juice, beef and mutton, sleep duration, adult residents in Dalian, body mass index

1 Introduction

Metabolic syndrome (MS) is a clinical entity characterized by a cluster of abdominal obesity, hyperglycemia (diabetes or impaired glucose tolerance), dyslipidemia (elevated triglycerides and/or reduced high-density lipoprotein levels), and hypertension—factors that collectively exert a substantial influence on systemic health. It comprises a constellation of metabolically interrelated risk elements (1), and is a multifaceted pathophysiological condition primarily stemming from an imbalance in caloric intake and energy expenditure, yet it is also modulated by factors such as an individual's genetic/epigenetic constitution and lifestyle behaviors. The pathogenesis of MS is mainly mediated by increased free fatty acids leading to insulin resistance and chronic low-grade inflammation induced by pro-inflammatory cytokines (2). Over recent decades, the global incidence of MS has markedly increased, now affecting nearly one-quarter of the global population, which translates to over 1 billion individuals (3). Its treatability remains uncertain, combination of drug therapy and dietary adjustments, could be helpful in the prevention and management of MS (2). In China, rapid economic expansion accompanied by shifts in dietary patterns and lifestyle behaviors has further intensified the MS burden. Current research estimates that 19.58% of the Chinese population is affected by MS (4), with prevalence rates surging to 36.9% among the elderly demographic (5). MS has attracted much attention from scholars since it was proposed. Its high incidence of endpoint events, especially cardiovascular and cerebrovascular events, has become the first of the three causes of death, which seriously threatens human health. Research on the risk factors of metabolic syndrome can not only further explore its formation mechanism, but also accelerate the drug development process of related targets, timely urge people to improve their lifestyles, and enhance the health awareness of the whole population, which is of great significance for the prevention and treatment of MS. While factors such as age, body mass index (BMI), and insulin resistance are consistently recognized as key contributors, other risk factors remain unclear or yield inconsistent associations across different populations and geographical regions. A study conducted among elderly individuals in Shenzhen, China, identified regular rice consumption as a potential protective factor against MS, while reporting no significant association between alcohol intake and MS risk (6). In contrast, research involving Swedish adults suggested a possible protective effect of alcohol consumption for individuals with MS (7). Meanwhile, findings from a Korean cohort indicated that high rice intake may elevate the risk of abdominal obesity, a condition closely linked to the pathogenesis and progression of MS (8). As a historically significant coastal city, Dalian exhibits distinct dietary customs and lifestyle patterns. The city's rapid socioeconomic development has led to an increasingly fast-paced lifestyle, contributing to a rise in metabolic disorder-related conditions. A cross-sectional study in adult residents of Shenzhen, a coastal city in China, has shown that significant differences were found in MS groups with different sociodemographic or other characteristics, such as age, serum uric acid(UA) levels, gender, smoking status, drinking status, marital status, BMI, and educational level, and increased UA levels were positively associated with the prevalence of MS and its components (9). Despite these trends, investigations into MS risk factors within the Dalian population remain lacking. Accordingly, this study adopted a nested case-control design to identify risk factors for MS among adult residents of Dalian. We hypothesize that specific dietary habits (e.g., consumption of fresh juice, beef and mutton, and soda), lifestyle factors (e.g., sleep duration, aerobic activities, and smoking), basic information (e.g., diseases

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate aminotransferase; BMI, Body Mass Index; DBP, Diastolic Blood pressure; FINS, Fasting Insulin; FT3, Triiodothyronine; FT4, Free Thyroxin; FPG, Fasting Plasma Glucose; FFQ, Food Frequency Questionnaire; 2hPG, 2 Hours Plasma Glucose; GGT, Gamma-Glutamyl Transferase; HbA1c, Glycosylated Hemoglobin; HC, Hip Circumference; HOMA–IR, Homeostatic Model Assessment for Insulin Resistance; HR, Heart Rate; HDL-C, High density lipoprotein cholesterol; IPAQ, International Physical Activity Questionnaire; LDL-C, Low-Density Lipoprotein Cholesterol; MS, Metabolic Syndrome; OGTT, Oral Glucose Tolerance Test; REACTION, Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal Study; SBP, Systolic Blood Pressure; Scr, Serum creatinine; TG, Triglyceride; TSH, Thyroid-stimulating Hormone; TgAb, Thyroglobulin Antibodies; TPOAb, Thyroid Peroxidase Antibodies; TC, Total Cholesterol; UA, Serum Uric Acid; WC, Waist Circumference.

history and anthropometric assessments), and relevant biochemical markers (e.g., LDL-C, GGT, UA, HOMA-IR) are associated with an increased risk of MS among adult residents in Dalian.

The nested case-control design, an advanced epidemiological methodology, integrates the methodological rigor of cohort studies with the efficiency of case-control frameworks. It is based on the follow-up observation of a pre-determined cohort, and then the design concept of case-control studies (mainly matching case-control studies) is applied for research and analysis, integrates the strengths of cohort and case-control designs. This approach improves research efficiency and cost management, while offering greater statistical robustness and diagnostic precision relative to traditional case-control models (10). Currently, this method is widely used in medical scientific research.

Utilizing data from the Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal (REACTION) Study, a follow-up cohort was established to investigate MS among adult residents in the Dalian community. Through a matched nested case-control framework, the study assessed the associations between the onset of MS and a comprehensive range of biochemical indicators, demographic characteristics, medical history, and lifestyle variables—including dietary patterns, physical activity, and habitual behaviors. The objective was to optimize early detection of risk factors, support timely intervention strategies, and reduce MS incidence, thereby minimizing its broader personal, familial, and social burden.

2 Materials and methods

2.1 Study participants

The REACTION Study, a multicenter prospective cohort investigation, enrolled Chinese adults aged ≥40 years from the Dalian community who participated in the baseline epidemiological survey at the Dalian subcenter between August and December 2011 (n=10208, 2807 males and 7401 females), followed by re-evaluation from July to December 2014(n=5354, 1369 males and 3985 females). Longitudinal data were obtained through standardized physical examinations, biochemical assessments, and structured data collection at both time points. A nested case-control design was employed in this study. Each incident MS case identified within the cohort was matched to one or more controls who remained free of MS at the time of diagnosis. Case group: A total of 536 cases newly diagnosed MS during the follow-up period (2014) from the study population were included, as per the 2020 Chinese Diabetes Society diagnostic criteria (see Section 2.2). Control group: Controls were selected from the same cohort among individuals who remained free of MS at follow-up (2014). To minimize confounding, controls were matched to cases in a 4:1 ratio based on the following criteria:1) Gender: Exact matching (male/female). 2) Age: ± 3 years from the cases' age at baseline. Controls were required to have completed both baseline and follow-up assessments, with no missing data on MS diagnostic components. Matching was performed using a stratified random sampling approach within each gender-age stratum to avoid overmatching. Exclusion criteria included missing data on biochemical or physical examinations(n=7), a prior diagnosis of MS(n=2367), clinically relevant cardiac, hepatic, or renal dysfunction(n=6), or chronic glucocorticoid therapy(n=2). The protocol was approved by the REACTION Study Ethics Committee [Approval No (2011). LLS No (14).], and all participants provided written informed consent.

2.2 Study methods

(1) Prior to survey implementation, the research personnel—including endocrinologists, postgraduate trainees, and nurses from Dalian Municipal Central Hospital Affiliated to Dalian University of Technology—received standardized training conducted by Ruijin Hospital, Shanghai Jiaotong University School of Medicine. All questionnaire data collection and anthropometric measurements were performed by trained staff according to a standard protocol. Informed consent was obtained from all enrolled community residents before data collection commenced.

(2) Baseline characteristics and outcome indicators were systematically collected. Participants completed structured questionnaires, underwent physical assessments, and provided venous blood specimens. Documented variables included demographic data (gender, age), individual and familial disease histories, marital and educational status, pharmacological treatments, sleep patterns, emotional well-being, and lifestyle parameters including dietary intake, physical activity, and daily routines. Clinical measurements included systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), height, weight, waist and hip circumference (HC), and BMI was subsequently derived. Blood sampling was performed in the morning after an overnight fast of at least 8-14h. Fasting plasma glucose(FPG), 2 hours plasma glucose(2hPG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS), and several biochemical markers—alanine aminotransferase (ALT), Aspartate aminotransferase(AST), gamma-glutamyl transferase (GGT), serum creatinine(Scr), total cholesterol (TC), Triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), High density lipoprotein cholesterol (HDL-C), UA, triiodothyronine (FT3), free thyroxin (FT4), thyroid-stimulating hormone (TSH), thyroglobulin antibodies (TgAb), and thyroid peroxidase antibodies (TPOAb)—were measured. In addition, all participants underwent an oral glucose tolerance test(OGTT).

(3) Biochemical Evaluation: Fasting venous blood was collected in standard biochemical tubes, centrifuged immediately(within 2 hours), aliquoted into 0.5-mL Eppendorf tubes, stored at -20°C, and transported within 3 weeks under cold-chain conditions to Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai Institute of Endocrine and Metabolic Diseases, which is certified by the College of American Pathologists, for centralized analysis. Levels of Scr, TC, LDL-C, HDL-C, and TG were measured on an autoanalyzer (c16000 system, ARCHITECT ci16200 analyzer; Abbott Laboratories, Lake Bluff, IL) in the central laboratory. FINS was measured with chemiluminescent immunoassay (i2000SR

system, Architect ci16200 analyzer; Abbott Laboratories). The levels of HbA1c were assayed by means of high-performance liquid chromatography method (Variant II and D-10 Systems; Bio-Rad, Hercules, CA).FPG and 2hPG levels were measured from NaF-anticoagulated blood using the hexokinase method on an automated biochemical analyzer (ADVIA 2400 system). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the mathematical formula as follows: HOMA-IR = FPG (mmol/L) × FINS (μU/mL)/22.5 (11).UA concentrations were determined from fasting venous samples using the uricase colorimetric method on the ADVIA Chemistry XPT system. Thyroid function was evaluated via chemiluminescence immunoassay (Abbott I2000, Abbott reagent).

Data Collection: Epidemiological data were collected via one-on-one questionnaires, encompassing sociodemographic characteristics, lifestyle factors, and medical histories. The REACTION study questionnaire was developed through a systematic review of questionnaires related to MS, diabetes, and cancer both domestically and internationally(e.g., the International Physical Activity Questionnaire, IPAQ, Food Frequency Questionnaire, FFQ), and a working group composed of experts from multiple disciplines including endocrinology, epidemiology, and nutrition decided the content and structure of the questionnaire. Information on intensity, duration, and frequency of physical activity was gathered using the short form of the IPAQ. In the dietary section of the questionnaire, data were obtained regarding usual dietary intake over the past 12 months. The questionnaire was designed to capture information on frequency and quantity of major food items such as red meat, fruits and vegetables, dairy, and Chinese traditional food such as pickles and salty vegetables. The questionnaire has previously been evaluated and validated in other cohort studies (12–14).

Anthropometric assessments followed standardized procedures: weight was measured in the morning following an overnight fast, and height was recorded with participants standing upright, feet together, and arms relaxed. Height and weight were measured with participants wearing light-weight clothes and no shoes. BMI was calculated by dividing weight (in kilograms) by weight (in meters) squared. Blood pressure and HR were measured at 5-minute intervals on the non-dominant arm in a resting state, with the mean of three readings recorded (1 mmHg = 0.133 kPa), using an automated electronic device (Omron Model HEM-725 FUZZY; Omron Co, Dalian, China). Waist circumference(WC)was assessed at the midpoint between the lower rib and the anterior superior iliac spine, with participants standing upright, feet 25–30 cm apart, and breathing normally. HC was measured at the maximal circumference of the hips while standing, with legs together and arms relaxed.

(4) Diagnostic and allocation criteria (1): MS diagnostic criteria: In accordance with the 2020 Guidelines of the Chinese Diabetes Society for the Prevention and Treatment of Type 2 Diabetes, a diagnosis of MS was established when at least three of the following five conditions were met: 1) Abdominal obesity, defined by a waist circumference ≥ 90 cm in men or ≥ 85 cm in women; 2) Hyperglycemia, determined by FPG ≥ 6.1 mmol/L and/or 2hPG ≥ 7.8 mmol/L, or a documented history of diabetes under treatment; 3) Hypertension, defined by blood pressure ≥ 130/85 mmHg, or a history of hypertension with ongoing treatment; 4) Elevated fasting triglycerides (≥ 1.70 mmol/L); 5) Decreased fasting HDL-C (< 1.04 mmol/L) (2). Case and control groups: A nested case-control design was employed. Each incident MS case identified within the cohort was matched to one or more controls who remained free of MS at the time of diagnosis. Ultimately, 2,680 participants (605 males and 2075 females) were included in the final analysis (Figure 1). A total of 536 newly diagnosed MS cases from the study population were included. A matching ratio of 1:4 was applied, with 2144 subjects without MS selected as controls. The controls were matched by gender and age, ensuring an age difference of less than 3 years.

2.3 Statistical methods

Statistical analyses were performed using SPSS 27.0. The distribution of measurement data was first evaluated; data conforming to normal distribution were presented as mean ± standard deviation (SD), whereas those deviating from normality were expressed as M *(Q1, Q3)*. Group comparisons for continuous variables employed the *t*-test when normality was verified by *P–P* plots, and the rank sum test for non-normally distributed data. Significance was defined as $P < 0.05$. Categorical variables were summarized as counts (%), with comparisons between groups conducted using the χ^2 test under the same significance criterion. Variables identified as significant in univariate analysis were incorporated into a multivariate conditional logistic regression model. A 1:4 matched conditional logistic regression (forward LR method) was used to identify risk factors for MS, with entry and removal criteria set at $\alpha = 0.05$ and $\alpha = 0.10$, respectively. A two-tailed $P < 0.05$ was considered indicative of statistical significance. OR value: >1 indicates risk factor, = 1 indicates no association, <1 indicates protective factor. 95% CI: includes1 indicates no statistical significance, excludes 1 indicates statistically significant. A *t*-test is a statistical hypothesis test used to determine whether there is a significant difference between the means of two groups or between a sample mean and a known population mean, and the data should be (approximately) normally distributed. The rank sum test, is a non-parametric statistical method used to compare two independent or paired samples when the data do not follow a normal distribution. The χ^2 test is a statistical hypothesis test used to examine the association between categorical variables or to assess how well observed data fit an expected distribution, and the data must be in frequency counts. Conditional logistic regression is a specialized regression analysis method designed for matched or stratified data, commonly employed in matched case-control studies. Its fundamental principle involves using conditional likelihood functions to eliminate the effects of confounding factors, thereby enabling more accurate estimation of the association between exposure variables and outcomes. The forward LR (likelihood ratio) method represents a variable selection strategy that progressively incorporates statistically significant variables into the model based on likelihood ratio tests, optimizing the model's goodness-of-fit.

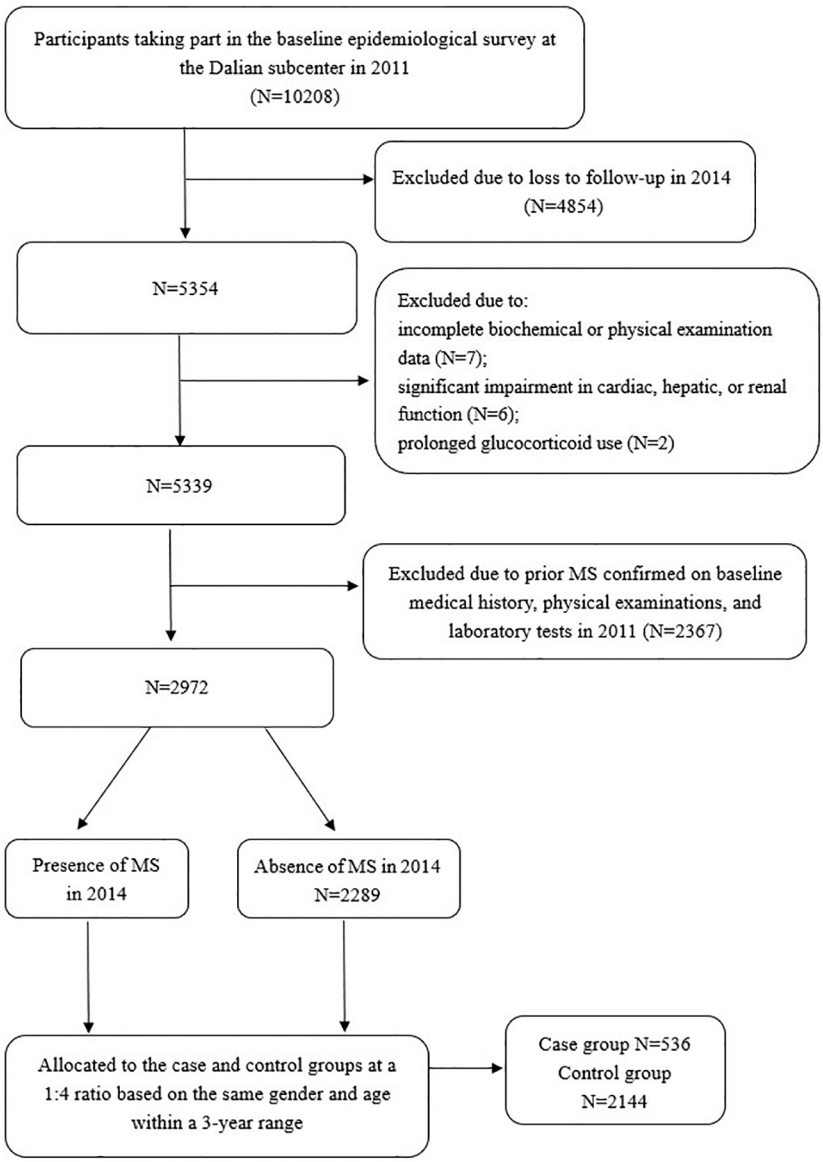

FIGURE 1
Flowchart of the study enrollment.

3 Results

3.1 Comparison of demographic and clinical data between groups

3.1.1 Baseline demographic characteristics

The case group (n=536, males=121,females=415) and control group (n=2144,males=484,females=1660) were well-matched in terms of age (56.34 ± 7.41 vs 56.26 ± 7.46 years, P=0.819) and sex distribution sex distribution (22.57% male in both groups) (Table 1).

3.1.2 Anthropometric and clinical measurements

The case group exhibited significantly higher values for weight (67.42 ± 9.77 vs 62.39 ± 9.31 kg, P<0.001), BMI (25.99 ± 3.36 vs 24.00 ± 3.14 kg/m^2, P<0.001), and HC (100.72 ± 6.47 vs 97.84 ± 6.38 cm, P<0.001) compared to controls. (Table 1).

3.1.3 Biochemical parameters

The case group demonstrated markedly altered metabolic profiles, including: LDL-C (3.38(2.79,3.96) vs 3.17(2.67,3.71) mmol/L, P<0.001), TC (5.54 ± 1.08 vs 5.40 ± 0.97 mmol/L, P=0.003).HOMA-IR (2.27 ± 1.19 vs 1.70 ± 0.92, P<0.001).GGT (22.00(17.00,33.00) vs 18.00 (14.00,27.00) U/L, P<0.001), ALT (16.00(13.00,21.00) vs 15.00 (11.00,19.00)U/L, P<0.001), UA(303.50(263.00,355.00) vs 281.00 (245.00,325.00)umol/L, P<0.001), HbA1c (5.93 ± 0.88 vs 5.75 ± 0.68%, P<0.001), and FINS (8.05(5.90,10.70) vs 6.15(4.60,8.30)mU/L, P<0.001). No significant differences were observed in thyroid function tests or other endocrine parameters (P>0.05, Table 1).

TABLE 1 Comparison of demographic and clinical data between groups.

Outcome measures	Case group (n=536)	Control group (n=2144)	*t*/Z value	*P* value
Age	56.34 ± 7.41	56.26 ± 7.46	0.229	0.819
Male [n (%)]	121 (22.57%)	484 (22.57%)		
Female [n (%)]	415 (77.43%)	1660 (77.43%)		
Height (cm)	160.95 ± 7.25	160.99 ± 7.66	-0.113	0.910
Weight (kg)	67.42 ± 9.77	62.39 ± 9.31	11.074	<0.001
BMI (kg/m^2)	25.99 ± 3.36	24.00 ± 3.14	12.935	<0.001
HC (cm)	100.72 ± 6.47	97.84 ± 6.38	9.383	<0.001
HR (bpm)	78.61 ± 11.08	78.13 ± 11.40	1.023	0.307
HOMA-IR	2.27 ± 1.19	1.70 ± 0.92	12.185	<0.001
TC (mmol/L)	5.54 ± 1.08	5.40 ± 0.97	2.963	0.003
LDL-C (mmol/L)	3.38 (2.79,3.96)	3.17 (2.67,3.71)	-5.133	<0.001
Scr (umol/L)	63.30 (57.73,70.40)	62.55 (57.70,68.88)	-1.699	0.089
ALT (U/L)	16.00 (13.00,21.00)	15.00 (11.00,19.00)	-5.299	<0.001
AST (U/L)	21.00 (18.00,25.00)	21.00 (18.00,24.00)	-0.954	0.340
GGT (U/L)	22.00 (17.00,33.00)	18.00 (14.00,27.00)	-7.913	<0.001
UA (umol/L)	303.50 (263.00,355.00)	281.00 (245.00,325.00)	-7.128	<0.001
HbA_{1c} (%)	5.93 ± 0.88	5.75 ± 0.68	4.917	<0.001
FINS (mU/L)	8.05 (5.90,10.70)	6.15 (4.60,8.30)	-11.217	<0.001
FT3 (pmol/L)	4.25 (3.99,4.46)	4.23 (3.99,4.50)	-0.180	0.857
FT4 (pmol/L)	13.04 (12.09,13.93)	13.10 (12.26,14.03)	-1.160	0.246
TSH (mIU/L)	2.04 (1.40,2.86)	2.01 (1.41,2.96)	-0.211	0.833
TPOAb (U/mL)	0.53 (0.27,1.23)	0.47 (0.27,1.14)	-1.168	0.243
TgAb (IU/mL)	1.62 (1.03,10.30)	1.52 (0.96,6.07)	-1.193	0.233

Normal data were represented by mean ± SD, and non-normal data were represented by M *(Q1, Q3)*. BMI, body mass index; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HC, hip circumference; HR, heart rate; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; UA, uric acid; HbA1c, glycosylated hemoglobin; FINS, fasting insulin; FT3, free T3; FT4, free T4; TSH, thyroid stimulating hormone; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody.

3.2 Comparison of lifestyle habits, medical history, and family history between groups

Key lifestyle differences between cases and controls included: Dietary habits: Higher consumption of fresh juice (17.99% vs 13.12%, *P*=0.004),beef and mutton (78.42% vs 74.07%, *P*=0.038), and soda water (20.15% vs 16.32%, *P*=0.049). Physical activity: Lower participation in aerobics (1.20% vs 2.92%, *P*=0.030). Sleep patterns: Shorter average sleep duration (7.55 ± 1.02 vs 7.69 ± 1.17 hours, *P*=0.028). Medical history: Higher prevalence of coronary heart disease (4.86% vs 2.87%, *P*=0.020) and habitual snoring (66.53% vs 54.96%, *P*<0.001). In contrast, no significant intergroup differences emerged in marital status, educational attainment, history of chronic gastroenteritis, smoking, alcohol intake, tea consumption, depression, insomnia, or dietary patterns involving grains, potatoes, pork, poultry, seafood, vegetables, fruits, eggs, milk, soy products, fried items, pickled vegetables, coffee, or animal offal. Measures of physical exertion such as daily vigorous exercise and tai chi, as well as familial predisposition to tumors or diabetes, screen time, and sedentary duration during weekdays, also demonstrated no statistically significant variation ($P > 0.05$) (Table 2).

3.3 Multivariate conditional logistic regression analysis of risk factors for MS

Multivariate conditional logistic regression analysis using the forward LR method was employed to investigate risk factors for MS, incorporating variables that demonstrated statistical significance in the univariate analysis. These variables included LDL-C, ALT, GGT, UA, HOMA-IR, HC, BMI, aerobics, consumption of soda water, fresh juice, beef and mutton, average daily sleep duration, history of coronary heart disease, and presence of snoring. Prior to modeling, collinearity diagnostics confirmed the absence of multicollinearity, with VIF values ranging from 1.005 to 1.901, confirming the absence of multicollinearity. The final model

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TABLE 2 Comparison of lifestyle habits and different medical histories between groups [n (%)].

Outcome measures	Case group (n=536)	Control group (n=2144)	χ^2 value	*P value*
Married Status	485 (90.49%)	1949 (90.90%)	0.209	0.648
High School Level or Above	290 (54.10%)	1067 (49.88%)	3.056	0.080
History of Coronary Heart Disease	26 (4.86%)	61 (2.87%)	5.375	0.020
History of Chronic Gastroenteritis	38 (7.12%)	165 (7.75%)	0.246	0.620
Snoring	336 (66.53%)	1102 (54.96%)	22.077	<0.001
Smoking	474 (89.10%)	1915 (89.74%)	0.187	0.665
Alcohol Consumption	388 (72.66%)	1624 (76.21%)	2.908	0.088
Drinking Tea	229 (42.96%)	868 (40.64%)	0.955	0.329
Feeling Depressed	84 (16.00%)	292 (14.04%)	1.306	0.253
Insomnia	138 (26.09%)	579 (27.53%)	0.377	0.539
Grains	533 (99.63%)	1782 (99.50%)	0.145	0.703
Potatoes	510 (95.68%)	2032 (96.17%)	0.262	0.609
Pork	503 (94.55%)	1971 (93.19%)	1.282	0.258
Beef And Mutton	418 (78.42%)	1557 (74.07%)	4.289	0.038
Poultry	407 (76.07%)	1593 (75.75%)	0.025	0.875
Seafood	511 (95.87%)	2017 (95.73%)	0.111	0.739
Vegetables	533 (99.63%)	2100 (99.43%)	0.306	0.580
Fruits	517 (96.82%)	2054 (97.35%)	0.445	0.505
Fresh Juice	95 (17.99%)	433 (13.12%)	8.258	0.004
Eggs	512 (96.06%)	2011 (95.26%)	0.619	0.431
Milk	383 (72.13%)	1543 (73.58%)	0.457	0.499
Soy Products	498 (93.43%)	1982 (93.93%)	0.184	0.668
Fried Food	258 (48.68%)	1018 (48.64%)	0.000	0.987
Soda Water	108 (20.15%)	350 (16.32%)	3.883	0.049
Pickled Vegetables	332 (62.29%)	1280 (60.72%)	0.440	0.507
Coffee	46 (8.66%)	221 (10.56%)	1.666	0.197
Animal Offal	145 (27.31%)	494 (23.57%)	3.216	0.073
Strenuous Exercise	36 (68.70%)	168 (7.95%)	0.682	0.409
Tai Chi	19 (3.54%)	82 (3.82%)	0.079	0.779
Aerobics	6 (1.20%)	59 (2.92%)	4.734	0.030
Family History of Tumor	104 (19.51%)	379 (17.77%)	0.874	0.350
Family History of Diabetes	126 (23.64%)	467 (21.89%)	0.751	0.386
Average Daily Sleep Duration (h)	7.55 ± 1.02	7.69 ± 1.17	-2.198	0.028
Average Daily Television Viewing Time (h)	2.98 ± 1.79	2.92 ± 1.62	0.746	0.456
Time Spent Sitting on Workdays (d)	4.94 ± 0.35	4.90 ± 0.49	1.726	0.085

Dietary habits indicate the consumption of specific foods, while strenuous exercise refers to engagement in intense physical activities within the past seven days. Tai Chi and aerobics assess participation in these exercises over the past 12 months. Snoring reflects whether it occurred during nighttime sleep over the previous year. Depression evaluates depressive feelings within the past two weeks, and insomnia pertains to sleep disturbances during the same period. The time spent sitting on workdays was calculated as the average number of days spent sitting from Monday through Friday.

identified the following factors remained significantly associated with metabolic syndrome (Table 3). Risk factors: LDL-C (OR=1.409, 95%CI 1.245-1.595,*P*<0.001), GGT (OR=1.004, 95% CI 1.001-1.008,*P*=0.017), UA (OR=1.005, 95%CI 1.003-1.007, *P*<0.001), HOMA-IR (OR=1.464, 95%CI 1.313-1.633,*P*<0.001), HC (OR=1.030, 95%CI 1.007-1.053,*P*=0.009), BMI (OR=1.118, 95%CI 1.064-1.174,*P*<0.001), fresh juice consumption (OR=1.846, 95%CI 1.315-2.592,*P*<0.001), and beef and mutton intake (OR=1.282, 95%CI 1.007-1.632,*P*=0.044).Protective factor: Longer sleep duration (OR=0.844, 95%CI 0.761-0.936,*P*=0.001). Among them, LDL-C showed the strongest positive association (41% increased odds per unit), fresh juice consumption conferred the highest modifiable risk (85% increased odds), sleep duration emerged as the most robust protective factor (16% risk reduction per hour).

4 Discussion

The primary endpoint in this study was MS. Statistically significant variables identified through univariate analysis—including LDL-C, ALT, GGT, UA, HOMA-IR, HC, BMI, engagement in aerobics, soda and fresh juice intake, consumption of beef and mutton, average daily sleep duration, history of coronary heart disease, and snoring—were entered into a multivariate conditional logistic regression model using the forward LR method. The analysis revealed that longer average sleep duration as a protective factor against MS risk. Conversely, elevated levels of LDL-C, GGT, UA, HOMA-IR, HC, and BMI, along with consumption of fresh juice and red meat (beef and mutton), were significantly associated with increased MS risk. Among the modifiable behavioral variables, average sleep duration demonstrated an inverse association with MS, whereas fresh juice and red meat(beef and mutton) consumption exhibited positive associations.

4.1 Sleep duration

Notably, our cohort exhibited shorter average sleep durations (7.55h in cases vs. 7.69h in controls), reflecting Dalian's fast-paced urban lifestyle. Current investigations into the association between sleep duration and MS yield inconsistent outcomes. One meta-analysis identified a U-shaped relationship, indicating increased MS risk at both extremes of sleep duration (15). In contrast, data from the China Health and Retirement Longitudinal Study revealed that sleep exceeding 8 h/d was linked to a 53% reduction in MS incidence compared to the 7–8 h/d reference group (16). A more recent meta-analysis including 11 studies with 343,669 participants found a higher MS prevalence among individuals reporting normal sleep duration than among those with either short or extended sleep durations. Regionally, North America exhibited the highest MS prevalence among both short and long sleepers, whereas in Asia, the highest rates were noted among those with typical sleep durations (17). No analogous research has been conducted in Dalian. Findings from the current analysis suggest that average daily sleep duration may exert a protective effect against MS. Potential mechanisms underlying this association include the synthesis and release of melatonin, which primarily occur at night and are inhibited by daytime light exposure. Melatonin exerts lipid-lowering, anti-inflammatory, and antioxidant effects, while also regulating blood pressure (18). Research (19) has identified significant differences in nocturnal melatonin secretion

TABLE 3 Multivariate conditional logistic regression analysis.

Variables	β value	SE value	Waldχ^2 value	*P* value	OR value	95%CI
LDL-C	0.343	0.063	29.525	<0.001	1.409	1.245-1.595
ALT	-0.003	0.006	0.324	0.569	0.997	0.986-1.008
GGT	0.004	0.002	5.695	0.017	1.004	1.001-1.008
UA	0.005	0.001	26.661	<0.001	1.005	1.003-1.007
HOMA-IR	0.381	0.056	46.899	<0.001	1.464	1.313-1.633
HC	0.029	0.011	6.747	0.009	1.030	1.007-1.053
BMI	0.112	0.025	19.891	<0.001	1.118	1.064-1.174
Aerobics	-0.620	0.475	1.703	0.192	0.538	0.212-1.365
Soda Water	-0.073	0.155	0.224	0.636	0.929	0.686-1.259
Fresh Juice	0.613	0.173	12.541	<0.001	1.846	1.315-2.592
Beef and Mutton	0.248	0.123	4.057	0.044	1.282	1.007-1.632
Snoring	-0.072	0.048	2.295	0.130	0.930	0.847-1.021
Average Daily Sleep Duration	-0.170	0.053	10.316	0.001	0.844	0.761-0.936
History of Coronary Heart Disease	0.476	0.320	2.208	0.137	1.609	0.859-3.015

Aerobic exercise indicates engagement in aerobics within the past 12 months. Dietary habits denote the frequency of specific food consumption. Snoring refers to the occurrence of snoring during nighttime sleep over the past 12 months.

between individuals with and without MS, with disruptions in circadian melatonin rhythms associated with MS onset. Additionally, MS patients exhibit heightened sympathetic nervous system activity (20). Reduced sleep duration, combined with elevated sympathetic drive, contributes to the development of hypertension (21). Sympathetic activation stimulates lipolysis through adipose tissue innervation, increasing circulating free fatty acids, which in turn diminishes insulin sensitivity and impair glucose tolerance (22, 23). Further evidence (24) also indicates that sleep deprivation influences hormones governing appetite and eating behavior, promoting increased food intake and subsequent weight gain, thereby predisposing to overweight and obesity. In parallel, reduced sleep duration has been shown to upregulate proinflammatory mediators (25, 26), which promote insulin resistance in both adipose and peripheral tissues (27), further increasing susceptibility to MS. Collectively, these mechanisms collectively explain our observed association between average daily sleep duration and MS. Future studies should assess sleep quality and napping habits, as Dalian residents rarely nap because of its short lunch breaks, potentially compounding sleep-related metabolic risks. Given the protective role of sleep duration, community-based initiatives could raise awareness about the importance of adequate sleep and provide practical tips for improving sleep duration, such as reducing screen time before bed, creating sleep-conducive environments, increasing the lunch break time.

4.2 Fresh juice consumption

In the questionnaire of this research, the definition of fresh juice is "juice extracted from fresh fruits", without any additional additives or processing procedures. Current evidence regarding the metabolic impact of fresh juice consumption remains inconsistent. Our finding that fresh juice intake increases MS risk contrasts with a cohort study reporting protective effects of pure fruit juice (28). This discrepancy may arise from differences in juice composition and consumption patterns. Conversely, other studies (29) align with the present findings, indicating a positive correlation between fresh juice consumption and MS development. In our study, "fresh juice" likely contains high in fructose but low in fiber. Unlike whole fruits, juicing removes dietary fiber, accelerating fructose absorption (30). Fructose undergoes hepatic metabolism distinct from that of glucose. In the absence of a rate-limiting enzyme and feedback inhibition, fructose catabolism yields high levels of uric acid, diglycerides, lactic acid, and other intermediates, which may trigger endoplasmic reticulum stress and inflammatory responses. These byproducts interfere with key metabolic pathways, promoting insulin resistance, lipogenesis, vascular endothelial impairment, central adiposity, elevated triglyceride concentrations, decreased HDL-C, hypertension, and impaired glucose tolerance—core features of MS. Furthermore, fructose modulates gut microbiota composition and activity (31), and the gut microbiota and metabolites have been proven to increase the risk of diabetes, metabolism-related fatty liver disease, carotid atherosclerotic plaque and MS (32, 33). Notably, Dalian's warm climate and abundant fruit markets may encourage frequent juice consumption, exacerbating these effects. Thus, public health campaigns in Dalian should emphasize whole fruit consumption over juicing, particularly among high-risk groups.

4.3 Red meat (beef and mutton) consumption

The results of this study align with previous research (34), indicating that the consumption of beef and mutton (red meat) may heighten the risk of MS. Although red meat essential nutrients such as amino acids, vitamins, and minerals (e.g., iron and zinc), growing evidence links its intake to an increased risk of various chronic diseases. Several biological pathways may account for the observed relationship between red meat consumption and MS development. One proposed mechanism involves the high heme iron content in beef and mutton, which functions as a potent pro-oxidant. Excessive intake of heme iron promotes oxidative stress, thereby triggering cellular damage and chronic systemic inflammation (35). Moreover, the processing and cooking techniques commonly applied to red meat appear to enhance its harmful metabolic effects (36). In Dalian, longstanding dietary practices such as hot pot and street barbecue are culturally ingrained, with beef and mutton as central ingredients. During these high-temperature cooking processes, significant levels of nitrates and nitrites are generated, which have been implicated in the induction of insulin resistance (37), potentially increasing susceptibility to MS. Additionally, the elevated content of total fat and saturated fatty acids in beef and mutton contributes to obesity, hyperinsulinemia, and hyperglycemia, exacerbate insulin resistance and further contributing to the onset of MS (38). Studies have also shown elevated levels of inflammatory mediators in individuals who regularly consume beef and mutton, and processed meats, potentially explaining the heightened risk of MS in this population (39). A longstanding belief in Dalian attributes tonic and restorative properties to the consumption of beef and mutton, and their broths, particularly mutton soup, which remains popular among locals. Although beef and mutton consumption is deeply embedded in Dalian's culinary culture, its association with MS calls for strategies to mitigate metabolic harm. For example, co-administration of compounds like Xiasangju, a traditional Chinese herbal formula, may attenuate red meat-induced oxidative stress and inflammation. Studies suggest that Xiasangju's noradrenaline-enhancing properties can activate brown adipose tissue, thereby increasing energy dissipation and improving lipid profiles (40). This synergistic approach that combines dietary factors that promote the occurrence of MS with those protect it could be explored in future public health campaigns.

4.4 Biomarkers: LDL-C, GGT, UA, HOMA-IR, HC, and BMI

Consistent with most previous studies, elevated LDL-C, GGT, UA, HOMA-IR, HC, and BMI are identified as significant indicators for increased risk of MS (41–43). LDL-C contributes to atherosclerosis by depositing oxidized lipids in arterial walls, while GGT, a marker of hepatic steatosis, reflects systemic oxidative stress (44). A recent study

highlighted the differences in the effects of lipids and lipoproteins on BP and pulse pressure. For pulse pressure, the dangerous effect of LDL-C bears the brunt among the major lipids (45). UA in both crystalline and soluble forms, plays a key role in the induction of inflammatory cascade and development of atherosclerotic diseases (46). HOMA-IR and HC underscore the centrality of insulin resistance and central obesity in MS pathogenesis. The increase of BMI drives higher ratio of 12,13-Epoxyoctadecenoic acid: Dihydroxyoctadecenoic acid in white adipose tissue and liver, which indicates the deterioration of the MS (47). Notably, Dalian's rapid urbanization has likely amplified sedentary behaviors and energy-dense diets, exacerbating these biomarkers. Clinicians should prioritize these metrics in routine screenings to enable early MS detection.

This study's nested case-control design enhances efficiency and reduces recall bias compared to traditional case-control studies. However, several methodological limitations warrant careful consideration regarding their potential impact on the results. First, possibility of residual confounding or the influence of unmeasured variables (e.g., sample contamination, diet before blood collection, impact of a woman's menstrual period, socioeconomic status, dietary additives, or environmental pollutants, etc.) cannot be ruled out. Second, the reliance on self-reported dietary data may introduce recall bias, particularly given the 3-year interval between baseline and follow-up. Third, due to participants' limited recall accuracy and over 50% missing data for portion size, analysis involving frequency and quantity is excluded. A binary variable (yes/no) is adopted for statistical modeling, potentially masking thresholds at which fresh juice or red meat intake becomes clinically significant. Moreover, the questionnaire does not differentiate cooking methods for beef and mutton or specify the types and preparation techniques of fresh juice. Finally, while the study adjusted for key confounders (e.g., age, sex), the absence of longitudinal assessments limits causal inference. For example, the association between short sleep duration and MS might be bidirectional, as MS-related metabolic disturbances could also disrupt sleep. Despite these limitations, the consistency of our findings with prior mechanistic research supports their biological plausibility.

The present study reveals a significant correlation between the occurrence of MS in adult residents of Dalian and several factors, including elevated levels of LDL-C, GGT, UA, HOMA-IR, HC, and BMI, as well as reduced daily sleep duration, consumption of beef and mutton, and intake of fresh juice. These results align with some existing literature but also underscore the need for targeted interventions and further research to address these factors in the Dalian population. Future research should employ longitudinal designs to establish causal relationships between identified risk factors and MS. For example, tracking changes in dietary habits, sleep patterns, and biomarker levels over time could elucidate their long-term impact on MS development, providing stronger evidence for causality and inform public health strategies. In addition, targeted public health campaigns should be carried out, such as providing targeted dietary advice, strengthening publicity on the importance of sleep, and launching projects for regular monitoring of relevant biological indicators in community hospitals. By addressing dietary habits, sleep duration, and biomarker monitoring, Dalian might reduce the burden of MS and improve overall metabolic health.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The raw data from REACTION's study has not yet been released. Requests to access these datasets should be directed to 18840859380@163.com.

Ethics statement

The studies involving humans were approved by Ethics Committee of Shanghai Jiao Tong University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RR: Data curation, Software, Writing – original draft. LL: Methodology, Writing – review & editing. XL: Conceptualization, Formal analysis, Writing – review & editing. ZG: Data curation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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Association between triglyceride glucose–body mass index and acute kidney injury and renal replacement therapy in critically ill patients with sepsis: analysis of the MIMIC-IV database

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Background: Previous studies have linked kidney damage to insulin resistance (IR), yet the association between triglyceride glucose–body mass (TyG–BMI) index, a reliable marker of IR, and acute kidney injury (AKI) remains unclear.

Methods: Patient data were collected from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. AKI was set as the primary endpoint, and renal replacement therapy (RRT) was set as the secondary endpoint to represent the progression of AKI. TyG–BMI index and study endpoints were analyzed using Cox regression and restricted cubic spline (RCS) analyses.

Results: A total of 1,117 patients with sepsis were enrolled, of whom 559 (50.0%) developed AKI. The result of Cox regression revealed that the TyG–BMI index was closely related to AKI (P = 0.032), and RCS analysis depicted a nonlinear correlation (P for nonlinear = 0.013). For RRT, similar results were observed. Compared with the simple severity of illness scores (SOFA, APSIII, SAPSII, and SIRS), when combined with the TyG–BMI index, their predictive ability for sepsis-related AKI significantly increased (AUCs: 0.745, 0.732, 0.708, and 0.566 vs. 0.756, 0.747, 0.728, and 0.661; all $P < 0.05$).

Conclusions: For critically ill patients with sepsis, an elevated TyG–BMI index implies a possible increased risk of AKI. The TyG–BMI index has the potential to be a valuable predictor.

KEYWORDS

acute kidney injury, sepsis, triglyceride glucose-body mass index, predictor, insulin resistance

Background

Sepsis, a life-threatening disease, is characterized by multi-organ damage induced by the dysfunction of the host's immune response to infection (1). Annually, nearly 50 million cases are diagnosed globally, with sepsis-related deaths accounting for more than 50% of in-hospital deaths (2, 3). Despite advancements in medical technology, the mortality rates for sepsis have not significantly improved (4). Sepsis may impair renal function, with approximately 60% of patients experiencing acute kidney injury (AKI) (5, 6). Once it occurs, it increases sepsis mortality by three to five times, leading to worse clinical outcomes (7). Therefore, the early detection of patients with a tendency to develop AKI and timely intervention are crucial to improve the prognosis.

Sepsis is often accompanied by insulin resistance (IR), which may be caused by systemic inflammation (8). Additionally, IR can inhibit the autophagic activity of podocytes, leading to kidney injury, and is positively correlated with kidney injury molecule-1 (9, 10). The triglyceride–glucose (TyG) index, an innovative marker, has been considered a convenient replacement indicator for IR (11). More importantly, the degree of IR in the body is more accurately reflected when used in conjunction with body mass index (BMI) (12). The findings above seem to suggest that TyG–BMI index may predict the occurrence of AKI, which would help to identify high-risk patients and thus enable early intervention. For certain diseases, such as hypertension, myocardial infarction, and chronic kidney disease, a strong association exists between their incidence and TyG–BMI index (13–15). However, it remains unclear whether this correlation exists in individuals with sepsis-associated AKI.

Consequently, the current study hypothesizes an association between TyG–BMI index and sepsis-associated AKI and intends to explore the issue utilizing this large cohort, with a view to guiding clinical practice.

Methods

Study population

Clinical data were retrospectively extracted from the MIMIC-IV database. One author (WSJ) successfully passed all of the required examinations for accessing the database and obtained approval to use the dataset (certification number: 56051808). The review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center approved the database for medical health-related research without requiring informed consent.

All patients with sepsis met the Sepsis 3.0 criteria, defined as the presence of infection and sequential organ failure assessment (SOFA) score ≥2 (16). The Kidney Disease: Improving Global Outcomes (KDIGO) guideline was used to confirm the presence of AKI (17). The exclusion criteria were as follows: (1) age <18 years, (2) only the first data were extracted if multiple ICU admissions for sepsis existed, (3) missing fasting blood glucose (FBG), triglyceride, and BMI data within 24 h of ICU admission, (4) diagnosed with AKI prior to ICU admission, (5) and missing AKI data within 48 h. Finally, 1,117 patients with sepsis were enrolled, and the cohort was divided according to the TyG–BMI quartile (Figure 1).

Data collection

Data on the basic characteristics of the patients were extracted using PostgresSQL and Navicat Premium software and merged with Stata software. Detailed clinical data included demographics (age, sex, race, height, weight, and BMI), laboratory test results (international normalized ratio [INR], blood urea nitrogen [BUN], low-density lipoprotein [LDL], sodium, chloride, aspartate aminotransferase [AST], albumin, red blood cell [RBC],

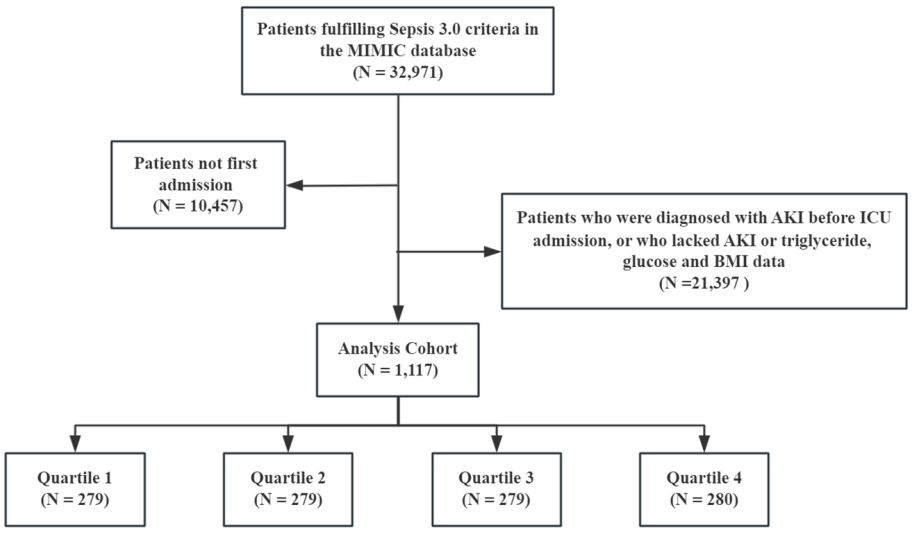

FIGURE 1
Flow of the included patients.

high-density lipoprotein [HDL], neutrophils, hemoglobin, platelets, hematocrit, total bilirubin, prothrombin time [PT], C-reactive protein [CRP], serum creatinine [SCr], alanine aminotransferase [ALT], white blood cells [WBC], alkaline phosphatase [ALP], calcium, lymphocytes, anion gap, activated partial thromboplastin time [APTT], blood glucose, triglycerides, potassium, and total cholesterol [TC]), medication (statin, insulin, and metformin), vital signs, and severity of illness scores. Since the MIMIC database does not explicitly specify which values represent FBG, all values are simply labeled as "blood glucose". Therefore, we inferred based on patients' medication use to exclude interference from insulin, glucose injection, and enteral nutrition on blood glucose values as much as possible. Data on the blood collection time for glucose tests on the first day of ICU admission as well as the start times of insulin, glucose injections, and enteral nutrition were extracted. If the blood collection occurred after the start of any of these interventions, the corresponding glucose value was considered interfered and excluded. Specific procedures and codes are provided in the supplementary methods. The International Classification of Diseases (9th and 10th) was used to identify comorbidities, including chronic kidney disease (CKD), cancer, diabetes, hypertension, arterial fibrillation (AF), and heart failure (HF). Within 24 h of ICU admission, all test indicators and scores were collected, and the SCr level and urine output were continuously monitored throughout the hospital stay. Information on medication use in the 24 h prior to ICU admission was collected. The timings of initial AKI and renal replacement therapy (RRT) were determined. Follow-up continued from the date of admission to all study endpoints.

TyG–BMI index formula: ln [triglyceride (mg/dL) × FBG (mg/dL)/2] × BMI (18). For the variables included in this study, multiple interpolation (multiple imputation by chained equations) was used to fill in those with missing values <20%, while those with missing values >20% were deleted (12). Lymphocytes, neutrophils, albumin, HDL, LDL, CRP, and TC contained more than 20% missing value.

Endpoints of interest

AKI was set as the primary endpoint. KDIGO guidelines were utilized: SCr was 1.5-fold higher than baseline within 7 days or elevation of SCr by 0.3 mg/dL in 48 h or urine output less than 0.5 mL/kg per hour for at least 6 h. The reference baseline of SCr was determined as the lowest recorded value within 7 days prior to ICU admission (276 patients), and if this information was not available, the SCr first measured at admission to ICU was used (841 patients). RRT, representing disease progression to AKI, was used as a secondary endpoint. Meanwhile, ICU, in-hospital, 28-day, and 1-year mortality were also specified as secondary endpoints.

Statistical analysis

The proportional hazards assumption was verified using Schoenfeld residual plots, and no violation was detected (Supplementary Figure S1). The occurrence of primary and secondary endpoints was depicted by the Kaplan–Meier curve. By utilizing Cox regression analysis, the study excluded confounders to identify independent association (survival package, version 3.5–5 and survminer package, version 0.4.9). The Fine–Gray model was constructed to analyze the competitive risk in order to evaluate the stability of the results (cmprsk package). To evaluate the possible influence of unmeasured confounding on the observed hazard ratios, E-values were analyzed. To avoid multicollinearity, variables were excluded when the variance inflation factor was greater than 5 (car package). To depict the dose–response effects, restricted cubic spline (RCS) analysis was conducted (ggrcs package, version 0.4.0). Furthermore, subgroup analyses of hypertension, HF, CHD, CKD, AF, diabetes, age, sex, and BMI were conducted (jstable package, version 1.1.7). The interactions were assessed with likelihood ratio tests.

The area under the curve (AUC) was used to reflect the predictive power of existing severity of illness scores for AKI when incorporating the TyG–BMI index (timeROC package). Integrated discrimination improvement (IDI) was computed by subtracting the difference in the probability of positivity predicted by the difference between the different models for the disease group from the difference in the probability of positivity predicted by the old and new models for the non-disease group (19). Reclassified by event occurrence, the net reclassification improvement (NRI) performed a net magnitude synthesis and quantified the degree of improvement. These two indexes allow the risk reclassification of the model (survIDINRI package, version 1.1–2). The analysis and visualization were conducted using R (version 4.1.3) and SPSS (version 27.0). Statistical significance in the current study was defined as P <0.05.

Results

Patient characteristics

A total of 1,117 patients with sepsis were enrolled, of whom 559 (50.0%) developed AKI and 201 (18.0%) received RRT. Meanwhile, 204 (18.5%) ICU deaths and 250 (22.4%) in-hospital deaths occurred.

According to the TyG–BMI index, the overall patients were grouped by quartiles [quartile (Q) 1: <244.37; Q2: 244.37–291.05; Q3: 291.06–355.40; Q4: >355.40]. Patients in the Q4 group had higher BMI, heart rate, and severity of illness scores but were younger. The prevalence of diabetes was higher, and that of CHD was lower in this group. With regard to laboratory indicators, the Q4 group showed higher WBC, anion gap, total bilirubin, ALT, AST, BUN, SCr, FBG, triglycerides, and potassium ions but lower platelets, chloride, and calcium levels. With increasing TyG–BMI index, the incidence of AKI and RRT in the four groups gradually increased (AKI: 36.2% vs. 43.7% vs. 53.4% vs. 66.8%, P < 0.001; RRT: 5.7% vs. 11.8% vs. 24.7% vs. 29.7%, P < 0.001). However, no statistical differences were observed in the in-hospital, ICU, 28-day,

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TABLE 1 Baseline characteristics according to TyG–BMI index quartiles.

Variables	Overall (*N* 1,117)	Q1 (*N* 279)	Q2 (*N* 279)	Q3 (*N* 279)	Q4 (*N* 280)	*P*-value
Demographics						
Age (years)	63.52 (51.72, 74.82)	66.16 (51.35, 79.72)	66.53 (53.44, 80.29)	60.96 (51.75, 70.31)	61.42 (48.61, 69.38)	<0.001
Sex (male)	680 (60.9%)	155 (55.6%)	170 (60.9%)	194 (69.5%)	161 (57.5%)	0.004
Race (white)	849 (76.0%)	210 (75.3%)	217 (77.8%)	213 (76.3%)	209 (74.6%)	0.315
Height (cm)	170 (163, 178)	170 (160, 175)	170 (163, 178)	173 (165, 178)	170 (163, 178)	<0.001
Weight (kg)	85.1 (70.0, 101.8)	63.6 (55.2, 72.0)	77.3 (70.0, 87.5)	95.0 (84.4, 102.8)	112.9 (98.5, 129.9)	<0.001
BMI (kg/m^2)	28.96 (25.05, 34.04)	22.42 (20.52, 24.30)	27.16 (25.72, 28.62)	31.23 (29.38, 33.33)	38.66 (35.31, 44.11)	<0.001
Infection site						
Lung	353 (31.6%)	82 (29.4%)	88 (31.5%)	86 (30.8%)	97 (34.6%)	0.688
Abdomen	175 (15.7%)	39 (14.0%)	46 (16.5%)	47 (16.9%)	43 (15.4%)	
Urinary system	261 (23.4%)	62 (22.2%)	71 (25.5%)	66 (23.7%)	62 (22.1%)	
Other	328 (29.4%)	96 (34.4%)	74 (26.5%)	80 (28.7%)	78 (27.9%)	
Infection type						
Gram-positive	388 (34.7%)	97 (34.8%)	87 (31.2%)	98 (35.1%)	106 (37.9%)	0.572
Gram-negative	343 (30.7%)	87 (31.2%)	85 (30.5%)	82 (29.4%)	89 (31.8%)	
Other	386 (34.6%)	95 (34.1%)	107 (38.4%)	99 (35.5%)	85 (30.4%)	
Laboratory tests						
Hemoglobin (g/dL)	10.6 (8.6, 12.3)	10.6 (8.5, 12.2)	10.6 (8.8, 12.3)	10.4 (8.5, 12.5)	10.6 (8.7, 12.4)	0.855
Platelets (K/uL)	204 (146, 280)	217 (154, 296)	202 (141, 271)	199 (141, 274)	198 (147, 267)	0.048
Hematocrit (%)	31.9 (26.3, 37.1)	31.9 (26.0, 36.6)	32.0 (26.5, 36.9)	31.7 (25.7, 37.8)	31.9 (26.5, 37.4)	0.553
WBC (K/uL)	14.4 (10.3, 19.0)	13.7 (10.0, 17.8)	13.5 (9.8, 17.6)	15.1 (10.3, 19.8)	15.7 (11.3, 21.2)	<0.001
RBC (K/μL)	3.81 (3.24, 4.39)	3.70 (3.14, 4.35)	3.81 (3.27, 4.32)	3.84 (3.17, 4.39)	3.96 (3.31, 4.51)	0.060
Anion gap (mEq/L)	17 (15, 20)	16 (14, 19)	17 (15, 20)	17 (15, 22)	18 (15, 21)	<0.001
Total bilirubin (mg/dL)	0.8 (0.5, 1.6)	0.8 (0.5, 1.1)	0.8 (0.6, 1.5)	0.8 (0.5, 1.8)	0.9 (0.5, 2.1)	<0.001
INR	1.3 (1.2, 1.6)	1.3 (1.1, 1.6)	1.3 (1.1, 1.6)	1.3 (1.2, 1.8)	1.3 (1.2, 1.6)	0.072
Prothrombin time	14.4 (12.8, 17.8)	14.3 (12.6, 17.5)	14.4 (12.7, 17.4)	14.7 (13.0, 19.8)	14.4 (12.8, 17.4)	0.101
APTT	33.1 (28.2, 50.6)	32.5 (28.6, 50.8)	31.5 (27.7, 46.5)	34.7 (28.5, 57.6)	33.7 (28.1, 48.1)	0.039
ALT (U/L)	41 (21, 88)	36 (16, 78)	39 (21, 85)	48 (23, 131)	42 (25, 94)	0.003
ALP (U/L)	82 (66, 109)	80 (64, 108)	80 (63, 103)	84 (66, 111)	86 (67, 114)	0.096
AST (U/L)	65 (32, 117)	54 (28, 127)	64 (28, 179)	70 (36, 272)	71 (37, 186)	0.005
BUN (mg/dL)	24 (16, 40)	20 (15, 34)	21 (15, 34)	25 (18, 45)	29 (19, 48)	<0.001
Serum creatinine (mg/dL)	1.2 (0.9, 2.1)	1.1 (0.7, 1.5)	1.2 (0.8, 1.7)	1.3 (1.0, 2.4)	1.6 (1.0, 2.7)	<0.001
Glucose (mg/dL)	159 (129, 226)	140 (116, 183)	150 (126, 205)	178 (135, 258)	191 (143, 254)	<0.001
Triglycerides (mg/dl)	123 (85, 207)	89 (65, 123)	113 (82, 164)	137 (97, 228)	205 (119, 382)	<0.001
Sodium (mEq/L)	141 (138, 144)	141 (138, 144)	141 (138, 144)	141 (138, 144)	140 (137, 144)	0.143
Chloride (mEq/L)	106 (102, 110)	107 (103, 111)	106 (103, 110)	106 (102, 110)	105 (101, 109)	0.021
Potassium (mEq/L)	4.5 (4.1, 5.0)	4.3 (4.0, 4.8)	4.4 (4.1, 4.8)	4.5 (4.1, 5.3)	4.7 (4.1, 5.5)	<0.001

(Continued)

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TABLE 1 Continued

Variables	Overall (*N* 1,117)	Q1 (*N* 279)	Q2 (*N* 279)	Q3 (*N* 279)	Q4 (*N* 280)	*P*-value
Laboratory tests						
Calcium (mg/dL)	8.0 (7.3, 8.5)	8.0 (7.5, 8.4)	8.1 (7.4, 8.7)	7.9 (7.2, 8.4)	7.8 (7.1, 8.4)	0.005
Vital signs						
SBP (mmHg)	118 (107,133)	118 (107,134)	120 (108, 134)	117 (107,133)	116 (105, 130)	0.308
DBP (mmHg)	63 (56, 71)	63 (56, 71)	64 (57, 72)	64 (51, 71)	62 (55, 70)	0.224
MBP (mmHg)	79 (72, 87)	78 (67, 87)	88 (80, 99)	79 (72, 87)	77 (71, 86)	0.074
Heart rate (beats/min)	86 (75, 99)	82 (70, 95)	84 (74, 96)	85 (75, 98)	92 (78, 106)	<0.001
Medication						
Statin	138 (12.4%)	28 (10.0%)	31 (11.1%)	37 (13.3%)	42 (15.0%)	0.283
Insulin	176 (15.8%)	36 (12.9%)	46 (16.5%)	46 (16.5%)	48 (17.1%)	0.505
Metformin	38 (3.4%)	7 (2.5%)	6 (2.2%)	16 (5.73%)	9 (3.2%)	0.084
Severity of illness scores						
SOFA score	6 (4, 10)	5 (3, 8)	5 (3, 9)	7 (4, 11)	8 (5, 11)	<0.001
SIRS score	3 (2, 4)	3 (2, 3)	3 (2, 3)	3 (2, 4)	3 (3, 4)	<0.001
APSIII	50 (37, 69)	44 (35, 60)	45 (33, 59)	47 (34, 62)	51 (36, 75)	<0.001
SAPSII	39 (30, 50)	37 (29, 47)	38 (29, 48)	40 (30, 53)	42 (30, 53)	<0.001
Comorbidities						
Hypertension	479 (42.9%)	102 (36.6%)	129 (46.2%)	121 (43.4%)	127 (45.4%)	0.087
Heart failure	207 (18.5%)	46 (16.5%)	50 (17.9%)	62 (22.2%)	49 (17.5%)	0.314
CHD	261 (23.4%)	72 (25.8%)	76 (27.2%)	72 (25.8%)	41 (14.6%)	0.001
Arterial fibrillation	150 (13.4%)	37 (13.3%)	44 (15.8%)	32 (11.5%)	37 (13.2)	0.521
CKD	151 (13.5%)	34 (12.2%)	34 (12.2%)	39 (14.0%)	44 (15.7%)	0.562
Diabetes	318 (28.5%)	49 (17.6%)	65 (23.3%)	76 (27.2%)	128 (45.7%)	<0.001
Cancer	112 (10.0%)	30 (10.8%)	32 (11.5%)	26 (9.3%)	24 (8.6%)	0.655
Outcomes						
AKI	559 (50.0%)	101 (36.2%)	122 (43.7%)	149 (53.4%)	187 (66.8%)	<0.001
RRT	201 (18.0%)	16 (5.7%)	33 (11.8%)	69 (24.7%)	83 (29.7%)	<0.001
ICU mortality	204 (18.5%)	43 (15.4%)	48 (17.2%)	59 (21.1%)	54 (19.4%)	0.323
In-hospital mortality	250 (22.4%)	56 (20.1%)	63 (22.6%)	70 (25.1%)	61 (21.8%)	0.552
28-day mortality	285 (25.5%)	75 (26.9%)	71 (25.5%)	73 (26.2%)	66 (23.7%)	0.827
1-year mortality	430 (38.5%)	115 (41.2%)	108 (38.7%)	102 (36.6%)	105 (37.5%)	0.697

TyG–BMI index: Q1 (<244.37), Q2 (244.37–291.05), Q3 (291.06–355.40), and Q4 (>355.40).
BMI, body mass index; WBC, white blood cell; RBC, red blood cell; INR, international normalized ratio; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; APSIII, acute physiology score III; SAPSII, simplified acute physiological score II; CHD, coronary heart disease; CKD, chronic kidney disease; AKI, acute kidney injury; RRT, renal replacement therapy; ICU, intensive care unit.

and 1-year mortality among the groups ($P = 0.552$, $P = 0.323$, $P = 0.827$, and $P = 0.697$, respectively) (Table 1).

Further grouping was determined by the presence of AKI (Table 2). The prevalence of HF, CKD, cancer, and diabetes was higher in the AKI group but with a lower prevalence of hypertension. Meanwhile, the BMI and severity of illness scores were also higher. For laboratory indicators, the AKI group had significantly higher levels of WBC, anion gap, total bilirubin, INR, PT, APTT, ALT, ALP, AST, BUN, SCr, FBG, triglycerides, and potassium. More importantly, the AKI patients showed a higher TyG–BMI index ($P < 0.001$).

TABLE 2 Baseline characteristics of the AKI and non-AKI groups.

Variables	Overall (*N* 1,117)	Non-AKI (*N* 558)	AKI (*N* 559)	*P*-value
Demographics				
Age (years)	63.52 (51.72, 74.82)	62.58 (50.47, 76.73)	64.17 (52.93,74.08)	0.422
Sex (male)	680 (60.9%)	308 (55.2%)	372 (66.5%)	<0.001
Race(white)	849 (76.0%)	425 (76.2%)	424 (75.8%)	0.387
Height (cm)	170 (163, 178)	170 (163, 178)	173 (163, 178)	<0.001
Weight (kg)	85.1 (70.0, 101.8)	80.2 (67.9, 96.3)	90.0 (72.6, 106.1)	<0.001
BMI (kg/m2)	28.96 (25.05, 34.04)	27.95 (24.19, 32.67)	30.16 (25.78, 35.74)	<0.001
Infection site				**0.023**
Lung	353 (31.6%)	169 (30.3%)	184 (32.9%)	
Abdomen	175 (15.7%)	72 (12.9%)	103 (18.4%)	
Urinary system	261 (23.4%)	141 (25.3%)	120 (21.5%)	
Other	328 (29.4%)	176 (31.5%)	152 (27.2%)	
Infection type				**0.113**
Gram-positive	388 (34.7%)	208 (37.3%)	180 (32.2%)	
Gram-negative	343 (30.7%)	172 (30.8%)	171 (30.6%)	
Other	386 (34.6%)	178 (31.9%)	208 (37.2%)	
Laboratory tests				
Hemoglobin (g/dL)	10.6 (8.6, 12.3)	11.1 (9.5, 12.8)	9.9 (8.0, 11.8)	<0.001
Platelets (K/uL)	204 (146, 280)	221 (165, 299)	185 (129, 259)	<0.001
Hematocrit (%)	31.9 (26.3, 37.1)	33.5 (28.8, 38.3)	29.8 (24.5, 35.5)	<0.001
WBC (K/uL)	14.4 (10.3, 19.0)	13.8 (10.1, 17.6)	14.9 (10.7, 21.1)	<0.001
RBC (K/μL)	3.81 (3.24, 4.39)	3.97 (3.38, 4.46)	3.71 (3.03, 4.3)	<0.001
Anion gap (mEq/L)	17 (15, 20)	16 (14, 18)	19 (16, 24)	<0.001
Total bilirubin (mg/dL)	0.8 (0.5, 1.6)	0.8 (0.5, 1.0)	1.0 (0.6, 2.7)	<0.001
INR	1.3 (1.2, 1.6)	1.2 (1.1, 1.4)	1.4 (1.2, 1.9)	<0.001
PT	14.4 (12.8, 17.8)	13.7 (12.5, 15.8)	15.4 (13.3, 21.1)	<0.001
APTT	33.1 (28.2, 50.6)	31.3 (27.2, 39.8)	36.3 (30.2, 58.5)	<0.001
ALT (U/L)	41 (21, 88)	36 (20, 68)	50 (23, 165)	<0.001
ALP (U/L)	82 (66, 109)	80 (65, 97)	86 (66, 128)	0.001
AST (U/L)	65 (32, 117)	50 (27, 108)	98 (41, 375)	<0.001
BUN (mg/dL)	24 (16, 40)	17 (13, 23)	36 (24, 58)	<0.001
SCr (mg/dL)	1.2 (0.9, 2.1)	0.9 (0.7, 1.1)	2.0 (1.4, 3.1)	<0.001
Glucose (mg/dL)	159 (129, 226)	147 (122, 197)	178 (137, 250)	<0.001
Triglycerides (mg/dl)	123 (85, 207)	109 (75, 172)	141 (98, 252)	<0.001
TyG–BMI index	290.88 (244.64, 355.93)	274.58 (233.96, 330.39)	309.96 (256.67, 384.85)	<0.001
Sodium (mEq/L)	141 (138, 144)	141 (139, 144)	141 (137, 144)	0.111
Chloride (mEq/L)	106 (102, 110)	106 (103, 110)	106 (101, 111)	0.067
Potassium (mEq/L)	4.5(4.1, 5.0)	4.3 (4.0, 4.7)	4.7 (4.2, 5.4)	<0.001

(Continued)

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TABLE 2 Continued

Variables	Overall (*N* 1,117)	Non-AKI (*N* 558)	AKI (*N* 559)	*P*-value
Laboratory tests				
Calcium (mg/dL)	8.0 (7.3, 8.5)	8.1 (7.6, 8.6)	7.7 (6.9, 8.2)	<0.001
Vital signs				
SBP (mmHg)	118 (107, 133)	121 (109, 136)	114 (104, 127)	<0.001
DBP (mmHg)	63 (56, 71)	65 (58, 73)	62 (55, 69)	<0.001
MBP (mmHg)	79 (72, 87)	80 (68, 88)	76 (70, 84)	<0.001
HR (beats/min)	86 (75, 99)	83 (72, 95)	89 (78, 103)	<0.001
Severity of illness scores				
SOFA score	6 (4, 10)	5 (3, 7)	9 (6, 12)	<0.001
SIRS score	3 (2, 4)	3 (2, 3)	3 (3, 4)	<0.001
APSIII	50 (37, 69)	41 (31, 51)	64 (48, 84)	<0.001
SAPSII	39 (30, 50)	33 (26, 42)	47 (37, 57)	<0.001
Medication				
Statin	138 (12.4%)	60 (10.8%)	78 (13.9%)	0.104
Insulin	176 (15.8%)	85 (15.2%)	91 (16.3%)	0.631
Metformin	38 (3.3%)	17 (3.0%)	21 (3.8%)	0.513
Comorbidities				
Hypertension	479 (42.9%)	263 (47.1%)	216 (38.6%)	0.004
Heart failure	207 (18.5%)	81 (14.5%)	126 (22.5%)	0.001
CHD	261 (23.4%)	128 (22.9%)	133 (23.8%)	0.736
Arterial fibrillation	150 (13.4%)	79 (14.2%)	71 (12.7%)	0.475
CKD	151 (13.5%)	37 (6.6%)	114 (20.4%)	<0.001
Diabetes	318 (28.5%)	135 (24.1%)	183 (32.7%)	0.002
Cancer	112 (10.0%)	45 (8.1%)	67 (12.0%)	0.002

BMI, body mass index; WBC, white blood cell; RBC, red blood cell; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SCr, serum creatinine; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; APSIII, acute physiology score III; SAPSII, simplified acute physiological score II; CHD, coronary heart disease; CKD, chronic kidney disease.

Primary and secondary endpoints

In order to describe the occurrence of study endpoints, Kaplan–Meier method was employed. For AKI, significant differences were observed; the Q4 group had the highest incidence of AKI ($P < 0.001$) (Figure 2a). As for RRT, similar results were observed ($P < 0.001$) (Figure 2b). The cumulative incident curves of AKI and RRT were plotted using the CIF method, and Gray's test was conducted, showing similar results to the data above ($P < 0.001$) (Supplementary Figure S2). Nevertheless, no statistical differences existed among the four groups for other secondary endpoints (all $P > 0.05$) (Supplementary Figure S3).

The variance inflation factors were calculated to exclude the collinearity of the factors included in the multivariate analysis (Supplementary Table S1). The TyG–BMI index was incorporated in Cox regression analysis to identify an independent association with AKI and RRT when, as a continuous variable in model 3, the risk of AKI increased by 1.1% for each 10-unit increase in the TyG–BMI index ($P = 0.032$) (Table 3). When incorporated as a nominal variable in model 3, the Q4 group showed a much higher risk of AKI compared to the Q1 group ($P = 0.012$) (Table 3); the E-value for this model was 1.73 (Supplementary Figure S4a). Similar results were shown for RRT, with a 2.6% increase in AKI risk for a 10-unit increase in the TyG–BMI index ($P < 0.001$) (Table 3). In the nominal variable model, significant differences were also observed between groups, with an E-value of 2.05 (Supplementary Figure S4b). Meanwhile, the results of the competitive risk analysis using the Fine–Gray model were similar to those of the Cox regression analysis (Supplementary Table S2). Furthermore, the RCS analysis demonstrated that the risk of both AKI (P for nonlinear = 0.013) and RRT (P for nonlinear = 0.003) were nonlinearly associated with increasing TyG–BMI index (Figure 3).

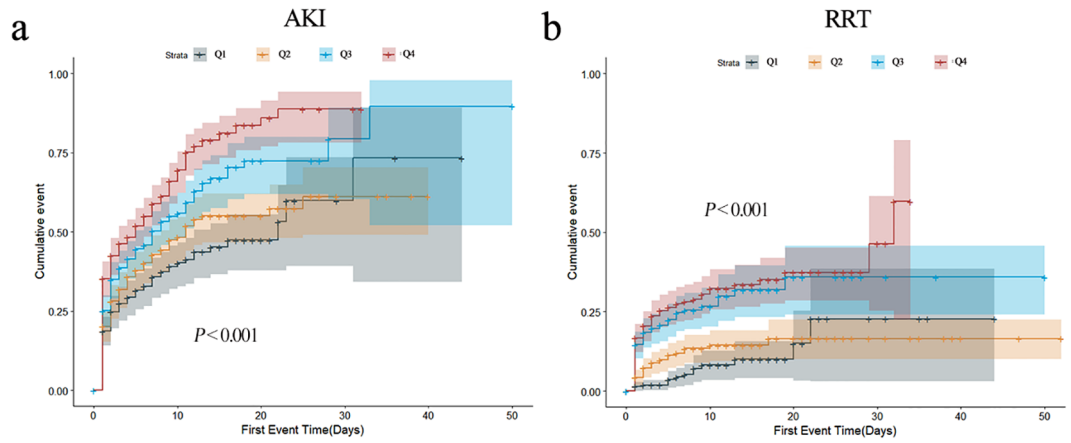

FIGURE 2
Cumulative event incidence curves for incidence of AKI **(a)** and requiring RRT **(b)**.

TABLE 3 Cox proportional hazard ratios (HR) for AKI and requiring RRT.

Categories	Model 1			Model 2			Model 3		
	HR (95% CI)	*P* value	*P* for trend	HR (95% CI)	*P* value	*P* for trend	HR (95% CI)	*P* value	*P* for trend
AKI incidence									
Continuous variable per 10 units	1.023 (1.015–1.030)	<0.001		1.024 (1.017–1.032)	<0.001		1.011 (1.001–1.021)	0.032	
Quartile			<0.001			<0.001			0.010
Q1 (*N* = 279)	Ref			Ref			Ref		
Q2 (*N* = 279)	1.197 (0.920–1.557)	0.180		1.185 (0.911–1.541)	0.206		1.121 (0.818–1.536)	0.477	
Q3 (*N* = 279)	1.567 (1.216–2.020)	<0.001		1.543 (1.195–1.993)	<0.001		0.998 (0.729–1.367)	0.990	
Q4 (*N* = 280)	2.056 (1.614–2.619)	<0.001		2.145 (1.680–2.738)	<0.001		1.485 (1.092–2.020)	0.012	
Requirement of RRT									
Continuous variable per 10 units	1.045 (1.035–1.056)	<0.001		1.044 (1.034–1.055)	<0.001		1.026 (1.011–1.041)	<0.001	
Quartile			<0.001			<0.001			0.040
Q1 (*N* = 279)	Ref			Ref			Ref		
Q2 (*N* = 279)	2.012 (1.110–3.646)	0.021		1.982 (1.093–3.592)	0.024		1.744 (0.882–3.449)	0.110	
Q3 (*N* = 279)	4.626 (2.681–7.982)	<0.001		4.269 (2.471–7.378)	<0.001		2.147 (1.115–4.132)	0.022	
Q4 (*N* = 280)	5.323 (3.118–9.088)	<0.001		5.044 (2.951–8.621)	<0.001		2.502 (1.312–4.770)	0.005	

Model 1, unadjusted; Model 2, adjusted for age and sex; Model 3, adjusted for age, sex, SOFA, SAPSII, SIRS, platelets, WBC, SCr, BUN, potassium, sodium chloride, ALT, total bilirubin, hemoglobin, RBC, INR, MBP, neutrophils, HF, CHD, AF, diabetes, and cancer.

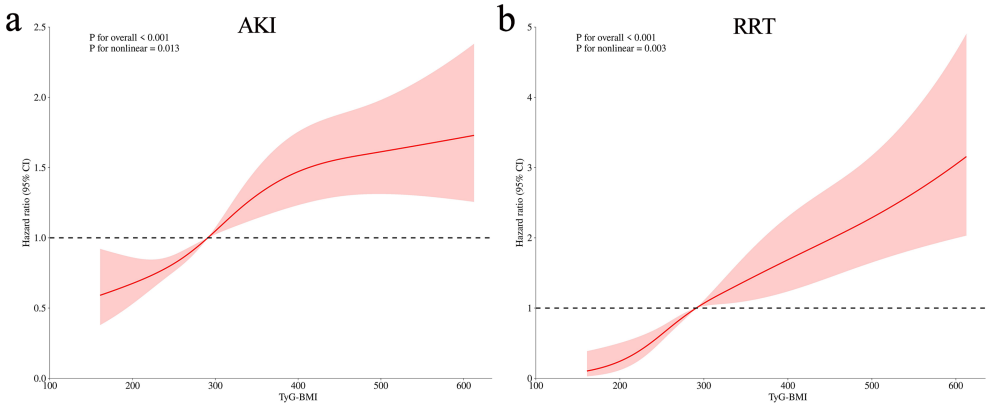

FIGURE 3
Restricted cubic spline analysis of TyG–BMI index with AKI **(a)** and requiring RRT **(b)**.

Subgroup analyses

To test whether these associations persist in specific populations, subgroup analyses were conducted. The significant association between AKI and the TyG–BMI index persisted in most subgroups, except for patients with HF and CKD (Figure 4a). Notably, the association was not as pronounced for patients with HF as it was for patients without HF (HR [95% CI] non-HF: 1.03 [1.02–1.04] vs. HF: 1.01 [0.99–1.02], *P* for interaction = 0.043). However, the prevalence of CKD did not influence the association between AKI and the TyG–BMI index (*P* for interaction = 0.498). Interestingly, all subgroups of the population experienced an increased risk of RRT with higher TyG–BMI index values (all $P < 0.05$; Figure 4b).

Added predictive value of the TyG–BMI index for AKI

To determine the predictive power of severity of illness scores and the combination with TyG–BMI index for sepsis-associated AKI, the AUCs were calculated. The findings indicated a slight increase in ACUs for SOFA, APSIII, SAPSII, and SIRS when the TyG–BMI index was included (Table 4). For assessing the risk reclassification power, the NRIs and IDIs were computed next. The results showed that, for severity of illness scores (SOFA, APSIII, SAPSII, and SIRS), the combined use of the TyG–BMI index led to a statistically significant increase in NRI and IDI (all $P < 0.05$) (Table 4).

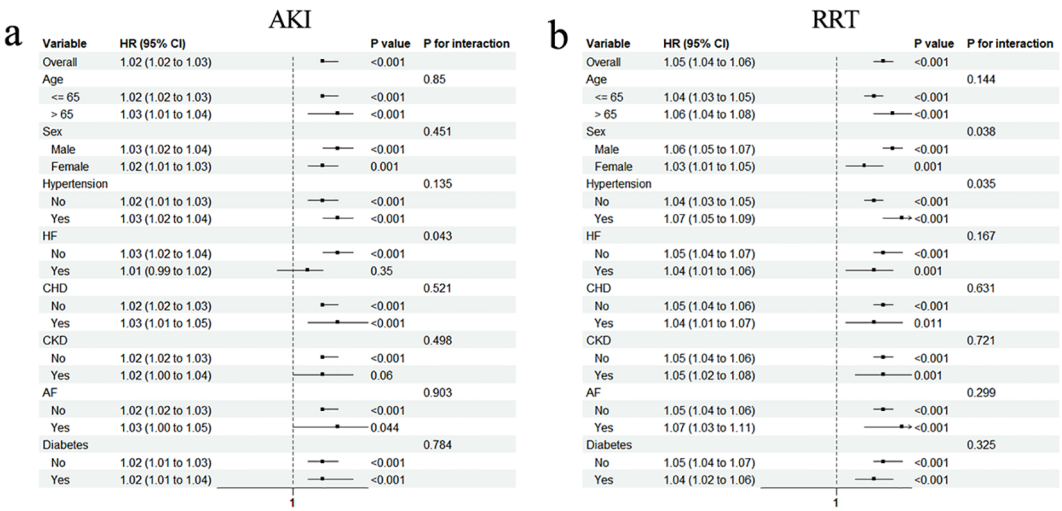

FIGURE 4
Subgroup analyses for the association of TyG–BMI index with AKI **(a)** and requiring RRT **(b)**. HR, hazard ratio; CI, confidence interval; HF, heart failure; CHD, coronary heart disease; CKD, chronic kidney disease; AF, arterial fibrillation.

TABLE 4 Performance metrics of severity of illness scores with and without TyG–BMI index to predict sepsis-associated AKI.

	AUC (95% CI)	*P*-value	NRI (95% CI)	*P*-value	IDI (95% CI)	*P*-value
SOFA	0.745 (0.713–0.788)	<0.001				
SOFA + TyG–BMI	0.756 (0.725–0.788)	<0.001	0.010 (0.001–0.022)	0.040	0.011 (0.001–0.020)	0.040
APSIII	0.732 (0.699–0.765)	<0.001				
APSIII + TyG–BMI	0.747 (0.715–0.779)	<0.001	0.007 (0.000–0.016)	0.039	0.006 (0.000–0.017)	<0.001
SAPSII	0.708 (0.674–0.742)	<0.001				
SAPSII + TyG–BMI	0.728 (0.695–0.761)	<0.001	0.028 (0.011–0.049)	<0.001	0.030 (0.009–0.046)	<0.001
SIRS	0.566 (0.531–0.601)	<0.001				
SIRS + TyG–BMI	0.661 (0.625–0.696)	<0.001	0.024 (0.006–0.042)	<0.001	0.019 (0.006–0.036)	0.02

AUC, area under the receiver operating characteristic curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; APSIII, acute physiology score III; SAPSII, simplified acute physiological score II.

Discussion

The present study is the first to examine the link between the TyG–BMI index and AKI in patients with sepsis. It determined that TyG–BMI exhibited an independent association with AKI, even following adjustment for potential confounding variables, providing a simple and effective predictive tool.

Sepsis often leads to AKI, which not only results in extremely high mortality but also increases the risk of chronic comorbidities (20). Despite ongoing efforts and research, the complex pathophysiology of sepsis-associated AKI has not yet been fully revealed (21). Systemic inflammation and microcirculatory disturbances in the organs were previously thought to be the key mechanisms leading to AKI, but metabolic disturbances during sepsis have attracted increasing attention in recent years (21). During sepsis, elevated catecholamines, release of inflammatory factors, and energy deficits may lead to abnormal lipid metabolism, which, in turn, promotes elevated levels of free fatty acids (22). Meanwhile, tumor necrosis factor can directly inhibit lipoprotein lipase, leading to elevated triglycerides (23). In addition, the release of inflammatory mediators increases liver gluconeogenesis and leads to peripheral IR, resulting in hyperglycemia, even in those without diabetes (24). Hyperglycemia can then trigger ketoacidosis and cause hyponatremia due to high osmolarity, exacerbating kidney damage (25–27). In addition, insulin-like growth factor-binding protein, an important factor involved in IR, has also been found to be directly involved in renal tubule injury (28–30). The abnormalities in blood glucose-related indices have also been shown to be associated with the prognosis of patients with aortic dissection and stroke (31, 32). IR is now recognized as an important causative factor in kidney injury (33).

The TyG–BMI index has been proposed in recent years and proven to better reflect systemic IR in stable populations. Septic patients often experience stress-induced hyperglycemia due to systemic inflammation and catecholamine surge, which may cause changes in the TyG–BMI index to be not only related to IR but also affected by glucose metabolic status (34). This implies that the TyG–BMI index may not accurately represent the state of IR in the body during stress. The specific mechanisms may need to be explored through glucose clamp technique, yet such studies have not been conducted in septic patients so far. Nevertheless, numerous studies have demonstrated its application value in septic patients. Fang et al. demonstrated an independent association between the TyG index and an increased risk of delirium in septic patients (35). In our study, after excluding many confounding factors, the TyG–BMI index was found to be closely related to AKI in the current study; those with a higher index were more prone to AKI. When AKI is progressively aggravated, RRT could address metabolic dysfunction and volume excess, reducing the burden on the kidneys (36). Therefore, the need for RRT is often regarded as an endpoint to represent the progression of AKI severity (37). In the current study, when the TyG–BMI index rose, the incidence of RRT also increased, with a non-linear correlation. Although whether the association between the TyG–BMI index and the study results is attributable to insulin resistance remains unclear, its predictive ability for sepsis-associated AKI and RT is still significant.

To further identify specific populations to which the TyG–BMI index applies, subgroup analyses were performed. The current study showed that the application value of the TyG–BMI index for AKI was not significantly altered by following clinical conditions, including age, sex, hypertension, CHD, AF, and diabetes. However, no significant correlation was found in patients with HF and CKD, which may be partly explained by the fact that HF and CKD are important precipitants to AKI (38, 39). In the context of these diseases, the role of IR and disordered glucose metabolism caused by severe sepsis in the development of AKI may be overshadowed.

The severity of illness scores is a useful tool to objectively quantify disease severity, which helps to identify the disease status and predict its endpoint (40). A previous study has shown that the SOFA score alone did not display a favorable predictive value for major renal adverse events associated with sepsis (41). It is of great value to explore whether combining the severity score with the TyG–BMI index could improve the predictive power. The current results show that the severity of illness scores, when combined with the TyG–BMI index, could significantly improve the ability to predict sepsis-associated AKI. Although it has previously been

demonstrated that combining SOFA score with some biomarkers such as calprotectin and cystatin C could also improve the prediction of AKI, these biochemical indices are not routinely tested in most patients, making it easy to miss high-risk patients (42). In contrast, the TyG–BMI index does not increase the financial burden on patients and has the advantages of being simple and easily accessible. The deficiency is that the increment of AUC after combining the TyG–BMI index is relatively small, which seems to lead to a limited clinical impact. However, due to the large number of patients with sepsis and the prevalence of AKI, even a limited increase may bring certain benefits to patients.

Study strengths and limitations

In the current study, a large cohort was used to confirm the relationship between the TyG–BMI index and sepsis-associated AKI for the first time, and the data were analyzed according to different populations. However, several limitations remain. First, given the retrospective nature of the study, selection bias was unavoidable. Second, some important clinical data, such as infection site, procalcitonin, and C-reactive protein, were not included in the study due to insufficient database information. Third, the current study focused only on assessing the baseline values of the TyG–BMI index, ignoring dynamic changes throughout the treatment period. Fourth, there is currently no direct evidence to establish that the association between the TyG–BMI index and AKI is entirely attributable to IR. Future studies using glucose clamp techniques are warranted to further elucidate this relationship. Finally, since the FBG is inferred rather than explicitly recorded in the database, it may lead to deviations from the true FBG. These deviations may affect the accuracy of the TyG–BMI index and cause discrepancies between subsequent clinical applications and study findings. Therefore, conducting prospective cohort studies in the future is essential.

Conclusions

The current study demonstrated that the TyG–BMI index is independently associated with AKI and RRT in critically ill patients with sepsis in a nonlinear manner. This suggests that the TyG–BMI index could be a valuable clinical risk classification tool. Strengthening the detection of patients' TyG–BMI index in clinical practice may help to identify those at a high risk of AKI and enable early intervention to improve the prognosis. Future studies should validate these findings in clinical practice and explore the underlying mechanisms.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by The review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because The study used a public, open database.

Author contributions

XW: Funding acquisition, Project administration, Resources, Visualization, Writing – review & editing. SW: Conceptualization, Formal Analysis, Investigation, Software, Writing – original draft, Writing – review & editing. RL: Data curation, Formal Analysis, Methodology, Software, Supervision, Writing – original draft. ZL: Project administration, Supervision, Validation, Writing – original draft. TX: Investigation, Project administration, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2025.1561228/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Visualization of Schoenfeld residuals.

SUPPLEMENTARY FIGURE 2
Cumulative incidence curves by cumulative incidence function. **(a)** AKI. **(b)** RRT.

SUPPLEMENTARY FIGURE 3
Kaplan–Meier survival analysis curve. **(a)** ICU. **(b)** In hospital. **(c)** 28 days. **(d)** 1-year mortality.

SUPPLEMENTARY FIGURE 4
E-value analysis. **(a)** AKI. **(b)** RRT.

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U-shaped relationship between the triglyceride glucose index and the risk of incident diabetes among MASLD adults: a retrospective cohort study

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Background: Previous research has indicated that the triglyceride glucose index (TyG-i) may serve as a potential risk factor for type 2 diabetes (T2D). However, there is a paucity of studies addressing the relationship between TyG-i and T2D, specifically in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Consequently, this longitudinal study aims to investigate the association between TyG-i and the onset of T2D in a cohort of Japanese adults with MASLD.

Methods: This retrospective cohort study included a total of 2,507 subjects diagnosed with MASLD. To evaluate the association between the TyG-i and the risk of developing T2D, Cox proportional hazards regression models were employed to estimate hazard ratios (HR) along with 95% confidence intervals (CI). Additionally, nonlinear associations between them were investigated utilizing restricted cubic spline models.

Results: During a mean follow-up period of 6.00 years, a total of 204 adults with MASLD developed T2D. After adjusting for potential confounding factors, elevated TyG-i was found to be independently associated with an increased risk of developing T2D (HR: 1.48, 95% CI: 1.05-2.09, P = 0.0256). Additionally, a U-shaped relationship between the TyG-i and the incidence of T2D was identified. A significant negative association was observed between TyG-i and T2D risk when TyG-i levels were below 7.94 (HR: 0.21, 95%CI: 0.07-0.66, P = 0.0072). Conversely, TyG-i values exceeding the threshold were positively correlated with T2D risk (HR: 1.76, 95% CI: 1.23-2.52, P = 0.0020).

Conclusion: A U-shaped association was identified between baseline TyG-i and the incidence of T2D in a Japanese population with MASLD. This inflection point in TyG-i serves as a valuable clinical indicator to differentiate individuals at lower versus higher risk of developing T2D. These findings indicate that maintaining TyG-i near the inflection point may be beneficial in reducing the risk of developing diabetes in patients with MASLD.

KEYWORDS

metabolic dysfunction-associated steatotic liver disease, type 2 diabetes, triglyceride, triglyceride glucose index, insulin resistance

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) represents the most prevalent chronic liver disorder globally (1–3), impacting approximately 32% of the world's population (4). This condition is marked by excessive lipid deposits in the liver, which can progress to inflammation and liver injury. Without intervention, these changes can advance to liver cirrhosis and potentially hepatocellular carcinoma (3, 5).

MASLD is linked not only to elevated liver-related health issues and mortality rates but also to an increased likelihood of developing cardiovascular diseases, type 2 diabetes (T2D), and overall mortality (1, 6–8). Research indicates that MASLD may act as a precursor to or exacerbate the onset of T2D (1, 9). Recent epidemiological investigations reveal that individuals diagnosed with MASLD face a two-fold greater risk of developing diabetes compared to those without the disease (10). Consequently, it is crucial to comprehend the fundamental risk factors that lead to glucose dysregulation in patients with MASLD, as this knowledge could guide the formulation of effective preventive measures against the onset of diabetes.

The triglyceride glucose index (TyG-i) has emerged as a significant biomarker for evaluating insulin resistance and predicting diabetes risk (11, 12). This index is derived from fasting triglyceride and glucose levels, offering a straightforward yet effective measure of metabolic health. Numerous studies have established substantial correlations between TyG-i and various health outcomes. Recent research has identified associations between TyG-i and conditions such as MASLD, cardiovascular disease, gestational diabetes, prediabetes, T2D, and all-cause mortality (13–16). Despite the increasing evidence linking TyG-i to T2D risk within general populations, its specific relationship with T2D among individuals with MASLD remains inadequately explored. Given the shared pathophysiological mechanisms of insulin resistance and dyslipidemia that characterize both MASLD and T2D, investigating TyG-i within the context of MASLD presents a unique opportunity to clarify its role as an early predictor of diabetes onset. Consequently, this retrospective study aims to examine the longitudinal association between TyG-i and the development of T2D among individuals with MASLD.

Abbreviations: TyG-i, lipid accumulation product; T2D, type 2 diabetes; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; HR, hazard ratio; SD, standard deviations; CI, confidence interval.

Methods

Data source and study participants

The data utilized in our research were obtained from the NAGALA database (17), which is hosted on the Dryad Data Platform. According to the service terms of the Dryad database, this dataset is available for analysis to support the exploration of new research hypotheses. The NAGALA database is a population-based longitudinal cohort study conducted at Murakami Memorial Hospital in Gifu Prefecture, Japan, spanning from 1994 to 2016 (17).

Participants in this study underwent a minimum of two physical examinations. In the initial study conducted by Okamura T et al. (17), medical data were extracted from a total of 20,944 participants. The exclusion criteria were as follows: (1) excessive alcohol consumption at baseline, defined as ≥30 g/day for females and ≥20 g/day for males (n = 1,952); (2) pre-existing liver disease (n = 416); (3) use of medications (n = 2,321); (4) missing data (n = 863); (5) a diagnosis of diabetes at baseline or fasting plasma glucose (FPG) levels exceeding 6.1 mmol/L (n = 1,131); and (6) participants not diagnosed with fatty liver disease (n = 11,744). Ultimately, our study included 2,507 participants with MASLD. The selection process for all participants is illustrated in Figure 1. Ethical approval for this research was obtained from the Clinical Research Ethics Committee of Shenzhen Second People's Hospital Dapeng New District Nan'ao Hospital. Additionally, the study was conducted in accordance with the principles set forth in the Declaration of Helsinki, ensuring adherence to all pertinent guidelines and regulatory requirements. To ensure data confidentiality, all personal identifiers were removed and the datasets were anonymized before analysis. Data were stored in secure servers with access restricted to authorized study personnel only. Throughout

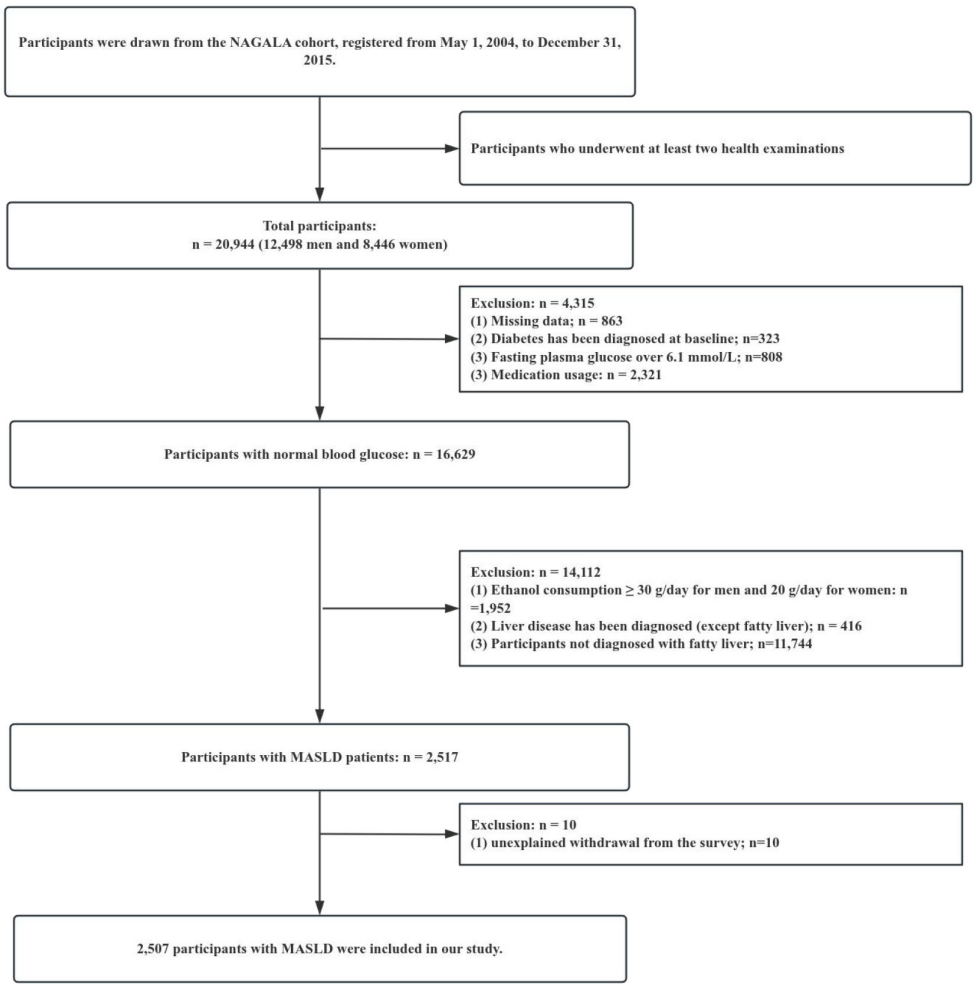

FIGURE 1
Study population.

the study, data handling adhered to applicable data protection laws and institutional policies, thereby safeguarding participant privacy and confidentiality.

Covariates

We choose covariates using clinical expertise and previous research results (14, 18–24). The covariates included (1) continuous variables: age, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), alcoholic intake, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), glycosylated hemoglobin (HbA1c), and FPG; (2) categorical variables: sex, smoking status, and exercise habits. The initial investigation employed a standardized self-administered questionnaire to collect comprehensive information on participants' medical backgrounds and lifestyle habits. Past-smoker is defined as individuals who have a history of smoking but has not engaged in smoking behavior within the 12 months preceding their enrollment in the study. Trained professionals conducted precise anthropometric measurements, including body mass and stature. The original study team obtained Laboratory test results using consistent procedures under controlled conditions.

TyG-i

The TyG-i was determined by applying the formula: Ln[FPG (mg/dL))×(TG (mg/dL)/2) (14).

Diagnosis of incident T2D

T2D was defined as having a self-reported history, HbA1c ≥ 6.5%, or FPG≥7.0 mmol/L (25).

Statistical analysis

Statistical analyses were conducted utilizing Empower-Stats. Participant baseline characteristics were assessed across quartiles

of the TyG-i. Data with normal distribution are expressed as means with standard deviations, whereas non-normally distributed data are reported as medians accompanied by interquartile ranges. Categorical variables underwent analysis via the chi-square test, while continuous variables were evaluated using Student's t-test for normally distributed data and the Mann-Whitney U test for data not following a normal distribution.

The association between the TyG-i and T2D risk was evaluated through three Cox regression models. DBP was omitted from the final multivariate Cox proportional hazards regression model following the collinearity assessment (Supplementary Table S1). Model 1 represents the unadjusted analysis. Model 2 incorporates adjustments for demographic and lifestyle variables, including sex, age, exercise habits, smoking status, alcoholic intake, and SBP. Model 3 further extends the adjustments to include biochemical parameters: ALT, GGT, AST, TC, HDL-C, and HbA1c. Throughout the study, we documented hazard ratios (HR) and 95% confidence intervals (CI). To explore the nonlinear association between the TyG-i and T2D risk, restricted cubic spline curves were generated based on Model 3 in the Cox proportional hazard analysis. This approach allows flexible modeling of the dose-response relationship without assuming linearity. When nonlinearity was detected, the inflection point was identified using a recursive algorithm designed to find the value of TyG-i at which the risk pattern changes. Subsequently, a two-piecewise Cox proportional hazards regression model was constructed on either side of the inflection point, enabling estimation of separate hazard ratios for TyG-i below and above this threshold to better characterize the relationship.

Hypertension and advanced age are well-documented risk factors for diabetes, as established by numerous scholarly studies. To assess the robustness of the relationship between TyG-i and T2D risk, sensitivity analyses were performed, excluding subjects with hypertension (SBP≥140 mmHg or DBP≥ 90 mmHg) or elderly (age≥60 years). In addition, to address potential residual confounding inherent in observational studies, the E-value was calculated as a sensitivity analysis metric. The E-value quantifies the minimum strength of association that any unmeasured confounder would need to possess with both the TyG-i and the incidence of diabetes, beyond the measured covariates, in order to completely explain away the observed association. This provides a quantitative measure of the robustness of our findings against unmeasured confounding.

A stratified analysis including age (≤60 years old or >60 years), gender, hypertension (DBP ≥90 mmHg or SBP ≥140 mmHg), BMI (<25, ≥25 kg/m^2), alcoholic intake (0, >0 g/wk), smoking status, and exercise habits was conducted to evaluate the potential effects of covariates. Statistical significance was defined as a two-tailed P value of < 0.05.

Results

Characteristics of the study population

The present study encompassed 2,507 participants diagnosed with MASLD, with an average age of 44.78 ± 8.33 years, of which 80.93% were male. Over an average follow-up duration of 6.00 years, 204 participants (8.14%) developed T2D. Participants were categorized into quartiles based on their TyG-i values: Q1 (TyG-i ≤ 8.21), Q2 (8.21 < TyG-i ≤ 8.58), Q3 (8.58 < TyG-i ≤ 8.94), and Q4 (TyG-i > 8.94) (Table 1). Individuals in the highest TyG-i quartile demonstrated higher levels of SBP, DBP, BMI, GGT, AST, ALT, TG, TC, age, alcoholic intake, HbA1c, and FPG, as well as a greater proportion of male participants and smokers. Additionally, these individuals exhibited lower levels of HDL-C.

The incidence rate of T2D

Table 2 further illustrates that during the follow-up period, 373 individuals developed T2D, corresponding to overall incidence rates of 4.63% (95%CI: 2.98%-6.27%), 6.56% (95%CI: 4.61%-8.51%), 8.12% (95%CI: 5.98%-10.26%), and 13.24% (95%CI: 10.58%-15.90%) across the first, second, third, and fourth TyG-i groups, respectively. The cumulative incidence rates per 100,000 person-years were 1,356.01 for the total study population and 792.88, 1,082.48, 1,326.71, and 2,210.45 for the first, second, third, and fourth TyG-i groups, respectively. The data indicate that higher TyG-i levels are associated with increased incidence and cumulative prevalence of T2D. Participants positioned within the higher TyG-i quartiles exhibited significantly elevated incidence rates of T2D. These findings are corroborated by the Kaplan-Meier curve illustrating cumulative hazard, as presented in Figure 2.

The results of the association between TyG-i and T2D risk

Since the TyG-i satisfied the proportional hazards assumption, the relationship between TyG-i and the risk of T2D was assessed using the Cox proportional hazards regression model. The outcomes from the adjusted multivariable Cox proportional hazards regression models are detailed in Table 3. An elevated TyG-i value was linked with the occurrence of T2D. In Models 1, 2, and 3, employing continuous TyG-i, significant associations between TyG-i and T2D risk were observed (Model 1: HR: 2.03, 95%CI: 1.57-2.63, P<0.0001; Model 2: HR: 2.13, 95%CI: 1.62-2.79, P<0.0001; Model 3: HR: 1.48, 95%CI: 1.05-2.09, P=0.0256). Furthermore, in Model 3, the highest quartile of TyG-i exhibited a 56% increased risk of T2D (HR: 1.56, 95%CI: 0.92-2.64) compared to the lowest quartile.

Sensitive analysis

To validate our results, we used extensive sensitivity analyses. Excluding participants with elevated blood pressure, we maintained a positive association between TyG-i and T2D (HR=1.45, 95% CI: 1.02-2.06, P=0.0380) (Table 4, Model 4). Similarly, excluding participants aged ≥60 years showed consistent results, with TyG-i remaining positively associated with T2D risk after adjusting for multiple

TABLE 1 The characteristics of participants and incidence rate of diabetes.

TyG-i	Q1 (≤8.21)	Q2 (8.21 to ≤8.58)	Q3 (8.58 to ≤8.94)	Q4 (>8.94)	P-value
Participants	627	625	628	627	
Sex					**<0.001**
Female	188 (29.98%)	143 (22.88%)	88 (14.01%)	59 (9.41%)	
Male	439 (70.02%)	482 (77.12%)	540 (85.99%)	568 (90.59%)	
Age(years)	44.74 ± 8.62	44.91 ± 8.45	45.03 ± 8.18	44.45 ± 8.07	0.641
Alcoholic intake (g/wk)	1 (0-18)	1 (0-36)	1 (0-44)	4.2 (1-60)	<0.001
Smoking status					**<0.001**
Never-smoker	350 (55.82%)	316 (50.56%)	269 (42.83%)	250 (39.87%)	
Past-smoker	152 (24.24%)	169 (27.04%)	161 (25.64%)	157 (25.04%)	
Current-smoker	125 (19.94%)	140 (22.40%)	198 (31.53%)	220 (35.09%)	
Exercise habits					**0.469**
No	528 (84.21%)	528 (84.48%)	529 (84.24%)	545 (86.92%)	
Yes	99 (15.79%)	97 (15.52%)	99 (15.76%)	82 (13.08%)	
SBP (mmHg)	120.61 ± 14.05	122.92 ± 15.19	123.66 ± 14.36	126.43 ± 15.14	<0.001
DBP (mmHg)	75.57 ± 9.87	77.39 ± 10.36	78.17 ± 9.60	80.11 ± 10.41	<0.001
BMI (kg/m^2)	24.81 ± 2.98	25.37 ± 3.44	25.80 ± 3.13	26.00 ± 2.81	<0.001
ALT (IU/L)	24 (18-32.50)	25 (19-35)	28 (21-40)	31 (23-45)	<0.001
AST (IU/L)	19 (16-24)	20 (16-25)	21 (17-26)	22 (18-28)	<0.001
GGT (IU/L)	18 (14-25)	22 (16-30)	24 (17-35)	29 (21-41)	<0.001
HDL-C (mg/dL)	52.64 ± 12.08	47.28 ± 10.28	43.77 ± 9.04	39.69 ± 8.18	<0.001
TG (mg/dL)	60 (49-69)	93 (84-101)	131 (120-142)	203 (176-252)	<0.001
TC (mg/dL)	196.03 ± 32.42	205.70 ± 29.39	215.83 ± 32.94	224.13 ± 32.64	<0.001
HbA1c (%)	5.28 ± 0.32	5.29 ± 0.34	5.30 ± 0.34	5.33 ± 0.33	0.033
FPG (mg/dL)	95.15 ± 6.75	96.97 ± 6.46	97.40 ± 6.32	99.17 ± 6.06	<0.001

Values are presented as n (%) or mean ± SD or median (quartile).
TyG-i, triglyceride glucose index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose.

covariates (HR=1.50, 95% CI: 1.03-2.17, P=0.0347) (Table 4, Model 5). Moreover, the calculated E-value of 2.32 surpasses the relative risk estimate of 1.78 attributed to both the TyG-i and plausible unmeasured confounding factors. This suggests that the impact of unidentified or unmeasured confounders on the detected association between TyG-i and T2D is probably limited.

The analyses of the non-linear association

Table 5, Figure 3 demonstrate a U-shaped relationship between the TyG-i and T2D. The two-piecewise Cox regression model identified a turning point at a TyG-i value of 7.94 (P-value for the log-likelihood ratio test = 0.004). Below this turning point, TyG-i exhibited an inverse relationship with T2D risk (HR: 0.21, 95%CI: 0.07-0.66, P=0.0072). Conversely, when the TyG-i exceeded this turning point, a significant positive relationship with T2D risk was observed (HR: 1.76, 95% CI: 1.23-2.52, P=0.0020).

The results of the subgroup analysis

Figure 4 outlines the findings from subgroup analyses designed to identify potential modifiers in the association between the TyG-i and T2D. The analyses revealed no significant interactions with T2D across various subgroups, including age (P for interaction = 0.3933), smoking status (P for interaction = 0.4720), gender (P for interaction = 0.7502), exercise habits (P for interaction = 0.8092), BMI (P for interaction = 0.4120), hypertension (P for interaction = 0.9640), and alcohol intake (P for interaction = 0.8001).

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TABLE 2 Incidence rate of incident diabetes.

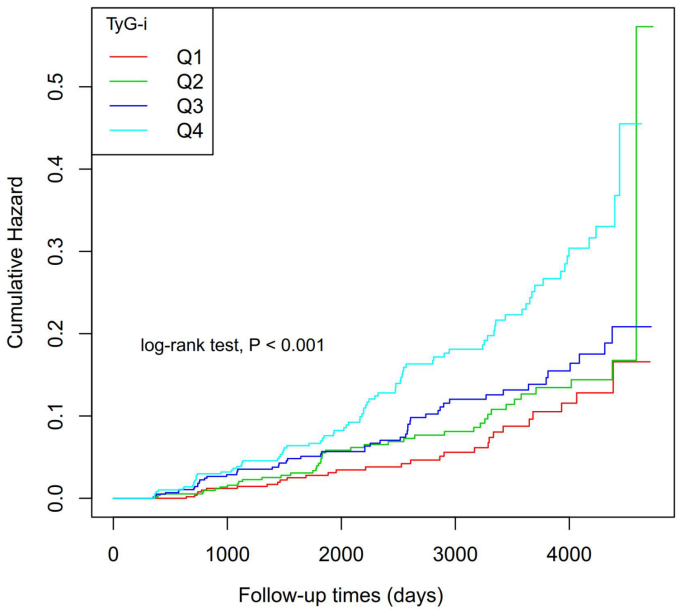
TyG-i	Participants (n)	Diabetes events (n)	Cumulative incidence (95% CI) (%)	Per 100,000 person-year
Total	2507	204	8.14 (7.07-9.21)	1,356.01
Q1	627	29	4.63 (2.98-6.27)	792.88
Q2	625	41	6.56 (4.61-8.51)	1,082.48
Q3	628	51	8.12 (5.98-10.26)	1,326.71
Q4	627	83	13.24 (10.58-15.90)	2,210.45
P for trend			<0.001	<0.001

TyG-i, triglyceride glucose index; CI, confidence interval; T2D, type 2 diabetes.

Discussion

In this retrospective cohort study involving 2,507 Japanese adults with MASLD, we identified a positive association between elevated TyG-i levels and the risk of T2D. Our findings further revealed a U-shaped relationship between TyG-i and an increased risk of T2D. Furthermore, sensitivity and subgroup analyses corroborated these results, reinforcing the robustness of our conclusions.

The TyG-i has been widely used as a surrogate for insulin resistance to predict the risk of metabolic diseases (26, 27). A meta-analysis that included 12 studies, including 105,365 participants, found that the TyG-i was positively associated with the risk of MASLD (OR: 2.84, 95%CI: 2.01-4.01) (28). In a longitudinal cohort study of 16,172 non-obese participants, individuals in the highest quartile of the baseline TyG-i had a 3.58-fold increased risk of developing MASLD relative to those in the lowest quartile (HR: 4.58, 95% CI: 3.48-6.02) (29). A meta-analysis encompassing 13 cohort studies with a total of 70,380 participants identified a significant and positive correlation between the TyG-i and T2D risk (HR: 2.44, 95% CI: 2.17-2.76) (30). In addition, a longitudinal cohort study that included 179541 Chinese adults found a positive nonlinear association between TyG-i and the risk of prediabetes and T2D after adjusting for confounders(HR: 1.67, 95%CI: 1.62-1.71, P< 0.001) (13). MASLD is a common chronic liver disease that is closely associated with metabolic syndrome (31). Past evidence has shown that the prevalence of diabetes is significantly increased in subjects with MASLD (8). However, there have been few studies discussing the relationship between TyG-i and T2D in the MASLD population. In our study, TyG-i was positively related to the risk of developing diabetes in people with MASLD when TyG-i > 7.94. Therefore, early intervention using the TyG-i may be effective in reducing the risk of diabetes in patients with MASLD.



The survival curves illustrate the proportion of participants from T2D over time. The differences in survival curves between the groups are statistically evaluated using the log-rank test (log-rank test, P < 0.001). A clear upward trend in cumulative diabetes risk is observed as the TyG index increases, suggesting a corresponding increase in the likelihood of developing T2D.

FIGURE 2
Kaplan–Meier event-free survival curve in females. Kaplan–Meier analysis of incident diabetes based on TyG-i quartiles (log-rank, P < 0.0001).

TABLE 3 Relationship between TyG-i and incident diabetes in different models.

Variable	Model 1 (HR, 95%CI, P)	Model 2 (HR, 95%CI, P)	Model 3 (HR, 95%CI, P)
TyG-i	2.03 (1.57, 2.63) <0.0001	2.13 (1.62, 2.79) <0.0001	1.48 (1.05, 2.09) 0.0256
TyG-i (quartile)			
Q1	Ref	Ref	Ref
Q2	1.33 (0.83, 2.15) 0.2349	1.33 (0.82, 2.14) 0.2455	1.01 (0.62, 1.66) 0.9545
Q3	1.63 (1.03, 2.57) 0.0361	1.63 (1.03, 2.60) 0.0386	1.28 (0.77, 2.12) 0.3375
Q4	2.76 (1.81, 4.21) <0.0001	2.82 (1.82, 4.37) <0.0001	1.56 (0.92, 2.64) 0.0967
P for trend	<0.0001	<0.0001	0.0403

Model 1: we did not adjust for any covariants.
Model 2: we adjusted for sex, age, alcoholic intake, smoking status, exercise habits, and SBP.
Model 3: we adjusted for sex, age, alcoholic intake, smoking status, exercise habits, SBP, ALT, AST, GGT, HDL-C, TC, and HbA1c.
HR, hazard ratio; CI, confidence interval; Ref, Reference; TyG-i, triglyceride glucose index.

Our research uncovered a U-shaped relationship between the TyG-i and T2D risk after controlling for confounders. Specifically, the analysis revealed that when TyG-i levels were below 7.94, there was a 79% decrease in the risk of T2D development for each one-unit increase in TyG-i. Conversely, a positive association was found between TyG-i and T2D risk when TyG-i levels exceeded 7.94. Understanding this U-shaped relationship is essential for identifying individuals exhibiting altered metabolic profiles across different TyG-i ranges. Those with values near the 7.94 inflection point may constitute a key population for targeted preventive interventions. Clinicians should closely monitor TyG-i as an early biomarker indicative of elevated T2D risk, particularly among patients with MASLD. Interventions aimed at sustaining TyG-i around the inflection point through lifestyle modifications—including dietary improvements, physical activity enhancement, and weight management—should be prioritized for individuals approaching this critical level. Such proactive measures could delay or prevent the progression from insulin resistance to overt T2D, thereby improving clinical outcomes. Additionally, the prospect of pharmacological strategies targeting the TyG-i warrants investigation. As the understanding of TyG-i's metabolic implications advances, clinical trials designed to assess treatments that modulate TyG-i are necessary to expand therapeutic options for high-risk populations. From a public health perspective, our findings underscore the importance of recognizing TyG-i as a valuable marker in T2D risk stratification. Health professionals and policymakers should consider integrating TyG-i assessments into preventive care frameworks to optimize resource allocation and intervention efficacy. Furthermore, educational programs aimed at raising awareness of the significance of metabolic health and elevated TyG-i levels could encourage early evaluation and engagement in risk-reducing behaviors.

The precise mechanisms underlying the U-shaped relationship between the TyG-i and the risk of developing diabetes in individuals with MASLD are still not fully understood. There is a notable positive association between higher TyG-i values and diabetes, likely linked to insulin resistance. Persistently high TG levels intensify liver fat accumulation, causing increased hepatic triglyceride production and worsening insulin sensitivity (32). This metabolic disturbance enhances lipogenesis, which further reduces insulin's effectiveness in managing glucose metabolism and increases liver lipid accumulation, eventually damaging pancreatic beta-cell functionality (33). The build-up of lipid droplets within pancreatic islets disrupts glucose-

TABLE 4 Relationship between TyG-i and incident T2D in different sensitivity analyses.

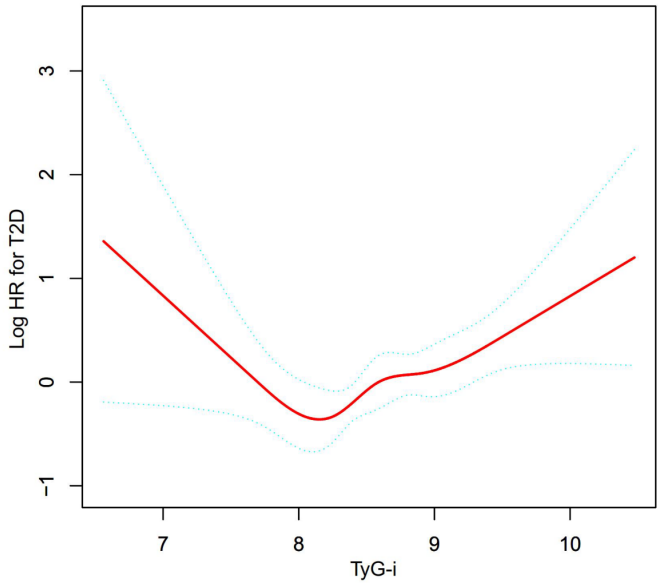
Exposure	Model 4 (HR, 95%CI, P)	Model 5 (HR, 95%CI, P)
TyG-i	1.45 (1.02, 2.06) 0.0380	1.50 (1.03, 2.17) 0.0347
TyG-i (quartile)		
Q1	Ref	Ref
Q2	1.04 (0.63, 1.72) 0.8763	1.21 (0.71, 2.06) 0.4947
Q3	1.25 (0.74, 2.09) 0.4024	1.36 (0.78, 2.39) 0.2760
Q4	1.54 (0.90, 2.63) 0.1135	1.76 (0.99, 3.15) 0.0548
P for trend	0.0568	0.0386

Model 4 was sensitivity analysis after excluding individuals with age≥60 years. We adjusted sex, age, alcoholic intake, smoking status, exercise habits, SBP, ALT, AST, GGT, HDL-C, TC, and HbA1c.
Model 5 was sensitivity analysis after excluding individuals with SBP≥140 mmHg or DBP≥ 90 mmHg. We adjusted sex, age, alcoholic intake, smoking status, exercise habits, SBP, ALT, AST, GGT, HDL-C, TC, and HbA1c.
HR, hazard ratios; CI, confidence; Ref, reference; TyG-i, triglyceride glucose index.

TABLE 5 The result of the two-piecewise Cox proportional hazards regression model.

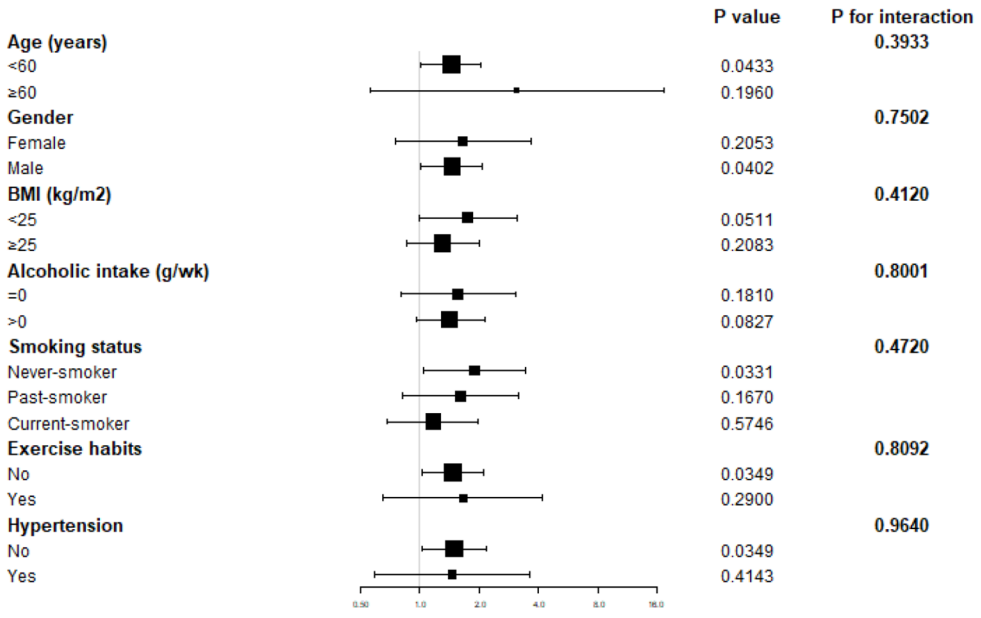
Incident Diabetes	HR (95%CI)	P-value
Fitting model by standard linear regression	1.48 (1.05, 2.09)	0.0256
Fitting model by two-piecewise Cox proportional hazards regression		
The inflection point of TyG-i	7.94	
≤7.94	0.21 (0.07, 0.66)	0.0072
>7.94	1.76 (1.23, 2.52)	0.0020
P for the log-likelihood ratio test	0.004	

We adjusted sex, age, alcoholic intake, smoking status, exercise habits, SBP, ALT, AST, GGT, HDL-C, TC, and HbA1c.
HR, hazard ratios; CI, confidence; TyG-i, triglyceride glucose index.



The x-axis represents the TyG-i values, while the y-axis represents Log HR for T2D. A nonlinear relationship between TyG-i and incident T2D was detected after adjusting for sex, age, alcoholic intake, smoking status, exercise habits, SBP, ALT, AST, GGT, HDL-C, TC, and HbA1c.

FIGURE 3
The nonlinear relationship between TyG-i and incident diabetes. The nonlinear relationship was detected after adjusting for sex, age, alcoholic intake, smoking status, exercise habits, SBP, ALT, AST, GGT, HDL-C, TC, and HbA1c.



Effect size of TyG-i on diabetes in prespecified and exploratory subgroups. The model was adjusted for sex, age, alcohol consumption, smoking status, exercise habits, systolic blood pressure, ALT, AST, GGT, HDL-C, total cholesterol, and HbA1c, excluding the stratification variable in each instance.

FIGURE 4
Effect size of TyG-i on diabetes in prespecified and exploratory subgroups. The model was adjusted for sex, age, alcohol consumption, smoking status, exercise habits, systolic blood pressure, ALT, AST, GGT, HDL-C, total cholesterol, and HbA1c, excluding the stratification variable in each instance.

induced insulin release, leading to diabetes onset (34, 35). Moreover, low TyG-i levels are similarly linked to an increased risk of developing diabetes. Interestingly, Black individuals exhibit unexpectedly low TG levels despite high insulin resistance or risk factors for diabetes, a phenomenon potentially explained by the inhibition of insulin-sensitive lipase activity and the consequent reduction in free fatty acid release from fat tissue due to hyperinsulinemia (36–39). Additionally, those with the PNPLA3 148M allele have lower triglyceride levels, increased insulin resistance, and greater vulnerability to diabetes (40). Pancreatic α-cells are vital for maintaining glucose, amino acid, and lipid balance (41). Malfunctions in these α-cells can result in hypoglycemia, which may indicate α-cell dysregulation, a core pathogenic process in diabetes development (42).

Our study is limited to a Japanese cohort, which may constrain the generalizability of our findings. It is essential to consider how genetic, dietary, and healthcare system differences might influence the observed associations between the TyG-i and the risk of T2D. Genetic predispositions play a significant role in metabolic regulation and the pathogenesis of diabetes. Ethnic variations in genes related to lipid metabolism and insulin sensitivity could modulate the relationship between the TyG-i and diabetes risk. For example, certain genetic polymorphisms prevalent in Asian populations may impact triglyceride levels and glucose homeostasis, potentially yielding risk profiles distinct from those in other ethnic groups (43). The traditional Japanese diet—characterized by high consumption of rice, fish, and soy products—imposes unique metabolic effects (44). Dietary patterns may interact with genetic factors to influence TyG-i levels and their associations with diabetes risk. Notably, omega-3 fatty acids abundant in fish have been documented to improve insulin sensitivity, which could affect metabolic outcomes within our cohort (45). Recognizing dietary variations across populations is critical when interpreting our results, as these differences could inform culturally tailored dietary recommendations for T2D prevention. Moreover, the Japanese healthcare system, with its emphasis on universal coverage and preventive care, may significantly impact the management of metabolic diseases (46, 47). Routine health screenings and early interventions are commonplace in Japan, potentially facilitating better management of conditions associated with the TyG-i, such as MASLD. This proactive healthcare approach may alter the observed relationship between TyG-i and diabetes risk, underscoring the need for caution when extrapolating our findings to populations with differing healthcare infrastructures. In light of these considerations, we stress the importance of further research involving diverse populations to validate the U-shaped association between the TyG-i and T2D risk. Future investigations should include a broad range of ethnic groups to examine the consistency and applicability of these findings across varied demographic and clinical contexts.

This study offers several notable advantages. Firstly, we identified a U-shaped association, allowing us to pinpoint the optimal inflection point where the TyG-i affects T2D risk. Secondly, we applied rigorous statistical adjustments to our results to reduce confounding factors, thereby enhancing their validity. Lastly, we employed a diverse array of sensitivity analyses to bolster the validity and reliability of our results, thereby enhancing the overall methodological strength of the study.

Despite these strengths, several limitations warrant consideration. Primarily, the research focused on a Japanese cohort, which may restrict the applicability of the results to other ethnic and geographic populations. Additionally, the definition of T2D employed in this study did not incorporate oral glucose tolerance testing, potentially resulting in an underestimation of T2D incidence. Secondly, although we have controlled for known confounding variables, the possibility remains that unmeasured factors—such as certain lifestyle habits or genetic predispositions—may have influenced the observed relationship between the TyG-i and T2D. Nevertheless, the calculated E-value of 2.32 exceeds the relative risk of 1.78 associated with both TyG-i and potential unknown confounders, implying that the effect of such unmeasured variables on this association is likely minimal. In future prospective investigations, we will strive to systematically collect and incorporate comprehensive information on lifestyle and genetic factors to further validate and strengthen our results. Thirdly, the absence of repeated measurements of the TyG-i precluded the assessment of the impact of longitudinal dynamic changes in TyG-i on T2D risk. The TyG-i, like other metabolic markers, is subject to fluctuations influenced by various factors, including dietary habits, physical activity, weight changes, and underlying metabolic conditions. These dynamic changes may significantly impact an individual's risk profile for T2D. Incorporating analyses of TyG-i variability over time could enhance our understanding of its relationship with diabetes risk. In light of these considerations, we plan to design future studies to investigate the relationship between changes in the TyG-i and diabetes prognosis.

Conclusion

This research revealed a U-shaped relationship between the TyG-i and the risk of T2D in adults with MASLD. These results underscore that early intervention using the TyG-i may effectively improve the risk of T2D in patients with MASLD.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://datadryad.org/stash/dataset/doi:10.5061%2Fdryad.8q0p192.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Murakami Memorial Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. This study also received approval

from the Clinical Research Ethics Committee of Shenzhen Second People's Hospital Dapeng New District Nan'ao Hospital. Full compliance with the principles of the Declaration of Helsinki, as well as all relevant guidelines and regulatory standards was ensured.

Author contributions

CC: Writing – original draft. XZ: Writing – original draft. YH: Writing – review & editing. HH: Writing – review & editing. YW: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Correlation of the triglyceride-glucose index with major adverse cardiovascular events in type 2 diabetes mellitus patients with acute myocardial infarction combined with HFpEF

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Aims: This study was conducted to evaluate the correlation between triglyceride-glucose index (TyG) and major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus (T2DM) and heart failure with preserved ejection fraction (HFpEF) after acute myocardial infarction (AMI).

Methods: This retrospective study at the First Affiliated Hospital of Dalian Medical University included 400 AMI patients with T2DM and HFpEF who underwent percutaneous coronary intervention (PCI) between 1 January 2018 and 1 January 2023. The study was conducted using univariate and multivariate Cox regression analyses, subgroup analyses, receiver operating characteristic (ROC) curves, and Kaplan–Meier survival curves to assess the correlation between the TyG index and MACE.

Results: Multivariate Cox regression analyses showed that in model 3 with variables fully adjusted, when TyG was used as a categorical variable, the risk of MACE in the TyG T2 and T3 groups was 1.622 times and 2.247 times higher than that in the T1 group, respectively ($P < 0.05$). When TyG was used as a continuous variable, the risk of MACE increased by 49.5% for every 1 unit increase in the TyG index ($P < 0.001$). In the subgroup analysis, elevated TyG index levels were consistently associated with an increased risk of MACE across multiple clinical subgroups ($P < 0.05$). ROC analysis showed that the TyG index significantly predicted the occurrence of MACE (AUC: 0.635, 95% CI: 0.580–0.691, $P < 0.001$), all-cause death (AUC: 0.565, 95% CI: 0.508–0.622, $P = 0.027$), non-fatal myocardial infarction (AUC: 0.617, 95% CI: 0.542–0.693, $P = 0.004$), and unplanned revascularization (AUC: 0.644, 95% CI: 0.578–0.710, $P < 0.001$). The Kaplan–Meier survival curves revealed statistically significant differences in survival probabilities for the occurrence of MACE, all-cause death, non-fatal

myocardial infarction, and unplanned revascularization across the three TyG index groups as the follow-up period progressed ($P < 0.05$).
Conclusions: The TyG index was independently associated with MACE in T2DM patients with AMI combined with HFpEF.

KEYWORDS

triglyceride-glucose index, acute myocardial infarction, heart failure with preserved ejection fraction, major adverse cardiovascular events, type 2 diabetes mellitus

1 Introduction

Over the past three decades, significant advances have been made in the treatment of coronary heart disease (CHD) and acute myocardial infarction (AMI). However, AMI, the most lethal and prevalent form of CHD, continues to be the most serious and dangerous type, remaining the leading cause of heart failure (HF) (1, 2). According to a systematic review and meta-analysis published in 2023 (with data updated through September 2022), the global prevalence of MI is 3.8% in individuals under 60 years old and rises to 9.5% in those over 60, indicating a marked age-related increase (3). MI is not only a critical manifestation of CHD but also a major precipitating factor for HF. In recent years, there has been increased attention on MI-related HF, particularly in the context of metabolic dysfunction. The prognostic value of this condition in CHD patients with type 2 diabetes mellitus (T2DM) is of paramount importance. Given that diabetes accelerates atherosclerosis and increases the risk of both MI and subsequent HF, understanding the interplay between these conditions is essential for improving risk stratification and guiding targeted interventions.

Several factors contribute to the risk of AMI, including poor glycemic control, hypertension, hyperlipidemia, mental stress, air pollution, and obesity (4, 5). If these risk factors are not effectively managed, they can lead to adverse left ventricular remodeling, thereby exacerbating the incidence of HF following AMI (6). Moreover, the prognosis of HF after AMI is notably worse in patients with T2DM compared to those without glucose disorders (7, 8). Furthermore, in a large cohort of 4,082 Chinese patients with HF, the 12-month follow-up revealed a high all-cause mortality rate of 19.6%, a rehospitalization rate of 24.4%, and a composite event rate of 40.15%, with overall health-related quality of life (HRQL) being poor as indicated by a mean MLHFQ score of 42.9—significantly higher in women than in men—and HRQL independently predicting both all-cause mortality and HF hospitalization (9). Despite this, current research predominantly focuses on the prevention and treatment of ischemic HF, with little attention given to further classifying HF post-AMI or exploring the link between glycemic metabolism abnormalities and HF onset, particularly in the context of heart failure with preserved ejection fraction (HFpEF) (10). This research gap is of critical importance, as HFpEF now accounts for approximately half of all HF cases and is closely associated with metabolic comorbidities such as diabetes, obesity, and hypertension, with emerging evidence indicating that systemic inflammation, microvascular endothelial dysfunction, and impaired myocardial energetics—often driven by glycemic dysregulation—play central roles in its pathogenesis (11). Therefore, it is crucial to examine whether risk factors associated with AMI in T2DM patients influence the outcomes of HFpEF or affect long-term cardiovascular outcomes following AMI.

One key factor in the development of cardiovascular diseases (CVD) is insulin resistance (IR), which is often a hallmark of metabolic disorders and systemic inflammation (12). IR frequently coexists with obesity, hypertension, and dyslipidemia, all of which are significant risk factors for CVD development and prognosis. The triglyceride-glucose index (TyG), derived from fasting triglyceride (TG) and fasting plasma glucose (FPG) levels, has emerged as a reliable indicator of IR in high-risk populations (13). In addition to its association with diabetes, the TyG index is also strongly linked to hypertension, dyslipidemia, metabolic syndrome, cardiovascular diseases, and mortality (13–17). Furthermore, Sun et al. demonstrated in a retrospective study of 2,055 ischemic HF patients undergoing percutaneous coronary intervention (PCI) that the TyG index was independently and positively associated with the risk of major adverse cardiovascular events (MACE), with higher TyG levels corresponding to an increased incidence of adverse outcomes (18). Additionally, in a multicenter cohort study of 277 patients with newly diagnosed ischemic cardiomyopathy and HFpEF undergoing coronary artery bypass grafting (CABG), Ruan et al. demonstrated that the TyG index was an independent predictor of MACE, showing a linear positive association with risk, and that incorporating the TyG index into traditional cardiovascular risk models significantly improved prognostic accuracy through enhanced discrimination, calibration, and reclassification metrics (19).

However, despite the accumulation of substantial research evidence, some studies—particularly those focusing on patients with T2DM complicated by AMI and HFpEF—have yet to establish a clear association between the TyG index and MACE. This indicates that further validation is needed to confirm the predictive value of the TyG index for MACE in this specific patient population. Therefore, to address this research gap, the present study aims to focus on T2DM patients with AMI and HFpEF who have undergone interventional therapy, exploring the association between the TyG index and MACE.

2 Methods

2.1 Study population and grouping

This was a single-center, retrospective cohort study that included patients with T2DM and AMI who were admitted to the Department of Cardiology at the First Affiliated Hospital of Dalian Medical University for PCI. These patients were diagnosed with HFpEF between 1 January 2018 and 1 January 2023. Patients with end-stage hepatic or renal failure, coagulation abnormalities, aortic coarctation, or incomplete data, as well as those lost to follow-up or who did not undergo PCI, were excluded from the study. After excluding these individuals, a total of 400 patients were finally included in the analysis. All procedures were conducted in compliance with the Declaration of Helsinki and its amendments. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital of Dalian Medical University. Informed consent was obtained from all participants prior to the collection of clinical data.

2.2 Data collection and definitions

All clinical data and study information were collected from Yidu Cloud, one of the largest medical databases in China, at the First Hospital of Dalian Medical University. These data included patient demographics, comorbidities, medication information, anthropometrics, blood biomarkers, medication regimens, echocardiographic results, and data related to PCI procedures.

Demographic data comprised age, gender, smoking, and family history of CHD. Smoking was defined as continuous or cumulative smoking for 6 months or more prior to enrollment. A CHD family history was defined as a genetic predisposition to the disease, with at least two or more close relatives affected.

Comorbidity data included hypertension, stroke, and atrial fibrillation (AF). Hypertension in adults was diagnosed based on a systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg (20). Diabetes was diagnosed in patients with symptoms such as polydipsia, polyuria, polyphagia, and weight loss, combined with a blood glucose level greater than 11.1 mmol/L at any time, a fasting blood glucose greater than 7.0 mmol/L, or hemoglobin A1c (HbA1c) ≥6.5%, or a 2-h oral glucose tolerance test blood glucose greater than 11.1 mmol/L (21). Stroke was defined as the impairment of blood circulation in the brain, leading to brain tissue damage due to the obstruction or rupture of cerebral blood vessels, including both ischemic and hemorrhagic stroke types (22). AF was defined as a rapid arrhythmia with disordered electrical activity in the atria, resulting in irregular and rapid fibrillation waves. The study included all forms of AF, including first diagnosis, paroxysmal, persistent, long-term persistent, and permanent atrial fibrillation (23). HFpEF was diagnosed based on the fulfillment of all the following three criteria: 1) the presence of typical HF symptoms and/or signs, such as shortness of breath, fatigue, or reduced exercise capacity; 2) a left ventricular ejection fraction (LVEF) of 50% or higher; and 3) objective indicators of diastolic dysfunction and/or elevated left ventricular filling pressures (24). These indicators included structural abnormalities (e.g., left atrial volume index >34 mL/m^2, left ventricular mass index ≥95 g/m^2 in women or ≥115 g/m^2 in men, or relative wall thickness >0.42), functional impairments (e.g., E/e′ ratio >9, tricuspid regurgitation velocity >2.8 m/s, or pulmonary artery systolic pressure >35 mmHg), and elevated levels of natriuretic peptides [N-terminal pro-B-type natriuretic peptide (NT-proBNP) >125 pg/mL or B-type natriuretic peptide (BNP) >35 pg/mL in sinus rhythm; NT-proBNP >365 pg/mL or BNP >105 pg/mL in atrial fibrillation] (24).

Anthropometric data included body mass index (BMI), SBP, and DBP. BMI was calculated using the formula: BMI = weight (kg)/height $(m)^2$. Additional data collected included the presence of ST-segment elevation myocardial infarction (STEMI) and Killip classification. STEMI was defined as marked ST-segment elevation on the electrocardiogram, usually caused by the rupture of an intracoronary plaque or thrombosis leading to coronary occlusion, which results in sustained myocardial ischemia and hypoxia, ultimately causing myocardial necrosis (25). The Killip classification, a grading system for assessing the cardiac functional status of patients with AMI, is divided into four grades (I–IV), with the condition progressively worsening (26).

Hematological biomarkers included FPG, HbA1c, albumin, uric acid (UA), estimate glomerular filtration rate (eGFR) [calculated using the Modification of Diet in Renal Disease (MDRD) equation: eGFR = $175 \times (\text{serum creatinine [(mg/dL)]})^{-1.234} \times (\text{age [years]})^{-0.179} \times 0.79$ (if female)] (27), TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fibrinogen (FIB), D-dimer, high-sensitivity C-reactive protein (Hs-CRP), cardiac biomarkers (troponin I), and B-type natriuretic peptide (BNP).

Discharge medication data included the use of antiplatelet agents (such as aspirin, clopidogrel, and ticagrelor), statins, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and β-blockers. Echocardiographic data included LVEF. All echocardiographic data were recorded by an experienced cardiac sonographer using a cardiac ultrasound machine. Procedure-related data included details on the multivessel disease. Multivessel disease was defined as lesions involving two or more coronary arteries with ≥50% stenosis.

2.3 Study endpoints and follow-up

In this study, patients were enrolled for follow-up starting from the date of their first hospitalization, with the follow-up period extending until either the patient's death or 31 July 2024. The median follow-up time was 24.63 months. The study endpoint was MACE, defined as a composite of one or more of the following: all-cause death, unplanned revascularization, and non-fatal myocardial infarction. To identify clinical characteristics associated with adverse cardiovascular outcomes, baseline variables were compared between patients with and without MACE. This grouping approach was intended to explore potential risk factors

for MACE. All enrolled patients were encouraged to monitor their condition regularly through outpatient services. For those who did not complete the follow-up program, efforts were made to contact them by telephone to ensure data completeness.

2.4 Calculation method of the TyG index

FPG and TG levels were collected for all patients during hospitalization. Specifically, blood samples were obtained in the early morning of the day following admission after an overnight fast of at least 8 h. All biochemical measurements were performed at the same clinical laboratory within the hospital using standardized procedures, ensuring consistency in both testing methods and fasting conditions. The formula for calculating the TyG index was as follows: TyG = Ln [fasting TG (mg/dL) × FPG (mg/dL)/2] (28). Based on the tertiles of the TyG index, patients were divided into three groups: T1 (≤8.76), T2 (8.77–9.51), and T3 (>9.51). This tertile-based stratification is widely used in metabolic and cardiovascular research to ensure statistical comparability across groups and avoid arbitrary threshold selection. Baseline characteristics were analyzed across these TyG tertiles to evaluate the association between metabolic risk status and clinical features or outcomes.

2.5 Statistical analysis

Statistical analyses were performed using SPSS statistical software version 26.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages. Continuous variables that were normally distributed were presented as means ± standard deviation, while non-normally distributed continuous variables were expressed as medians with interquartile ranges. To compare the differences between two or more groups, the chi-square test was used for categorical variables. For continuous variables, the independent samples *t*-test was applied for two-group comparisons with a normal distribution, while one-way ANOVA was used for comparisons involving three groups. For non-normally distributed data, the Mann–Whitney *U* test or Kruskal–Wallis test was applied, depending on the number of groups. Univariate and multivariate Cox regression analyses were performed to identify independent factors predicting the MACE. The proportional hazards assumption was tested using Schoenfeld residuals, and no significant violations were observed. Covariates included in the multivariate logistic regression analysis were those that showed a statistically significant association with MACE ($P < 0.05$) in the univariate logistic regression analysis. In addition, subgroup analyses were performed using Cox regression within different clinical subgroups (such as age, sex, hypertension, STEMI status, Killip classification, and multivessel disease) to evaluate the association between TyG tertiles and MACE in each category. The rationale for conducting subgroup analyses was to explore whether the predictive value of the TyG index for MACE remained consistent across various clinically relevant populations. These subgroups were selected based on their known associations with cardiovascular risk and their clinical importance in the context of HF, AMI, and MACE. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive power of the TyG index for the events. The area under the curve (AUC) was calculated for each endpoint to determine the diagnostic accuracy. Kaplan–Meier analysis was employed to estimate the cumulative incidence of clinical adverse events, while the log-rank test was applied to compare survival distributions across groups. A two-sided *P*-value of <0.05 was considered statistically significant.

3 Results

3.1 Baseline demographics and clinical characteristics

Table 1 presents the clinical characteristics of the population, grouped according to the occurrence of MACE. The results showed that, compared to the group without MACE, the MACE group had a higher median age; a higher probability of being classified as Killip class III–IV; and elevated SBP, FPG, FIB, D-dimer, BNP, and TyG index levels. Moreover, the MACE group had higher rates of clopidogrel use and multivessel disease ($P < 0.05$). In contrast, the MACE group had lower rates of STEMI and use of aspirin and ticagrelor and lower levels of eGFR ($P < 0.05$).

Table 2 displays the clinical characteristics of the cohort, grouped according to TyG tertiles. The TyG tertiles were defined as follows: TyG-T1: ≤8.76, TyG-T2: 8.77–9.51, and TyG-T3: >9.51. The results indicated that significant differences were observed among the three TyG groups in terms of age, Killip classification, SBP, DBP, FPG, HbA1c, TG, TC, LDL-C, HDL-C, UA, eGFR, FIB, use of β-blockers, LVEF, all-cause death, MACE, non-fatal myocardial infarction, and unplanned revascularization ($P < 0.05$). Specifically, the incidence of all-cause death, MACE, non-fatal myocardial infarction, and unplanned revascularization increased with higher TyG tertile levels ($P < 0.05$).

3.2 Association between TyG and MACE

Table 3 presents the results of the univariate Cox regression analysis for MACE. The analysis showed that age, STEMI, Killip classification III–IV, hypertension, SBP, FPG, eGFR, troponin I, BNP, aspirin, clopidogrel, ticagrelor, ACEI/ARB, multivessel disease, and the TyG index were all significantly correlated with the risk of MACE ($P < 0.05$).

Table 4 displays the results of the multivariate Cox regression analyses for TyG and MACE. In the unadjusted model 1, as well as in model 2 (which was adjusted for age, hypertension, STEMI, and Killip classification), both TyG as a categorical variable and as a continuous variable were strongly associated with the risk of MACE ($P < 0.05$). Furthermore, in model 3, which was fully adjusted for age, hypertension, STEMI, Killip classification, eGFR, aspirin, ACEI/ARB, and multivessel disease, when TyG was used as a categorical variable, the risk of MACE in the TyG-T2 and T3

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TABLE 1 Clinical characteristics according to MACE.

Variables	Total population	Non-MACE	MACE	P-value
Age, years	74.39 ± 11.15	71.84 ± 10.93	75.88 ± 11.03	<0.001
Male, n (%)	209 (52.3)	84 (56.8)	125 (49.6)	0.167
Smoking, n (%)	121 (30.3)	48 (32.4)	73 (29.0)	0.466
STEMI, n (%)	172 (43.0)	82 (55.4)	90 (35.7)	<0.001
Killip class, n (%)				0.027
I	197 (49.3)	82 (55.4)	115 (45.6)	
II	147 (36.8)	55 (37.2)	92 (36.5)	
III	32 (8.0)	7 (4.7)	25 (9.9)	
IV	24 (6.0)	4 (2.7)	20 (7.9)	
Family history of CHD, n (%)	62 (15.5)	23 (15.5)	39 (15.5)	0.986
Hypertension, n (%)	278 (69.5)	95 (64.2)	183 (72.6)	0.077
Stroke, n (%)	53 (13.3)	18 (12.2)	35 (13.9)	0.623
AF, n (%)	36 (9.0)	8 (5.4)	28 (11.1)	0.054
BMI, kg/m2	26.76 ± 3.95	26.93 ± 4.27	26.66 ± 3.76	0.515
SBP, mmHg	132.11 ± 29.59	128.16 ± 28.67	134.43 ± 29.93	0.040
DBP, mmHg	74.74 ± 15.31	74.46 ± 15.69	74.90 ± 15.11	0.779
FPG, mmol/L	8.84 (5.80, 13.44)	6.36 (5.21, 8.84)	10.56 (6.61, 14.84)	<0.001
HbA1c, %	7.40 (6.13, 8.80)	7.30 (6.00, 8.90)	7.50 (6.30, 8.80)	0.163
TG, mmol/L	1.28 (0.94, 1.84)	1.37 (0.98, 1.82)	1.25 (0.92, 1.85)	0.465
TC, mmol/L	4.67 ± 1.29	4.73 ± 1.32	4.63 ± 1.27	0.423
LDL-C, mmol/L	2.92 ± 0.93	2.95 ± 0.88	2.90 ± 0.95	0.549
HDL-C, mmol/L	1.02 ± 0.29	1.04 ± 0.31	1.02 ± 0.28	0.443
Albumin, g/L	35.97 ± 3.96	36.21 ± 4.10	35.83 ± 3.87	0.354
UA, μmol/L	387.55 ± 127.87	394.12 ± 121.86	383.69 ± 131.35	0.432
eGFR, mL/min	67.50 (46.25, 85.00)	71.00 (53.25, 88.50)	65.00 (40.00, 84.75)	0.008
Hs-CRP, mg/L	44.70 (24.00, 88.80)	44.70 (21.75, 90.05)	44.80 (24.35, 87.50)	0.880
FIB, g/L	3.59 (2.78, 4.43)	3.35 (2.59, 4.15)	3.73 (2.93, 4.49)	0.029
D-dimer, mg/L	240.00 (0.77, 779.37)	130.00 (0.60, 630.00)	310.00 (1.14, 779.37)	0.004
Troponin I, ng/mL	8.16 (1.50, 48.94)	9.76 (1.96, 94.86)	7.63 (1.40, 39.11)	0.100
BNP, pg/mL	696.59 (523.73, 1,078.49)	650.83 (508.30, 958.26)	735.39 (529.34, 1,146.09)	0.015
Discharge medication, *n* (%)				
Aspirin	295 (73.8)	121 (81.8)	174 (69.0)	0.005
Clopidogrel	234 (58.5)	73 (49.3)	161 (63.9)	0.004
Ticagrelor	166 (41.5)	75 (50.7)	91 (36.1)	0.004
Statins	374 (93.5)	138 (93.2)	236 (93.7)	0.873
ACEI/ARB	308 (77.0)	106 (71.6)	202 (80.2)	0.050
β-Blockers	274 (68.5)	101 (68.2)	173 (68.7)	0.932
LVEF, %	54.73 ± 3.05	54.86 ± 2.91	54.66 ± 3.13	0.528

(Continued)

TABLE 1 Continued

Variables	Total population	Non-MACE	MACE	P-value
Discharge medication, *n* (%)				
Multivessel disease, *n* (%)	189 (47.3)	59 (39.9)	130 (51.6)	0.023
TyG index	9.17 ± 0.75	8.95 ± 0.68	9.30 ± 0.77	<0.001

MACE, major adverse cardiovascular events; STEMI, ST-elevation myocardial infarction; CHD, coronary heart disease; AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; FIB, fibrinogen; BNP, B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; TyG index, triglyceride-glucose index.

TABLE 2 Clinical characteristics according to TyG tertiles.

Variables	T1	T2	T3	*P*-value
Age, years	76.70 ± 10.06	74.03 ± 11.16	72.44 ± 11.83	0.007
Male, *n* (%)	77 (57.9)	65 (48.9)	67 (50.0)	0.275
Smoking, *n* (%)	37 (27.8)	39 (29.3)	45 (33.6)	0.568
STEMI, *n* (%)	56 (42.1)	57 (42.9)	59 (44.0)	0.950
Killip class, *n* (%)				0.038
I	69 (51.9)	71 (53.4)	57 (42.5)	
II	50 (37.6)	49 (36.8)	48 (35.8)	
III	11 (8.3)	6 (4.5)	15 (11.2)	
IV	3 (2.3)	7 (5.3)	14 (10.4)	
Family history of CHD, *n* (%)	15 (11.3)	21 (15.8)	26 (19.4)	0.185
Hypertension, *n* (%)	85 (63.9)	91 (68.4)	102 (76.1)	0.091
Stroke, *n* (%)	20 (15.0)	14 (10.5)	19 (14.2)	0.515
AF, *n* (%)	13 (9.8)	6 (4.5)	17 (12.7)	0.061
BMI, kg/m^2	26.50 ± 4.28	26.43 ± 3.75	27.36 ± 3.77	0.099
SBP, mmHg	129.37 ± 31.25	129.62 ± 24.89	137.30 ± 31.65	0.045
DBP, mmHg	72.95 ± 15.11	73.54 ± 12.84	77.71 ± 17.30	0.021
FPG, mmol/L	5.53 (4.85, 6.24)	9.02 (6.55, 12.35)	14.34 (10.99, 17.13)	<0.001
HbA1c, %	6.50 (5.80, 7.50)	7.50 (6.15, 8.75)	8.30 (7.28, 9.60)	<0.001
TG, mmol/L	0.92 (0.74, 1.18)	1.31 (1.01, 1.65)	2.04 (1.45, 2.87)	<0.001
TC, mmol/L	4.24 ± 1.19	4.57 ± 1.07	5.19 ± 1.41	<0.001
LDL-C, mmol/L	2.80 ± 0.84	2.88 ± 0.93	3.07 ± 1.00	0.048
HDL-C, mmol/L	1.06 ± 0.33	1.04 ± 0.27	0.96 ± 0.26	0.012
Albumin, g/L	35.70 ± 3.79	36.15 ± 3.87	36.07 ± 4.21	0.613
UA, μmol/L	388.10 ± 133.64	366.77 ± 122.97	407.63 ± 124.41	0.033
eGFR, mL/min	71.00 (50.50, 86.00)	70.00 (51.00, 93.50)	57.50 (36.50, 79.25)	0.002
Hs-CRP, mg/L	47.20 (24.00, 89.85)	48.20 (29.90, 92.10)	41.50 (21.30, 83.60)	0.130
FIB, g/L	3.32 (2.59, 4.04)	3.51 (2.71, 4.36)	3.73 (3.13, 4.99)	0.001
D-dimer, mg/L	290.00 (1.20, 779.37)	130.00 (0.63, 690.00)	215.00 (0.97, 779.37)	0.086
Troponin I, ng/mL	9.95 (1.33, 69.68)	6.41 (1.79, 52.51)	8.06 (1.46, 41.50)	0.934

(Continued)

TABLE 2 Continued

Variables	T1	T2	T3	*P*-value
Killip class, *n* (%)				0.038
BNP, pg/mL	697.62 (529.29, 1,067.11)	656.07 (501.76, 968.20)	755.61 (540.76, 1,137.00)	0.117
Discharge medication, *n* (%)				
Aspirin	89 (66.9)	104 (78.2)	102 (76.1)	0.084
Clopidogrel	88 (66.2)	69 (51.9)	77 (57.5)	0.058
Ticagrelor	45 (33.8)	64 (48.1)	57 (42.5)	0.058
Statins	126 (94.7)	127 (95.5)	121 (90.3)	0.177
ACEI/ARB	97 (72.9)	102 (76.7)	109 (81.3)	0.262
β-Blockers	81 (60.9)	87 (65.4)	106 (79.1)	0.004
LVEF, %	55.43 ± 3.05	54.40 ± 2.90	54.37 ± 3.09	0.005
Multivessel disease, *n* (%)	57 (42.9)	68 (51.1)	64 (47.8)	0.397
All-cause death, *n* (%)	52 (39.1)	43 (32.3)	66 (49.3)	0.018
MACE, *n* (%)	67 (50.4)	81 (60.9)	104 (77.6)	<0.001
Non-fatal myocardial infarction, *n* (%)	13 (9.8)	18 (13.5)	29 (21.6)	0.021
Unplanned revascularization, *n* (%)	10 (7.5)	28 (21.1)	34 (25.4)	<0.001

TyG, triglyceride-glucose index; STEMI, ST-elevation myocardial infarction; CHD, coronary heart disease; AF, atrial fibrillation; CKD, chronic kidney disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; eGFR, estimated glomerular filtration rate; FIB, fibrinogen; BNP, B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events.

groups was 1.622 times and 2.247 times higher than that in the T1 group, respectively (HR: 1.622, 95% CI: 1.169–2.251, $P = 0.004$; HR: 2.247, 95% CI: 1.639–3.082, $P < 0.001$). When TyG was treated as a continuous variable, the risk of MACE increased by 49.5% for every 1-unit increase in the TyG index (HR: 1.495, 95% CI: 1.272–1.757, $P < 0.001$).

3.3 Hierarchical association of TyG and MACE

Table 5 presents the hierarchical association between the TyG index and MACE. The results indicated that in the subgroup analysis, elevated TyG index levels were consistently associated with an increased risk of MACE across multiple clinical subgroups. Among patients aged <75 years, the TyG-T2 and T3 groups had significantly higher MACE risks compared to T1 (HR = 2.060, $P = 0.014$; HR = 2.865, $P < 0.001$, respectively), and similar associations were observed in those aged ≥75 years (T2: HR = 1.630, $P = 0.019$; T3: HR = 1.942, $P = 0.001$). For women, both T2 and T3 groups showed significantly elevated risks (HR = 2.347 and 2.638, both $P \leq 0.001$), while in men, only the T3 group was significantly associated with increased MACE (HR = 2.052, $P = 0.001$). In non-STEMI patients, both the T2 and T3 groups were at significantly higher risk (HR = 1.944 and 2.244, both $P < 0.001$); among STEMI patients, the T3 group was significant (HR = 2.659, $P < 0.001$). The association remained robust in patients with hypertension (T2: HR = 1.477, $P = 0.050$; T3: HR = 1.994, $P < 0.001$) and was even stronger in those without hypertension (T2: HR = 2.308, $P = 0.008$; T3: HR = 2.899, $P = 0.001$). In Killip classification I patients, both the T2 and T3 groups were associated with higher MACE risk (HR = 1.850 and 2.842, $P = 0.011$ and <0.001), while in classification II–IV, only the T3 group showed significance (HR = 1.955, $P = 0.002$). Finally, in patients with or without multivessel disease, both the T2 and T3 tertiles were significantly linked to increased MACE risk, with the strongest association seen in the T3 group without multivessel disease (HR = 2.926, $P < 0.001$).

3.4 ROC curves and Kaplan–Meier curve analyses

As shown in Figure 1, ROC curve analysis demonstrated that the TyG index was a significant predictor for the risk of MACE (AUC: 0.635, 95% CI: 0.580–0.691, $P < 0.001$). It also predicted all-cause death (AUC: 0.565, 95% CI: 0.508–0.622, $P = 0.027$), new-onset myocardial infarction (AUC: 0.617, 95% CI: 0.542–0.693, $P = 0.004$), and second PCI (AUC: 0.644, 95% CI: 0.578–0.710, $P < 0.001$).

Additionally, as shown in Figure 2, the Kaplan–Meier survival curves revealed statistically significant differences in the survival probabilities for MACE, all-cause death, non-fatal myocardial infarction, and unplanned revascularization across the three TyG index groups over time (log-rank $P < 0.05$). Notably, patients in the

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TABLE 3 Univariate Cox regression analysis of MACE.

Variables	HR	95% CI	*P*-value
Age	1.026	1.013–1.039	<0.001
Male	0.834	0.651–1.068	0.151
Smoking	0.872	0.664–1.145	0.326
STEMI	0.599	0.463–0.776	<0.001
Killip class			
I	Ref		
II	1.186	0.902–1.561	0.222
III	1.605	1.041–2.476	0.032
IV	2.468	1.532–3.975	<0.001
Family history of CHD	1.092	0.776–1.536	0.615
Hypertension	1.382	1.048–1.824	0.022
Stroke	1.210	0.847–1.730	0.295
AF	1.472	0.993–2.182	0.054
BMI	0.995	0.965–1.025	0.720
SBP	1.006	1.002–1.010	0.004
DBP	1.001	0.993–1.009	0.757
FPG	1.068	1.048–1.089	<0.001
HbA1c	1.026	0.962–1.094	0.429
TG	1.026	0.904–1.165	0.689
TC	0.950	0.859–1.050	0.312
LDL-C	0.969	0.845–1.112	0.655
HDL-C	0.859	0.562–1.312	0.481
Albumin	0.986	0.956–1.017	0.378
UA	1.000	0.999–1.001	0.472
eGFR	0.993	0.989–0.997	0.001
Hs-CRP	1.000	0.998–1.002	0.890
FIB	1.049	0.963–1.143	0.272
D-dimer	1.000	1.000–1.000	0.321
Troponin I	0.999	0.998–1.000	0.047
BNP	1.000	1.000–1.000	0.001
Discharge medication			
Aspirin	0.634	0.485–0.829	0.001
Clopidogrel	1.402	1.084–1.814	0.010
Ticagrelor	0.713	0.551–0.922	0.010
Statins	1.085	0.654–1.800	0.752
ACEI/ARB	1.437	1.054–1.959	0.022
β Blockers	1.068	0.818–1.394	0.629
LVEF	0.987	0.949–1.027	0.529
Multivessel disease	1.318	1.029–1.688	0.029
TyG index	1.470	1.256–1.722	< 0.001

HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events; STEMI, ST-elevation myocardial infarction; CHD, coronary heart disease; AF, atrial fibrillation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; FIB, fibrinogen; BNP, B-type natriuretic peptide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; TyG, triglyceride-glucose index.

TyG T3 group demonstrated the steepest decline in event-free survival. The estimated HRs for MACE from Kaplan–Meier analysis were 1.535 (95% CI: 1.109–2.124, $P = 0.010$) for the TyG T2 group and 2.141 (95% CI: 1.573–2.915, $P < 0.001$) for the TyG T3 group, both compared with the T1 group.

4 Discussion

This study comprehensively investigated the association between the TyG index and the risk of MACE in patients with T2DM and HFpEF following AMI. Our findings revealed a clear and consistent relationship between elevated TyG levels and increased incidence of MACE. Patients in the highest TyG tertile (T3) had a more than twofold increased risk of MACE compared to those in the lowest tertile (T1), even after adjusting for multiple clinical confounders. Moreover, the risk of MACE increased by nearly 50% for each 1-unit rise in the TyG index. Subgroup analyses confirmed the robustness of this association across various clinical strata, including age, sex, hypertension status, Killip classification, and presence of multivessel disease. These findings were further supported by Kaplan–Meier survival curves and ROC analysis, where the TyG index demonstrated modest but significant predictive power for MACE and related outcomes.

Left ventricular dilation and dysfunction caused by ischemic heart disease—specifically, structural and functional remodeling of the left ventricle—can result in decreased LVEF or hemodynamic abnormalities. However, in many patients with ischemic heart disease, including those with CAD and coronary microvascular dysfunction, this dysfunction can be delayed, inhibited, or even reversed due to the widespread use of PCI. This phenomenon, referred to as HFpEF caused by either coronary large vessel obstruction or microvascular dysfunction, has become more widely recognized (29, 30). Increasingly, researchers have focused on the relationship between metabolic disorders and the development of HFpEF after myocardial infarction, especially in the context of glucose metabolism, a field that remains underexplored (31, 32).

In our study, the clinical characteristics grouped according to TyG tertiles revealed statistically significant differences in outcomes such as all-cause death, MACE, non-fatal myocardial infarction,

TABLE 4 Multivariate Cox regression analysis of TyG and MACE.

Variables	Model 1			Model 2			Model 3		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
T1	Ref			Ref			Ref		
T2	1.535	1.109–2.124	0.010	1.661	1.198–2.303	0.002	1.622	1.169–2.251	0.004
T3	2.141	1.573–2.915	<0.001	2.304	1.680–3.160	<0.001	2.247	1.639–3.082	<0.001
TyG index	1.470	1.256–1.722	<0.001	1.505	1.282–1.767	<0.001	1.495	1.272–1.757	<0.001

Model 1: unadjusted; model 2: adjusted for age, hypertension, STEMI, and Killip classification; model 3: adjusted for age, hypertension, STEMI, Killip classification, eGFR, aspirin, ACEI/ARB, and multivessel disease.
HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events; TyG, triglyceride-glucose index; T1, tertile 1; T2, tertile 2; T3, tertile 3; STEMI, ST-elevation myocardial infarction; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

and unplanned revascularization among the three TyG groups. The incidence of MACE, non-fatal myocardial infarction, and unplanned revascularization increased with higher TyG levels. Specifically, in patients with T2DM and HFpEF following AMI, those with a TyG index reaching or exceeding 9.51 (in the T3 group) should be closely monitored for potential MACE, non-fatal myocardial infarction, and unplanned revascularization events. After adjusting for confounding factors, the TyG index remained an independent predictor of MACE in this population.

While previous studies have not extensively investigated the correlation between the TyG index and ischemia-induced HFpEF or its adverse outcomes, multiple studies have reported correlations between the TyG index and various CVD as well as the risk of cardiovascular events. For instance, Lyu et al. (33) found a non-linear relationship between the TyG-BMI index and all-cause mortality and HF-related rehospitalizations in HF patients. They reported an inverse "J"-shaped curve, where the risk of all-cause mortality decreased when the TyG-BMI index was below 240.0. Similarly, Guo et al. (34) identified TyG and TG/HDL-C as significant predictors of in-hospital mortality in non-diabetic AMI patients. This finding aligns with the results of our study, where TyG remained a key predictor for poor outcomes in patients

TABLE 5 Stratified association of TyG and MACE.

Subgroups	T1	T2		T3		
	HR (95% CI)	HR (95% CI)	*P*	HR (95% CI)	*P*	*P* for trend
Age						
<75 years	Ref	2.060 (1.160–3.660)	0.014	2.865 (1.691–4.854)	<0.001	<0.001
≥75 years	Ref	1.630 (1.083–2.453)	0.019	1.942 (1.291–2.922)	0.001	0.004
Gender						
Male	Ref	1.132 (0.709–1.807)	0.603	2.052 (1.354–3.109)	0.001	0.002
Female	Ref	2.347 (1.443–3.818)	0.001	2.638 (1.620–4.297)	<0.001	<0.001
STEMI						
Yes	Ref	1.246 (0.713–2.176)	0.440	2.659 (1.583–4.468)	<0.001	<0.001
No	Ref	1.944 (1.294–2.922)	0.001	2.244 (1.512–3.332)	<0.001	<0.001
Hypertension						
Yes	Ref	1.477 (1.000–2.184)	0.050	1.994 (1.381–2.879)	<0.001	0.001
No	Ref	2.308 (1.245–4.279)	0.008	2.899 (1.520–5.532)	0.001	0.002
Killip classification						
I	Ref	1.850 (1.154–2.964)	0.011	2.842 (1.761–4.585)	<0.001	<0.001
II–IV	Ref	1.446 (0.915–2.284)	0.114	1.955 (1.284–2.976)	0.002	0.006
Multivessel disease						
Yes	Ref	1.646 (1.043–2.596)	0.032	1.850 (1.188–2.882)	0.007	0.016
No	Ref	1.714 (1.055–2.784)	0.030	2.926 (1.884–4.546)	<0.001	<0.001

HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events; TyG, triglyceride-glucose index; T1, tertile 1; T2, tertile 2; T3, tertile 3; STEMI, ST-elevation myocardial infarction.

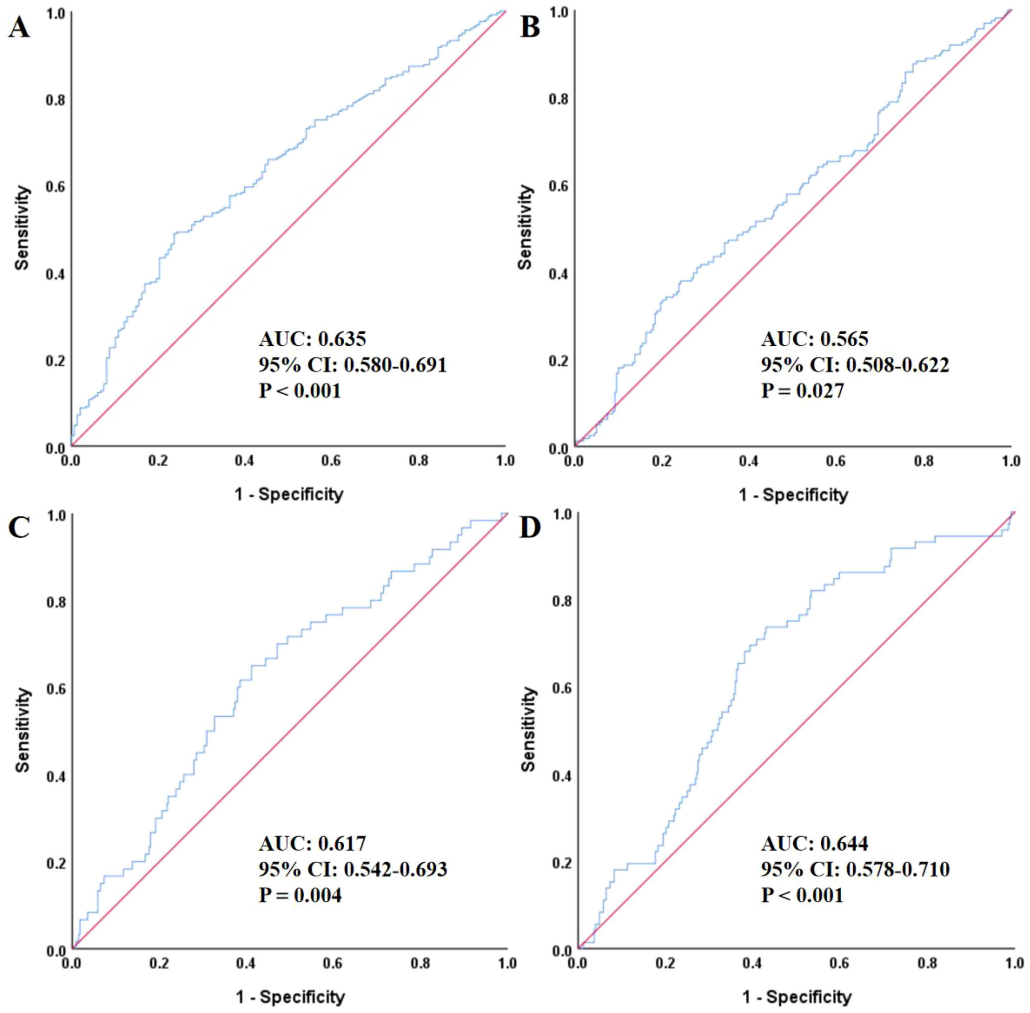

FIGURE 1
The ROC analysis of TyG for predicting MACE **(A)**, all-cause death **(B)**, non-fatal myocardial infarction **(C)**, and unplanned revascularization **(D)**. ROC, receiver operating characteristic; TyG, triglyceride-glucose index; AUC, area under the curve; CI, confidence interval; MACE, major adverse cardiovascular events.

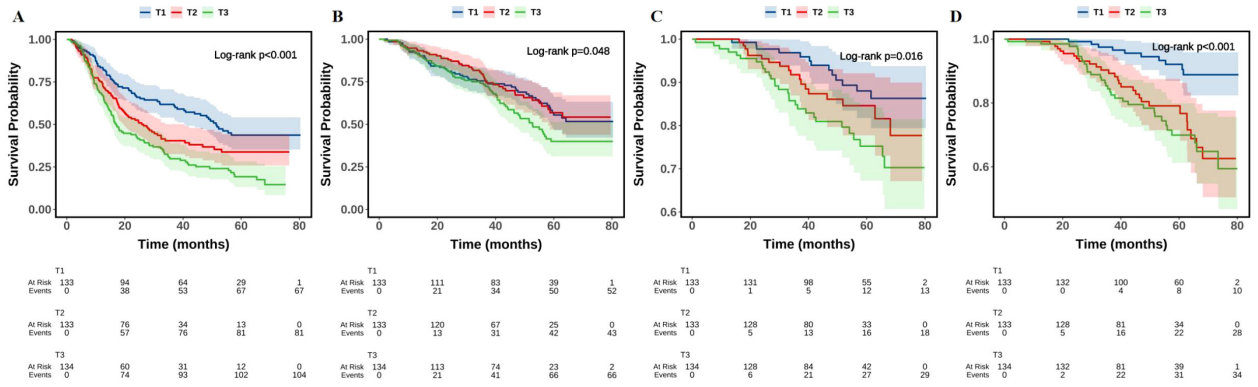

FIGURE 2
The Kaplan–Meier analysis of TyG with MACE **(A)**, all-cause death **(B)**, non-fatal myocardial infarction **(C)**, and unplanned revascularization **(D)**. TyG, triglyceride-glucose index; MACE, major adverse cardiovascular events.

with T2DM following AMI. Furthermore, Wang et al. (35) demonstrated that the TyG index independently predicted future MACE in diabetic patients with acute coronary syndrome (ACS), with Kaplan–Meier survival curves showing significant event-free survival differences between TyG quartiles. In our study, the stratified analysis demonstrated that elevated TyG index levels were consistently associated with an increased risk of MACE across multiple clinical subgroups. Among patients aged <75 years, the risk of MACE in the TyG T2 and T3 groups was 2.060 and 2.865 times higher than in the T1 group, respectively. In those aged ≥75 years, the risk was 1.630 times higher in T2 and 1.942 times higher in T3 compared to T1. In terms of sex, women in the T2 and T3 groups had 2.347-fold and 2.638-fold higher risks, respectively. Among men, only the T3 group showed a significant increase in risk (2.052-fold). In patients without STEMI, the T2 and T3 groups had 1.944-fold and 2.244-fold higher risks, respectively, while in STEMI patients, the T3 group showed a 2.659-fold increase. For patients with hypertension, the MACE risk was 1.477 times higher in T2 and 1.994 times higher in T3. Among those without hypertension, the risk increased to 2.308 times in T2 and 2.899 times in T3. Among patients with Killip classification I, the T2 and T3 groups had 1.850-fold and 2.842-fold higher risks, respectively. In those with Killip classification II–IV, only the T3 group showed a notable increase (1.955-fold). For patients with or without multivessel disease, both T2 and T3 groups demonstrated elevated MACE risks. Notably, in patients without multivessel disease, the T3 group had the highest risk, with a 2.926-fold increase. In summary, the TyG index was positively associated with MACE across various subgroups, with particularly stronger predictive value in women, non-STEMI patients, those without hypertension, and those without multivessel disease—highlighting its potential utility in risk stratification for targeted management in high-risk populations.

Beyond its cardiovascular implications, the TyG index has been explored as a non-invasive marker for various diseases. Liu and colleagues found that the TyG index was an effective predictor for non-alcoholic fatty liver disease and related hepatic conditions, including hepatic fibrosis, when coupled with TyG-derived indices like TyG-BMI (36, 37). Additionally, research by Jiang et al. (38) suggested that the TyG index was causally associated with a reduced stroke risk, a finding that aligns with our results. In our study, ROC curve analysis revealed that the TyG index significantly predicted the risk of MACE, all-cause death, non-fatal myocardial infarction, and unplanned revascularization, all with statistically significant predictive value. Moreover, the Kaplan–Meier survival curves showed significant differences between the TyG tertiles in the survival probabilities for MACE, all-cause death, non-fatal myocardial infarction, and unplanned revascularization over time. Patients in the higher TyG groups exhibited the fastest decline in survival probability, suggesting that a higher TyG index (above 9.51) correlates with worse clinical prognosis. In conclusion, while the TyG index has been linked to the prediction of a range of diseases, including CVD, liver fibrosis, and stroke, its association with ischemia-induced HFpEF remains underexplored. However, our study demonstrated that the TyG index was significantly correlated with the occurrence of MACE in T2DM patients with AMI and HFpEF. Therefore, clinicians should maintain a high level of vigilance for MACE, non-fatal myocardial infarction, and unplanned revascularization in patients with higher TyG indices, particularly when the index exceeds 9.51.

The mechanisms by which the TyG index contributes to MACE in HFpEF patients following AMI are likely multifactorial. First, TyG is a recognized surrogate marker of IR, a metabolic state that promotes myocardial lipid accumulation, fibrosis, and impaired ventricular relaxation, all of which contribute to diastolic dysfunction and the development of HFpEF (39–42). Second, elevated TyG levels have been associated with microvascular dysfunction, particularly in diabetic populations. This dysfunction, characterized by reduced nitric oxide bioavailability and endothelial inflammation, leads to coronary microcirculatory impairment, exacerbating myocardial ischemia and remodeling (43, 44). Third, IR-induced alterations in myocardial calcium handling and activation of profibrotic signaling pathways promote left ventricular hypertrophy and reduced compliance, further worsening diastolic performance (45, 46). These pathophysiologic processes—IR, microvascular dysfunction, and diastolic impairment—together may explain the observed association between higher TyG index values and increased MACE risk in HFpEF patients. Our findings underscore the importance of early glycemic-lipid metabolic assessment and intervention, especially in T2DM patients post-AMI with preserved ejection fraction, to mitigate cardiovascular risk and improve long-term outcomes.

This study had several limitations. First, being retrospective in nature, selection bias may be unavoidable. Second, patients with HFpEF were primarily diagnosed using transthoracic echocardiography, which lacks the sensitivity of exercise stress echocardiography and may lead to missed diagnoses. Third, the lack of statistical significance for some survival analysis outcomes could be attributed to the small sample size and single-center design of the study. Fourth, the study population was confined to Liaoning Province, China, which may limit the generalizability of the findings to other populations. Fifth, this study did not employ propensity score matching (PSM) or inverse probability of treatment weighting (IPTW) to further control for potential confounding. The primary reasons for this were the relatively small sample size and missing data in some covariates, which limited the feasibility and stability of such analyses. While multivariable Cox regression was used to adjust for known clinical covariates, unmeasured confounding cannot be entirely excluded. Future prospective studies with larger and more diverse populations should consider incorporating PSM or IPTW to strengthen causal inference and reduce residual bias. Sixth, patients lost to follow-up and those who did not undergo interventional procedures were excluded from the analysis. While this was done to ensure data completeness and treatment consistency, it may have introduced survivorship bias, as individuals with early adverse events could have been inadvertently excluded. We acknowledge this potential bias and recommend that future studies adopt strategies such as prospective design, improved follow-up systems, or multiple imputation to minimize its impact. Seventh, although the TyG index was found to be statistically associated with MACE, its overall predictive value was limited. This suggests that,

while the TyG index may have some prognostic relevance, it alone may not provide strong discriminatory power in clinical practice. Moreover, this study did not compare the TyG index with established risk scoring systems such as the Global Registry of Acute Coronary Events (GRACE) score and the Thrombolysis in Myocardial Infarction (TIMI) score, due to the unavailability of complete data required for those calculations. This lack of comparison limits the ability to contextualize the TyG index within existing clinical risk assessment frameworks. Future studies should include these established tools to better evaluate the added value of the TyG index in cardiovascular risk stratification. Eighth, while the TyG index was found to be associated with MACE, the underlying biological mechanisms—such as insulin resistance, chronic inflammation, or endothelial dysfunction—were not directly investigated in this study. As this was a retrospective analysis based on routine clinical records, mechanistic biomarkers such as fasting insulin (for Homeostasis Model Assessment of Insulin Resistance), inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-alpha), or markers of oxidative stress were not collected. This limits the ability to explore the potential pathophysiological pathways linking TyG to adverse cardiovascular outcomes. Future prospective studies incorporating metabolic and inflammatory biomarkers are warranted to better elucidate the biological basis of the observed associations. Lastly, although the TyG index shows promise in predicting and assessing various diseases, there remains no standardized range or critical value for the index across studies. Further research with larger, multicenter, and prospective designs is necessary to clarify the diagnostic cutoff points and prognostic value of the TyG index in different diseases.

5 Conclusions

Our study found that in T2DM patients with HFpEF combined with AMI, the incidence of MACE was higher, and the prognosis worsened as the TyG index increased. The TyG index proved to be an independent predictor of MACE and could serve as a valuable tool for risk stratification and prognosis in this population. Clinicians should be particularly alert to the risks associated with left ventricular dysfunction in patients with elevated TyG indices during the management of AMI.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XDZ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. NN: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. SY: Conceptualization, Writing – review & editing. XXZ: Conceptualization, Writing – review & editing. XC: Conceptualization, Writing – review & editing. MY: Conceptualization, Writing – review & editing. WZ: Conceptualization, Writing – review & editing. YL: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing. ZW: Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of nine different exercise interventions on insulin sensitivity in diabetic patients: a systematic review and mesh meta-analysis

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Objective: This study aimed to assess the impact of nine exercise interventions (resistance training [BT, ball training [BT], resistance + walking [RT+W alk], resistance + running [RT + Running], resistance + cycling [RT + bicycle], running, and Tai Chi) on insulin sensitivity in patients with diabetes.

Methods: A systematic search of five databases (PubMed, EMBASE, Cochrane, Web of Science, and CNKI) for RCTs investigating the effects of exercise interventions on insulin sensitivity in patients with diabetes was conducted. The quality of the included studies was assessed using the Cochrane Manual version 5.1.0 Risk of Bias Assessment Tool (ROB). Data analysis software was used for the synthesis and analysis.

Results: This Meta-analysis comprised 21 randomized controlled trials involving 1140 participants. Cycling significantly reduced the fasting glucose index in individuals with diabetes (SUCRA score=90.7%). Resistance exercise exhibited superior efficacy in enhancing insulin sensitivity compared with alternative interventions in patients with diabetes (SUCRA score=71.8%). Furthermore, the combination of resistance exercise and running resulted in a noteworthy decrease in HOMA-IR levels (SUCRA score=64.2%).

Conclusion: Cycling, resistance training, and combined aerobic and resistance exercises have been shown to effectively enhance fasting blood glucose levels, insulin secretion, and insulin sensitivity in individuals with diabetes. However, additional studies with longer follow-up periods and more rigorous methodologies are required to further validate these findings.

Systematic review registration: https://ww.crd.york.ac.uk/PROSPERO/, identifier CRD42023450107.

KEYWORDS

exercise, insulin resistance, diabetes patients, network meta-analysis, systematic review

1 Introduction

Diabetes has emerged as a critical global health challenge, with the 2023 Global Burden of Disease Study reporting approximately 529 million affected individuals worldwide and projecting a rise to 1.31 billion by 2050 (1). Type 2 diabetes (T2DM), characterized by insulin resistance and impaired insulin secretion, accounts for over 90% of diabetes cases and imposes substantial economic burdens exceeding $1 trillion USD annually in healthcare expenditures (2, 3).

Physical exercise is a cornerstone of T2DM management, with distinct modalities operating through specific physiological pathways to improve glycemic control. Aerobic exercise enhances insulin sensitivity primarily through GLUT4 translocation in the skeletal muscle, facilitating glucose uptake independent of insulin signaling (4). This process is amplified by mitochondrial biogenesis via the AMPK-PGC1α pathway, which improves oxidative capacity (5), while concurrent reductions in pro-inflammatory cytokines (TNF-α and IL-6) ameliorate adipose tissue dysfunction (6). Resistance training exerts complementary effects through muscle hypertrophy, which expands the glucose storage capacity (7), enhances post-receptor insulin signaling via IRS-1/PI3K/Akt phosphorylation cascades (8), and suppresses hepatic gluconeogenesis (9). Combined aerobic-resistance training synergizes these mechanisms, with recent meta-analyses confirming superior HbA1c reductions compared to single-modality interventions (Δ = -0.17%, $p < 0.01$) (10). Despite these advances, the comparative efficacy of specific exercise modalities is unclear. This network meta-analysis directly evaluated nine interventions, including resistance training, aerobic modalities (cycling and running), combined regimens, and mind-body exercises, to provide evidence-based guidance for optimizing exercise prescriptions in diabetes care.

2 Materials and methods

This systematic review was registered in the Prospero database (ID: CRD42023450107) under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) and the Cochrane Intervention Review.

2.1 Search strategy

We conducted a comprehensive search across multiple databases, including PubMed, Embase, Cochrane Library, Web of Science, and CNKi, from January 2004 to December 2022, to identify eligible studies. The search keywords were formulated based on the PICOS framework, and the search strategies were developed by PICOS principles: (P) population, diabetic patients; (I) intervention, exercise; (C) comparator, control group receiving only usual care and appropriate rehabilitation measures (placebo or other forms of exercise); and (O) Outcome - Exercise tests in diabetic patients. Finally, we focused on randomized controlled trials as the preferred study design. Taking PubMed as an example, detailed search strategies are provided in Table 1.

2.1.1 Definition of exercise interventions

The nine exercise interventions evaluated in this study are abbreviated as follows:

RT: Resistance training
BT: Ball training
RT+Walk: Combined resistance training and walking
RT+Running: Combined resistance training and running
RT+Bicycle: Combined resistance training and cycling

TABLE 1 Search strategy on PubMed.

#1	"Exercise"[MeSH]
#2	((((((((((((((((((((Exercises[Title/Abstract])OR Physical Activity[Title/Abstract])OR Activities, Physical[Title/Abstract])OR Activity, Physical[Title/Abstract])OR Physical Activities[Title/Abstract])OR Exercise, Physical[Title/Abstract])OR Exercises, Physical[Title/Abstract])OR Physical Exercise[Title/Abstract])OR Physical Exercises[Title/Abstract])OR Acute Exercise[Title/Abstract])OR Acute Exercises[Title/Abstract])OR Exercise, Acute[Title/Abstract])OR Exercises, Acute[Title/Abstract])OR Exercise, Isometric[Title/Abstract])OR Exercises, Isometric[Title/Abstract])OR Isometric Exercises[Title/Abstract])OR Isometric Exercise[Title/Abstract])OR Exercise, Aerobic[Title/Abstract])OR Aerobic Exercise[Title/Abstract])OR Aerobic Exercises[Title/Abstract])OR Exercises, Aerobic[Title/Abstract])OR Exercise Training[Title/Abstract])OR Exercise Trainings[Title/Abstract])OR Training, Exercise[Title/Abstract])
#3	#1 OR #2
#4	"Insulin"[MeSH]
#5	((((((((((Insulin[Title/Abstract])OR Insulin, Regular[Title/Abstract])OR Regular Insulin[Title/Abstract])OR Soluble Insulin[Title/Abstract])OR Insulin, Soluble[Title/Abstract])OR Insulin A Chain[Title/Abstract])OR Sodium Insulin[Title/Abstract])OR Insulin, Sodium[Title/Abstract])OR Novolin[Title/Abstract])OR Iletin[Title/Abstract])OR Insulin B Chain[Title/Abstract])OR Chain, Insulin B[Title/Abstract])
#6	#4 OR #5
#7	Randomized controlled[Publication Type]
#8	#3 AND #6 AND #7

Bicycle: Cycling training alone

Running: Running training alone

Taichi: Tai Chi practice

CON: Control group (no exercise intervention, routine care only)

All combined training involved sequential sessions of resistance and aerobic exercise within the same day.

2.2 Inclusion criteria

(1) Randomized controlled clinical trials involving patients with diabetes. (2) The experimental group utilizes various exercise methods as interventions for diabetes. (3) The control group receives conventional care only. (4) Active cooperation of participants in the experimental process is required. (5) Outcome measures include at least one of the following: Fasting blood glucose levels (FBG), Homeostasis Model Assessment of insulin Resistance (HOMA-IR), fasting insulin level (FI), and homeostasis model of insulin resistance.

2.3 Exclusion criteria

(1) Papers with incomplete or insufficient data or reporting information are excluded. (2) Non-randomized controlled trials, animal studies, conference reports, literature reviews, abstracts, and protocols are excluded.

2.4 Study selection

The two researchers used NoteExpress, a literature management software, to screen and exclude duplicate articles. Initially, they reviewed the titles and abstracts to exclude non-randomized controlled trials, systematic reviews, conference papers, protocols, and communications while retaining the remaining literature. Subsequently, both researchers independently read through the remaining literature and conducted further screening. Only when there was agreement on inclusion criteria did an article finally get included; otherwise, a third researcher was consulted for discussion and resolution.

2.5 Data extraction

Two researchers independently extracted the data and assessed study quality using the Cochrane Handbook, while a third individual addressed any issues that arose post-data extraction. The extracted data encompassed authorship details (author, year, country of publication), average age, sample size, intervention duration, and outcome indicators such as risk of bias assessment.

2.6 Risk of bias in individual studies

We assessed the literature quality based on the Risk Bias Assessment Tool (ROB) outlined in the Cochrane Manual 5.1.0, considering seven key domains for evaluating randomized controlled trials: (1) Random sequence generation, (2) Allocation concealment, (3) Blinding of participants and personnel, (4) Blinding of outcome assessors, (5) Handling of incomplete outcome data, (6) Selective outcome reporting, and (7) Other potential sources of bias.

2.7 Subgroup analysis and outcome indicators

We conducted a subgroup analysis to categorize the experiments based on medication status. Specifically, 13 trials received metformin treatment, five received insulin treatment, and the remaining three did not receive any hypoglycemic drugs. The findings of our meta-analysis remained robust across these subgroups, indicating that exercise intervention benefits blood glucose levels independently of drug therapy. Our primary outcome measure was the change in fasting plasma glucose (ΔFPG) levels from baseline (mmol/L). We also compared fasting insulin concentration (ΔFI; μU/ml) and HOMA-IR index (ΔHOMA-IR) between the experimental and control groups.

We quantified between-study heterogeneity using I^2 statistics. For fasting blood glucose (FBG), I^2 = 62% (95%CI: 48-75%), indicating moderate heterogeneity. For fasting insulin, I^2 = 45% (95%CI: 28-59%), suggesting low-moderate heterogeneity. For HOMA-IR, I^2 = 68% (95%CI: 52-80%), reflecting moderate heterogeneity. These values align with expected variations in exercise interventions across diverse populations.

2.8 Data analysis

Sensitivity analyses excluding studies with high/unclear risk of bias in ≥3 Cochrane domains (n=5 studies) confirmed robustness: FBG reduction with cycling [MD = -50.21 mmol/L, 95%CI -92.15 to -8.27], fasting insulin with RT *vs.* BT [MD = -25.94 μU/ml, 95%CI -49.83 to -2.05], and HOMA-IR ranking of RT+Running (SUCRA=62.1%). In our included studies involving various exercise interventions, all variables were continuous and expressed as the mean and standard deviation (SD) with a 95% confidence interval (CI) (11). The mean difference (MD) was used to represent the net change in the measured variables between the experimental and control groups, with a negative MD value indicating a greater reduction in the experimental group (12). A random-effects model was employed for the meta-analysis while calculating the SUCRA values to rank the interventions. Funnel plots were used to assess publication bias, and frequency analysis of random-effects models was conducted to evaluate the effectiveness of multiple interventions in addressing potential differences among studies (13).

The effectiveness of multiple interventions in addressing potential differences between studies was evaluated using a frequency analysis of random-effects models (13). Stata software (version 15.1) was employed to model four chains using the Markov chain Monte Carlo (MCMC) method. The fit and consistency of the model were assessed using the Deviation Information Criterion (DIC). Network diagrams illustrating the different motion interventions were generated using Stata software (version 15.1). In case a closed-loop mesh appeared in the network, node splitting analysis was conducted to examine local consistency, with a passing consistency test defined as a P value >0.05. The network diagram consists of nodes and lines connecting them, where the width of each node and connecting line is proportional to the sample size of the respective study (14). Furthermore, the interventions were ranked based on their SUCRA values, and a ranking table was created to compare their relative effectiveness. To assess potential bias between the studies, heterogeneity was examined by constructing a funnel plot (15). The degree of intervention was summarized as an S value representing the area under the cumulative ranking curve; larger values indicated better intervention effects within a scoring range of 0-1. Similarly, the SUCRA values ranged from 0% to 100%, with higher scores indicating superior intervention effects. However, caution should be exercised when interpreting these scores unless genuine clinical differences exist between the interventions (16).

To address potential confounding by exercise duration, we calculated the metabolic equivalents (MET-min) for each intervention using standard compendium values (17). For example:

- Cycling: 8.0 METs
- Running: 10.0 METs
- Resistance training: 6.0 METs

Sensitivity analyses were performed to assess whether duration-adjusted energy expenditure influenced primary outcomes.

3 Results

3.1 Study and identification and selection

A total of 7761 articles were retrieved from five electronic databases, and three were retrieved. After excluding 2281 duplicate references, 5, 125 articles were eliminated based on the evaluation of their titles and abstracts, resulting in 5480 remaining references. Subsequently, a comprehensive review was performed on the remaining 355 papers by reading them in their entirety. Following this assessment, an additional 334 papers were excluded, ultimately leading to the inclusion of only 21 studies for the meta-analysis. (Show in Figure 1).

3.2 Quality evaluation of the included studies

Given the diverse range of movement modes of these interventions, achieving blinding for both subjects becomes challenging. Consequently, informed consent was obtained from all participants and their families before the experiment.

The risk-of-bias assessment across seven domains is summarized in Figure 2, revealing consistent limitations in participant blinding due to exercise intervention nature."

3.3 Features of the included study

Table 2 presents the baseline characteristics of the included studies. The present study included 21 randomized controlled trials involving 1140 participants. The 21 trials, conducted between 2004 and 2022, encompassed a diverse age range of 10–69 years. The exercise interventions comprised resistance training (RT), aerobic training (such as cycling and running), combination training, Tai Chi, and ball games. The control group received standard treatment and daily care without exercise intervention. Control group interventions consisted of combined resistance and walking exercise training (18, 19), combined resistance and running exercise training (15, 20, 21), combined resistance and cycling exercise training (22), bicycle training (23–25), combined resistance and cycling exercise training along with Tai Chi Qigong practice (24, 26, 27), ball game exercises (28, 29), running exercises (20, 30–34) as well and standalone resistance exercises (22, 30, 31, 35, 36). FBG was employed as an outcome indicator in 19 studies, while fasting insulin was an outcome indicator in all included studies. HOMA-IR was used in 15 studies for evaluation. These studies were conducted in various countries, including China, South Korea, the United States, Brazil, Iran, Turkey, the Netherlands, Greece, the United Kingdom, and Germany. The detailed characteristics of the included studies are provided in Table 2.

3.4 Network meta-analysis

The complete network diagram is shown in Figures 3a, 4a, and 5a.

3.4.1 Fasting blood glucose index results of diabetic patients

The meta-analysis results demonstrated that the intervention effect in the bicycle group was superior. Specifically, when comparing the cycling group with both anaerobic and running groups [MD=-46.63, 95%CI (-91.96,-1.29)], and when comparing the running group with the cycling group [MD=-52.19, 95%CI (-101.70,-2.68)], significant differences were observed in favor of the bicycle group's intervention effect (Figure 3b). Furthermore, compared to the control group [MD=-52.64, 95%CI (-95.72,-9.55)], ball games [MD=-56.11, 95%CI (-103.29,-8.94)], and Tai Chi group [MD=-73.02, 95%CI (-120.-17,-25-86)], fasting insulin sensitivity exhibited a more pronounced improvement in insulin sensitivity (Figure 3b). Regarding the SUCRA ranking score (Figure 3b), cycling practice ranked first with a SUCRA score of 90%. Pairwise comparisons between the interventions are presented in Table 3.

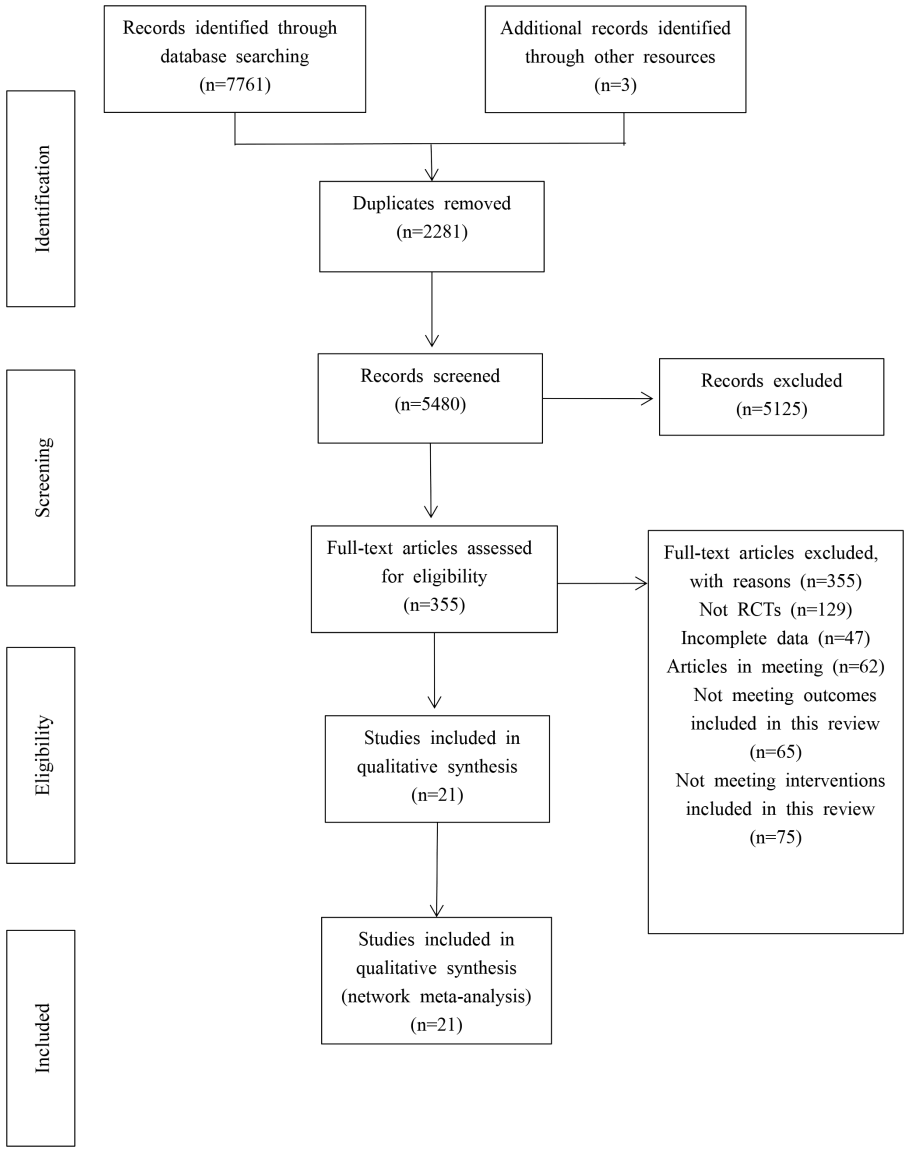

FIGURE 1
Flow diagram of literature selection.

Notably, cycling interventions had longer session durations (mean 90 min) compared to running (mean 45 min) and resistance training (mean 50 min). However, after adjusting for MET-minutes, cycling remained superior in reducing FBG [MD = -38.72, 95%CI (-75.15, -2.29)].

3.4.2 Fasting insulin index results of diabetic patients

In comparison to ball games, resistance exercise demonstrated a significant impact on enhancing insulin sensitivity [MD=-26.71, 95% CI (-51.23, -2.19)].The Qigong exercise group exhibited significant differences compared to the aerobic exercise group [MD=33.04, 95% CI (4.82, 61.26)], bicycle exercise group [MD=30.54, 95% CI (4.41, 56.67)], aerobic walking combined exercise group [MD=26.03, 95% CI (0.40, 51.66)], aerobic running combined exercise group [MD=29.74, 95% CI (4.16, 55.32)], running exercise group [MD=29.68,95%CI (4.10,55.26)], the general control group[MD=28.54,95%CI (5.22,51.86)], and the aerobic and bicycle combined exercise group [MD=28. 21,95%CI(2.30,54.12)], the results suggest that the Qigong exercise intervention had limited impact on improving insulin sensitivity parameters. The bicycle group (SUCRA: 90.7%) exhibited superior efficacy in enhancing insulin sensitivity parameters, as demonstrated in Figure 4b of the SUCRA analysis. The effect size of the key comparison indicates that, Resistance training *vs.* Ball training: MD = -26.71 μU/ml, 95%CI (-51.23, -2.19);Qigong *vs.* Control: MD = -28.54 μU/ml, 95%CI (-51.86, -5.22);Cycling *vs.* Control: MD = -2.00 μU/ml, 95%CI (-13.79, 9.79). The MD for Resistance Training versus Ball Training and Qigong versus control

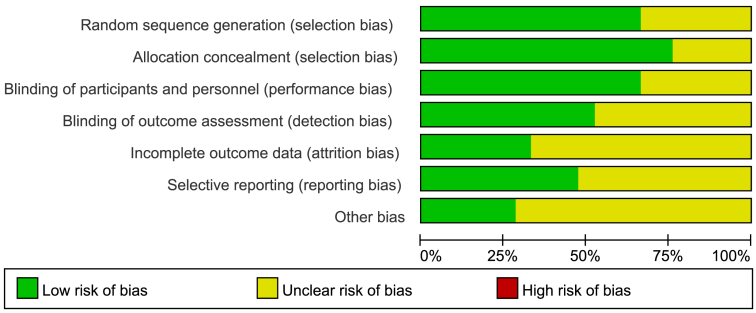

FIGURE 2
Risk of bias graph (percentage form). The "X-axis" lists bias domains (e.g."Random sequence generation"), and the "Y-axis" represents the "percentage of studies" falling into each risk category(Low/Unclear/High). The color-coded legend (green/yellow/red) explicitly defines each risk level, eliminating the need for additional axis units.

was statistically significant. A comparison of the various interventions is shown in Table 4.

3.4.3 Results of the HOMA-IR index for diabetic patients

The meta-analysis chart results (Figure 5b) revealed no statistically significant differences in the reduction of HOMA-IR index among the intervention groups. The SUCRA value indicated that the combination of aerobic exercise and running exhibited the highest ranking for reducing HOMA-IR values, thus proving to be the most effective approach compared to other exercises (SUCRA: 64.2%). Ball games ranked next (SUCRA: 62.7%), as shown in Figure 4b. HOMA-IR changes versus control:RT+Running: MD = -1.20, 95%CI (-11.70, 9.30); ball training: MD = -3.83, 95%CI (-17.84, 10.19); Cycling: MD = -0.10, 95%CI (-3.93, 3.73); Although RT+Running had the highest SUCRA ranking, its effect versus control did not reach statistical significance (95%CI crosses zero). The pairwise comparison of the interventions is presented in Table 5.

3.5 Publication bias test

The included trials were assessed using the Cochrane risk assessment tool and were determined to have a low-to-moderate risk of bias. Additionally, no significant publication bias was observed in the funnel plots (Figures 6a–c).

4 Discussion

In this meta-review and meta-analysis, we incorporated data from studies conducted across multiple continents, including the United States, Europe, Asia, and Australia, to augment the sample size and enhance the generalizability of our findings. By comparing the effects of nine different exercise interventions, we observed that cycling, resistance exercise, and combined resistance with running exercise exhibited comparatively superior enhancements. Specifically, cycling showed the largest FBG reduction [MD = -52.64 mmol/L *vs.* control], resistance training significantly improved insulin sensitivity over ball games [MD = -26.71 μU/ml], and RT+Running had the highest probability (SUCRA=64.2%) for HOMA-IR reduction despite non-significant effects versus control [MD = -1.20].

By comparing the effects of nine different exercise interventions on fasting blood glucose, fasting insulin, and HOMA-IR levels among patients with diabetes, we observed that cycling, resistance exercise, and combined resistance with running exercise demonstrated relatively superior improvements in glycemic control indicators, including FPG, FI, and HOMA-IR index. Cycling is most likely to reduce fasting plasma glucose (FPG) levels, which is consistent with previous evidence indicating that cycling recruits a more significant number of type I muscle fibers and improves glucose utilization (37, 38). The extensive engagement of muscles and the absence of weight-bearing characteristics make cycling a safer and more effective exercise option for individuals with type 2 diabetes mellitus (T2DMM) (39). Utilizing bicycles mobilizes large muscle groups and eliminates leg weight-bearing and ground friction, making it remarkably safe and effective for patients with T2DMM. Cycling elicits greater recruitment of type I muscle fibers, which demonstrate higher insulin sensitivity and GLUT4 density (4, 39). Li et al. demonstrated that both high-intensity interval cycling and moderate-intensity cycling significantly reduced fasting glucose in T2DMM patients (40).

During exercise under normoglycemic-hyperinsulinemic conditions, skeletal muscles account for nearly all human glucose uptake. The increase in muscle glucose uptake during exercise is attributed to enhanced contraction activity and increased blood flow within the muscles, which facilitates glucose transport (41). The higher level of glucose utilization observed during cycling compared with running may be due to the greater contraction activity resulting from the larger active muscle mass. Muscle fiber recruitment and glycogen utilization patterns differ among various forms of exercise. It has been discovered that the effect on muscle glycogen supply by type I fibers was superior in the group undergoing cycling interventions compared to those undergoing running interventions. Type I fibers possess higher insulin content, are more sensitive to insulin stimulation, and can recruit more GLUT4 transport proteins, thereby enhancing the skeletal muscle's ability to take up and transport glucose, an effect associated with

TABLE 2 Detailed characteristics of the studies included in meta-analysis.

Country	Year	Age (mean+SD)	Total/male/female	Intervention	Control	Outcome
Korea	2019	T+C:36.8 (6.9)	T:11/7/4 C:6/4/2	RT+walk Length of Intervention: 6 weeks Freq: 3 times a week Duration:1 hour	CON	FBG Fasting insulin HOMA-IR
Holland	2004	T+C:60 (9)	T:36/25/11 C:25/20/5	RT+Walk Length of Intervention: 26 weeks Freq: 4 times a week Duration: 1 hour	CON	FBG Fasting insulin
USA	2021	T: 53.7 (8) C:50.1 (9.6)	T:49/49/0 C:54/54/0	RT+Running Length of Intervention: 20 weeks Freq: 3 times a week Duration: 50 min	CON	FBG Fasting insulin HOMA-IR
Germany	2018	T:14.6 (1) C:14.8 (1)	T:20/0/20 C:20/0/20	RT+Running Length of Intervention: 12 weeks Freq: 5 times a week Duration: 1 hour	CON	FBG Fasting insulin HOMA-IR
Britain	2009	T:67.6 (4.2) T1:69.1 (6.5) C:66.5 (5.3) C1:66.7 (3.7)	RT:36/15/21 AT:37/17/20 RT+AT:35/14/21 C:28/11/17	RT Length of Intervention: 24 weeks Freq: 3 times a week Duration: 20 min Runing Length of Intervention: 24 weeks Freq: 3 times a week Duration: 30 min RT+Running Length of Intervention: 24 weeks Freq: 3 times a week Duration: 50 min	CON	Fasting insulin
Iran	2018	SIT:55.36 (5.94) A+R:54.14 (5.43) C:55.71 (6.40)	T:52/0/17 T1:52/0/17 C:52/0/18	RT Length of Intervention: 10 weeks Freq: 3 times a week Duration: 30 min RT+Bicycle Length of Intervention: 10 weeks Freq: 3 times a week Duration: 30 min	CON	FBG Fasting insulin HOMA-IR
Los Lagos	2017	T:38 (8) C:33 (7)	T:18/0/18 C:17/0/17	Bicycle Length of Intervention: 12 weeks Freq: 3 times a week Duration: 3 hours	RT Length of Intervention: 12 weeks Freq: 3 times a week Duration: 3 hour	FBG Fasting insulin HOMA-IR

(Continued)

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TABLE 2 Continued

Country	Year	Age (mean+SD)	Total/male/female	Intervention	Control	Outcome
Brazil	2013	T:32.4 (7) C:30.1 (5.5)	T:17/8/9 C:18/8/10	Bicycle Length of Intervention: 4 weeks Freq: 3 times a week Duration: 40 min	CON	Fasting insulin insulin, HOMA-IR
USA	2015	T:13.8 (2.2) C:12.1 (1.2)	E:10/8/2 C:8/5/3	Bicycle Length of Intervention: 8 weeks Freq: 3 times a week Duration: 35 min	CON	FBG Fasting insulin HOMA-IR
China	2009	T:58.1 (13.4) C:56.6 (13.3)	T:28/12/16 C:32/16/16	Taichi training Length of Intervention: 12 weeks Freq: 4 times a week Duration: 1 hour	CON	FBG
Korea	2014	T:48.4 (8.6) C:48.3 (8.2)	T:18/9/9 C:17/10/7	Taichi training Length of Intervention: 12 weeks Freq: 3 times a week Duration: 45 min	CON	FBG Fasting insulin HOMA-IR
China	2011	T+C:57.8 (6.3)	T:20/8/12 C:21/8/13	Taichi training Length of Intervention: 12 weeks Freq: 3 times a week Duration: 1-1.5 hours	CON	FBG Fasting insulin
Turkey	2019	T:14.41 (1.06) C:14.47 (1.06)	T:34/17/0 C:34/17/0	Ball game Length of Intervention: 6 weeks Freq: 3 times a week Duration: 30 min	CON	FBG Fasting insulin
Brazil	2019	T+C:61.1 (6.4)	41/20/21 T:19 C:22	Ball game Length of Intervention: 12 weeks Freq: 3 times a week Duration: 40 min	CON	FBG Fasting insulin HOMA-IR
USA	2005	T:12.5 (0.5) C:12.5 (0.7)	T:27/13/14 C:23/13/10	Running Length of Intervention: 6 weeks Freq: 5 times a week Duration: 2 hours	CON	FBG Fasting insulin
Greece	2007	T:59.33 (4.76) C:63.82 (7.03)	T:30/13/17 C:30/12/18	Running Length of Intervention: 24 weeks Freq: 4 times a week Duration: 1 hour	CON	FBG Fasting insulin HOMA-IR
Korea	2014	T:24.86 (2.75) C:26.8 (2.8)	T:29/29/0 C:10/10/0	Running Length of Intervention: 8 weeks Freq: 4 times a week Duration: 1 hour	CON	FBG Fasting insulin HOMA-IR

(Continued)

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TABLE 2 Continued

Country	Year	Age (mean+SD)	Total/male/female	Intervention	Control	Outcome
Iran	2015	T:49.29 (5.82) C:49 (8.16)	T:27/0/27 C:26/0/26	Running Length of Intervention: 12 weeks Freq: 3 times a week Duration: 50 min	CON	FBG Fasting insulin
USA	2014	T:60 (1) C:61 (1)	T:37/0/37 C:40/0/40	Running Length of Intervention: 24 weeks Freq: 3 times a week Duration: 45 min	CON	FBG Fasting insulin HOMA-IR
Britain	2015	T:21 (1) C:21 (1)	T:6/6/0 C:9/3/6	RT Length of Intervention: 2 weeks Freq: 3 times a week Duration: 2 hours	CON	FBG Fasting insulin HOMA-IR
Iran	2014	RT:40.4 (5.2) AT:39.6 (3.7) C:38.9 (4.1)	RT:12/12/0 AT:12/12/0 C:10/10/0	RT Length of Intervention: 12 weeks Freq: 3 times a week Duration: 45–60 min Running Length of Intervention: 12 weeks Freq: 3 times a week Duration: 30 min	CON	FBG Fasting insulin HOMA-IR

CON, control group with routine care (no exercise); T, experimental group; C, control group; RT, resistance training; AT, Aerobic training; T+C, The ages of the experimental and control groups were not reported separately in the study. Only the overall age was reported; FBG, Fasting blood glucose; HOMA-IR, Homeostasis model assessment of insulin resistance.

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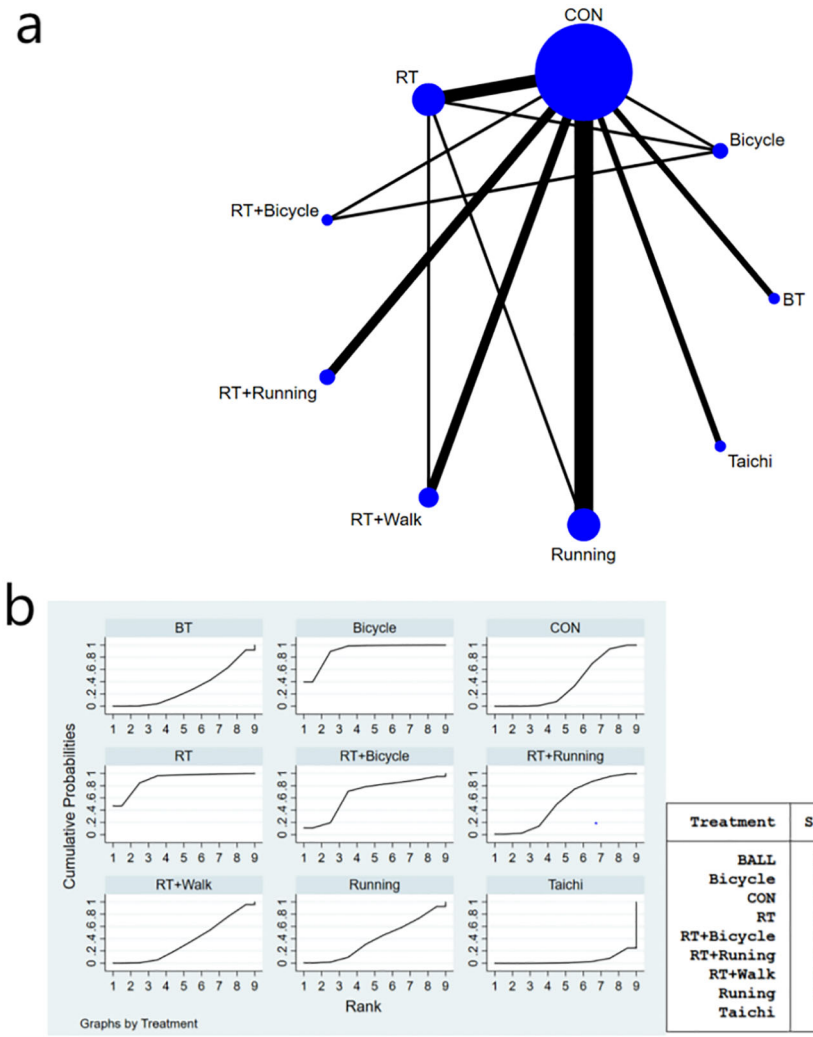


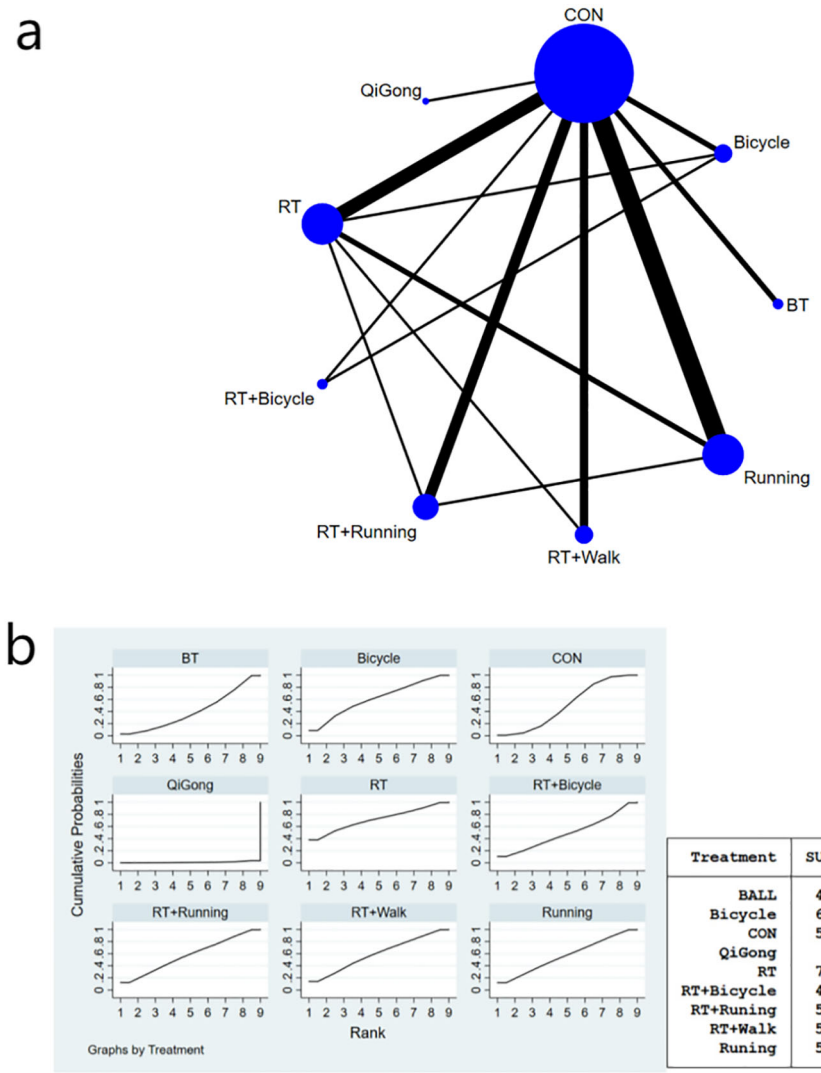
Treatment	SUCRA	PrBest	MeanRank
BALL	30.7	0.2	6.5
Bicycle	90.7	39.7	1.7
CON	38.1	0.0	5.9
RT	90.3	47.1	1.8
RT+Bicycle	66.8	11.1	3.7
RT+Runing	53.0	0.9	4.8
RT+Walk	36.4	0.2	6.1
Runing	39.3	0.7	5.9
Taichi	4.8	0.0	8.6

FIGURE 3
(a) Network meta-analysis figure for FBG; **(b)** SUCRA plot for FBG. The "X-axis" is labeled "Rank", indicating the relative efficacy ranking of interventions (1=most effective). The "y-axis" is labeled "Cumulative Probability", representing the probability of each intervention being ranked as the best option.

increased insulin-stimulated glucose uptake capability (37, 39). These findings suggest that cycling elicits greater recruitment of type I fibers and higher glucose utilization than running does.

This study suggests that resistance training is beneficial for improving insulin utilization in patients with type 2 diabetes. Compared to conventional exercise, resistance training can more effectively promote skeletal muscle glucose utilization and uptake due to its ability to increase muscle mass and cross-sectional area (42, 43), thereby facilitating insulin signaling and peripheral tissue glucose uptake (44, 45). Resistance training can augment glucose phosphorylation in skeletal muscle cells, facilitating the conversion of blood sugar into simple sugars, thereby promoting optimal insulin secretion and maintaining blood sugar homeostasis (44, 45). Long-term (>12 weeks) high-intensity resistance training has been shown to significantly enhance insulin sensitivity and sustain physical function for a duration that surpasses that of aerobic exercise (46). The findings of various studies have demonstrated that engagement in resistance exercise can significantly enhance metabolic health during weight recovery, including the reduction of fasting blood glucose levels and enhancement of insulin sensitivity (47). In a 24-week study, a comparison between resistance training and aerobic exercise revealed that the former enhanced insulin sensitivity and glucose uptake in muscles mediated by insulin (46). In general, resistance training enhances insulin sensitivity and improves fasting glucose levels in individuals diagnosed with type 2 diabetes (46, 48).

The combination of running and anaerobic exercise demonstrated superior efficacy in alleviating insulin resistance, as supported by a significant reduction in the HOMA-IR index, indicating an enhanced improvement in insulin sensitivity. The underlying mechanisms potentially involve augmented lipid oxidation and glycogen utilization (38), improved mitochondrial function (49), and enhanced muscle mass and cardiorespiratory



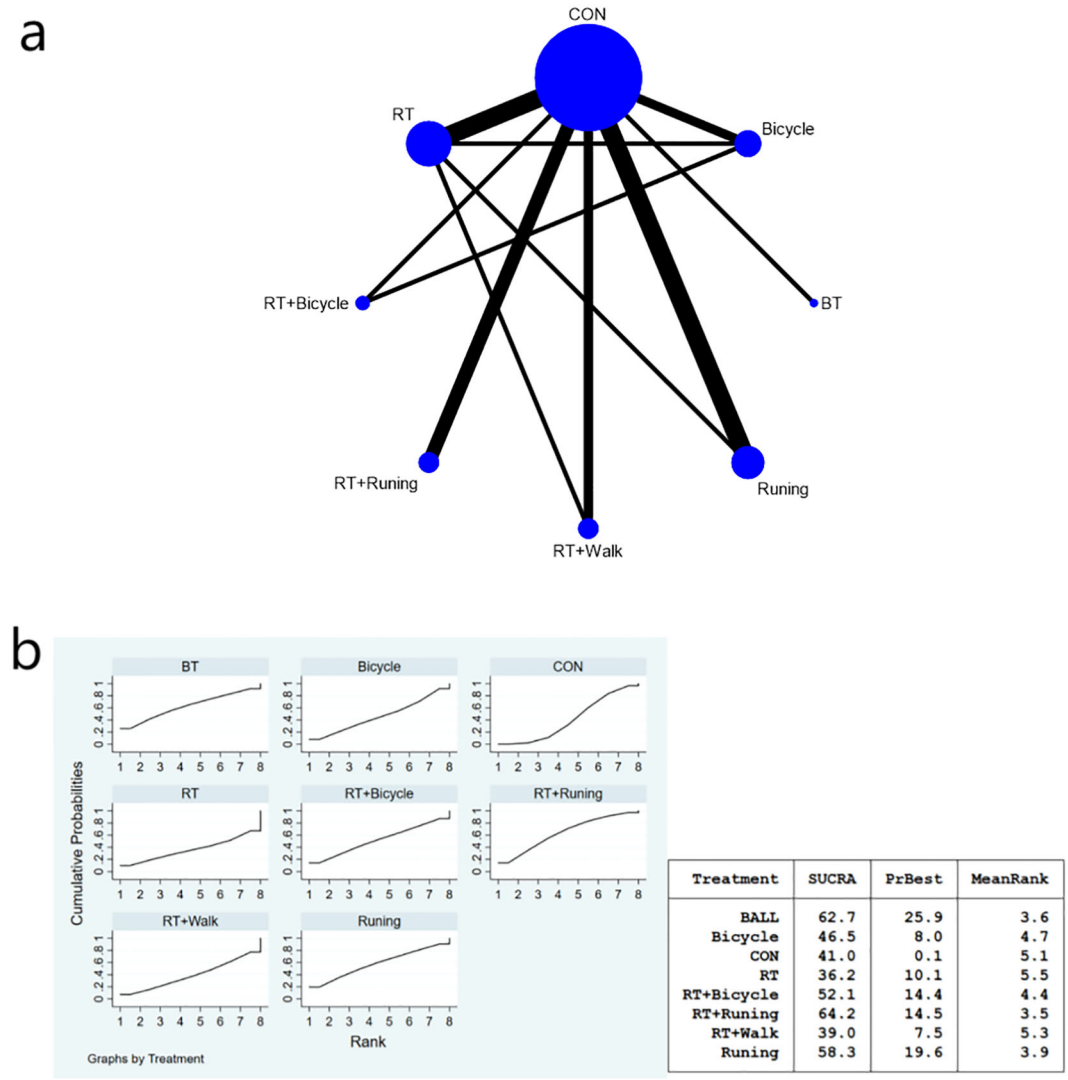
Treatment	SUCRA	PrBest	MeanRank
BALL	40.6	2.9	5.8
Bicycle	61.2	8.7	4.1
CON	50.6	0.8	5.0
QiGong	1.1	0.1	8.9
RT	71.8	38.0	3.3
RT+Bicycle	49.7	10.7	5.0
RT+Runing	57.8	12.4	4.4
RT+Walk	59.9	14.3	4.2
Runing	57.2	12.2	4.4

FIGURE 4
(a) Network meta-analysis figure for fasting insulin; **(b)** SUCRA plot for fasting insulin. The "X-axis" is labeled "Rank", indicating the relative efficacy ranking of interventions (1=most effective). The "y-axis" is labeled "Cumulative Probability", representing the probability of each intervention being ranked as the best option.

fitness (40). Type 2 diabetes is characterized by insulin resistance (IR) and relative insulin insufficiency, leading to glucose intolerance and subsequent elevation of blood glucose levels (40). However, preserving islet β-cell function may be pivotal in preventing T2DM onset (49, 50). Notably, the combined impact of running and resistance training on β-cell function surpasses that achieved through either aerobic or resistance training alone (51), likely attributable to the prolonged duration and heightened intensity associated with combined training regimens. Low-load high-repetition resistance training has emerged as an alternative form of aerobic-based resistance training capable of promoting muscle hypertrophy and strength gains similar to those observed with high-load low-repetition protocols (51, 52). In the context of combined training approaches, increased fat loss during resistance exercise aids in augmenting glucose uptake while concurrently enhancing skeletal muscle mitochondrial oxidative capacity. This synergistic effect maximizes reductionions in body fat content while expediting glycogen consumption during aerobic exercise sessions (53).

5 Advantages and limitations

The methodology employed in this study was highly rigorous and systematic. We conducted a comprehensive search across five electronic databases, strictly adhering to predefined criteria, and identified 21 articles encompassing a substantial sample size of 1140 patients with diabetes. To ensure accuracy, the selected articles underwent double-checking procedures, and we incorporated various specific joint exercise measures targeting both aerobic and anaerobic activities, thereby providing updated and more comprehensive evidence-based recommendations on how exercise can effectively reduce blood glucose levels and enhance insulin sensitivity.



Treatment	SUCRA	PrBest	MeanRank
BALL	62.7	25.9	3.6
Bicycle	46.5	8.0	4.7
CON	41.0	0.1	5.1
RT	36.2	10.1	5.5
RT+Bicycle	52.1	14.4	4.4
RT+Runing	64.2	14.5	3.5
RT+Walk	39.0	7.5	5.3
Runing	58.3	19.6	3.9

FIGURE 5
(a) Network meta-analysis figure for HOMA-IR; **(b)** SUCRA plot for HOMA-IR.

Nevertheless, certain limitations of this meta-analysis should be acknowledged.

1. Cycling duration confounder: The observed superiority of cycling (e.g., FBG MD=-52.64 *vs* control) must be interpreted in the context of its typically longer session durations (35 min-3 h *vs* 30 min-2 h for running). While our MET-adjusted analysis suggested that duration alone did not fully explain efficacy (54), energy expenditure differentials remained a potential confounder.
2. Surrogate markers: Reliance on FBG/FI/HOMA-IR rather than gold-standard measures (for example, hyperinsulinemic-eug clamps);
3. Language bias: The inclusion of the CNKI database may limit generalizability, although funnel plots showed symmetry.
4. Blinding impossibility: Participant blinding was unattainable due to the nature of the exercise intervention.

Future directions: (a) Match interventions by MET-minutes to isolate modality effects; (b) validate findings with direct insulin sensitivity measures; (c) extend follow-up beyond 6 months.

6 Conclusion

Our study conducted a systematic review and network meta-analysis to compare the effects of different exercise interventions on glycemic control in patients with diabetes. The results demonstrated that cycling, resistance training, and combined resistance and aerobic training effectively improved fasting blood glucose levels,

TABLE 3 League table on FBG.

Bicycle	RT	RT+Bicycle	RT_Running	Running	CON	RT+Walk	BT	Taichi
Bicycle	-0.96 (-25.93,24.02)	26.37 (-21.52,74.26)	46.63 (1.29,91.96)	52.19 (2.68,101.70)	52.64 (9.55,95.72)	35.71 (-15.40,86.82)	56.11 (8.94,103.29)	73.02 (25.86,120.17)
0.96 (-24.02,25.93)	RT	27.33 (-26.68,81.33)	47.58 (-4.15,99.31)	53.15 (-2.28,108.57)	53.59 (3.82,103.36)	36.67 (-20.19,93.53)	-52.39 (-105.07,0.29)	73.97 (20.64,127.30)
-26.37 (-74.26,21.52)	-27.33 (-81.33,26.68)	RT+Bicycle	20.26 (-36.01,76.52)	25.82 (-33.86,85.50)	26.27 (-28.20,80.74)	9.34 (-51.68,70.36)	-50.85 (-108.21,6.52)	46.65 (-11.10,104.39)
-46.63 (-91.96,-1.29)	-47.58 (-99.31,4.15)	-20.26 (-76.52,36.01)	RT+Running	5.56 (-22.62,33.75)	6.01 (-8.11,20.13)	-10.92 (-41.83,20.00)	-53.42 (-108.84,2.01)	26.39 (2.55,50.23)
-52.19 (-101.70,-2.68)	-53.15 (-108.57,2.28)	-25.82 (-85.50,33.86)	-5.56 (-33.75,22.62)	Running	0.45 (-23.95,24.84)	-16.48 (-53.24,20.28)	29.75 (-28.03,87.52)	20.83 (-10.22,51.87)
-52.64 (-95.72,-9.55)	**-53.59 (-103.36,-3.82)**	-26.27 (-80.74,28.20)	-6.01 (-20.13,8.11)	-0.45 (-24.84,23.95)	CON	-16.93 (-44.43,10.57)	3.48 (-15.90,22.86)	20.38 (1.18,39.57)
-35.71 (-86.82,15.40)	-36.67 (-93.53,20.19)	-9.34 (-70.36,51.68)	10.92 (-20.00,41.83)	16.48 (-20.28,53.24)	16.93 (-10.57,44.43)	RT+Walk	57.07 (3.72,110.42)	37.31 (3.77,70.84)
-56.11 (-103.29,-8.94)	52.39 (-0.29,105.07)	50.85 (-6.52,108.21)	53.42 (-2.01,108.84)	-29.75 (-87.52,28.03)	-3.48 (-22.86,15.90)	**-57.07 (-110.42,-3.72)**	BT	-9.49 (-33.45,14.47)
-73.02 (-120.17,-25.86)	**-73.97 (-127.30,-20.64)**	-46.65 (-104.39,11.10)	**-26.39 (-50.23,-2.55)**	-20.83 (-51.87,10.22)	**-20.38 (-39.57,-1.18)**	**-37.31 (-70.84,-3.77)**	9.49 (-14.47,33.45)	Taichi

Bold values: indicate statistically significant differences (P < 0.05).

TABLE 4 League table on fasting insulin.

RT	Bicycle	RT+Walk	RT+Running	Running	CON	RT+Bicycle	BT	QiGong
RT	-2.50 (-13.15,8.15)	-7.01 (-26.12,12.11)	-3.30 (-22.34,15.75)	-3.36 (-22.41,15.70)	-4.50 (-20.38,11.39)	-4.83 (-24.32,14.66)	26.71 (2.19,51.23)	**-33.04 (-61.26,-4.82)**
2.50 (-8.15,13.15)	Bicycle	-4.51 (-20.38,11.37)	-0.80 (-16.59,14.99)	-0.86 (-16.66,14.95)	-2.00 (-13.79,9.79)	-2.33 (-18.65,13.99)	3.01 (-13.10,19.12)	**-30.54 (-56.67,-4.41)**
7.01 (-12.11,26.12)	4.51 (-11.37,20.38)	RT+Walk	3.71 (-11.23,18.65)	3.65 (-11.31,18.61)	2.51 (-8.12,13.14)	2.18 (-13.32,17.68)	6.01 (-13.16,25.17)	**-26.03 (-51.66,-0.40)**
3.30 (-15.75,22.34)	0.80 (-14.99,16.59)	-3.71 (-18.65,11.23)	RT+Running	-0.06 (-10.56,10.44)	-1.20 (-11.70,9.30)	-1.53 (-16.95,13.89)	3.82 (-15.23,22.87)	**-29.74 (-55.32,-4.16)**
3.36 (-15.70,22.41)	0.86 (-14.95,16.66)	-3.65 (-18.61,11.31)	0.06 (-10.44,10.56)	Running	-1.14 (-11.66,9.38)	-1.47 (-16.90,13.96)	7.04 (-12.02,26.09)	**-29.68 (-55.26,-4.10)**
4.50 (-11.39,20.38)	2.00 (-9.79,13.79)	-2.51 (-13.14,8.12)	1.20 (-9.30,11.70)	1.14 (-9.38,11.66)	CON	-0.33 (-11.62,10.96)	-3.83 (-17.84,10.19)	**-28.54 (-51.86,-5.22)**
4.83 (-14.66,24.32)	2.33 (-13.99,18.65)	-2.18 (-17.68,13.32)	1.53 (-13.89,16.95)	1.47 (-13.96,16.90)	0.33 (-10.96,11.62)	RT+Bicycle	7.53 (-24.40,39.45)	**-28.21 (-54.12,-2.30)**
-26.71 (-51.23,-2.19)	-3.01 (-19.12,13.10)	-6.01 (-25.17,13.16)	-3.82 (-22.87,15.23)	-7.04 (-26.09,12.02)	3.83 (-10.19,17.84)	-7.53 (-39.45,24.40)	BT	1.83 (-5.75,9.41)
33.04 (4.82,61.26)	**30.54 (4.41,56.67)**	**26.03 (0.40,51.66)**	**29.74 (4.16,55.32)**	**29.68 (4.10,55.26)**	**28.54 (5.22,51.86)**	**28.21 (2.30,54.12)**	-1.83 (-9.41,5.75)	QiGong

Bold values: indicate statistically significant differences (P < 0.05).

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TABLE 5 League table on HOMA-IR.

RT+Running	BT	Running	RT+Bicycle	Bicycle	CON	RT+Walk	RT
RT+Running	0.96 (-5.50,7.42)	0.20 (-4.10,4.49)	0.51 (-3.79,4.80)	0.88 (-3.58,5.33)	0.98 (-1.30,3.25)	0.19 (-4.13,4.50)	1.58 (-4.20,7.35)
-0.96 (-7.42,5.50)	BT	1.70 (-4.87,8.27)	-1.27 (-7.31,4.77)	-0.17 (-5.47,5.13)	1.00 (-4.45,6.45)	-1.38 (-7.82,5.06)	1.10 (-2.78,4.98)
-0.20 (-4.49,4.10)	-1.70 (-8.27,4.87)	Running	0.31 (-4.85,5.47)	0.68 (-4.61,5.97)	0.78 (-2.87,4.43)	-0.01 (-5.18,5.16)	1.38 (-5.06,7.82)
-0.51 (-4.80,3.79)	1.27 (-4.77,7.31)	-0.31 (-5.47,4.85)	RT+Bicycle	0.37 (-4.92,5.66)	0.47 (-3.18,4.12)	-0.32 (-5.49,4.85)	1.07 (-5.37,7.51)
-0.88 (-5.33,3.58)	0.17 (-5.13,5.47)	-0.68 (-5.97,4.61)	-0.37 (-5.66,4.92)	Bicycle	0.10 (-3.73,3.93)	-0.69 (-5.99,4.61)	0.70 (-2.97,4.37)
-0.98 (-3.25,1.30)	-1.00 (-6.45,4.45)	-0.78 (-4.43,2.87)	-0.47 (-4.12,3.18)	-0.10 (-3.93,3.73)	CON	-0.79 (-4.46,2.88)	0.60 (-4.70,5.90)
-0.19 (-4.50,4.13)	1.38 (-5.06,7.82)	0.01 (-5.16,5.18)	0.32 (-4.85,5.49)	0.69 (-4.61,5.99)	0.79 (-2.88,4.46)	RT+Walk	1.39 (-5.06,7.84)
-1.58 (-7.35,4.20)	-1.10 (-4.98,2.78)	-1.38 (-7.82,5.06)	-1.07 (-7.51,5.37)	-0.70 (-4.37,2.97)	-0.60 (-5.90,4.70)	-1.39 (-7.84,5.06)	RT

Bicycle, bicycle training; RT+Running, resistance training and Running; BT, ball training; RT, resistance training; RT+Running, resistance training and Running; RT+bicycle, resistance training and bicycle; RT+walk, CON, resistance training and walk; control group (no exercise).

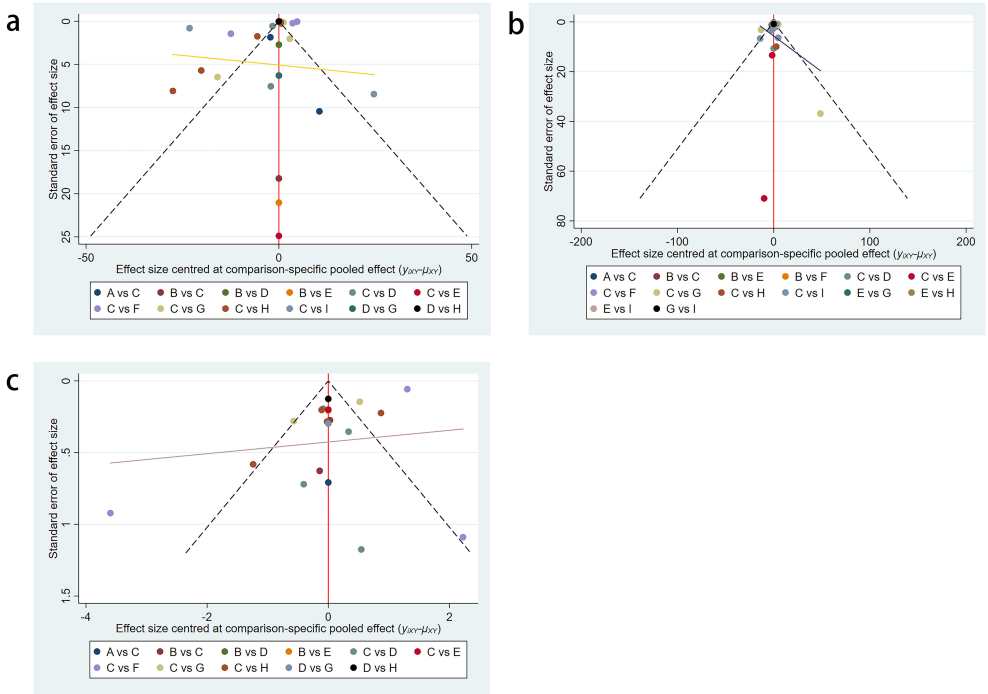

FIGURE 6
Funnel plot on publication bias. **(a)** FBG; **(b)** fasting insulin; **(c)** HOMA-IR.

insulin levels, and insulin resistance. These findings have significant implications for the management of diabetes. We recommend prioritizing cycling to reduce blood glucose levels, incorporating resistance training to enhance insulin sensitivity, and implementing combined training to address insulin resistance. Exercise has been proven effective in regulating glycemia and should be widely recommended as an essential non-pharmacological treatment for individuals with diabetes.

Future studies should further validate the benefits of diverse exercise regimens on blood glucose regulation in a broader population. The genetic background and type of diabetes may influence individual variations in response to exercise interventions; thus, we advocate for future trials with expanded sample sizes encompassing various ethnicities to corroborate our current findings. Additionally, exploring the interaction between exercise and antidiabetic drugs is imperative. Longitudinal trials

with larger sample sizes are also necessary to investigate the long-term effects of exercise interventions on maintaining blood glucose control among patients with diabetes while providing more personalized exercise recommendations.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Author contributions

YP: Writing – original draft, Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Writing – review & editing. PW: Writing – review & editing, Investigation, Software, Visualization. CY: Writing – review & editing, Resources, Software. CL: Writing – review & editing, Formal Analysis, Resources, Software.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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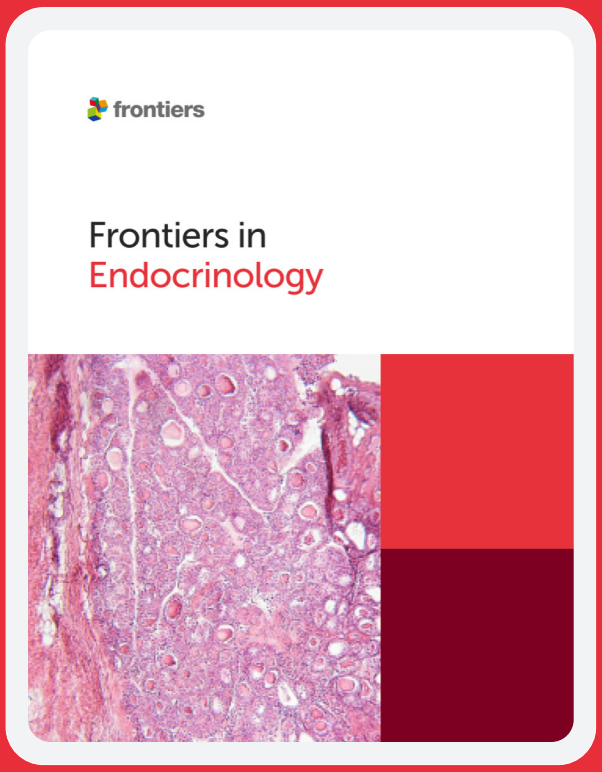

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