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# Cardiovascular diseases related to diabetes and obesity, volume III

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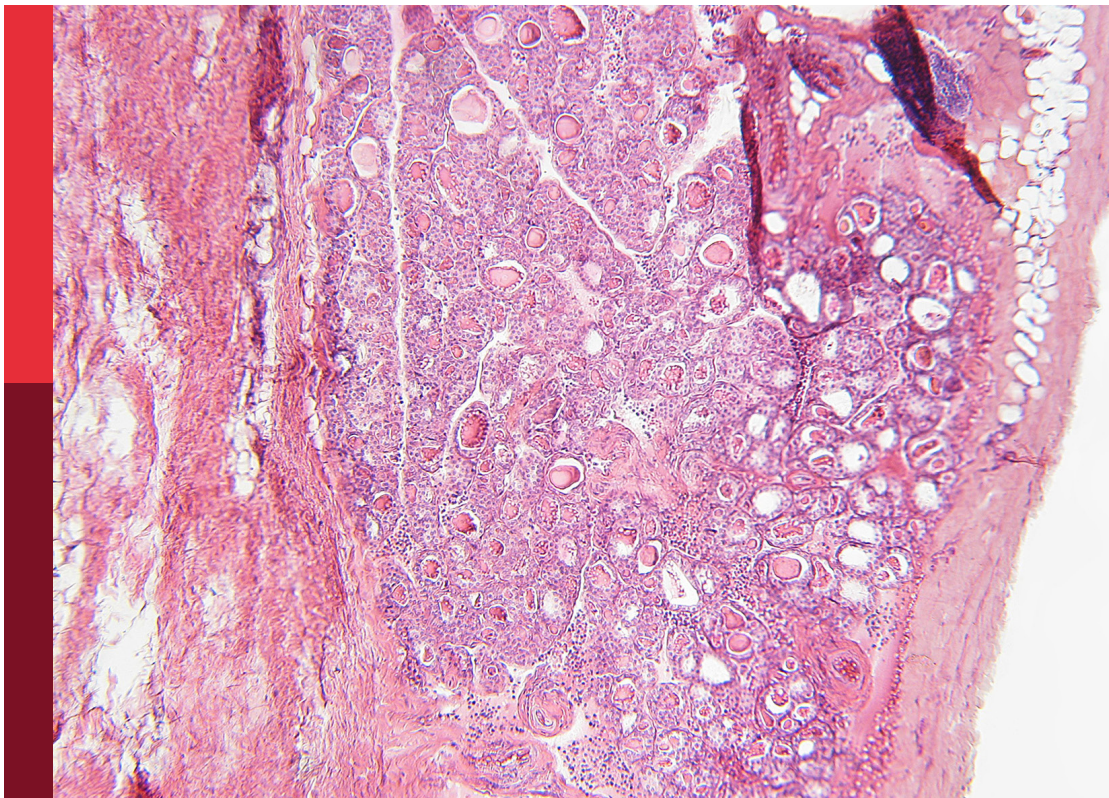
**Published in**
Frontiers in Endocrinology



ISSN 1664-8714
ISBN 978-2-8325-4511-9
DOI 10.3389/978-2-8325-4511-9

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# Cardiovascular diseases related to diabetes and obesity, volume III

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**Citation**

Cai, L., Xin, Y., Young, J. L., Mohanraj, R., eds. (2024). *Cardiovascular diseases related to diabetes and obesity, volume III*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-4511-9

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frontiers | Frontiers in Endocrinology

TYPE Editorial
PUBLISHED 13 February 2024
DOI 10.3389/fendo.2024.1381446



OPEN ACCESS

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RECEIVED 03 February 2024
ACCEPTED 05 February 2024
PUBLISHED 13 February 2024

CITATION
Xin Y, Wise JY, Rajesh M and Cai L (2024) Editorial: Cardiovascular diseases related to diabetes and obesity, volume III.
*Front. Endocrinol.* 15:1381446.
doi: 10.3389/fendo.2024.1381446



# Editorial: Cardiovascular diseases related to diabetes and obesity, volume III

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KEYWORDS

**metabolic syndrome, obesity, diabetes, cardiovascular disease, CVD biomarkers**

Editorial on the Research Topic
Cardiovascular diseases related to diabetes and obesity, volume III

Obesity is a chronic, multifactorial metabolic disease responsible for over 4 million deaths each year (1). Globally, the population of obese people is expected to reach more than 1 billion by 2030, accounting for 20% of the total adult population (2). An interaction of genetic, environmental and lifestyle factors (i.e., increased consumption of high-energy food, growth of sitting work patterns, and decreased intensity of physical activity) all contribute to the perpetual rise of disease prevalence. Obesity significantly increases the incidence of many metabolic diseases, and is the primary cause of the global epidemics of diabetes mellitus (DM), hypertension, and cardiovascular disease (CVD) (3). Several cohort studies have also confirmed that obesity is associated with an increase in the mortality from CVD (4). Existing medications fail to cure CVD associated with obesity, DM, and metabolic syndrome, although lifestyle changes, balanced diets, and exercise are available to prevent or delay the complications. Therefore, it is crucial to explore the pathogenesis and early screening approaches of obesity and DM-associated CVD for more effective interventions. This Research Topic developed the third volume, collected ten publications, including 8 clinical studies and 2 reviews, all which have strengthened the understanding of the pathogenesis and early detection of these chronic diseases, providing a platform for the creation of more individualized therapeutic regimens.

CVD is a major contributor to the mortality in the global population; therefore, it is essential to explore effective screening measures to identify high-risk individuals for early intervention. As one of the common pathogenic mechanisms and characteristics of CVD, DM and obesity, insulin resistance (IR) has the potential to be used as an early indicator of disease. However, the application of homeostasis model assessment IR (HOMA-IR), the common assessment approach for measuring IR, is restricted due to its inconvenience and cost. Therefore, Wang et al. performed a prospective cohort study that included 4,712 participants in Xinjiang to estimate the relevance of the metabolic IR score (METS-IR) and triglyceride-glucose (TyG) index, two alternative markers of IR, with the cumulative morbidity of CVD. They revealed that elevated baseline METS-IR and TyG indices were independent risk factors for new-onset CVD, and their trajectory patterns were linked to an

increased risk of CVD. Therefore, both METS-IR and TyG index are predicted as early effective assessments for CVD identification in large-scale epidemiological surveys. Furthermore, IR may correlate with the high risk of heart failure (HF) in patients with DM or prediabetes, and recently the triglyceride glucose-body mass index (TyG-BMI) was reported to predict IR better than the TyG index. Thereby, Yang et al. conducted a cross-sectional study involving 7,472 participants, including 329 patients with HF, to investigate the relationship between TyG-BMI and HF. Their study revealed that DM and prediabetes participants with high TyG-BMI were more susceptible to HF, therefore indicating an urgent need to develop strategies to reduce TyG-BMI for HF prevention.

Glycemic variability (GV) refers to fluctuations in glucose levels and has been recognized as a critical risk factor for cardiovascular events, such as HF, diabetic cardiovascular complications, and hypertension. To assess the impact of GV on myocardial recovery in failing hearts and onset of hypertension, the following clinical studies were performed. Among HF patients, a substantial proportion whose ejection fraction (EF) was improved after adherence to guideline-directed medications, is described as HFimpEF, showing better prognosis. A cohort study in 591 consecutive HF patients with a reduced EF (HFrEF, EF ≤40%), hospitalized between 2013 and 2020, was conducted by Yang et al. Duplicate echocardiograms were taken at baseline and after 12 months. Multivariate analysis showed that long-term GV was independently associated with the compromised development of HFimpEF irrespective of glycemic levels. Another large prospective cohort study performed by Huang et al. assessed the correlation of HbA1c, an indicator of GV, with hypertension. This study enrolled a total of 4,074 participants with DM combined with or without hypertension from the China Health and Nutrition Survey (CHNS). Huang et al. (2023) reported a linear and positive correlation between HbA1c and hypertension. These two studies suggest that more steady control of blood glucose is necessary to decrease hypertension and promote cardiac functional recovery in HF patients.

Diabetic cardiomyopathy (DCM), a diabetes-induced microvascular complication, is manifested by myocardial remodeling, diastolic and systolic dysfunction, and poor prognosis, which can ultimately result in clinical HF. Therefore, to improve early assessment of cardiac impairment in DM, Cao et al. designed a study to evaluate left ventricular (LV) function with a non-invasive myocardial work technique. They recruited 67 type 2 diabetes mellitus (T2DM) patients and 28 healthy controls in the study. The results demonstrated that the peak strain dispersion (PSD), global wasted work (GWW) and global work efficiency (GWE) were more sensitive for diagnosing subclinical LV dysfunction among patients with only a small number of changes in diastolic function parameters, while the ejection fraction remained normal. Discordant LV myocardial strain may contribute to the increased GWW and decreased GWE. These findings are very informative, since the uncoordinated LV myocardial strain and abnormal GWW and GWE obtained by this non-invasive technique may serve as early indicators for DCM or other cardiac impairment in T2DM patients. Furthermore, Zhao et al. summarized the DCM literature from the last 40 years, discussing the overall view of DCM, stages of progression, potential clinical indicators, screening and diagnosis criteria, and clinical treatment. In this review, the authors specified five specific spatio-temporal models of DCM and briefly summarized their pathological mechanisms, as well as proposed the hypothesis that a subclinical hyperfunction may be present in the ultra-early stages of DCM. However, more observational clinical trials should be conducted to improve and to explore available metrics and effective drugs for DCM.

Emerging evidence highlighted that visceral adipose tissue might regulate the cardiovascular and metabolic systems through several pathways. Patients with metabolic syndrome (MetS) are considered at high risk for developing CVD, and visceral obesity is the most evident clinical feature of MetS. Chinese Visceral Adiposity Index (CVAI) is utilized for assessing dysfunction of visceral fat and outperforms other indicators in the diagnosis of DM and hypertension among the Chinese population. Given the impact of visceral fat dysfunction on cardiovascular risk, Liu et al. carried out a study aimed at exploring the relationship between CVAI and stroke risk in MetS patients. With 6,732 individuals meeting the criteria for MetS in the Hunan province and a 2-year follow-up, it was found that CVAI showed an independent positive correlation with incident stroke in MetS patients. There is a reduced risk of stroke for MetS patients when the CVAI was below 110.91. Meanwhile, previous studies have found epicardial fat thickness (EFT) isindependently correlated with subclinical carotid atherosclerosis (SCCA), and a recent study showed that perirenal adipose tissue also plays an important role in SCCA. Therefore, Guo et al. undertook a study of 670 T2DM participants to investigate the association between perirenal fat thickness (PrFT) and SCCA for the identification of the novel risk factors. The findings confirmed that PrFT was independently related to carotid intima-to-media thickness (cIMT), plaques, and SCCA. Furthermore, subgroup analysis after stratification for age, sex, smoking, hypertension, and body mass index, also indicated a correlation between PrFT and SCCA. Accordingly, T2DM or MetS with the excessive accumulation of visceral fat, including perirenal fat, ought to attract more attention. In compliance with our call for studies on natural products with potential application in individuals with Mets, a systematic review and meta-analysis of randomized controlled trials was conducted by Qiu et al. to evaluate the efficacy and safety of curcumin on metabolism, inflammation, and oxidative stress among patients with MetS. A total of 785 participants from 13 randomized controlled trials were included, with intervention durations ranging from 4 to 12 weeks. This study confirmed that curcumin improved MetS-related metrics, including high-density lipoprotein cholesterol, inflammatory cytokine levels (i.e., tumor necrosis factor-a and C-reactive protein), and oxidative stress (indicated by MDA). Nevertheless, more studies are needed to confirm these results due to the limited and heterogeneous evidence included.

In addition to obesity and DCM, coronavirus disease 2019 (COVID-19) has emerged as a high risk factor for DM and CVD. In fact, COVID-19 may even be a greater risk factor than obesity and DCM. To evaluate the relation between COVID-19, incidence of CVD, and all-cause mortality among patients with DM, Jung and

Choi conducted a study included 16,779 COVID-19 patients and 16,779 matched controls between 2017 and 2021. The results showed that DM patients with COVID-19 experienced higher morbidity and mortality from CVD, coronary heart disease, and stroke compared to uninfected DM patients, which indicates that more prevention and management should be given to DM and MetS patients with COVID-19.

## Author contributions

YX: Conceptualization, Writing – original draft, Writing – review & editing. JW: Writing – review & editing. MR: Writing – review & editing. LC: Conceptualization, Writing – original draft, 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.

## Publisher's note



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frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 07 December 2022
DOI 10.3389/fendo.2022.1032268



OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

RECEIVED 30 August 2022
ACCEPTED 22 November 2022
PUBLISHED 07 December 2022

CITATION
Zhao X, Liu S, Wang X, Chen Y, Pang P, Yang Q, Lin J, Deng S, Wu S, Fan G and Wang B (2022) Diabetic cardiomyopathy: Clinical phenotype and practice.
*Front. Endocrinol.* 13:1032268.
doi: 10.3389/fendo.2022.1032268



# Diabetic cardiomyopathy: Clinical phenotype and practice

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Diabetic cardiomyopathy (DCM) is a pathophysiological condition of cardiac structure and function changes in diabetic patients without coronary artery disease, hypertension, and other types of heart diseases. DCM is not uncommon in people with diabetes, which increases the risk of heart failure. However, the treatment is scarce, and the prognosis is poor. Since 1972, one clinical study after another on DCM has been conducted. However, the complex phenotype of DCM still has not been fully revealed. This dilemma hinders the pace of understanding the essence of DCM and makes it difficult to carry out penetrating clinical or basic research. This review summarizes the literature on DCM over the last 40 years and discusses the overall perspective of DCM, phase of progression, potential clinical indicators, diagnostic and screening criteria, and related randomized controlled trials to understand DCM better.

KEYWORDS

**diabetic cardiomyopathy, phase of progression, screening, diagnosis, treatment, review**

## Introduction

The current diabetes mellitus (DM) prevalence is 463 million, 9.3% of the world population (1). In this vast group, heart failure (HF) has emerged as the most common cardiovascular complication of diabetes (2). Meanwhile, patients with type 2 diabetes mellitus (T2D) are more likely to be hospitalized and re-admitted for HF and have a higher risk of cardiovascular and all-cause mortality than those without diabetes and HF (3, 4); this may be due to long-term DM leading to pathological changes that contribute to the development and progression of HF, including myocardial structural, functional,

and metabolic changes (5), independent of myocardial ischemia or atherosclerotic disease processes.

This distinct clinical entity was first proposed by Lundbaek (6) in 1954 as diabetic heart disease independent of hypertension and coronary artery disease (CAD) that commonly coexist with T2D. In 1972, the existence of DCM had been confirmed through postmortem pathological findings in four patients with diabetes who manifested HF symptoms, and DCM became validated as a distinct entity (2). Bertoni et al. (7) conducted a large nationwide case-control study in the United States in 1995, which confirmed an association between nonischemic idiopathic cardiomyopathy and diabetes. After these initial studies, DCM gained increased attention from epidemiologists and clinicians.

Despite the rapid increase in the number of preclinical and clinical studies on diabetic cardiomyopathy in the past decades, the process of DCM remains unclear. As a result, no consensus has been reached regarding the most effective preventive or therapeutic approaches to diabetic cardiomyopathy. For this reason, this review summarizes the recent theory and clinical finding achievements to understand this controversial disease better.

## Phases of progression

Diabetic cardiomyopathy is organic heart disease. The exact evolution of DCM pathological changes has not been fully studied. The existing Spatio-temporal evolution models of DCM are generally divided into two categories. One, which is the traditional understanding, is that DCM has only one phenotype, from diastolic to systolic dysfunction, and is accompanied by structural remodeling such as left ventricular hypertrophy (LVH), which is a gradual development process. The other believes that DCM is a disease with two independent phenotypes. The diastolic dysfunction phenotype eventually develops into HFpEF, and the systolic dysfunction phenotype finally develops into HFrEF, which is a new understanding.

Specifically, five specific Spatio-temporal models have been proposed, and their pathological mechanisms have been briefly summarized (Figure 1). Moreover, a hypothesis is argued: there may be subclinical hyperfunction in the ultra-early stage of DCM.

### Single clinical phenotype

#### Dichotomy

The simplest model describes DCM as two stages, mainly in the left ventricle (8). The first is the stage of diastolic dysfunction, which is asymptomatic, but has a series of characteristics of ultrasonic cardiogram (9): elevated LV end-diastolic pressure, increased ventricular stiffness, and possibly accompanied by left ventricular concentric hypertrophy and left atrial enlargement.

The second stage of HF displays clinical symptoms and signs based on systolic dysfunction and severe cardiac remodeling, such as LVH and terminal LV dilatation.

#### Trichotomy

Scholars who hold the trisection view believe diabetic cardiomyopathy successively involves cardiac function – cardiac structure – microvascular (10–20). It takes years to induce significant LV dysfunction by gradually accumulating subcellular structural damage at the beginning (10). Diastolic dysfunction is the earliest clinical abnormality, with myocardial fibrosis and hypertrophy as the main reason. Systolic dysfunction only develops in the late stage of the disease (10) and often coexists with severe CAD and cardiac autonomic neuropathy (CAN) (11).

The early stage lasts only a short time. The entire initial stage is completely asymptomatic (12). At the very beginning, hyperglycemia and insulin resistance (IR) of DM patients have led the metabolic disorders in their hearts (21). At this stage, the heart structure is close to normal as a result of the compensatory adaptation of the heart to metabolic disorders, and only changes in myocardial cell substructure and endothelial dysfunction are observed (22–24). First, the level of GLUT4 on myocardial cell membrane decreases (25), and the activity of PPARα increases (26), which decreases the level of intracellular glucose oxidation (GLOX) (27). On the other hand, the signal transduction mediated by insulin receptor increases (28), which promotes the transport of fatty acid transferase (FAT/CD36) to the plasma membrane (29), and then increases the uptake of FA and the level of fatty acid oxidation (FAO). These unbalanced substrate metabolisms reduce the efficiency of myocardial ATP production, so that work efficiency of cardiomyocytes deteriorates. Discrete subclinical diastolic dysfunction can be detected clinically. The initial characteristics of DCM are increased atrial filling, decreased ventricular early diastolic filling, and increased myocardial relaxation damage and stiffness (10). The ventricular filling reduction is characterized by a slow E acceleration peak, deceleration peak, and peak filling rate, which can be captured by magnetic resonance imaging (30). Echocardiographic findings of ventricular septal annual wall motion damage also confirmed this (13). It is worth mentioning that the decrease of myocardial blood flow reserve can be identified by load imaging technology (31), which may be related to impaired insulin signal transduction (14).

In the middle stage, the aggravation of myocardial cell injury makes diastolic cardiac function significantly abnormal, but the ejection function is only slightly affected (EF 40%-50%) (15). With the progress of the disease, the effects of metabolic disorders gradually expand, in which dysfunctional mitochondria is a key role (32). The increase of FAO and the

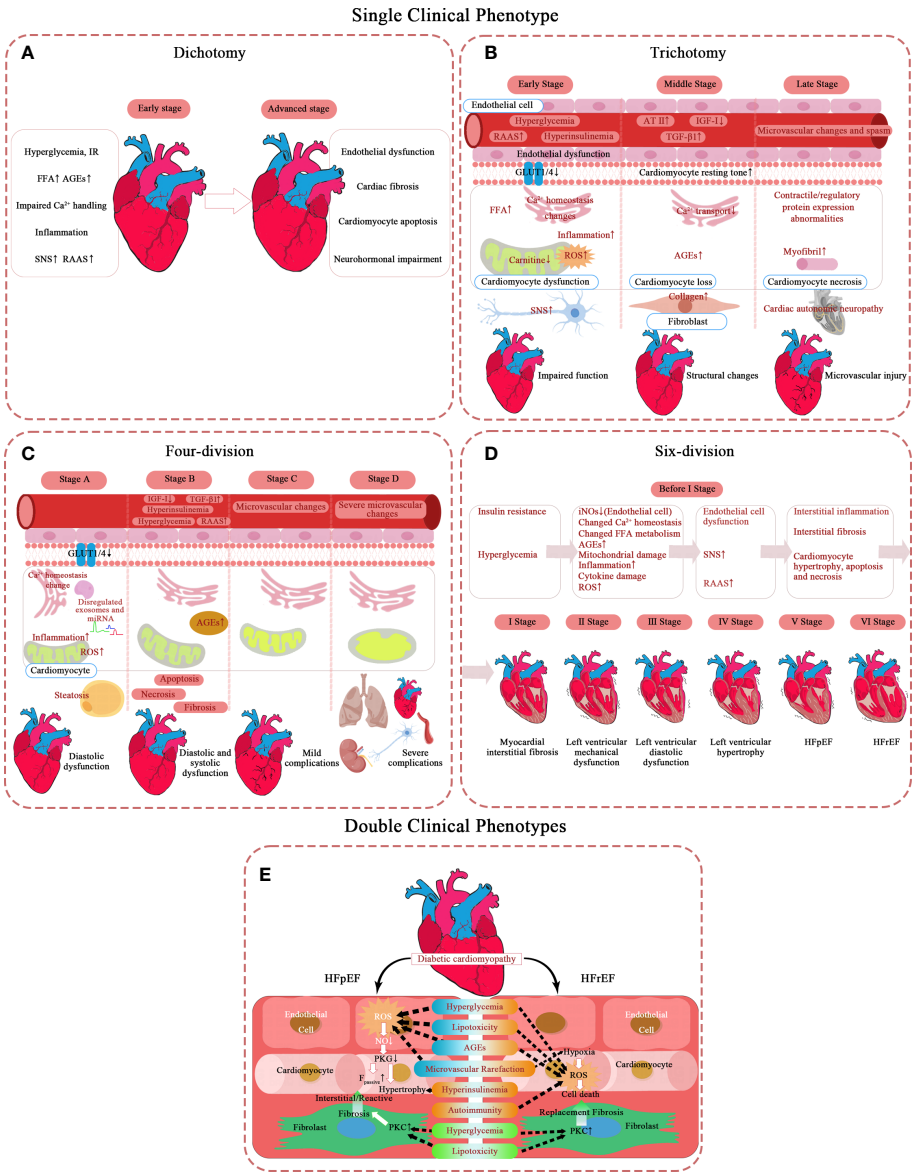


FIGURE 1
Pathological mechanism of DCM in different types of phases of progression. **(A–D)** Single clinical phenotype. **(E)** Double clinical phenotypes. AT-II, angiotensin II; AGEs, advanced glycation end-products; $F_{passive}$, cardiomyocyte resting tension; FFA, free fatty acid; GLUT1, glucose transporter 1; GLUT4, glucose transporter 4; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; IR, insulin resistance; IGF-I, insulin-like growth factor 1; NO, nitric oxide; PKC, protein kinase C; PKG, protein kinase G; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TGF-β1, transforming growth factor β1.

decrease of GLOX lead to the accumulation of toxic lipid metabolites, like DAG and ceramide, and the increase of oxidative stress, especially the release of ROS and NOS in cardiomyocytes (33, 34). Lipotoxicity caused by toxic lipid metabolites can lead to the remodeling of mitochondrial membrane, and oxidative stress can damage the proteins involved in oxidative phosphorylation (35) and activate uncoupling protein (UCP) (36), further destroying the function of mitochondria. In addition, under the influence of hyperglycemia, the levels of advanced glycation end products (AGE) increases both inside and outside the cells, and their formation on the SERCA2a and Ryr of the sarcoplasmic reticulum interfered with the dynamics of Ca2+ (37, 38), thus affecting the function of mitochondria (39). Mitochondria plays as a mediator in this process, which activates the apoptotic cascades under the influence of abovementioned factors (40). In short, the subcellular mechanisms, such as impaired insulin signal transduction, mitochondria metabolic disorders and

impaired calcium dynamics, lead to cardiomyocyte loss and fibrosis, and may lead to mild CAN (15). This stage begins to show clinical symptoms. Although the change in cardiac structure is still slight, it can be detected by conventional echocardiography: LV diameter, wall thickness, or mass increases, and compliance decreases (14). Myocardial microvascular structural damage is not obvious at this stage.

This stage is a critical period of fibrosis progression because cardiac magnetic resonance (CMR) can detect diffuse fibrosis (16). The increase of perivascular and myofibrillar interstitial fibrosis was observed in the myocardial samples without coronary heart disease and hypertension (41). Stiff collagen and its crosslinks accumulate in the heart interstitial, causing the gradual loss of muscle cells. Notably, this collagen deposition and accumulation of advanced glycation end products (AGEs) are important features of increased LV stiffness in heart failure patients with reduced EF, which may be related to the impairment of ejection function (41).

In the last stage, cardiac interstitial fibrosis exacerbates and eventually turns into HFrEF. Patients will have prominent exercise intolerance (12). The change in myocardial microcirculation is noticeable now. Severe collagen deposition results in coronary arteriolar sclerosis, basement membrane thickening, and capillary microaneurysm (20). Cardiac remodeling exceeds myocardial repair capacity. LV mass, volume, and wall thickness continue to increase (12, 15), accompanied by LV dilatation. At this time, focal fibrosis can be detected by positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI) (16). Based on diastolic dysfunction, the signs of systolic dysfunction begin to appear, manifested as shortened ejection period, prolonged performance before ejection, and increased filling pressure. Ischemic heart disease and severe CAN are the two major complications at this stage (17–20). At the subcellular level, increased ROS and inflammation (13), contractile and regulatory protein expression abnormalities, and impaired myocardial insulin signal transduction lead to decreased endothelial nitric oxide synthase activation and bioavailable nitric oxide levels (42).

Even if this trisection model seems perfect, some believe that LVH is the first performance of the first stage rather than in the middle (15). Because at the cellular level, the activation of neurohumoral mechanisms such as hyperglycemia, insulin resistance, renin-angiotensin-aldosterone system (RAAS), and sympathetic nervous system (SNS) lead to cardiomyocyte hypertrophy, stiffness, and fibrosis, which is sufficient to trigger this process. Meanwhile, free fatty acid (FFA) accumulation, calcium homeostasis imbalance, and GLUT-1 and -4 depletion contribute to myocyte injury at the molecular level (15).

Furthermore, some pathological mechanisms like microvascular perfusion damage remain debatable (16). The microcirculation disturbance is recognized in the late stage of this disease, but it is not clear in the early stage. The current known decrease in myocardial blood flow reserve is most likely related. DCM is undoubtedly a DM microcirculation complication if microcirculation disturbance runs through the process.

## Four-division

Some scholars divide DCM into four stages with a clear hierarchy based on NYHA classification and AHA staging (43–46). They emphasize that DCM is the earliest contributor to HF in patients with DM in an ideal state. In this model, the presence or absence of comorbidities is regarded as the watershed of HF. The early stages (stages A and B) are characterized by simple DCM, mainly caused by the pathophysiology of diabetes. The latter stages (stages C and D) show that DCM coexists with other complications, and diabetes is a secondary factor. This scheme extends the traditional definition of diabetic cardiomyopathy, considering the pathophysiological characteristics, echocardiography changes, and periodic changes in serum biomarkers. The stages are:

Stage A (diastolic dysfunction): no clinical symptoms. Patients usually have normal cardiac structure and function, at most subclinical cardiac structure and function abnormalities, normal ejection fraction (LVEF), and no non-DCM complications. However, patients often show hypertrophic and restrictive phenotypes because LVH increases ventricular stiffness, leading to diastolic dysfunction. This is the earliest stage of DCM and can be detected in 28% to 75% of asymptomatic diabetic patients (14). Finally, 36.9% of patients with stage A will progress to symptomatic heart failure (47).

Stage B (systolic and diastolic dysfunction): mild/moderate physical activity limitation. Structural and functional abnormalities appear in the heart, but no non-DCM complication exists. In addition to diastolic dysfunction, patients may have decreased ventricular dilatation and ejection fraction. Secondary complications such as coronary heart disease and hypertension are possible but are not severe.

Stage C (mild complications): severe physical activity limitation. Cardiac dysfunction and LVEF decline worsen. Non-DCM complications, such as hypertension, microvascular disease, and viral heart disease, begin to appear. Patients may have myocarditis and coronary atherosclerosis but no coronary heart disease (14).

Stage D (severe complications): there are still symptoms or imminent death at rest. Biventricular refractory heart failure lasts. Non-DCM complications are severe, including dilatation, fibrosis, microvascular and macrovascular lesions, and obvious native coronary heart disease. It can also be combined with myocardial overload after myocardial infarction, with or without hypertensive heart disease.

In addition, there are different beliefs. Because DM is a clear risk factor for HF, some researchers believe it enters phase A as long as it occurs. Further progress is manifested as simple

diastolic dysfunction; this is a split in phase A of the above program, but this model does not refer to complications. The specific stages can be summarized as follows: stage A (risk factor stage): simple diabetes; stage B (HFpEF): left ventricular diastolic dysfunction (LVDD) without symptoms but with LVH; phase C (HFrEF): EF decreased with obvious symptoms and signs such as dyspnea and pulmonary congestion; stage D (terminal stage): heart failure that is difficult to treat (48).

### Six-division

After nearly 30 years of accumulation of CMR-derived myocardial mechanics data, according to the order of structure and dysfunction, a view of the DCM six points method was created (49).

In the first stage, myocardial interstitial fibrosis occurs; this is detected in a diagnostic test. Researchers used sensitive methods to measure the left ventricle's multidirectional strain and strain rate. The overall longitudinal, circumferential, and radial strains were not significantly different compared to the healthy control group, but ECV (extracellular volume, representing interstitial fibrosis) in T2D patients was significantly high (50). AGEs accumulation or myocardial interstitial neovascularization may cause ECV dilatation. An animal study also showed that ECV first increased after three months of diabetes induction. The ultrasonic-derived LV radial strain rate changed after six months, and radial strain damage was observed after nine months (51). These studies have confirmed that extracellular fibrosis develops first, and mechanical function impairs. The early stage of interstitial fibrosis may not be sufficient to cause mechanical damage to the left ventricle, which is the reason for independently dividing it into stages.

The second stage of diabetic cardiomyopathy is LV mechanical dysfunction. Echocardiography and nuclear magnetic resonance studies have shown that in the systolic and early diastolic stages (52), the multidirectional strain of myocardial layers in diabetic patients decreased significantly (53–56), and a few strains increased compensatorily (53). Liu et al. (57) confirmed the decrease of diastolic longitudinal and circumferential strain rates in patients with T2D. In contrast, longitudinal strain and peak systolic longitudinal strain rates decreased in patients with T2D over 5 years (57).

The third stage is LVDD. Nuclear magnetic resonance (30, 58) studies have shown diastolic dysfunction in pre-diabetes (59), type 1 diabetes (T1D) (60, 61), and T2D (55) patients (children (62) and adults (63)). Moreover, from this stage on, changes can be detected by conventional echocardiography (55, 59, 60).

The fourth stage is LVH, the fifth stage is HFpEF, and the final stage is HFrEF. Not all diabetic patients will progress through all stages.

## Double clinical phenotypes

One thing in common in the above views regardless of the number of DCM phases: admitting that DCM has only one phenotype. However, some scholars believe that DCM has two phenotypes. Furthermore, these two phenotypes are not continuous stages of DCM but independently evolved into heart failure with LVEF preservation or reduction (64).

Researchers have found the phenotype-specific mechanisms of HFpEF and HFrEF, namely coronary microvascular endothelial dysfunction in HFpEF and myocardial cell death in HFrEF. The involvement priority of endothelial cell or cardiomyocyte cell compartments determines the development direction of DCM. In obese patients with T2D, abnormal glucose, lipid metabolism, and insulin resistance coexist and tend to occur in DCM's restrictive/HFpEF phenotype. T1D patients with autoimmune tendency are more likely to develop into dilated/HFrEF phenotype.

## A hypothesis: subclinical hyperfunction

Early DCM was not well understood. It was generally believed before that the cardiac function of patients with DCM remained normal initially. However, a new hypothesis is that DCM has a stage of myocardial systolic hyperfunction (65). This myocardial hyperdynamic state is short-lived and is the onset of the asymptomatic subclinical stage.

Based on the findings of a clinical study, this hypothesis adds to the early stage of DCM evolution. Hensel KO et al. used speckle tracking echocardiography to study the short course (4.3 ± 3.5 years) of type 1 diabetic adolescents without complications (62). Compared to the healthy control group, patients with type 1 diabetes showed overall longitudinal and circumferential LV myocardial systolic ability enhancement under rest and load. However, this situation is more evident in patients with a longer disease course, indicating that a high dynamic state may continue for several years.

Some evidence has been found in human and animal models. M-mode and Doppler ultrasound studies found that LV systolic ability increased in children with simple diabetes (66, 67). This phenomenon occurred only in normal albuminuria. When microalbuminuria occurred, LV systolic ability returned to normal (68). Studies on MRI also found that young adults with T1D showed signs of increased LV torsion at the early stage (69, 70). Few studies have revealed its pathophysiological mechanism. Only one animal model study suggests that it may be associated with increased plasma volume and sympathetic activation (27).

In short, this high LV systolic capacity is more like compensation for reduced myocardial efficiency. However, this is not widely reported because myocardial hypercontraction has

no clinical symptom and can only be detected using sensitive methods. Therefore, more clinical data are required to confirm this hypothesis.

## Overall clinical findings

Many studies have reported that DCM does not have any obvious clinical manifestations. It has nonspecific symptoms and signs of heart failure only when it progresses to the advanced stage. Therefore, auxiliary examination methods are the only ways to diagnose DCM. Previously, it was difficult to diagnose DCM because noninvasive techniques were inaccurate. Restrictive phenotype determination still required cardiac catheterization, while dilated phenotype required myocardial biopsy (48, 71); this made it difficult for humans to uncover the mysterious veil of DCM.

Noninvasive cardiac imaging has come a long way in the last 40 years, and because of its safety, simplicity, and accuracy, it is becoming increasingly important in diagnosing DCM. Nowadays, people can characterize DCM in metabolism, structure, and function. Numerous diagnostic clinical findings have been accumulated. They are summarized and listed below (Tables 1–3). All cardiac indicators differ meaningfully between diabetic patients and healthy people are included. Because DCM's clinical phenotypes and mechanisms are different in T1D and T2D, we sorted them out according to the type (64, 166). Given that the mixed population study (including T1D and T2D) still has a certain reference value, we summarized these studies together because it represents the general rule of DM.

Serological markers, echocardiography, cardiac magnetic resonance imaging, and positron emission tomography are widely used as the main tools to explore the changes in DCM heart. Because CMR is readily unavailable and expensive and has contraindications, and may not be suitable for patients with autism or metal implants, the application of CMR remains in the field of scientific research. Although echocardiography has inter-observer variability, and the assessment of right ventricular structure and function is often more nonstandard in the heart's four chambers, it is generally the preferred method for diagnosing DCM and tracking disease progression (48). Adding a series of new serological markers makes it more possible to implement a large screening because this is the simplest method. Many plasma/serum substances reflect changes in myocardial metabolism, structure, and function and may indicate prognosis (167). Metabolic changes in DCM can be detected using emerging magnetic resonance spectroscopy imaging, which appears to be the earliest detectable change in DCM. We also included DCM heart changes found by invasive techniques (Tables 2, 3), hoping to present a full spectrum of DCM lesions.

## Screening and diagnosis criteria

### Screening criterion

Diabetic cardiomyopathy screening knowledge is still insufficient to build up a criterion, but some useful information has emerged. Asymptomatic patients with T1D or T2D are considered to need further examination when they have risk factors as follows (168) (1): Longstanding DM (2); Poorly controlled DM (3); Microvascular complications of DM: diabetic kidney disease (↑UACR, ↓eGFR), retinopathy, and neuropathy. It is thought to be more suspicious if evidence of cardiac LV dysfunction or LVH as well as exercise intolerance can be found by doppler ultrasound or cardiopulmonary exercise test (168, 169). Additionally, five serological or urinary markers may be currently available for screening. Earlier researches have shown that, while BNP is a more visible indicator of diastolic dysfunction than hs-CRP, its sensitivity and specificity are low (170, 171). However, with the advancement of research, increasing evidence has confirmed that BNP or NT-proBNP is closely related to heart failure and is still recommended as an early screening for DCM (172, 173). Two prospective randomized controlled trials have confirmed that a new standard (BNP≥50 pg/mL or NT-proBNP>125 pg/ml) can screen high-risk DM populations properly to reduce the incidence of cardiovascular hospitalizations/death or heart failure (173, 174). A study has also shown that NT-proBNP level below 125 pg/mL helps role out the possibility of

TABLE 1 Main clinical findings of biomarkers for cardiac dysfunction in T1D and T2D patients.

| Biomarkers | | T1D | T2D | DM (T1D+T2D) |
|---|---|---|---|---|
| Conventional indicators | NT-proBNP | ↑ (72) | ↑ (73) | ↑ (74) |
| | hs-cTnT, BNP, NLR | | ↑ (75–78) | |
| | TNF-α, IL-6, AGEs, Creatinine | | ↑ (79) | |
| | GDF-15, Galectin-3, MMP-7, PIP, CT-1 | | ↑ (80–84) | |
| MiRNA | mir-223 | | ↑ (85) | |
| | mir-21 | | ↓ (86) | |
| LncRNA | lncRNA NKILA | | | ↑ (87) |

NLR, Neutrophil to lymphocyte ratio.
↑ means the figure is higher than that of healthy people, while ↓ means the figure is lower than that of healthy people.

asymptomatic LV dysfunction in the DM population (73). What's more, $HbA_1c$ levels are proportional to the degree and frequency of diastolic dysfunction (175). Interestingly, testing microalbuminuria in people with diabetes helps identify their risk of diastolic dysfunction (78). However, the detection results of these indicators cannot directly confirm myocardial changes, so they must be determined by imaging tests.

TABLE 2 Main clinical findings of ultrasound for cardiac dysfunction in T1D and T2D patients.

| Instrumental examination | | | | | T1D | T2D | DM (T1D +T2D) |
|---|---|---|---|---|---|---|---|
| Conventional Doppler Echocardiography | Epicardium | Structure | EFT | | ↑ (88, 89) | ↑ (90) | ↑ (91) |
| | LA | Structure | LAV index | | | ↑ (55, 92, 93) | |
| | | Function | LAEF | | | ↓ (94, 95) | |
| | | | LAEV | | | ↓ (94) | |
| | | | atrial filling fraction | | | | ↑ (96, 97) |
| | LV | Structure | interventricular septum thickness | | | ↑ (55) | |
| | | | posterior wall thickness | | | ↑ (55) | ↑ (97) |
| | | | relative wall thickness | | | ↑ (55, 92, 94) | |
| | | | LV mass index | | ↑ (98) | ↑ (55, 92, 94) | |
| | | | LVEDV | | ↓ (99) | | |
| | | Function | EDT | | ↑ (61, 100, 101) | ↑ (55, 92, 102, 103) | ↑ (104) |
| | | | | | | ↓ (93) | |
| | | | E/A | | ↓ (61–63, 100, 105) | ↓ (55, 83, 92–94, 102, 103, 106) | ↓ (97, 104, 107) |
| | | | | | ↑ (108) | | |
| | | | IVRT | | ↑ (99–101, 105) | ↑ (92, 102, 103) | ↑ (97) |
| | | | | | | ↓ (93) | |
| | | | LVEF | | | ↓ (92) | |
| | | | fractional shortening | | | ↓ (92) | |
| | RV | Function | IVRT | | ↑ (61) | | |
| | | | MPI | | ↑ (61) | | |
| | | | E/A | | ↓ (63, 109) | ↓ (83) | |
| TDI | LA | Function | strain | | | ↓ (95) | |
| | LV | Function | E/e′ | | | ↑ (55, 93, 110, 111) | ↑ (104) |
| | | | | | | ↓ (72, 92) | |
| | | | MPI | | | ↓ (92, 112) | |
| | | | interventricular septum | systolic strain | | | ↓ (54) |
| | | | | SRs | | | ↓ (54) |
| | | | | SRe | | | ↓ (54) |
| | | | lateral wall | systolic strain | | | ↓ (54) |
| | | | | SRs | | | ↓ (54) |
| | | | | SRe | | | ↓ (54) |
| | | | GRS | | | ↓ (113) | |
| | | | longitudinal strain | global | ↓ (108, 114) | ↓ (113) | |
| | | | | endocardia | | ↓ (113) | |
| | | | | mid-myocardial | | ↓ (113) | |
| | | | | epicardial | | ↓ (113) | |
| | | | circumferential strain | global | | ↓ (113) | |
| | | | | endocardia | | ↓ (113) | |
| | | | | mid-myocardial | | ↓ (113) | |
| | | | | epicardial | | ↓ (113) | |

*(Continued)*

TABLE 2 Continued

| Instrumental examination | | | | | T1D | T2D | DM (T1D +T2D) |
|---|---|---|---|---|---|---|---|
| | | | LV twist | | | ↑ (113) | |
| | RV | Function | basal segment | systolic strain | | | ↓ (54) |
| | | | | SRs | | | ↓ (54) |
| | | | | SRe | | | ↓ (54) |
| | | | apical segment | systolic strain | | | ↓ (54) |
| | | | | SRs | | | ↓ (54) |
| | | | | SRe | | | ↓ (54) |
| | | | GLS | | ↓ (109) | | |
| | | | FWLS | | ↓ (108) | | |
| 2D STE | LA | Structure | LAV index | | | | ↑ (115) |
| | | Function | strain | global | | | ↓ (115) |
| | | | | reservoir | ↓ (116) | | |
| | | | | conduit | ↓ (116) | | |
| | | | LA stiffness | | ↑ (116) | | |
| | LV | Function | GWI | | | ↓ (117) | |
| | | | GWE | | | ↓ (117) | |
| | | | GWW | | | ↑ (117) | |
| | | | longitudinal strain | global | ↓ (118) | ↓ (92, 110, 117, 119) | ↓ (120) |
| | | | | endocardial | ↓ (121) | ↓ (55) | |
| | | | | mid-myocardial | ↓ (121) | ↓ (55) | |
| | | | | epicardial | ↓ (121) | ↓ (55) | |
| | | | circumferential strain | global | ↓ (118) | | |
| | | | | endocardial | | ↓ (55) | |
| | | | | mid-myocardial | ↓ (121) | ↓ (55) | |
| | | | | epicardial | ↓ (121) | ↓ (55) | |
| | | | radial strain | basal | ↓ (118) | | |
| | | | | subendocardial | | ↓ (119) | |
| | RV | Function | free wall strain | | | ↓ (122) | |
| | | | GLS | | ↓ (118) | | |
| 3D E | LA | Structure | LAV index | | | ↑ (123) | |
| | | Function | LAEF | | | ↓ (123) | |
| | | | GLS | | | ↓ (124) | |
| | | | GCS | | | ↓ (124) | |
| | | | GAS | | | ↓ (124) | |
| 3D STE | LV | Function | GLS | | ↓ (125) | | ↓ (126) |
| | | | GCS | | | | ↓ (126) |
| | | | GRS | | | | ↓ (126) |
| | | | GAS | | | | ↓ (126) |
| Physical SE | LV | Function | GLSR at rest and during exercise | | ↑ (62) | | |
| | | | GCSR at rest | | ↑ (62) | | |
| | | | longitudinal reserve index | diastolic | | ↓ (127) | |
| | | | | systolic | | ↓ (127) | |
| Pharmacological SE | LV | Function | rotation | apical | | ↓ (128) | |
| | | | | basal | | ↓ (128) | |
| | | | LV twist | | | ↓ (128) | |
| | | | ΔLVEF | | | ↓ (129) | |

*(Continued)*

TABLE 2 Continued

| Instrumental examination | | | | T1D | T2D | DM (T1D +T2D) |
|---|---|---|---|---|---|---|
| Stress Doppler wire | Coronary Artery | Structure | coronary diameter | | ↓ (129) | |
| | | Function | maximal hyperemic flow | | ↓ (129) | |
| | | | coronary flow velocity | | ↑ (129) | |
| | | | CFR | | ↓ (129) | |

Conventional doppler echocardiography contains 2D, M-mode, color, pulsed, and continuous-wave doppler echocardiography. Doppler echographies based on tissue doppler imaging are included in "TDI", for example, SRI. Physical stress echocardiography contains tissue doppler echocardiography and speckle tracking echocardiography. Pharmacological stress echocardiography contains conventional echocardiography and speckle tracking echocardiography.
CFR, coronary flow reserve; EDT, E deceleration time; EFT, Epicardial fat thickness; E/A, ratio of the early to the late peak diastolic transmitral flow velocity; FWLS, free wall longitudinal strain; GRS, global radial strain; GLS, global longitudinal strain; GCS, global circumferential strain; GWI, global myocardial work index; GWW, global wasted work; GWE, global work efficiency; GAS, global area strain; GLSR, global longitudinal strain rate; GCSR, global circumferential strain rate; IVRT, isovolumic relaxation time; LV, left ventricular; RV, right ventricular; LAV, left atrial volume; LVEF, left ventricular ejection fraction; LA, left atrium; LAEF, left atrial ejection fraction; MPI, myocardial performance index; RA, right atrium; SRs, peak systolic strain rate; SRe, peak early diastolic strain rate; SE, stress echocardiography; TDI, tissue doppler imaging; 2D STE, two-dimensional speckle tracking echocardiography; 3D E, three-dimensional echocardiography; 3D STE, three-dimensional speckle tracking echocardiography.
↑ means the figure is higher than that of healthy people, while ↓ means the figure is lower than that of healthy people.

TABLE 3 Main clinical findings of CT/MRI/PET and other methods for cardiac dysfunction in T1D and T2D patients.

| Instrumental examination | | | | | Pre-DM | T1D | T2D | DM (T1D +T2D) |
|---|---|---|---|---|---|---|---|---|
| ECG | QTc max. interval | | | | | | ↑ (130) | |
| | QTc dispersion | | | | | | ↑ (130) | |
| | T peak-Tend dispersion | | | | | | ↑ (130) | |
| | QRS-T angle | | | | | | ↑ (131) | |
| CT | LV mass | | | | | ↓ (132) | | |
| | LV volume | | | | | ↓ (132) | | |
| | RV volume | | | | | ↓ (132) | | |
| MRI | LA | Function | GCS | | | | ↓ (133) | |
| | | | GRS | | | | ↓ (133) | |
| | | | GLS | | | | ↓ (133) | |
| | | | LA ejection fraction | total | | | ↓ (134, 135) | |
| | | | | passive | | | ↓ (135) | |
| | LV | Structure | LV mass | | | | ↑ (5) | ↑ (136) |
| | | | LV mass index | | | | ↑ (5, 137, 138) | |
| | | | LVEDV | | | | ↓ (135) | |
| | | | LVEDV index | | | | ↓ (134, 139) | |
| | | | LVESV index | | | | ↓ (139) | |
| | | | LV mass/volume | | | | ↑ (5, 134, 135, 137, 139) | |
| | | | LV wall thickness | | ↑ (140) | | ↑ (138, 140) | |
| | | Function | diastolic strain rate | inferior septal | | ↓ (141) | | |
| | | | | free wall region | ↓ (141) | | | |
| | | | diastolic relaxation fraction | | | ↑ (141) | | |
| | | | systolic stretch fraction | | | ↑ (141) | | |
| | | | apical FD | | | | ↑ (137) | |
| | | | torsion angle | | | | | ↑ (136) |
| | | | E peak | acceleration | | | ↓ (30) | |
| | | | deceleration | | | ↓ (30) | | |

*(Continued)*

TABLE 3 Continued

| Instrumental examination | | | | | Pre-DM | T1D | T2D | DM (T1D +T2D) |
|---|---|---|---|---|---|---|---|---|
| | | | filling rate | | | ↓ (30) | | |
| | | | E/A | | | ↓ (30) | | |
| | | | peak strain | longitudinal | | | ↓ (142) | |
| | | | circumferential | | | ↓ (142) | | |
| | | | peak diastolic strain rate | longitudinal | | | ↓ (57, 137, 142) | |
| | | | circumferential | | | ↓ (5, 57, 142) | | |
| | | | radial | | | ↓ (57, 142) | | |
| | RV | Structure | RVEDV | | | | ↓ (143) | |
| | | | RVESV | | | | ↓ (143) | |
| | | Function | GLS | | | | ↓ (133) | |
| | | | stroke volume | | | | ↓ (143) | |
| | | | pulmonary flow acceleration time | | | | ↑ (143) | |
| | | | PERPV | | | | ↓ (143) | |
| | | | PFRE | | | | ↓ (30, 143) | |
| | | | PDGE | | | | ↓ (30, 143) | |
| | Global | Metabolism | Lactate | | | | ↑ (144) | |
| | | | Bicarbonate | | | | ↓ (144) | |
| | | | Bicarbonate/Lactate | | | | ↓ (144) | |
| | | myocardial perfusion | upslope | | | | ↓ (57, 145) | |
| | | | max signal intensity | | | | ↓ (57, 145) | |
| | | | time to maximum signal intensity | | | | ↑ (57, 145) | |
| | | | BOLD SID | | | | ↓ (146) | |
| | | | MPR | | | ↓ (70) | ↓ (146, 147) | ↓ (136) |
| MRI $T_1$-mapping | Structure | LV mass/volume | | | ↑ (148) | | ↑ (145, 147) | ↑ (148) |
| | | native $T_1$ values | | | | ↑ (149) | | |
| | | ECV | | | ↓ (148) | ↑ (149) | ↑ (150, 151) | ↓ (148) |
| | | cell volume | | | ↑ (148) | | | ↑ (148) |
| | Function | myocardial function | myocardial $T_1$ time | | | | | ↓ (152) |
| | | | LVEDV | | | | ↓ (138, 147) | |
| | | | LVEDV index | | | | ↓ (147) | |
| | | | systolic strain | | | | ↓ (138) | |
| | | | systolic torsion | | | ↑ (149) | | |
| | | | systolic torsion rate | | | ↑ (149) | | |
| | | | systolic $E_{cl}$ | | | ↑ (149) | | |
| | | | rates of systolic $E_{cl}$ | | | ↑ (149) | | |
| | | | rates of diastolic $E_{cl}$ | | | ↑ (149) | | |
| | | | LV stroke volume | | | | ↓ (147) | |
| | | | LV stroke volume index | | | | ↓ (147) | |
| | | Microvascular function | $\Delta T_1$ | | | | ↓ (147) | |
| $^1$H-MRS | Myocardial lipid content | | | | | | ↑ (5, 144, 153) | |
| $^{31}$P-MRS | PCr/ATP | | | | | | ↓ (5, 30, 144, 146, 154) | |
| G-Spect | phase bandwidth | | | | | | ↑ (155) | |
| PET | myocardial glucose metabolism | uptake | | | | ↓ (156) | ↓ (157–159) | ↓ (160) |
| | | uptake/plasma insulin | | | | | ↓ (161) | |

*(Continued)*

TABLE 3 Continued

| Instrumental examination | | | Pre-DM | T1D | T2D | DM (T1D +T2D) |
|---|---|---|---|---|---|---|
| | | utilization | | ↓ (162) | ↓ (157) | |
| | | utilization rate/insulin | | ↓ (163) | | |
| | | oxidation | | ↓ (156) | ↓ (157) | |
| | | glycogen deposition | | | ↓ (157) | |
| | | glycolysis | | ↓ (156) | ↓ (157) | |
| | | glycogen synthesis | | ↓ (156) | | |
| | myocardial fatty acid metabolism | uptake | | | ↑ (159) | |
| | | utilization | | ↑ (162) | ↑ (158, 161) | |
| | | oxidation | | ↑ (162) | ↑ (158, 161) | |
| | | percent oxidation | | ↑ (162) | ↓ (161) | |
| | | esterification | | | ↑ (161) | |
| | myocardial oxygen consumption | $MVO_2$ | | ↑ (162, 163) | | |
| | myocardial perfusion | ΔCBF | | | ↓ (164) | |
| Cardiopulmonary Exercise Testing | peak oxygen uptake | | | | ↓ (55) | |
| | peak oxygen consumption | | | | ↓ (95) | |
| | oxygen pulse | | | | ↓ (55) | |
| | ventilation/carbon dioxide slope | | | | ↑ (55, 95) | |
| Coronary Angiography | microvascular function | CFR | | | ↓ (165) | |
| | | MRR | | | ↓ (165) | |

apical FD, apical fractal dimension of trabeculations; BOLD SID, blood-oxygen level-dependent signal intensity change; CT, computed tomography; CBF, coronary blood flow; CFR, coronary flow reserve; EDV, end-diastolic volume; ESV, end-systolic volume; E/A, ratio of the early to the late peak diastolic transmitral flow velocity; ECG, electrocardiograph; ECV, extracellular volume; $E_{cl}$, the shear strain component associated with twist; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LA, left atrium; LV, left ventricle; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; MRS, nuclear magnetic resonance spectrum; MPR, myocardial perfusion reserve; MVR, ratio of left ventricular mass at end diastole to end-diastolic volume; MRR, microvascular resistance reserve; $MVO_2$, myocardial oxygen consumption; PET, positron emission tomography; PSDR, peak diastolic strain rate; PERPV, peak ejection rate across the pulmonary valve; PFRE, peak filling rate of the early filling phase; PDGE, peak deceleration gradient of the early filling phase; RA, right atrium; RV, right ventricle.
↑ means the figure is higher than that of healthy people, while ↓ means the figure is lower than that of healthy people.

## Diagnosis criterion

As mentioned above, diabetic cardiomyopathy shows metabolic, structural, and functional changes. Therefore, many scholars are trying to find a cut-off point to establish the diagnosis of DCM. A study published in 2013 provided initial diagnosis clues of DCM (176). After other heart diseases are ruled out, changes as follows should be evaluated: The structural changes include (1) LV hypertrophy assessed by 2D echocardiography or CMR (2); Increased integrated backscatter in the LV (septal and posterior wall); and (3) Late Gd-enhancement of the myocardium in CMR. The functional changes include (1) LVDD assessed by pulsed Doppler echocardiography and TDI (2); LV systolic dysfunction (LVSD) demonstrated by TDI/SRI; and (3) Limited systolic and/or diastolic functional reserve assessed by exercise TDI. The metabolic changes include (1) Reduced cardiac PCr/ATP detected by $^{31}$P-MRS; (2) Elevated myocardial triglyceride content detected by $^{1}$H-MRS.

In 2015, researchers proposed different phenotypes of DCM development and their diagnostic criteria (64). The phenotypes should both meet the following conditions first: (1) Presence of DM; (2) Exclusion of CAD, valvular, or congenital heart disease; and (3) Exclusion of hypertensive heart disease (=DBP<90 mmHg). Based on this, the diagnostic criterion of Dilated/HFrEF Phenotype should include (1) Exclusion of viral myocarditis by endomyocardial biopsy; (2) LVEF<50%, LVEDVI>97 mL/m$^2$. While the criterion of Restrictive/HFpEF Phenotype should include: (1) Exclusion of infiltrative heart disease by endomyocardial biopsy; (2) LVEF>50%, LVEDVI<97 mL/m$^2$; and (3) E/e' >15 or 8<E/e' <15+LAVI>40 mL/m$^2$ or 8<E/e' <15+BNP>200 pg/mL or 8<E/e' <15+atrial fibrillation or 8<E/e'<15+LVH (LVMI♀>122 g/m$^2$; LVMI♂>149 g/m$^2$).

In 2021, a study (168) put forward a new diagnostic criterion based on the four-division method. Acknowledging only one phenotype exists, they believe stage B is the best time to diagnose DCM. Patients should have at least one of the following echocardiographic abnormalities: (1) LVH, defined as LV mass

index (LVMi) > 115 g/m$^2$ in men and > 95 g/m$^2$ in women; (2) LAE, defined as left atrial volume index (LAVi) ≥ 34 mL/m$^2$; (3) abnormal ratio of mitral inflow peak early diastolic velocity (E) to tissue Doppler mitral annular early diastolic velocity (e'), defined as E/e' ≥ 13; (4) impaired GLS, defined as GLS < 18%.

# Clinical practice

Currently, the treatment for DCM is mainly divided into three kinds: conventional cardiovascular drugs, anti-glycemic drugs, and new therapies such as CoQ10, MicroRNA and Stem cell therapy (14). Many reviews have focused on the outcomes of the trials of these therapies (14, 168, 177). Although the number of the trials is large, most of them recruited mixed population, resulting in invalid data for judging whether it is effective for treating DCM. What's worse, each kind has certain limitations now. For example, conventional cardiovascular drugs only apply when DCM develops into more obvious cardiac symptoms. Conventional anti-glycemic drugs have an insignificant benefit, and only SGLT2i (a new kind of anti-glycemic drug) is recommended as the first-line medicine for DCM. Moreover, new therapies still have defects such as clinical trial failure and insignificant safety. Therefore, more studies must be conducted to find suitable drugs. The following table (Table 4) summarizes the randomized controlled trials (RCTs) related to DCM in the last 10 years, hoping to inspire clinical drug use.

# Discussion

## Phase of progression

Although the progression phase contains some theoretical components, it stems from our understanding of the entire disease process, which has important guiding significance for clinical practice and scientific research. The differences among them are mainly reflected in three points: the phenotypes of the disease, the beginning of the disease, and the stages of the disease. Different phenotypes require different treatments, which is relevant to developing guidelines. If DCM only has one phenotype, it is necessary to consider the secondary prevention of HFpEF progression to HFrEF, and appropriate animal models should also be considered in basic research. If DCM exhibits two distinct phenotypes, clinical trials and basic research must be divided into sub-fields to be further investigated. It is also important to define the beginning of the disease. Although many researchers agree that the myocardial injury caused by diabetes begins at the onset of diabetes, some scholars have pointed out through epidemiological analysis that the natural history of diabetic cardiomyopathy has begun as early as the metabolic syndrome period. Patients who have elevated inflammatory markers and microalbuminuria are at risk of developing heart failure (14). Therefore, clarifying the starting point of DCM is of great value for formulating disease screening strategies, and early treatment can delay the progress of DCM. Furthermore, the division of disease stages, which provides strong support for clinicians in evaluating the severity of DCM patients and selecting the intervention time, should not be ignored. Moreover, it also affects the evaluation of drug efficacy because drugs have different benefits for different stages.

We have summarized all the proposed DCM Spatio-temporal evolution models (Table 5). The dichotomy is the most concise model for clinicians to master and can be easily popularized in communities. However, it should be noted that structural and metabolic changes that go unnoticed are the culprits of dysfunction. The trisection model does not advance much more than the dichotomy but emphasizes the discreteness, concealment, and progressive fibrosis of early dysfunction. Unless in medical institutions with advanced technological means, the clinical practice remains a dichotomy because early changes cannot be detected promptly.

Due to the origin of AHA and NYHA classification, the quartering model has strong practicability and popularity, which is definitely a good paradigm for examining DCM from a macro perspective and considering DCM complications. Six-division model is based on nuclear magnetic resonance, so it is more inclined to stage DCM from the perspective of imaging. If MRI is easy to obtain, this model is undoubtedly more refined, which is significant for clinical research. Unfortunately, although patients can be stratified, we lack the drugs to treat the lesions at each stage, particularly interstitial fibrosis, LV mechanical change, LVH, and HFpEF.

If DCM has two independent phenotypes, its value is enormous because it can save a lot of clinical resources to distinguish the stage and monitor the progression. The clinical test results of active cardiovascular drugs on HFpEF and HFrEF are different (64). However, the two-phenotype theory has a mixed reputation. LVSD is scattered in T2D. Most literature shows that resting LVEF in patients with T2D is normal. Therefore, whether T2D eventually develops into HFrEF is a controversial issue (9). Seferovic et al. proposed the hypothesis that T1D and T2D evolved respectively, which is convincing (64), but more research is required to confirm it. However, it was reported that LVEF in patients with relatively simple T2D at rest has a downward trend (194, 195). In fact, observational studies are mostly cross-sectional. Usually, only one of diastolic dysfunction and systolic dysfunction is included. Moreover, there is no prospective study to observe whether patients progress from diastolic to systolic dysfunction, so the evolution of DCM phenotype over time is still unknown. In addition, LVEF may improve or deteriorate during follow-up (196), and the measurement has a certain variability (197), which makes accurate classification difficult.

TABLE 4 Main RCTs on diabetic cardiomyopathy.

| Author (Year) | Target | Drug | Queue size | Outcomes | Refs |
|---|---|---|---|---|---|
| Hiroki Oe, Kazufumi Nakamura, Hajime Kihara (2015) | DPP4 | Sitagliptin VS Voglibose | 100 | Sitagliptin reduced $HbA_1c$ levels more greatly than voglibose does, but neither was associated with improvement in the echocardiographic parameters of LV diastolic function in patients with diabetes. | (178) |
| Hirotsugu Yamada, Atsushi Tanaka, Kenya Kusunose (2017) | DPP4 | Sitagliptin | 115 | Adding sitagliptin to conventional antidiabetic regimens for 24 months in T2D patients attenuated the exacerbation in E/e′, the echocardiographic parameter of diastolic dysfunction. | (179) |
| Alexander J.M. Brown, Chim Lang, Rory McCrimmon (2017) | SGLT-2 | Dapagliflozin | 66 | Dapagliflozin treatment significantly reduced left ventricular mass accompanied by reductions in systolic BP, body weight, visceral and subcutaneous adipose tissue, insulin resistance, and hs-CRP. | (180, 181) |
| Daisuke Matsutani, Masaya Sakamoto, Yosuke Kayama (2018) | SGLT-2 | Canagliflozin | 37 | Canagliflozin could improve left ventricular diastolic function within 3 months in patients with T2DM, which was especially apparent in patients with substantially improved hemoglobin values. | (182) |
| Satoshi Oka, Takahiko Kai, Katsuomi Hoshino (2021) | SGLT-2 | Empagliflozin | 35 | The positive effects of empagliflozin on LV dysfunction were more remarkable in early than in advanced DCM. | (183) |
| Sharmaine Thirunavukarasu, Nicholas Jex, Amrit Chowdhary (2021) | SGLT-2 | Empagliflozin | 18 | Empagliflozin ameliorated the cardiac energy metabolism, regressed adverse myocardial cellular remodeling, and improves cardiac function. | (184) |
| Rebecca L. Scalzo, Kerrie L. Moreau, Cemal Ozemek (2017) | GLP1R | Exenatide | 23 | Administrating exenatide improved cardiac function and reduced arterial stiffness; however, these changes were not accompanied by improved exercise capacity. | (185) |
| Weena J. Y. Chen, Michaela Diamant, Karin de Boer (2017) | GLP1R/ IR | Exenatide VS Insulin Glargine | 33 | Exenatide or insulin glargine had no effects on cardiac function, perfusion or oxidative metabolism. | (186) |
| Vaia Lambadiari, George Pavlidis, Foteini Kousathana (2018) | GLP1R/ AMPK | Liraglutide VS Metformin | 60 | Six-month treatment with liraglutide improved arterial stiffness, LV myocardial strain, LV twisting and untwisting and NT-proBNP in subjects with newly diagnosed T2D, which is related to anti-oxidative stress. | (187) |
| Maurice B. Bizino, Ingrid M. Jazet, Jos J. M. Westenberg (2019) | GLP1R | Liraglutide | 49 | Liraglutide reduced early LV diastolic filling and LV filling pressure, thereby unloading the left ventricle. LV systolic function reduced and remained within normal range. | (188) |
| Elisabeth H.M. Paiman, Huub J. van Eyk, Minke M.A. van Aalst (2020) | GLP1R | Liraglutide | 47 | Liraglutide did not affect LV diastolic and systolic function, aortic stiffness, myocardial triglyceride content, or extracellular volume in Dutch South Asian type 2 diabetes patients with or without coronary artery disease. | (189) |
| Ignatios Ikonomidis, George Pavlidis, John Thymis (2020) | GLP-1R/ SGLT-2 | Liraglutide + Empagliflozin | 160 | Treatment with GLP-1RA, SGLT-2i, and their combination within 12 months showed a greater improvement of vascular markers and effective cardiac work than insulin treatment in T2DM. The combined therapy was superior to either insulin or GLP- 1RA and SGLT-2i separately. | (190) |
| Elisa Giannetta, Andrea M. Isidori, Nicola Galea (2012) | PDE5 | Sildenafil | 54 | Selective phosphodiesterase type 5 inhibitor, sildenafil, acts directly on the myocardium through its anti-remodeling effect to ameliorate LV concentric hypertrophy associated with altered myocardial contractility dynamics in the early stages of diabetic cardiomyopathy. | (191) |
| S. Giannattasio, C. Corinaldesi, M. Colletti (2019) | PDE5 | Sildenafil | 46 | Sildenafil can control DCM progression through IL-8 targeting at the systemic and cellular levels. | (192) |
| Peng Zhao, Jie Zhang, Xian-Gang Yin (2013) | 3-KAT | Trimetazidine | 80 | Trimetazidine treatment can improve cardiac function and physical tolerance and decrease the inflammatory response. | (193) |

AMPK, Adenosine 5'-monophosphate-activated protein kinase; DPP4, Dipeptidyl-Peptidase 4; GLP1R, glucagon-like peptide 1 receptor; IR, insulin receptor; PDE5, phosphodiesterase type 5; SGLT-2, sodium-dependent glucose transporters 2; 3-KAT, long-chain 3-ketoacyl coenzyme A thiolase.

Notably, existing Spatio-temporal evolution models are mostly theoretical because the clinical diagnosis of DCM is challenging, so their data are mainly from experimental models (12). However, the proposed stages allow clinicians and researchers to see the whole picture. Moreover, the full spectrum of DCM clinical indicators will help optimize the evolution model and contribute to improvements in diagnosis since they all come from human studies.

## An overall picture of DCM

There is evidence that early in pre-diabetes, cardiometabolic recession appears alone (153, 158), followed by myocardial hypertrophy (148). Moreover, LVDD may appear. However, until the early stage of diabetes, heart damage remains tiny and discrete. As the disease progresses, the following phenomena occur (Figure 2):

TABLE 5 Summary of Phases of Progression.

| | | Stages | Cellular mechanisms | Tissue and organ changes | Metabolism changes | Functional changes | Structural changes | Common complications | Means of auxiliary examination |
|---|---|---|---|---|---|---|---|---|---|
| Single clinical phenotype | Dichotomy | Early stage | Hyperglycemia, insulin resistance, impaired $Ca^{2+}$ handling, hyperactivation of the SNS and RAAS, and inflammation | / | Increased FFA and AGE deposition | Diastolic dysfunction, increase in left atrial filling pressure, and elevated LV end-diastolic pressure | LV concentric hypertrophy, increased ventricular stiffness, and left atrial enlargement | / | / |
| | | Advanced stage | Microvascular endothelial dysfunction, neurohormonal impairment, inflammation, impaired $Ca^{2+}$ handling | Cardiac fibrosis and cardiomyocyte apoptosis | / | Diastolic dysfunction, systolic dysfunction | LV dilation, cardiac remodeling, and LV hypertrophy | / | / |
| | Trichotomy | Early stage | Depletion of GLUT-1 and -4, $Ca^{2+}$ homeostasis changes, hyperglycemia, insulin resistance, endothelial dysfunction, activated RAAS and SNS, oxidative stress, and inflammation | Very small pathophysiological changes in myocytes, such as cardiomyocyte substructural changes | Increased FFA and Carnitine deficiency | Prolonged isovolumetric relaxation, increased atrial filling, impaired early diastolic filling, increased cardiac relaxation and stiffness | Decreased myocardial blood flow reserve | / | Sensitive methods such as strain, strain rate, and myocardial tissue velocity, MRI, CTA, and IVUS |
| | | Middle stage | Defects in $Ca^{2+}$ transport, hormone disorders (increased AT II and TGF-β1, reduced IGF-I), activated RAAS, accumulation of AGEs, collagen deposition | Cardiomyocyte loss and fibrosis, high cardiomyocyte resting tone | / | Diastolic dysfunction, slightly impaired ejection function, increased left ventricular stiffness | Left ventricular hypertrophy, slightly increased LV mass, wall thickness or size | Mild CAN | Conventional echocardiography, sensitive methods (the same as techniques above) |
| | | Late stage | Myofibril reduction, contractile and regulatory protein expression abnormalities, increased formation and deposition of collagen | Advanced cardiac fibrosis, cardiomyocyte necrosis, microvascular changes and spasm | / | Significant deterioration of coronary microcirculation and systolic and diastolic function | Significantly increased LV size, wall thickness and mass | Hypertension, ischemic Heart Disease, Severe CAN | Conventional echocardiography |
| | Four-division | Stage A (diastolic dysfunction) | Altered $Ca^{2+}$ homeostasis, depletion of GLUT-1 and -4, increased ROS and inflammation, disregulated miRNA and exosomes | Steatosis | / | Diastolic dysfunction with normal EF, mild decrease in systolic strain of both atria and ventricles | Increased LV mass, decreased tissue velocities | / | LGE ,$^{1}$H-Spectroscopy, and $^{31}$P-Spectroscopy |
| | | Stage B (systolic and diastolic dysfunction) | Stage A mechanisms + Acticated RAAS, cytokine damage (reduced IGF-I and increased TGF-β1), hyperglycemia, AGE formation, insulin resistance | Apoptosis, necrosis, and fibrosis | loss of cardiac metabolic flexibility | Combined systolic and diastolic dysfunction, right and left atrial and ventricular involvement | Increased LV wall thickness and mild cavity dilatation | Mild CAN | LGE, $^{1}$H-Spectroscopy, and $^{31}$P-Spectroscopy |
| | | Stage C (mild complications) | Stage A and Stage B mechanisms + microvascular changes | Apoptosis, necrosis, and fibrosis | Overt DM | Diastolic dysfunction, systolic dysfunction, decreased LVEF, and pulmonary hypertension | Concentric hypertrophy or indeterminate hypertrophy (magnification) or | Microvascular disease/coronary atherosclerosis without obstructive | LGE, $^{1}$H-Spectroscopy, and $^{31}$P-Spectroscopy |

*(Continued)*



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TABLE 5 Continued

| | Stages | Cellular mechanisms | Tissue and organ changes | Metabolism changes | Functional changes | Structural changes | Common complications | Means of auxiliary examination |
|---|---|---|---|---|---|---|---|---|
| | | | | | | eccentric hypertrophy, cavity dilatation, Abnormal EMB | CHD, HTA, severe CAN | |
| | Stage D (severe complications) | the same as Stage C mechanisms, but more severe | Apoptosis, necrosis, and fibrosis | Overt DM | Moderate-severe systolic dysfunction and biventricular refractory heart failure | Eccentric hypertrophy | Overt ischemia/ infarct causing HF, micro- and macroangiopathic complications (e.g. CHD and CKD), severe CAN | LGE, $^{1}$H-Spectroscopy, and $^{31}$P-Spectroscopy |
| Six-division | / | Hyperglycemia, insulin resistance, changed $Ca^{2+}$ homeostasis, increased ROS and inflammation, mitochondrial damage, cytokine damage, inactive iNOs, endothelial cell dysfunction, activated SNS and RAAS (before I stage) | Interstitial inflammation, interstitial fibrosis, cardiomyocyte hypertrophy, myocyte apoptosis and necrosis, cardiac stiffness, arterial stiffness and increase of afterload (I stage) | Changed FFA metabolism, accumulation of AGEs (I stage) | LV mechanical impairment (II stage); LV diastolic dysfunction (III stage); HFpEF (V stage); HFrEF (VI stage) | LV hypertrophy (IV stage) | / | Conventional echocardiography and CMR (II and III stages) |
| Double clinical phenotypes | HFpEF phenotype | Hyperglycemia, lipotoxicity, hyperinsulinemia, and insulin resistance | Coronary microvascular endothelial inflammation, coronary microvascular stenosis, stiff and hypertrophied cardiomyocyte with a high resting tension | Accumulation of AGEs, impaired glucose metabolism, collagen deposition | LV diastolic dysfunction | Concentric LV remodeling, normal-sized, hypertrophied, and stiff LV | / | / |
| | HFrEF phenotype | Autoimmunity, lipotoxicity, reactive interstitial fibrosis, replacement fibrosis, loss of sarcomeres | Cardiomyocyte apoptosis, cardiomyocyte necrosis, coronary microvascular stenosis | Accumulation of AGEs and collagen deposition | Diastolic dysfunction | Eccentric LV remodeling, enlarged LV | / | / |
| A hypothesis | Subclinical hyperfunction | Impaired mitochondrial metabolism, activation of RAAS, impaired collagen crosslinking, loss of t-tubule structure, impaired $Ca^{2+}$ sequestration of the sarcoplasmic reticulum, and oxidative stress | / | Formation of AGEs | Increased LV contractility and impaired diastolic function | Increased LV torsion and altered myocardial perfusion | / | Quantitative stress echocardiography |

AT, angiotensin; AGEs, advanced glycation end products; CAN, cardiac autonomic neuropathy; CHD, coronary heart disease; CKD, chronic kidney disease; CTA, computed tomography angiography; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; FFA, free fatty acid; GLUT, glucose transporter; HTA, arterial hypertension; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IVUS, intravascular ultrasound; IGF, insulin-like growth factors; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; PCr/ATP, phosphocreatine/adenosine triphosphate; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TGF-β, transforming growth factor beta.



10.3389/fendo.2022.1032268

- The myocardial energy metabolism substrates lose flexibility. Specifically, glucose uptake and utilization decrease, and fatty acid uptake and utilization increase, resulting in a large number of triglyceride deposition and a decrease in ATP production (144). Although the relationship between cardiac diastolic function and energy metabolism parameters is uncertain (30, 159), it has been confirmed that cardiac triglyceride deposition and myocardial energy damage are related to concentric LV remodeling and systolic dysfunction (138).
- Myocardial deformability decreases before diastolic dysfunction. Three layers of LV myocardium, including subendocardial (longitudinal fiber), medium (radial fiber), and subepicardial (circumferential fiber), are all damaged. Similar to the coronary ischemic myocardial injury (198), the damage to the subendocardial myocardium is the most serious, followed by the middle myocardium and the subepicardial myocardium (55). As for the left atrium, the function of all segments in the whole cardiac cycle is damaged (115). The unique feature of T1D is that the myocardial deformability of children is intact. The circumferential strain of the epicardium and middle layer and the longitudinal strain of the whole layer begins to decrease in late adolescence, followed by the decrease of conventional cardiac parameters years after (121).
- Remodeling involves in three chambers (left atrium, left and right ventricle), with systolic and diastolic function all impaired. LV remodeling is concentric hypertrophy characterized by an absolute and relative increase in LV wall thickness, increased LV mass (about 3.5 g) (136), and reduced LV cavity volume. RV remodeling is also restrictive, characterized by increased right ventricular stiffness and reduced right ventricular volume, similar to LV (143). In many diabetic patients, systolic and diastolic dysfunction often go hand in hand (103). In severe cases, LVEF and RVEF decreases.
- The epicardial adipose tissue becomes thickened.
- Myocardial perfusion decreases in both coronary artery and microvessels. This change is sufficient to be detected at rest and more obvious at stress (dobutamine and exercise).
- Cardiopulmonary function decreases, manifested as a decrease in myocardial oxygen uptake, and increase in oxygen consumption.

Except these alterations, the pulmonary artery adjacent to the RV is not spared. As early as 2005, the link between T2D and PAH (Pulmonary Artery Hypertension) had been demonstrated by an epidemiological study, showing an increased risk of PAH in diabetic patients independent of smoking, coronary heart disease, hypertension, or congestive heart failure (199). PAH is a disease characterized by pulmonary vascular remodeling, which

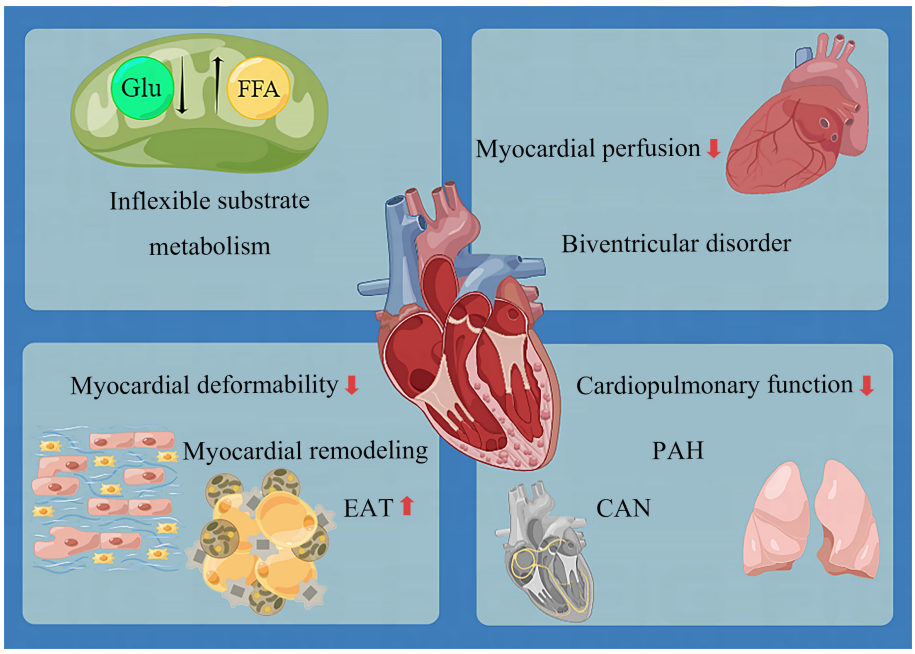


FIGURE 2
Overview of lesions in the development of DCM. CAN, cardiac autonomic neuropathy; EAT, epicardial adipose tissue; FFA, free fatty acid; Glu, glucose; PAH, pulmonary artery hypertension.

accelerates the pace of right heart failure by increasing the right ventricular afterload. Insulin resistance, frequently found in diabetic patients with increased pulmonary artery pressure, increases pulmonary stiffness and decreases pulmonary elasticity (48). The prognosis of PAH is poor, and the 10-year survival rate of PAH patients with diabetes is worse (200). DCM may be a cardiopulmonary disease to some extent. Unfortunately, interventions to improve RV function and prognosis in patients with DCM are yet to be studied.

DCM eventually develops into biventricular disorder (48, 201). Although the original research data on T1D are not as detailed as those of T2D, we can find that the cardiac phenotype changes of T1D and T2D are approximately the same. The only noteworthy finding was evidence of cardiac hyperdynamic contraction in T1D but not T2D; this may be attributed to the fact that the course of disease of patients included in T2D research is generally too long, and the opportunity to find this phenomenon is missed. In addition, only sporadic studies have focused on the exact changes in the heart of patients with pre-diabetes. More data accumulation is still needed to understand the impact of pre-diabetes on the heart.

Some scholars believe that DCM affects the whole heart (46). However, we are temporarily unable to decide the situation of right atrium (RA). Although some studies (202–204) found that DM causes RA volume expansion and systolic and diastolic function decline, the subjects were mixed with CAD or hypertension patients, making accurate judgments difficult. However, we confirm that the impact of diabetes on the heart will damage the heart metabolism, structure, function, perfusion, epicardium, and pulmonary vascular, which is comprehensive. In addition to the changes in the heart itself, DM will also cause a series of hematological changes, mainly on the entry of information substances secreted by the heart and other tissues into the plasma.

Another fact is that the pathogenesis of DCM includes CAN (14), making it difficult to separate these two diseases. There is evidence that in T2D patients with normal blood pressure, CAN precedes LVH and diastolic dysfunction, which is a very early change in the heart of DM (205). Furthermore, CAN is gradually aggravated parallel to the progression of cardiomyopathy. Because of the close relationship between nerve and muscle in the heart, the extent of CAN participation in DCM is worth exploring because it is related to the essence of DCM, either nerve-muscle or simple muscle disease.

## Diagnostic marker

### ECG

Changes in myocardial electrophysiology can be found in DCM patients, such as the prolongation of QT interval, the increase of QT dispersion, and T peak-Tend dispersion. These repolarization abnormalities represent the asynchronous myocardial movement and have been reported to reflect LVDD (130). However, ECG is not specific, making it difficult to diagnose DCM simply by ECG.

### Serum marker

Some new markers appear to be promising for use in clinical diagnosis and treatment. Fibrotic markers play a major role. The increase of active MMP-9 and MMP-7 and the decrease of TIMP-1/active MMP-9 ratio have been detected in DM-DD (diastolic dysfunction) (82). It was also found that serum PIP level was negatively correlated with A-Ar (estimated passive diastolic function) in early T2D, suggesting that fibrosis might indeed be the cause of diastolic dysfunction (83). Some other markers have also been studied. GDF-15 is a stress response cytokine that is elevated in asymptomatic DCM and significantly associated with E/e' (diastolic function index) (80). IGFBP-7 is expected to be a marker for DCM as it increased progressively in patients with DM, DM-DD, and DM-SD (systolic dysfunction) and did not increase in DD patients without diabetes (79). Another study confirmed that NLR was positively correlated with impaired LVDD and was an independent risk factor for subclinical DCM (77), but NLR is also well correlated with other diabetic complications (206). In addition, some crucial biomarkers deserve attention: FABP3, activin A, CT-1, YKL40, galectin-3, and FGF21. They are involved in various pathological mechanisms and have good early diagnostic potential (207).

In recent years, non-coding RNA has been developing rapidly in the field of diagnosis, but many original studies have focused on DM, and there are few studies on DCM markers (208). miRNAs are small non-coding RNAs responsible for post-transcriptional regulation of gene expression. miRNAs can be isolated from tissues and body fluids, and its level can be detected by qPCR, *in situ* hybridization array, and RNA sequencing (209). Two DCM-related miRNAs (Table 1) have been found. It is striking that one study seems to have found a specific lncRNA marker for DCM. Researchers reported that lncRNA NKILA was up-regulated in the plasma of DCM patients but not in patients with other complications (87). Plasma lncRNA NKILA mRNA levels six months before diagnosis were sufficient to screen DCM in DM patients. Eight years of follow-up research revealed that the expression of the lncRNA NKILA was specifically up-regulated when DCM was present. LncRNA NKILA is a molecule that promotes cardiomyocyte apoptosis, which may be involved in the occurrence and development of DCM and has a bright future in diagnosis or treatment (87).

Some argue that DCM cannot be diagnosed by a single serological marker, so a combination may be needed to solve this problem. Some researchers had begun to endeavor. A study showed that the AUCs of IL-6, TNF-α, and AGEs were 0.905, 0.845, and 0.807, respectively, which could not diagnose DCM.

However, the combination of these biomarkers significantly increased AUC to 0.924, with a sensitivity of 84.8% and a specificity of 88.2% (79). The union of TNF-α, AGEs, creatinine, and insulin helped diagnose DM-DD (AUC 0.913, specificity 100%) (79). Nevertheless, the combination of IL-6 and AGEs was found helpful for further differential diagnosis of DM-SD and DM-DD, with an AUC of 0.795 and sensitivity of 90.6%, which was significantly better than that of a separate diagnosis (79).

### Echocardiogram

In recent years, LV GLS has become the most commonly used strain value (117) for evaluating LV function in diabetic patients. GLS damage is likely the first ultrasonic sign of preclinical diabetic cardiomyopathy, confirmed in both T1D and T2D (98, 103). In theory, longitudinal myocardial fibers are more prone to ischemia and fibrosis because compensatory ventricular remodeling may increase short-axis function (210). A meta-analysis showed that (126) three-dimensional GLS was 2.4% lower in diabetic patients than in healthy controls, and it is the most obvious indicator of three-dimensional LV systolic strain in all directions. GLS can also be used to exclude DCM. The detection of NPV is up to 0.94 when joined with Gal-3 (81). It should not be ignored that LA strain has changed before LV strain changes, so as an early parameter, it may be more sensitive than LV strain for detecting early DCM (133); this is because LA is a fragile monolayer wall and is sensitive to subtle stimuli (211).

### Cardiac magnetic resonance

CMR is accurate for myocardial imaging. Furthermore, one-stop detection of DM heart may be realized in the future due to its excellent differential diagnosis ability of coronary atherosclerotic heart disease and lack of need for a contrast agent (212).

The participation of myocardial microvascular dysfunction in DCM remains uncertain because even ischemia has been excluded, obese patients are inevitably mixed in T2D, and it can also aggravate the adverse effect of diabetes on microvascular function. However, a new study has confirmed that, rather than BMI, HbA1c is the only independent risk factor for myocardial microvascular function in T2D patients (145). Myocardial microvascular dysfunction begins in the early stage of T2D and accumulates with the course extension. A CMR study has reported upslope, Max SI (max signal intensity), and TTM (time to maximum signal intensity) changes, which are indicators of coronary microcirculation impairment in T2D. Multivariate regression analysis shows that TTM and upslope are independently associated with longitudinal PSSR (peak systolic strain rate), suggesting that there might be a mechanical linkage between myocardial perfusion impairment and subclinical myocardial dysfunction in T2D patients (57).

As a result of the application of T1 mapping technology, interstitial fibrosis becomes easy to measure. The more severe interstitial fibrosis is, the worse LV diastolic function becomes (152). ECV can measure dilated ECM (extracellular matrix), so ECV can reflect myocardial fibrosis when there is no myocardial edema or protein deposition (150). The ECV value of diabetic patients has been proven significantly increased, especially those with poor blood glucose control (150). So it may be a sensitive parameter to detect early remodeling before dysfunction. A study between obese adolescents and healthy volunteers found that increased ECV occurred parallel with changes in LV mass and volume, but LV function remained unchanged (151).

As for T1D, researchers introduced a new CMR marker, DRF indice, which can detect ventricular diastolic efficiency and dynamic changes in the diabetic heart between 16-21 years old so that it may be a sensitive marker of cardiac dysfunction in adolescents (141). However, the study of CMR in T1D patients is still lacking.

The diagnostic marker of DCM should be a humoral or structural/functional indicator directly related to its pathogenesis and has good exclusiveness. Unfortunately, no mature auxiliary examination marker has been reliably tested in large clinical trials to diagnose DCM up to this point.

## Clinical treatment

### hypoglycemic drugs

For DCM treatment, people's first consideration is whether the hypoglycemic drugs can inhibit the process of impaired cardiac function in DM patients. However, the results are still a little far from satisfaction. Among conventional oral antidiabetic drugs, only gliclazide significantly reduced LVM (213), and their cardiac benefits are tiny (14).

Some scientists focused on DPP4i (sitagliptin, alogliptin, and saxagliptin). All three agents have been evaluated in large clinical trials, but they did not affect the composite primary outcome, which included cardiovascular (CV) mortality, nonfatal MI, and nonfatal stroke (214). As for the influence on DCM, Sitagliptin had a better hypoglycemic effect than voglibose, but it did not improve LV function in 24 weeks of treatment (178). While years later, another study showed that the addition of sitagliptin to the conventional hypoglycemic regimen for 24 months alleviated LVDD (179).

GLP-1RA (liraglutide, exenatide, semaglutide, lixisenatide, and dulaglutide) has attracted much attention as a new star, because it has been shown to have CV protective effects as well as weight loss (215), but its performance is mediocre in DCM. Liraglutide is an injection drug given once a day, whose 3-point MACE (major adverse CV events) benefits has been proved by LEADER trial (216). Two studies have shown that early application of liraglutide (for about six months) improved cardiac function (187, 188), and Liraglutide is more effective

than sitagliptin and linagliptin, both in terms of improving diastolic function and proteinuria (217). While another study has shown that the exact duration of liraglutide treatment did not improve cardiac function in patients (189). As for once-weekly Exenatide, who showed no influence on 3-point MACE (218), a study showed that it can improve cardiac function and reduce arterial stiffness, but it is not accompanied by an improvement in exercise capacity (185). However, there is also evidence that exenatide does not affect cardiac function, perfusion, or oxidative metabolism in T2D patients with LVSD (186). Despite Liraglutide seems a little better than Exenatide in CV effect, its frequent injections and increase of heart beats should not be ignored (219). But in any case, these drugs have a positive effect on coronary atherosclerotic events (215). Although not all five GLP-1RA have CV benefits, their CV safety is indisputable, so they are still worthy of consideration in obese DCM patients with mixed atherosclerotic disease.

Of note, SGLT-2i, which includes Dapagliflozin, Empagliflozin and Canagliflozin, have all been proved to help decrease the rate of CV events or heart failure and even death (220–222). When it comes to DCM, Dapagliflozin can prevent and reverse the development of ventricular remodeling (180, 181). The efficacy of Empagliflozin is diverse. 12 weeks' empagliflozin treatment not only enhances cardiac function, attenuates adverse remodeling, but also improves myocardial energy metabolism, which is not found in the other two (184). And another study showed that the earlier the intervention implements, the better the improvement in left ventricular diastolic and systolic function will be (183). There is a study which has shown that 3 months of canagliflozin treatment can improve left ventricular diastolic function, but it should be noted that the study population was mixed with ischemic heart disease patients, limiting the reference value (182).

Besides, both Dapagliflozin and Canagliflozin showed significant renal benefits (220, 221). It is highly likely that DCM is associated with renal injury because microalbuminuria is associated with early DCM as mentioned above, which makes these two drugs worthy of further investigation. By the way, a meta-analysis showed that the efficacy of SGLT-2i was sex specific, which reduces MACE better in men than in women. However, GLP-1RA did not show this difference (223). In general, SGLT-2i is more promising than GLP-1RA in DCM. Because the former has better performance in preventing heart failure and improving renal outcomes while similar to the latter in atherosclerotic benefits, and is injection-independent (224). In addition to this, GLP-1RA on top of SGLT-2i is a hopeful direction. Preliminary studies have shown that the combination of liraglutide and empagliflozin for 12 months significantly improves effective myocardial work and cardiac function in patients with type 2 diabetes mellitus in high CV risk. However, similar work needs to be done in patients excluding coronary heart disease and hypertension to determine whether the effect persists.

## Cardiovascular drugs

Although conventional cardiovascular drugs (ACEI, ARB, and β blocker) are widely used in the diabetic population, there is a lack of evidence regarding the clinical efficacy of DCM. But new heart failure drugs are likely to play an important role in DCM induced HFrEF in the near future. Large studies have shown that patients with combined use of new drugs (ARNi, β-blocker, MRA and SGLT2i) can delay 2.7 years (80 years) to 8.3 years (55 years) without death from cardiovascular disease or first hospitalization for heart failure, and increase life expectancy by 1.4 years (80 years) to 6.3 years (55 years), compared with conventional therapies (225). Notably, three large cohorts each had more than 30% of patients with DM, heralding a promising future for these agents in DM.

Sacubitril/valsartan inhibits neprilysin through its active metabolite of sacubitril, and at the same time blocks angiotensin II type 1 receptor through valsartan, which plays an anti-heart failure role. Sacubitril/valsartan reduced NT-proBNP to a greater extent than valsartan at 12 weeks and was well tolerated in patients with HFpEF (226). And the benefit of Sacubitril/valsartan is across all age groups from 18 to 96 years old (227). However, in patients with HFpEF (EF ≥45%), sacubitril/valsartan did not significantly reduce heart failure hospitalizations or cardiovascular mortality (228). Unexpectedly, the investigators also found a beneficial effect of sacubitril/valsartan on glycemic control. In patients with diabetes and HFrEF enrolled in the PARADIGM-HF study, long-term reductions in HBA1C and delayed time to initiation of oral glucose-lowering therapy were observed (229).

Vericiguat, approved by the U.S. FDA in 2021, is the first soluble guanylate cyclase (sGC) agonist for the treatment of patients with symptomatic HFrEF. Patients with chronic HFrEF who received vericiguat had a lower incidence of cardiovascular death or hospitalization for heart failure than those who received placebo (230). However, in patients with decompensated HFpEF, vericiguat treatment for 24 weeks did not improve activity tolerance and quality of life which were measured by KCCQ (231). The safety and tolerability profile of vericiguat were good when sacubitril/valsartan was used together for at least 3 months, suggesting that the combination may provide additional benefit (232).

Elevated resting heart rate is a risk factor for poor outcomes in heart failure (233). when heart rate is ≥70 beats/min, the risk of cardiovascular outcomes increases in patients with CAD and LVSD (234). This sparked scientists' interest in Ivabradine, a drug that lowers the heart rate. Ivabradine was shown to be effective and safe in patients with HFrEF regardless of diabetes status, and significantly reduced the primary composite endpoint (PCE) in both diabetic and non-diabetic patients (235). However, a randomized, double-blind, placebo-controlled trial found that heart rate reduction with ivabradine did not improve outcomes in HFpEF patients (236).

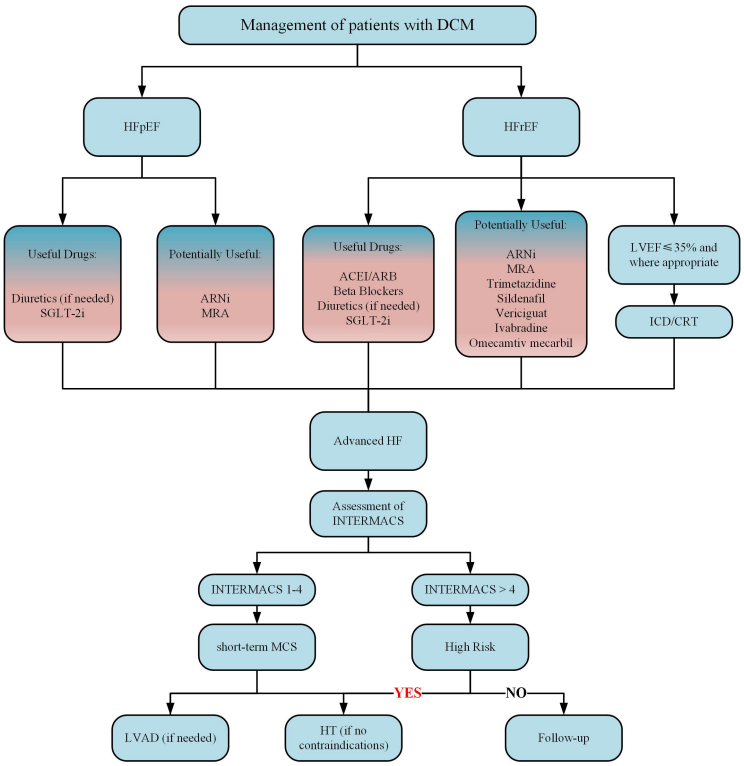


FIGURE 3
Treatment algorithm of DCM. ACEI, indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CRT, cardiac resynchronization therapy; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HT, heart transplant; ICD, implantable cardioverter-defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Omecamtiv mecarbil is the first potent cardiac myosin activator that can specifically activate the cardiac myosin S1 structure. A preclinical report has shown that it increases myocardial contractility without increasing myocardial oxygen consumption (237), and in clinical trials, it improved the composite rate of heart failure events or death from cardiovascular causes (238). The improvement of cardiac function by Omecamtiv was also very significant. Omecamtiv treatment for 20 weeks directly improved LV myocardial deformation in patients with HFrEF, whch means improved GLS by about 0.8%, and also improved GCS, while reducing heart rate and NT-proBNP concentrations, significantly increasing systolic ejection time, stroke volume, and reversing LV remodeling have been reported (239). Each 1% improvement in GLS is statistically associated with a 24% reduction in the risk of HF hospitalization and death (240). What's more, omecamtiv also results in a small reduction in heart rate (241). Unfortunately, omecamtiv did not improve exercise capacity compared with placebo over a period of 20 weeks in patients with chronic HFrEF (242).

Other than those, some non-classical cardiovascular drugs appear to show some different potential. The critical role of inflammatory cytokines in developing cardiovascular disease in individuals with and without diabetes is well established. A study has shown that trimetazidine treatment could significantly improve cardiac function and physical tolerance, accompanied by a reduction in inflammation (193), but it could not explain if there is a link between inflammation and the outcome. Another study found that sildenafil could control DCM progression by targeting IL-8 at the systemic and cellular levels (192). A previous study had also shown that sildenafil could achieve its anti-remodeling effect by reducing LV concentric hypertrophy in patients with early DCM (191). In addition, an aldosterone receptor antagonist, Spironolactone, has been proven to be failed to improve DCM's changes in myocardial structure and diastolic function (243).

According to the existing drug research results and HF guidelines (244, 245), we summarized a therapeutic algorithm (Figure 3). To date, neither the long-term survival problem caused by HFpEF nor the limitation of exercise in HF patients

can be improved by any drug. To make matters worse, no drug independently treats DCM as a primary role.

## Conclusion

As a complication of DM, DCM has been studied for 50 years. The vast accumulation of knowledge has painted the outline of DCM so humans can overlook the panorama of clinical phenotypes. More observational clinical studies are needed to continuously improve the undiscovered corners of DCM, correct previous studies' results, and explore indicators that can be used for accurate diagnosis. Screening criteria still need to be further defined, which is vital for finding high-risk populations of DCM. Nevertheless, it is gratifying that the diagnostic criteria have been established, which allows the real focus on implementing clinical intervention studies of DCM, even if the threshold is high. The accumulation of DCM research is significant. When achieving development of safe and effective diabetic cardiomyopathy drugs, whether combined with diabetes will affect the classification, diagnosis, and treatment of HF and change the dilemma that the prognosis of HF patients with diabetes is worse than that of HF patients alone. And the dawn will eventually come.

## Author contributions

XZ: Writing- Original draft preparation. SL: Writing-Reviewing and Editing. GF: Conceptualization, Methodology. BW: Supervision. XW: Software, Visualization. SW: Funding acquisition. PP, QY, SD and JL: Data curation. YC: Methodology. All authors contributed to the article and approved the submitted version.

## Funding

This work is supported by National Administration of Traditional Chinese Medicine (No: ZYYCXTD-D-202207, and National Chinese Medicine Education Letter [2022] No.75).

## 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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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 16 January 2023
DOI 10.3389/fendo.2022.1098012



OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

RECEIVED 14 November 2022
ACCEPTED 22 December 2022
PUBLISHED 16 January 2023

CITATION
Huang X, Qin C, Guo X, Cao F and Tang C (2023) Association of hemoglobin A1c with the incidence of hypertension: A large prospective study.
*Front. Endocrinol.* 13:1098012.
doi: 10.3389/fendo.2022.1098012



# Association of hemoglobin A1c with the incidence of hypertension: A large prospective study

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**Background:** Although hemoglobin A1c (HbA1c) is closely related to diabetes, its relationship with the incidence of hypertension is still unknown, so we aimed to evaluate the relationship between HbA1c and the incidence of hypertension in the general population.

**Method:** In this large prospective cohort study with a median follow-up of 2 years, we included 4,074 participants from the China Health and Nutrition Survey (CHNS). Multivariate COX regression, subgroup analysis, receiver operator characteristic (ROC) curve and restricted cubic spline (RCS) were used to evaluate the relationship between HbA1c and incidental hypertension.

**Results:** Compared with participants without incident hypertension, participants with incident hypertension had higher levels of HbA1c ($P < 0.05$). In univariate COX regression analysis, HbA1c was associated with the risk of hypertension (HR: 1.161, 95% CI: 1.105-1.221, $P < 0.001$). In multivariate COX regression analysis adjusted for confounding variables, HbA1c was still closely related to the risk of hypertension (HR: 1.102, 95% CI: 1.006-1.206, $P = 0.037$). And subgroup analysis showed that the relationship between HbA1c and hypertension remained significant in female, lower than high school and non-obese subgroups ($P < 0.05$). ROC curve also showed that HbA1c could predict the risk of hypertension (AUC = 0.583, 95% CI: 0.568-0.598, $P < 0.001$). Further RCS analysis showed that HbA1c was positively correlated with the risk of hypertension (P for nonlinearity = 0.642).

**Conclusion:** HbA1c was linearly and positively associated with the incidence of hypertension.

KEYWORDS

glycated hemoglobin, hemoglobin A1c, hypertension, prevalence, incidence

# 1 Introduction

Currently, arterial hypertension (hereinafter referred to as hypertension) is a very common disease and one of the most important risk factors for cardiovascular disease and premature death (1). In 2 years, it is expected that more than 1.5 billion people will suffer from hypertension, which undoubtedly indicates that hypertension has gradually become a major global public health problem (2). The reasons for the dramatic increase in hypertension stem not only from an aging population, unhealthy lifestyles and unhealthy diets, but also from other metabolic problems, such as fluctuating blood glucose or diabetes (3).

Similar to hypertension, at present, diabetes is also a major global public health problem. In 2019, nearly 463 million people developed diabetes (9.3%), and this percentage is expected to rise by 0.9% and 1.6% by 2030 and 2045, respectively (4). As two major risk factors for cardiovascular disease and mortality, hypertension and diabetes tend to coexist in the same metabolically dysregulated individual and they share some common abnormal metabolic pathways, such as obesity, insulin resistance, inflammation and oxidative stress (5–7). Current evidence has shown that diabetes is closely related to hypertension (8, 9), while it is uncertain whether blood glucose fluctuations are associated with hypertension. Hemoglobin A1c (HbA1c) is not only one of the most important tools for diagnosing diabetes superior to fasting blood glucose, but also an indicator of blood glucose fluctuations and the efficacy of glycemic control over the last 3 months (10, 11). Although the relationship between HbA1c and cardiovascular disease and mortality has been reported in many studies (12–14), the research on its relationship with the prevalence and incidence of hypertension is still few and not unified. As mentioned earlier, the harm of hypertension and diabetes is great, so it is necessary to control the incidence of hypertension and diabetes to reduce the socio-economic burden and public health. HbA1c is not only a diagnostic factor of diabetes, but also has been proved to be closely related to cardiovascular disease and mortality. Assuming that there is a causal relationship between HbA1c and the incidence of hypertension, then controlling the level of HbA1c not only reduces the incidence of hypertension but also reduces the burden of diabetes, which is not only a treatment of killing two birds with one stone, but also has far-reaching significance in reducing the economic burden, the incidence of metabolic-related diseases and the reduction of premature death.

Therefore, in order to enrich this research area and provide more evidence for evidence-based medicine, this study aimed to explore the relationship between HbA1c and the incidence of hypertension in a general population in the Chinese community.

# 2 Subjects, materials and methods

## 2.1 Study population

This was a large prospective cohort study based on community populations, with all participants from the 2009 China Health and Nutrition Survey (CHNS 2009). After excluding individuals with baseline hypertension and those without HbA1c and follow-up data, a total of 4,074 individuals were enrolled in the study (Figure 1). The CHNS was approved by the institutional review committees at the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. Every participant signed a written informed consent form when participating in the CHNS, and the study protocol was carried out in accordance with the Declaration of Helsinki.

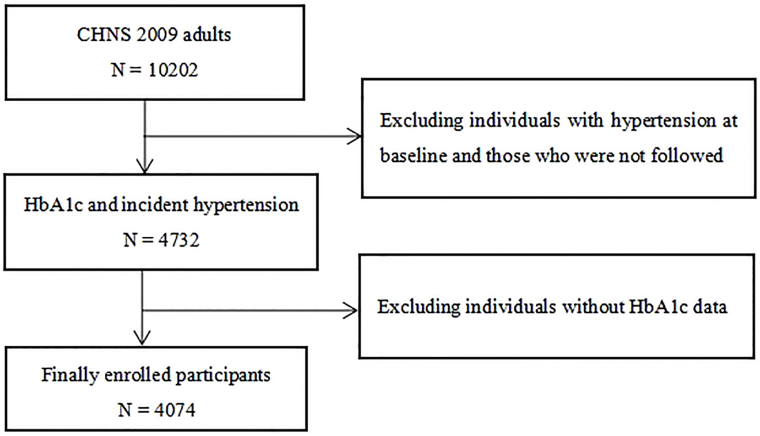


FIGURE 1
Flow chart of the study population. CHNS, China Health and Nutrition Survey; HbA1c, hemoglobin A1c.

## 2.2 Data collection and definitions

All the data included in this study were from CHNS 2009, including demographic data, complications data, drug treatment data, biomarker data and follow-up data, in which the educational level was divided into three groups: lower than high school, high school and higher than high school. Marital status was divided into two groups: married and non-married. Smoking status was divided into three groups: now, ever and never. Drinking status was divided into five groups: every day, 3-4 times/week, 1-2 times/week, ≤ 2 times/month and no drinking (15). Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L, HbA1c ≥ 6.5%, or using hypoglycemic drugs, or having a history of diabetes diagnosis (16). Incidental hypertension was defined as newly diagnosed hypertension when non-hypertensive individuals participating in CHNS 2009 re-participated in CHNS 2011 and 2015 by asking for medical history and blood pressure measurements, such as systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥ 140/90 mmHg. Anthropometric data, including body mass index (BMI), SBP, DBP, were measured by trained staff from CHNS in accordance with standard measurement procedures. Blood markers, including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), creatinine (CR), fasting plasma glucose (FPG), HbA1c and high-sensitivity C-reactive protein (Hs-CRP), were collected by trained CHNS staff and sent to a standard laboratory for determination according to standard operating procedures, of which HbA1c was determined by high performance liquid chromatography (model HLC-723 G7; Tosoh Corporation, Tokyo, Japan), and the levels of FPG, blood lipids and Hs-CRP were measured by GODPAP method (Randox Laboratories Ltd., UK), glycerol-phosphate oxidase method and the PEG-modified enzyme method (Kyowa Medex Co., Ltd, Tokyo, Japan), and immunoturbidimetric method (Hitachi 7600 automated analyzer, Hitachi Inc., Tokyo, Japan) respectively (17).

## 2.3 Statistical analysis

The continuous variables with normal or skewed distribution were expressed by mean ± standard deviation or median (first quartile, third quartile), respectively, and the differences between groups were tested by independent sample T test or Mann-Whitney U test. The classification variables were presented by frequency (percentage), and the differences between groups were compared by chi-square test and Fisher's exact test. Univariate COX regression analysis was used to evaluate the relationship between each variable and the incidence of hypertension, and then the covariates with P < 0.05 and significant variables were selected to construct a multivariate COX proportional hazard regression model to evaluate the relationship between HbA1c and the incidence of hypertension. Subgroup analysis based on age, sex, educational level, diabetes, and obesity was used to evaluate the relationship between HbA1c and the incidence of hypertension in these subgroups and the potential interaction between HbA1c and these stratified variables. Receiver operator characteristic (ROC) curve was used to evaluate the ability of HbA1c to distinguish hypertension. Restricted cubic spline (RCS) was used to explore the potential nonlinear association between HbA1c and the risk of hypertension. Using SPSS 26.0, MedCalc 19.6.1 and R 3.6.3 for statistical analysis. A two-tailed P value < 0.05 was determined to be statistically significant.

# 3 Results

## 3.1 Baseline characteristics of study population

As shown in Table 1, participants with incident hypertension had higher age, higher rates of education below high school, current smoking, daily alcohol consumption, diabetes, and hypoglycemic drugs use, and higher levels of BMI, SBP, DBP, TG, TC, LDL-C, ApoB, uric acid, FPG, Hs-CRP, and HbA1c compared with participants without incident hypertension (P < 0.05). However, there was no significant difference in marital status, HDL-C, ApoA1 and CR between the two groups (P > 0.05).

## 3.2 Association of HbA1c with the incidence of hypertension

As shown in Table 2, HbA1c was associated with the risk of hypertension in univariate COX regression analysis (HR: 1.161, 95% CI: 1.105-1.221, P < 0.001), and age, sex, educational level, smoking status, drinking status, diabetes, hypoglycemic drugs, BMI, SBP, DBP, TG, TC, LDL-C, ApoB, CR, uric acid, FPG and Hs-CRP were also associated with the risk of hypertension (P < 0.05). In multivariate COX regression analysis, higher HbA1c was still associated with higher risk of hypertension after adjusting for age, sex, educational level, marital status, smoking status, drinking status, diabetes, hypoglycemic drugs, BMI, SBP, DBP, TG, TC, LDL-C, ApoB, CR, uric acid, FPG and Hs-CRP (HR: 1.102, 95% CI: 1.006-1.206, P = 0.037). And in the subgroup analysis of Table 3, the association was still significant in women, lower than high school and non-obese subgroups (HR: 1.158, 95% CI: 1.007-1.331, P = 0.039; HR: 1.127, 95% CI: 1.022-1.243, P = 0.017; HR: 1.073, 95% CI: 1.007-1.142, P = 0.029; respectively), whlie

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the relationship between HbA1c and new-onset hypertension no longer existed in the subgroups of < 60 years, ≥ 60 years, male, high school, higher than high school, diabetes, non-diabetes and obesity (P > 0.05). In addition, ROC analysis showed that HbA1c could predict the occurrence of hypertension (AUC = 0.583, 95% CI: 0.568-0.598, P < 0.001) (Figure 2). Further RCS analysis showed that there was a positive linear correlation between HbA1c and the risk of hypertension (P for nonlinearity = 0.642) (Figure 3). In addition, as shown in Table 4, we conducted a sensitivity analysis showing that higher HbA1c was still associated with a higher risk of hypertension (P < 0.05).

TABLE 1 Baseline characteristics of participants stratified by the hypertension.

| | Total population | Non-hypertension | Hypertension | P value |
|---|---|---|---|---|
| Age, years | 48.25 ± 13.14 | 45.80 ± 12.82 | 53.13 ± 12.39 | < 0.001 |
| Sex, male, n (%) | 1868 (45.90%) | 1195 (44.10%) | 673 (49.40%) | 0.001 |
| Educational level, n (%) | | | | < 0.001 |
| Lower than high school | 3139 (77.00%) | 2037 (75.10%) | 1102 (80.90%) | |
| High School | 499 (12.20%) | 350 (12.90%) | 149 (10.90%) | |
| Higher than high school | 431 (10.60%) | 321 (11.80%) | 110 (8.10%) | |
| Marital status, n (%) | | | | 0.769 |
| Married | 3630 (89.10%) | 2411 (88.90%) | 1219 (89.50%) | |
| Non-married | 436 (10.70%) | 295 (10.90%) | 141 (10.40%) | |
| Smoking status, n (%) | | | | 0.035 |
| Now | 1170 (28.70%) | 750 (27.70%) | 420 (30.80%) | |
| Ever | 98 (2.40%) | 58 (2.10%) | 40 (2.90%) | |
| Never | 2804 (68.80%) | 1902 (70.10%) | 902 (66.20%) | |
| Drinking status, n (%) | | | | < 0.001 |
| Every day | 369 (9.10%) | 205 (7.60%) | 164 (12.00%) | |
| 3-4 times/week | 181 (4.40%) | 110 (4.10%) | 71 (5.20%) | |
| 1-2 times/week | 325 (8.00%) | 203 (7.50%) | 122 (9.00%) | |
| ≤ 2 times/month | 475 (11.70%) | 345 (12.70%) | 130 (9.50%) | |
| No drinking | 2724 (66.90%) | 1849 (68.20%) | 875 (64.20%) | |
| Diabetes, n (%) | 309 (7.60%) | 168 (6.20%) | 141 (10.40%) | < 0.001 |
| Hypoglycemic drugs, n (%) | 47 (1.20%) | 21 (0.80%) | 26 (1.90%) | 0.004 |
| BMI, $kg/m^2$ | 22.98 ± 3.23 | 22.58 ± 3.09 | 23.78 ± 3.35 | < 0.001 |
| SBP, mmHg | 116.60 ± 11.23 | 114.45 ± 11.03 | 121.05 ± 10.30 | < 0.001 |
| DBP, mmHg | 76.01 ± 7.46 | 74.89 ± 7.51 | 78.35 ± 6.78 | < 0.001 |
| TG, mmol/L | 1.19 (0.81, 1.81) | 1.13 (0.78, 1.72) | 1.33 (0.91, 2.02) | < 0.001 |
| TC, mmol/L | 4.80 ± 0.96 | 4.73 ± 0.93 | 4.95 ± 1.01 | < 0.001 |
| LDL–C, mmol/L | 2.93 ± 0.91 | 2.87 ± 0.86 | 3.05 ± 1.01 | < 0.001 |
| HDL–C, mmol/L | 1.45 ± 0.46 | 1.45 ± 0.47 | 1.44 ± 0.44 | 0.442 |
| ApoA1, g/L | 1.15 ± 0.37 | 1.15 ± 0.35 | 1.17 ± 0.41 | 0.074 |
| ApoB, g/L | 0.89 ± 0.25 | 0.87 ± 0.24 | 0.93 ± 0.26 | < 0.001 |
| CR, umol/L | 86.20 ± 21.32 | 85.83 ± 23.52 | 86.94 ± 16.05 | 0.118 |

*(Continued)*

TABLE 1 Continued

| | Total population | Non-hypertension | Hypertension | P value |
|---|---|---|---|---|
| Uric acid, umol/L | 299.12 ± 100.95 | 294.89 ± 103.64 | 307.54 ± 94.82 | < 0.001 |
| FPG, mmol/L | 5.28 ± 1.29 | 5.18 ± 1.15 | 5.46 ± 1.51 | < 0.001 |
| HbA1c, % | 5.54 ± 0.78 | 5.47 ± 0.68 | 5.68 ± 0.94 | < 0.001 |
| Hs-CRP, mg/L | 1.00 (0, 2.00) | 1.00 (0, 2.00) | 1.00 (1.00, 2.75) | < 0.001 |
| Follow-up time, years | 2.00 (2.00, 6.00) | 2.00 (2.00, 2.00) | 6.00 (2.00, 6.00) | < 0.001 |

Data were expressed as mean ± SD, median (interquartile range), or n (%). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CR, creatinine; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; Hs-CRP, high-sensitivity C-reactive protein.

TABLE 2 Univariate and multivariate COX regression analysis of incident hypertension.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Age | 1.025 (1.020, 1.029) | < 0.001 | 1.022 (1.017, 1.027) | < 0.001 |
| Male | 1.135 (1.021, 1.263) | 0.019 | 1.081 (0.914, 1.279) | 0.361 |
| Higher than high school | 0.737 (0.606, 0.897) | 0.002 | 0.809 (0.662, 0.989) | 0.038 |
| Married | 0.964 (0.810, 1.148) | 0.684 | 0.925 (0.774, 1.105) | 0.389 |
| Smoking status: Never | 0.888 (0.791, 0.997) | 0.045 | 0.941 (0.811, 1.091) | 0.420 |
| Drinking status: No drinking | 0.776 (0.657, 0.917) | 0.003 | 0.899 (0.743, 1.087) | 0.270 |
| Diabetes | 1.390 (1.168, 1.655) | < 0.001 | 0.889 (0.696, 1.135) | 0.346 |
| Hypoglycemic drugs | 1.712 (1.161, 2.523) | 0.007 | 1.151 (0.738, 1.796) | 0.534 |
| BMI | 1.048 (1.031, 1.066) | < 0.001 | 1.039 (1.020, 1.058) | < 0.001 |
| SBP | 1.032 (1.026, 1.038) | < 0.001 | 1.010 (1.004, 1.016) | 0.001 |
| DBP | 1.035 (1.026, 1.045) | < 0.001 | 1.009 (0.999, 1.018) | 0.064 |
| TG | 1.056 (1.022, 1.091) | 0.001 | 1.027 (0.972, 1.084) | 0.349 |
| TC | 1.115 (1.058, 1.176) | < 0.001 | 0.982 (0.874, 1.103) | 0.754 |
| LDL−C | 1.085 (1.030, 1.143) | 0.002 | 0.992 (0.877, 1.123) | 0.902 |
| HDL−C | 0.971 (0.864, 1.092) | 0.626 | | |
| ApoA1 | 1.077 (0.961, 1.208) | 0.203 | | |
| ApoB | 1.610 (1.312, 1.976) | < 0.001 | 1.133 (0.720, 1.783) | 0.588 |
| CR | 1.002 (1.000, 1.004) | 0.033 | 1.000 (0.996, 1.004) | 0.987 |
| Uric acid | 1.001 (1.000, 1.001) | 0.007 | 1.000 (0.999, 1.001) | 0.840 |
| FPG | 1.075 (1.041, 1.111) | < 0.001 | 0.984 (0.929, 1.043) | 0.590 |
| Hs-CRP | 1.010 (1.004, 1.016) | 0.002 | 1.005 (0.997, 1.012) | 0.208 |
| HbA1c | 1.161 (1.105, 1.221) | < 0.001 | 1.102 (1.006, 1.206) | 0.037 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CR, creatinine; FPG, fasting plasma glucose; Hs-CRP, high-sensitivity C-reactive protein; HbA1c, hemoglobin A1c; HR, hazard ratio; CI, confidence interval.

TABLE 3 Subgroups analyses for the association between HbA1c and the incidence of hypertension.

| | HR (95% CI) | P value | P for interaction |
|---|---|---|---|
| Age | | | 0.270 |
| < 60 years | 1.082 (0.961, 1.217) | 0.191 | |
| ≥ 60 years | 1.139 (0.979, 1.324) | 0.092 | |
| Sex | | | 0.672 |
| Male | 1.062 (0.938, 1.201) | 0.342 | |
| Female | 1.158 (1.007, 1.331) | 0.039 | |
| Educational level | | | 0.901 |
| Lower than high school | 1.127 (1.022, 1.243) | 0.017 | |
| High School | 0.981 (0.671, 1.434) | 0.921 | |
| Higher than high school | 0.922 (0.627, 1.355) | 0.678 | |
| Diabetes | | | 0.925 |
| Yes | 1.119 (0.972, 1.290) | 0.118 | |
| No | 1.096 (0.954, 1.259) | 0.197 | |
| Obesity | | | 0.423 |
| Yes | 1.307 (0.881, 1.938) | 0.183 | |
| No | 1.073 (1.007, 1.142) | 0.029 | |

The multivariate adjusted model used in the subgroups analysis consisted of all covariates used in the multivariate adjusted models in Table 2 except for the variable (as a categorical variable) that was used for stratification. The HR was examined by per 1-unit increase of HbA1c. The interaction of HbA1c and variables used for stratification was examined by likelihood ratio tests. HbA1c, hemoglobin A1c; HR, hazard ratio; CI, confidence interval.

## 4 Discussion

Although there is evidence that HbA1c is associated with hypertension, the relationship between them in people from CHNS is unknown. In this large prospective cohort study, we not only confirmed that HbA1c was closely related to the incidence of hypertension during follow-up, but also confirmed that this significant correlation still existed in women, lower than high school and non-obese subgroups, and further confirmed that there was a linear positive correlation between HbA1c and the risk of hypertension, which not only filled the knowledge gap of CHNS, but also stabilized the stability of the relationship between HbA1c and hypertension in Chinese population.

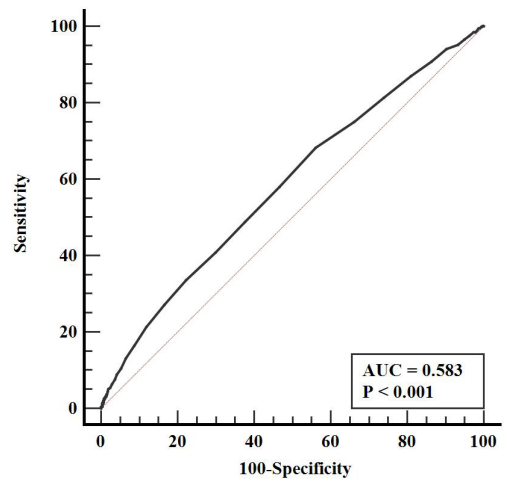


FIGURE 2
ROC curve evaluating diagnostic performance of HbA1c for incident hypertension. HbA1c, hemoglobin A1c; ROC, receiver operator characteristic; AUC, area under the curve.

Although our study had made meaningful findings, there are still few studies on the relationship between HbA1c and hypertension and no unified conclusion has been reached. For example, Britton et al. found in a large prospective cohort study of 19,858 women in 2011 that higher HbA1c was closely associated with the risk of developing hypertension during an average follow-up period of 11.6 years, while this correlation could not be independent of BMI (18). A large longitudinal study from Japan also found no independent association between HbA1c and future new-onset hypertension (19). The evidence from a large medical center also only revealed the relationship between fasting blood glucose and the incidence of hypertension in prediabetes, and did not confirm the independent predictive effect of HbA1c on the incidence of hypertension (20). Similar to the above studies, Tatsumi et al. also only found an independent predictive effect of fasting blood

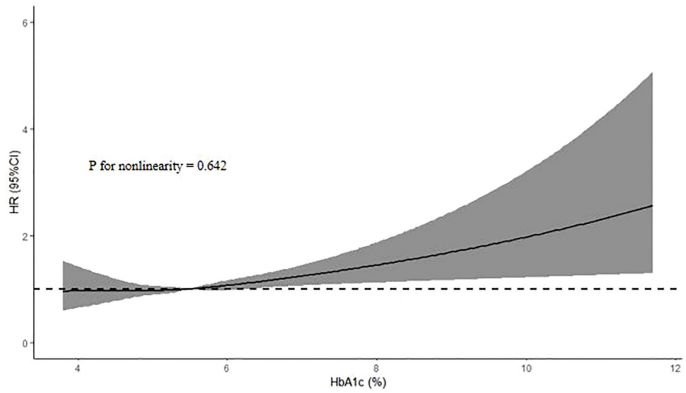


FIGURE 3
HR (95% CI) for the incidence of hypertension according to HbA1c. The association was adjusted for variables included in the multivariate adjusted models in Table 2. HbA1c, hemoglobin A1c; HR, hazard ratio; CI, confidence interval.

glucose on new-onset hypertension in the cohort from Japan, and failed to confirm the independent correlation between HbA1c and new-onset hypertension (21). A Mendelian randomized study showed that in a univariate linear Mendelian random analysis, each 1 mmol/mol increase in HbA1c predicted by the gene increased the risk of hypertension by 2%, but this correlation no longer existed after adjusting for hemoglobin (22). Besides, another multicenter clinical study from China showed that the higher baseline HbA1c was not an independent risk factor for the incidence of hypertension in the multivariate adjusted model, while the absolute rate of change in HbA1c levels was independently associated with the risk of hypertension (23). However, Omar et al. confirmed a positive correlation between HbA1c levels and the risk of newly diagnosed hypertension in a small cross-sectional study (24). And in a study involving 9,603 middle-aged people, Julie et al. showed that higher HbA1c was not only independently associated with the prevalence of hypertension, but also with the incidence of hypertension (25). And a Mendelian randomized study using the UK Biobank data showed that higher HbA1c was not only closely associated with the risk of hypertension, but also positively correlated with SBP (26). Furthermore, Song et al. not only confirmed a strong correlation between HbA1c and the risk of hypertension in a Chinese population, but also unexpectedly found that it could also increase the risk of isolated systolic hypertension (27). Thus it can be seen that the relationship between HbA1c and the prevalence and incidence of hypertension has not reached a unified conclusion, and the causal relationship between HbA1c and hypertension has not been determined. What is encouraging is that our study found meaningful results that higher HbA1c was closely associated with a higher risk of hypertension, independent of traditional cardiovascular risk factors, including age, SBP, and BMI. In addition, The annual incidence of hypertension in this study was 10%, while the annual incidence of hypertension in the cohort study conducted by Lou et al. was 2.64% (28), and the probability in the study conducted by Heianza et al. was 2.29% (19). It can be seen that the incidence of hypertension in our study participants was higher than that in other studies, which was mainly related to the heterogeneity of the study population, and their study participants are mainly people without diabetes, which means that the cardiovascular metabolic risk of these people is relatively low, so the incidence of hypertension is relatively low.

In addition to hypertension, some studies have also shown that HbA1c is not only closely related to cardiovascular disease and poor cardiovascular outcomes (12–14, 22), but also inextricably related to all-cause mortality (14). These findings suggest that controlling HbA1c in the best range can not only reduce the incidence of diabetes, but also reduce the incidence of diabetic complications, cardiovascular disease morbidity, cardiovascular mortality and all-cause mortality, and further reduce the socio-economic burden and the health burden of the people, which is undoubtedly a great blessing for public health problems.

Additionally, not only the association between HbA1c and hypertension has not been agreed, but also the pathological mechanism of the harmful effects of higher HbA1c on hypertension is still unknown. There may be the following mechanisms involved in the pathogenic effect of HbA1c on hypertension. For example, higher HbA1c often reflects insulin resistance, and there is evidence that insulin resistance can promote the release of inflammatory factors, which in turn leads to endothelial dysfunction and the increase of sympathetic nerve tension, and may accelerate the reabsorption of sodium and water by renal tubules at the same time, eventually leading to the occurrence and development of hypertension (29–31). In addition, high HbA1c can reflect the state of continuously rising blood

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TABLE 4 Sensitivity analysis for the association between HbA1c and the incidence of hypertension.

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | HR (95% CI) | P value | HR (95% CI) | P value |
| Age | 1.022 (1.018, 1.027) | < 0.001 | 1.023 (1.019, 1.028) | < 0.001 |
| Male | 1.081 (0.929, 1.258) | 0.315 | 1.153 (1.036, 1.285) | 0.009 |
| Higher than high school | 0.804 (0.658, 0.983) | 0.033 | | |
| Married | 0.927 (0.776, 1.107) | 0.401 | | |
| Smoking status: Never | 0.944 (0.814, 1.095) | 0.446 | | |
| Drinking status: No drinking | 0.893 (0.738, 1.080) | 0.242 | | |
| Diabetes | 0.889 (0.696, 1.135) | 0.345 | 0.899 (0.708, 1.142) | 0.382 |
| Hypoglycemic drugs | 1.136 (0.729, 1.771) | 0.574 | | |
| BMI | 1.040 (1.022, 1.059) | < 0.001 | 1.040 (1.022, 1.058) | < 0.001 |
| SBP | 1.010 (1.004, 1.016) | 0.001 | 1.010 (1.004, 1.016) | 0.001 |
| DBP | 1.009 (0.999, 1.018) | 0.064 | 1.009 (1.000, 1.018) | 0.059 |
| TG | 1.022 (0.973, 1.073) | 0.389 | 1.023 (0.973, 1.074) | 0.376 |
| TC | 0.981 (0.873, 1.101) | 0.743 | 0.990 (0.881, 1.112) | 0.862 |
| LDL−C | 0.988 (0.872, 1.119) | 0.848 | 0.986 (0.867, 1.121) | 0.832 |
| HDL−C | | | | |
| ApoA1 | | | | |
| ApoB | 1.144 (0.729, 1.795) | 0.559 | 1.102 (0.702, 1.731) | 0.674 |
| CR | | | | |
| Uric acid | | | | |
| FPG | 0.987 (0.932, 1.045) | 0.652 | 0.988 (0.933, 1.046) | 0.669 |
| Hs-CRP | | | | |
| HbA1c | 1.100 (1.006, 1.204) | 0.037 | 1.101 (1.007, 1.205) | 0.035 |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; CR, creatinine; FPG, fasting plasma glucose; Hs-CRP, high-sensitivity C-reactive protein; HbA1c, hemoglobin A1c; HR, hazard ratio; CI, confidence interval.

glucose, while persistently high glucose may induce the formation of advanced glycation end products, promote oxidative stress and activate protein kinase, thus damaging the stability and balance of endothelial cells and smooth muscle cells, leading to hypertension (32–35).

Despite our valuable results, there were several limitations that warrant discussion. First, although this was a prospective cohort study, it was still an observational study, so the causal link between HbA1c and hypertension was unknown in this population. Second, because the variable of physical activity was missing more in our study, we did not include this variable in our analysis and could not determine the extent of its effect on the association between HbA1c and hypertension. Third, due to the limitations of the data, we were unable to evaluate the effects of chronic kidney disease and hypothyroidism on the association between HbA1c with hypertension. Additionally, since HbA1c was measured only once at baseline, it was not possible to evaluate the impact of the trajectory of HbA1c change on hypertension. Besides, because our study lacked the variable of family history of hypertension, we were unable to evaluate the effect of family history of hypertension on the association between HbA1c and hypertension risk. And in this study, the annual incidence of hypertension was higher than that of other studies, so according to the epidemiological diagnostic criteria, the incidence of hypertension might not be so accurate. Finally, since all participants were from the CHNS, there was no systematic assessment of the causes of hypertension, so secondary hypertension could not be ruled out.

## 5 Conclusion

In this prospective cohort study from Chinese population, we found that there was a close linear positive correlation between HbA1c and the risk of hypertension, which not only further strengthened the close relationship between blood glucose fluctuation and the risk of hypertension, but also reminded us to pay attention not only to the traditional risk factors of hypertension, but also to the effect of blood glucose fluctuation on blood pressure level or hypertension.

## 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 human participants were reviewed and approved by institutional review committees at the University of North Carolina at Chapel Hill and the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

XH conceived, designed the study. CQ contributed to initial data analysis and interpretation. XH and XG drafted the initial manuscript. CQ, FC, and CT revised the manuscript. FC and CT were the guarantor of this work and had full access to all the data in the study and take responsibility for its integrity and the accuracy of the data analysis. All authors read and approved the final manuscript.

## Funding

This work was supported by the National Natural Science Foundation of China (81820108019, and 91939303), Innovative Project of Chinese PLA General Hospital (CX19028), Key Health Care Projects of National Health Commission (2020ZD05), Basic Research Reinforcement Project (2021-JCJQ-JJ-1079). National Key Research and Development Projects (2022YFC3602400); the Key Health Care Projects of National Health Commission (2020ZD05); Basic Research Reinforcement Project (2022-JCJQ-ZD-079-00), and Project of National Clinical Research Center for Geriatric Diseases (NCRCG-PLAGH-2022007).

## Acknowledgments

This research uses data from China Health and Nutrition Survey (CHNS). We are grateful to research grant funding from the National Institute for Health (NIH), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) for R01 HD30880, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for R01DK104371 and R01HL108427, the NIH Fogarty grant D43 TW009077 for financial support for the CHNS data collection and analysis files since 1989, and the China-Japan Friendship Hospital, Ministry of Health for support for CHNS 2009, Chinese National Human Genome Center at Shanghai since 2009, and Beijing Municipal Center for Disease Prevention and Control since 2011. We thank the National Institute for Nutrition and Health, China Center for Disease Control and Prevention, Beijing Municipal Center for Disease Control and Prevention, and the Chinese National Human Genome Center at Shanghai.

## 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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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 29 June 2023
DOI 10.3389/fendo.2023.1218905



OPEN ACCESS

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RECEIVED 08 May 2023
ACCEPTED 15 June 2023
PUBLISHED 29 June 2023

CITATION
Liu Z, Huang Q, Deng B, Wei M, Feng X, Yu F, Feng J, Du Y and Xia J (2023) Elevated Chinese visceral adiposity index increases the risk of stroke in Chinese patients with metabolic syndrome. *Front. Endocrinol.* 14:1218905. doi: 10.3389/fendo.2023.1218905



# Elevated Chinese visceral adiposity index increases the risk of stroke in Chinese patients with metabolic syndrome

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**Introduction:** Patients with Metabolic Syndrome (MetS) are considered at high-risk for incident stroke. An indicator of visceral adiposity dysfunction, the Chinese Visceral Adiposity Index (CVAI) is used to evaluate the dysfunction of visceral fat. Given the impact of visceral adiposity dysfunction on elevating cardiovascular hazards, this study aimed to examine the association between CVAI and stroke risk in MetS patients.

**Method:** Between November 2017 and December 2018, a total of 18,974 individuals aged ≥40 underwent standardized in-person clinical interviews in Hunan Province, with 6,732 meeting the criteria for MetS. After the baseline survey was completed, subsequent surveys were conducted biennially. The study was split into two stages performed at baseline and after two years. During the former, receiver-operating characteristic curves were used to assess the accuracy of using baseline CVAI in diagnosing MetS. After two years, we examined the association between CVAI and incident stroke in MetS patients using logistic regression, subgroup analysis, and restricted cubic spline (RCS) analysis.

**Result:** As evidenced by a higher AUC (AUC:0.741), CVAI demonstrated superior diagnostic performance relative to body mass index (AUC:0.631) and waist circumference (AUC:0.627) in diagnosing MetS. After a 2-year follow-up, 72 MetS patients had a stroke event. There was a robust positive correlation between incident stroke and CVAI in patients with MetS. Each 1 SD increase in CVAI was associated with a 1.52-fold higher risk of stroke after adjustment for confounding factors (aOR=1.52, 95%CI: 1.18-1.95). The RCS demonstrated a reduced risk of stroke for MetS patients when the CVAI was below 110.91. However, no significant correlation was detected between CVAI and stroke in non-MetS patients.

**Conclusion:** Our findings recommend CVAI as a superior screening tool for detecting MetS and suggest that reducing CVAI can mitigate the risk of stroke in patients with MetS.

KEYWORDS

Chinese visceral adiposity index, stroke, metabolic syndrome, obesity, visceral fat tissue

# 1 Introduction

Stroke ranks third in terms of morbidity and second in terms of disability-adjusted life-years worldwide (1, 2), resulting in an economic burden greater than 721 billion USD, which is equivalent to 0.66% of the global gross national product (3).

Due to an aging population, the stroke burden in China is escalating. In 2020, a nationwide survey of 676,394 adults aged ≥40 years revealed an estimated incidence and mortality rate for stroke of 502.2 per 100,000 person-years and 343.4 per 100,000 person-years, respectively (4). It is therefore important to identify effective primary prevention and early intervention strategies for stroke (5).

Metabolic syndrome (MetS) is an umbrella term that refers to multiple metabolic abnormalities, including hypertension, central obesity, impaired glucose regulation, and atherogenic dyslipidemia (6). The improvement in the general standard of living has accompanied a significant rise in the incidence of MetS (7), as well as a concomitant elevation in the risk of stroke (8–10).Identifying risk factors for incident stroke in patients with MetS would help to mitigate the anticipated rise in stroke burden resulting from the increased morbidity of MetS. As such, it is essential to identify the risk factors of incident stroke for MetS patients.

Adipose tissue is important not only for storing energy but also regulating endocrine function through the secretion of adipokines (11). Adipose tissue is categorized as either visceral fat tissue (VAT) or subcutaneous fat tissue (SAT) according to its location. The accumulation of VAT is strongly associated with increased cardiometabolic risk (12–15). The study conducted by Huang et al. demonstrated significant correlations between VAT mass and a wide range of CVD outcomes, including but not limited to coronary heart disease, cardiac arrhythmia, vascular diseases, and stroke (16). Additionally, another Mendelian Randomization Study furnished proof of a substantial causal link between VAT and ischemic stroke, as opposed to intracerebral hemorrhage (17). In general, visceral obesity is among the most evident clinical features of MetS (18). Obese patients with MetS have a higher risk of developing cardiovascular disease (CVD) than non-obese patients (19). However, whether a higher degree of visceral adiposity in MetS patients is associated with an increased risk of incident stroke remains poorly characterized.

At present, body mass index (BMI) and waist circumference (WC) are the most common methods for estimating adiposity and assessing central obesity in patients with MetS. However, these metrics are limited: BMI cannot distinguish between the accumulation of fat-free mass and fat, leading to the misdiagnosis of muscular individuals as overweight or obese (20); WC is marred by poor reliability and is inadequate for differentiating between subcutaneous and visceral fat (21). While more technologically advanced alternatives, such as magnetic resonance imaging and computed tomography, are considered gold standards, their technical complexity and high cost prohibit their use in routine clinical practice (22). The need for a reliable and low-cost indicator of visceral adiposity has prompted the development of novel indices based on combining anthropometric and biochemical assessments: e.g., the visceral adiposity index (VAI) and Chinese visceral adiposity index (CVAI) (23). In 2016, a CVAI was established that utilizes clinically available metabolic parameters, including age, BMI, WC, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) (24). CVAI is highly correlated with visceral fat area and outperforms BMI, WC, or VAI in the diagnosis of diabetes and hypertension among Chinese population (25, 26). Furthermore, elevated CVAI is significantly associated with increased risks of carotid plaque and CVD (27–29). Few studies, however, have investigated an association between CVAI and incident stroke in patients with MetS. To resolve this dearth in the literature, the present study investigates the relationship between CVAI and incident stroke in a Chinese population.

# 2 Materials and methods

## 2.1 Study design and population

The present study used patient data collected by the China Stroke High-risk Population Screening and Intervention Program (CSHPSIP): an ongoing population-based screening project conducted by the China Stroke Prevention Project Committee (30). The program aims to mitigate stroke risk by addressing the prevalence of stroke risk factors through screening, physical examination, and comprehensive interventions. The CSHPSIP enrolled community-dwelling adults who were (1) aged >40 years, (2) resided in the community for >6 months, and (3) provided informed consent (4). The protocol for the program were reviewed and approved by the Institutional Review Board at the Capital Medical University Xuanwu Hospital (No. 2012045).

The present study used data obtained from individuals residing in Hunan Province, a region featuring a relatively elevated incidence of stroke within China (4). 54338 individuals enrolled from twenty-six

communities (thirteen urban areas and thirteen rural areas) in the province were administered a baseline survey between January 2017 and December 2018. All eligible participants underwent standardized in-person clinical interviews. After the baseline survey was completed, subsequent surveys were conducted biennially.

A total of 20,487 respondents participated in the follow-up survey two years after completing the baseline survey. Individuals with incomplete sociodemographic information, missing anthropometric measures, or lacking laboratory assay results due to unsuccessful blood collection were excluded from the study.

Of the 18,974 participants included in the final analysis, 6,732 were diagnosed with MetS according to the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2020 edition). The criteria for defining the detailed components of MetS were as follows (31): (1) abdominal obesity, ascertained by a WC of ≥ 90 cm in males or ≥ 85 cm in females; (2) hypertension, defined as a blood pressure of ≥ 130/85 mmHg or a history of hypertension; (3) hyperglycemia, indicated by a fasting plasma glucose (FBG) level of ≥ 6.10 mmol/L, a 2-h plasma glucose level of ≥7.8 mmol/L, or a diagnosis of type 2 diabetes mellitus; (4) high TG, determined by a fasting TG level of ≥1.70 mmol/L; and (5) low HDL-C, indicated by an HDL-C level of ≤ 1.04 mmol/L. Patients who fulfilled any three of the aforementioned five criteria were diagnosed with MetS.

In parallel with the survey schedule, the study was split into two stages performed at baseline and after two years (Supplemental Figure 1). During the former, we examined the associations between baseline CVAI levels and MetS diagnosis, as well as assessed the diagnostic efficacy of CVAI in detecting MetS. After two years, we investigated the relationship between CVAI and incident stroke risk among patients diagnosed with MetS.

## 2.2 Baseline data collection and anthropometry measurements

Data on medical, socio-demographic, anthropometric, and lifestyle-related variables were obtained by trained interviewers or medical staff. Demographic information, including age, sex, education level, economic status, lifestyle risk factors (tobacco use, alcohol consumption, and physical activity), medical history (hypertension, diabetes mellitus, dyslipidemia, stroke, and atrial fibrillation), and family medical history of stroke was collected. Education level was classified as "primary school or below," "middle school," and "high school or above." Income was stratified as "<5000 Chinese Yuan (CNY)," "5000–9999 CNY," "10000–19999 CNY," and "≥20,000 CNY." The definition of alcohol consumption in this study was the regular intake of alcoholic beverages at a frequency of three or more times per week, with a minimum of 100 mL per drinking episode. Smoking was defined as the act of smoking continuously or cumulatively for a period exceeding six months. Physical inactivity refers to the absence of moderate-to-vigorous physical activity for >150 minutes/week or vigorous-intensity physical activity for >75 minutes/week (4). Diabetes was defined as a fasting plasma glucose level of ≥ 7.0 mmol/L (126 mg/dL), a previous diagnosis of diabetes mellitus, or the use of antidiabetic medication or insulin (32). Hypertension was defined as a blood pressure of ≥140/90 mmHg, a history of hypertension, or the use of antihypertensive medication (33). Dyslipidemia was defined as serum total cholesterol (TC) concentration ≥ 6.22 mmol/L (240 mg/dL), and/or low-density lipoprotein cholesterol (LDL-C) concentration ≥ 4.14 mmol/L (160 mg/dL), and/or TG concentration ≥ 2.26 mmol/L (200 mg/dL), and/or HDL-C concentration <1.04 mmol/L (40 mg/dL), or previous history of hyperlipidemia and currently taking lipid-lowering drugs (34). Atrial fibrillation was defined as electrocardiographic evidence of atrial fibrillation or treatment for atrial fibrillation.

Each participant underwent a physical examination conducted by a qualified nurse or physician. Height and weight were measured to a precision of 0.1 cm and 0.1 kg, respectively. BMI was calculated by dividing body mass (kilograms) by the height (meters) squared. The WC was measured to a precision of 0.1 cm at the highest point of the iliac crest during minimal respiration. In accordance with previous studies, general obesity was defined as a BMI of ≥25 kg/m$^2$ following Asian-specific criteria (35); abdominal obesity as a WC of ≥90 cm for men and a WC of ≥85 cm for women (31). Blood pressure was measured twice by an examining nurse or physician at an interval of 15 min. The average between the two measurements was used as the final datum.

## 2.3 Biochemical measurements

Blood samples were collected after an 8-hour fast and analyzed using the HP-AFS/3 automatic immunoassay system A3 Specific Protein Analyzer with supporting reagents (Shijiazhuang Hebo Biotechnology Co., Ltd., Shijiazhuang, China) on the same day of collection. The biochemical indicators assessed included fasting blood glucose (FBG), Hemoglobin A1c (HbA1c), TC, TG, LDL-C, and HDL-C.

## 2.4 Definition of CVAI

CVAI scores were computed using sex-specific formulas as follows (36):

Males: CVAI = −267.93 + 0.68 × age (years) + 0.03 × BMI (kg/m$^2$) + 4.00 × WC (cm) + 22.00 × log10(TG [mmol/L]) − 16.32 × HDL-C (mmol/L);

Females: CVAI= −187.32 + 1.71 × age (years) + 4.32 × BMI (kg/m$^2$) + 1.12 × WC (cm) + 39.76 × log10(TG [mmol/L]) − 11.66 × HDL-C (mmol/L).

## 2.5 Definition of outcome incident stroke

All incidents of stroke, including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, were documented during the survey period. The diagnosis of stroke was confirmed either through neurological imaging (brain computed tomography or magnetic resonance imaging) or a diagnosis certificate from a secondary or higher medical unit. However, due to limitations in data collection methods, we were unable to record the exact onset time of stroke.

## 2.6 Statistical analysis

All continuous variables were non-normally distributed and are presented as medians with interquartile ranges (IQR). Categorical variables are presented as percentages. The baseline characteristics of participants without MetS were compared to those of patients with MetS using the Mann-Whitney test for continuous variables and the Chi-square test for categorical variables. The baseline characteristics of MetS patients with and without stroke were analyzed in the same manner. Furthermore, to demonstrate the baseline characteristics of CVAI, we stratified patients into quartiles based on their initial CVAI levels. Differences in baseline variables between groups were assessed using either the Jonckheere-Terpstra trend test or the Chi-square test for trends.

Multivariate logistic regression models were used to assess the correlation between CAVI and MetS diagnosis. Various multivariable models with different levels of adjustment were employed. Model 1 incorporated individual characteristics, such as age, sex, education level, and economic status. Model 2 further included lifestyle risk factors, like smoking, alcohol consumption, and physical activity; medical history of hypertension, diabetes mellitus, dyslipidemia, and stroke; and family medical history of stroke. The variables included in the models all met the criteria of tolerance > 0.1 and variance inflation factor < 10. The diagnostic performance of CVAI in detecting MetS was compared with that of BMI and WC using receiver operating characteristic (ROC) curve analyses. In addition, we employed a restricted cubic spline to evaluate the dose-response relationship between CVAI and MetS (knots on the 5th, 25th, 75th, and 95th percentiles).

After a 2-year follow-up, multivariate logistic regression models were used to evaluate the correlation between stroke risk in MetS patients and CVAI, as well as other adiposity measures. The multivariable models were consistent with those described above. Model 1 contained individual characteristics (age, sex, education, economic status). Model 2 added lifestyle risk factors and medical history (smoking, alcohol drinking and physical activity, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, prior stroke, family medical history of stroke on the base of model 1. The odds ratio (OR) was calculated with a 95% confidence interval (CI) for the presence of incident stroke. The dose-response relationship between CVAI or other adiposity measures and stroke risk was evaluated with a restricted cubic spline. Subgroup analyses were further performed to investigate the relationship between CVAI and stroke in various subgroups based on age (≥60, <60 years), sex (male, female), diabetes (yes, no), hypertension (yes, no), dyslipidemia (yes, no), prior stroke (yes, no), current smoking status (yes, no), current drinking habits (yes, no), and physical activity level (lacking or not lacking exercise). The p-value for an interaction between a subgroup variable and CVAI was assessed in each subgroup analysis.

SPSS version 25.0 (IBM SPSS, Armonk, NY, USA) and R version 4.2.3 (R Development Core Team, Vienna, Austria) were used for all statistical analyses. A two-tailed P-value of <0.05 was considered to indicate statistical significance.

# 3 Results

## 3.1 Characteristics of the study participants

Of the 18,974 participants surveyed at both baseline and the two-year follow-up, 6732 were diagnosed with MetS at baseline. Table 1 outlines the demographic and clinical characteristics of these individuals. Notably, those with MetS had a significantly higher median CVAI compared to their non-MetS counterparts. Supplemental Table 1 presents the characteristics of all study participants stratified by CVAI quartile. The median CVAI for all study participants was 90.49 (IQR, 68.66–114.58).

## 3.2 Association between CVAI and MetS at baseline

As the CVAI increased, there was a corresponding increase in the prevalence of MetS (Figure 1A). Table 2 shows a correlation between CVAI and MetS. In the unadjusted model, for each additional SD increase in CVAI, the risk of MetS increased by 1.59. In all two adjusted models, CVAI demonstrated an independent association with MetS; the adjusted odds ratios are 2.68 (95% CI: 2.57-2.79), and 2.05 (95% CI: 1.95-2.16), respectively. When assessed as quartiles, CVAI was significantly associated with MetS in the second, third, and fourth quartiles—even after adjustment for all confounding factors (adjusted OR: 1.54, 95% CI: 1.34, 1.76; adjusted OR: 2.83, 95% CI: 2.48, 3.24; adjusted OR: 6.29, 95% CI: 5.47,7.23, respectively). Participants in the third and fourth CVAI quartiles were associated with a significantly higher risk of MetS compared to their counterparts in the first and second quartiles (adjusted OR: 3.13, 95% CI: 2.86, 3.44). Additionally, dose-response relationships between CVAI and MetS were evaluated by restricted cubic splines (Figure 1B). CVAI increases the risk of MetS when higher than 90.94.

ROC curve analysis was used to compare the diagnostic efficacy of CVAI with that of BMI and WC in detecting MetS (Figure 2). In the diagnosis of MetS, the CVAI demonstrated the highest AUC values (AUC: 0.741, 95% CI: 0.734-0.749), exceeding those of WC (AUC: 0.627, 95% CI: 0.619-0.635) and BMI (AUC: 0.631, 95% CI: 0.623-0.639). Table 3 presents the diagnostic performance of each anthropometric index in identifying MetS, encompassing sensitivity, specificity, and corresponding optimal cut-off values. CVAI exhibited the highest Youden indices (0.376) for identifying MetS, with an optimal cut-off of 99.15.

## 3.3 Comparison of baseline characteristics between MetS patients with and without stroke

Of the 6,732 patients with MetS, 72 experienced strokes during the two-year follow-up period; these individuals were more likely to be of advanced age and have a lower income at baseline relative to

10.3389/fendo.2023.1218905

TABLE 1 Baseline characteristics of all participants.

| Variable | Non-MetS (N=12242, 64.5%) | MetS (N=6732, 35.5%) | p value |
|---|---|---|---|
| Individual characteristics | | | |
| **Males, N (%)** | 5176 (42.3) | 3168 (47.1) | <0.0001 * |
| **Age, years** | 56 (49-66) | 61 (53-69) | <0.0001 * |
| **Education, N (%)** | | | <0.0001 * |
| Primary school or below | 4209 (34.4) | 2667 (39.6) | |
| Middle school | 4541 (37.1) | 2311 (34.3) | |
| High school or above | 3492 (28.5) | 1754 (26.1) | |
| **Annual Income, N (%)** | | | 0.002 * |
| <5000 CNY | 3097 (25.3) | 1770 (26.3) | |
| 5000-9999 CNY | 1379 (11.3) | 832 (12.4) | |
| 10000-19999 CNY | 1612 (13.2) | 935 (13.9) | |
| ≥20000 CNY | 6154 (50.3) | 3195 (47.4) | |
| Medical history and risk factor, N (%) | | | |
| Current smoking | 2435 (19.9) | 1567 (23.3) | <0.0001 * |
| Alcohol consumption | 1871 (15.3) | 1033 (15.3) | 0.911 |
| Physical inactivity | 3083 (25.2) | 1867 (27.7) | <0.0001 * |
| Hypertension | 2533 (20.7) | 4341 (64.5) | <0.0001 * |
| Diabetes | 1251 (10.2) | 2861 (42.5) | <0.0001 * |
| Dyslipidemia | 2528 (20.7) | 4410 (65.5) | <0.0001 * |
| Prior stroke | 293 (2.4) | 390 (5.8) | <0.0001 * |
| Family history of stroke | 1101 (9.0) | 803 (11.9) | <0.0001 * |
| General observation indexes | | | |
| SBP, mmHg | 123 (115-132) | 138 (130-150) | <0.0001 * |
| DBP, mmHg | 77(70-82) | 82 (76-90) | <0.0001 * |
| FBG, mmol/L | 5.02 (4.52-5.55) | 5.90 (4.99-7.59) | <0.0001 * |
| HbA1c, % | 5.30 (5.00-5.70) | 5.60 (5.10-6.70) | <0.0001 * |
| TG, mmol/L | 1.25 (0.98-1.55) | 2.05 (1.58-2.75) | <0.0001 * |
| TC, mmol/L | 4.62 (3.98-5.30) | 4.96 (4.20-5.67) | <0.0001 * |
| LDL-C, mmol/L | 2.56 (2.09-3.11) | 2.71 (2.10-3.29) | <0.0001 * |
| HDL-C, mmol/L | 1.37 (1.17-1.65) | 1.16 (0.97-1.43) | <0.0001 * |
| Indicators of adiposity | | | |
| BMI, $kg/m^2$ | 23.18 (21.39-24.98) | 24.54 (22.58-26.64) | <0.0001 * |
| WC, cm | 80.0 (76.0-86.0) | 84.0 (79.0-90.0) | <0.0001 * |
| CVAI | 80.89 (62.09-101.08) | 110.79 (88.45-133.32) | <0.0001 * |

MetS, metabolic syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin A 1c; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol; BMI, Body Mass Index, WC, waist circumferences, CVAI, Chinese visceral adiposity index. Statistical significance is considered at * $P < 0.05$.

those without a history of stroke. Hypertension, previous history of stroke, and family history of stroke were more prevalent among individuals with a stroke incident. Additionally, the stroke group exhibited significantly higher SBP levels, BMI, WC, and CVAI at baseline (Supplement Table 2).

Table 4 shows the characteristics of participants with MetS categorized by CVAI quartile. The median CVAI was 110.79 (IQR, 88.45–133.32). Participants in the upper CVAI quartile tended to be older, female, less educated, and have a higher income. They were also less physically active, and hypertension, dyslipidemia, prior

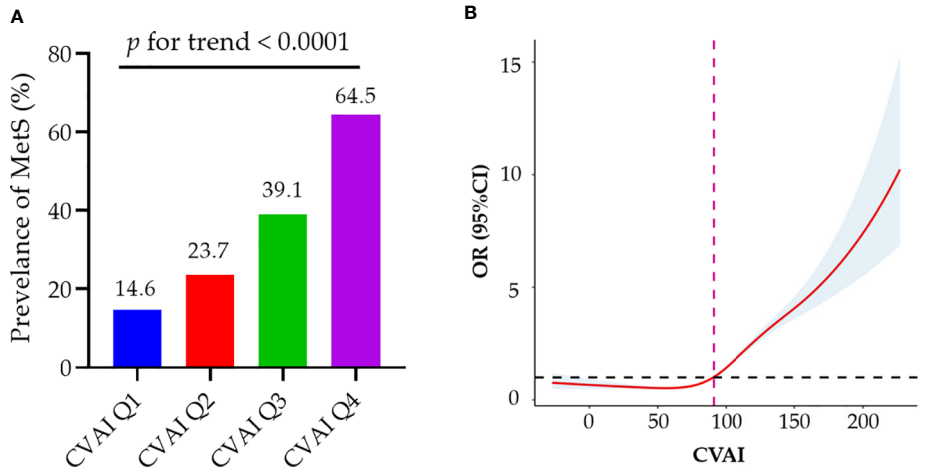


FIGURE 1
Associations of baseline CVAI with MetS. **(A)** As the CVAI increased, there was a corresponding rise in the prevalence of MetS; **(B)** Dose–response relationship of CVAI and MetS risk. CVAI could increase the risk of MetS when higher than 90.94. MetS, metabolic syndrome; CVAI, Chinese Visceral Adiposity Index; OR, odds ratio; CI, confidence interval.

stroke history, and family history of stroke were more prevalent among them. Furthermore, we observed a significant trend towards increasing SBP, TG, and TC levels, as well as decreasing HDL-C levels with increasing CVAI, among the participants who developed MetS.

## 3.4 Association between CVAI at baseline and incident stroke during the 2-year follow-up of MetS patients

There was a positive association between CVAI and the risk of incident stroke (Figure 3A). Table 5 presents the association between CVAI and incident stroke. In the unadjusted model, the risk of incident stroke increased by 64% (95% CI: 1.30, 2.06) for each SD of CVAI. In both adjusted model 1 and model 2, there was a significant association between the increase in CVAI and the occurrence of stroke, as evidenced by the adjusted ORs of 1.61 (95% CI: 1.26, 2.04) and 1.52 (95% CI: 1.18, 1.95), respectively. When assessing CVAI as quartiles, the associations between incident stroke and the second, third, and fourth CVAI quartiles were 3.22 (95% CI: 1.17-8.81), 4.04 (95% CI: 1.51-10.78), and 6.30 (95% CI: 2.44-16.24), respectively, relative to the first CVAI quartile. These association estimators did not change significantly after additional adjustment for individual

TABLE 2 Associations of baseline CVAI with MetS.

| Variants | No. of case (%) | Crude | | Model 1 [a] | | Model 2 [b] | |
|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | p Value | OR (95% CI) | p Value | OR (95% CI) | p Value |
| **Per SD increase** | | 2.59 (2.49-2.69) | <0.0001* | 2.68 (2.57-2.79) | <0.0001* | 2.05 (1.95-2.16) | <0.0001* |
| Quartiles | | | | | | | |
| Quartile 1 (< 68.66) | 694/4743 (14.6) | Reference | | Reference | | Reference | |
| Quartile 2 (≥ 68.66 & < 90.49) | 1126/4745 (23.7) | 1.82 (1.64-2.02) | <0.0001* | 1.88 (1.69-2.09) | <0.0001* | 1.54 (1.34-1.76) | <0.0001* |
| Quartile 3 (≥ 90.49 & < 114.58) | 1852/4741 (39.1) | 3.74 (3.39-4.13) | <0.0001* | 3.99 (3.60-4.43) | <0.0001* | 2.83 (2.48-3.24) | <0.0001* |
| Quartile 4 (≥ 114.58) | 3060/4745 (64.5) | 10.60 (9.59-11.71) | <0.0001* | 11.63 (10.44-12.96) | <0.0001* | 6.29 (5.47-7.23) | <0.0001* |
| *p* for trend | | | <0.0001* | | <0.0001* | | <0.0001* |
| Categories | | | | | | | |
| Quartile 1-2 (< 90.49) | 1820/9488 (19.2) | Reference | | Reference | | Reference | |
| Quartile 3-4 (≥ 90.49) | 4912/9486 (51.8) | 4.52 (4.24-4.83) | <0.0001* | 4.49 (4.19-4.82) | <0.0001* | 3.13 (2.86-3.44) | <0.0001* |

CVAI, Chinese visceral adiposity index; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval, SD, standard deviation.
[a] Model 1 contained individual characteristics (age, sex, education, economic status). [b] Model 2 added lifestyle risk factors and medical history (smoking, alcohol drinking and physical activity, hypertension, diabetes mellitus, dyslipidemia, prior stroke, family medical history of stroke on the base of model 1. Statistical significance is considered at * P < 0.05.

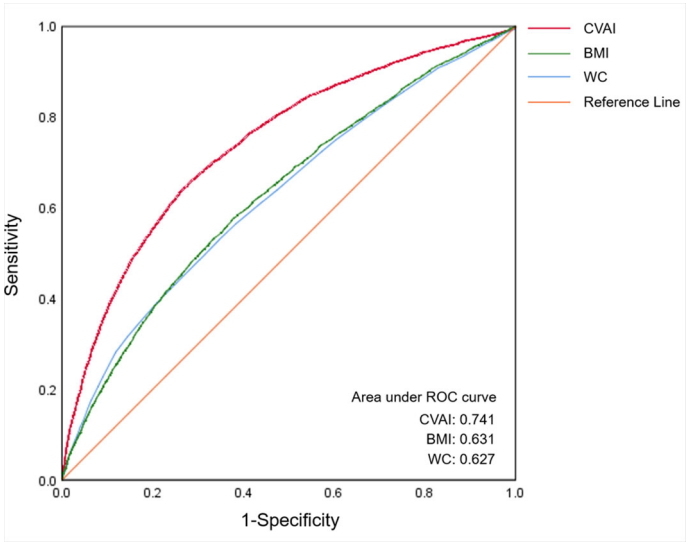


FIGURE 2
The ROC curves of CVAI, BMI and WC for MetS diagnosis. The area under the ROC curve of CVAI was 0.741 for diagnosing MetS, which is significantly superior to BMI and WC among Chinese adults (all $p < 0.05$). ROC, receiver-operating characteristic; CVAI, Chinese visceral adiposity index; BMI, body mass index; WC, waist circumference.

characteristics, medical history, and risk factors. Consistently, participants in the third and fourth CVAI quartiles showed a significantly higher risk of incident stroke than those in the first and second quartiles (adjusted OR: 2.14, 95% CI: 1.25, 3.69).

As demonstrated by the logistic regression models, our findings also indicate a positive correlation between WC and incident stroke in individuals with MetS. Participants exhibiting abdominal obesity had a relative risk of 2.73 (95% CI: 1.67, 4.46) for developing an incident stroke compared to their counterparts without abdominal obesity (Supplement Table 3). The fully adjusted model revealed significant associations between incident stroke and the third and fourth BMI quartiles in patients with MetS, but not the second quartile (Supplement Table 4). Although general obesity may be associated with an elevated risk of stroke, the association did not reach statistical significance after adjustment for confounding factors (adjusted OR: 1.60; 95% CI: 0.99, 2.59). We further used restricted cubic splines to visualize the relation of CVAI, WC, and BMI with incident stroke in patients with MetS. The risk of incident stroke was non-linearly associated with CVAI (Figure 3B) and followed an inverted U-shaped curve with respect to BMI (Supplement Figure 2A). A decreased risk of stroke was observed when the CVAI was below 110.91.

During the two-year follow-up period, 57 strokes occurred among the 12,242 patients without MetS. However, no significant correlation was detected between CVAI and stroke in non-MetS patients (Supplement Table 5).

## 3.5 Subgroup analyses of stroke risk factors

To evaluate any potential modifying effects of stroke risk factors on the association between CVAI (3-4 quartiles vs. 1-2 quartiles) and incident stroke, subgroup analyses were conducted (Table 6). We found no significant interaction between CVAI and covariates in relation to incident stroke.

TABLE 3 ROC for BMI, WC, and CVAI in predicting MetS and cut-off points.

| Parameter | BMI | WC | CVAI |
|---|---|---|---|
| Area under ROC curve (95% CI) | 0.631 (0.623-0.639) | 0.627 (0.619-0.635) | 0.741 (0.734-0.749) |
| *p* value | <0.0001* | <0.0001* | <0.0001* |
| Cut-off point | 83.25 | 23.98 | 99.15 |
| Youden Index | 0.184 | 0.200 | 0.376 |
| Sensitivity | 0.530 | 0.578 | 0.646 |
| Specificity | 0.654 | 0.622 | 0.730 |

ROC, receiver operating characteristic; BMI, body mass index; WC, waist circumference; CVAI, Chinese visceral adiposity index; MetS, metabolic syndrome; CI, confidence interval. Statistical significance is considered at * $P < 0.05$.

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TABLE 4 Baseline characteristics of MetS patients divided by CVAI quartiles.

| Variants | CVAI Q1 | CVAI Q2 | CVAI Q3 | CVAI Q4 | p for trend |
|---|---|---|---|---|---|
| **Range** | <88.45 | ≥ 88.45 & < 110.79 | ≥ 110.79 & < 133.32 | ≥133.32 | |
| **N** | 1683 | 1683 | 1683 | 1683 | |
| Individual characteristics | | | | | |
| **Males, N (%)** | 995 (59.1) | 714 (42.4) | 664 (39.5) | 795 (47.2) | <0.0001* |
| **Age, years** | 55 (49-64) | 59 (53-67) | 63 (55-69) | 66 (57-72) | <0.0001* |
| **Education, N (%)** | | | | | <0.0001* |
| Primary school or below | 596 (35.4) | 642 (38.1) | 688 (40.9) | 741 (44.0) | |
| Middle school | 633 (37.6) | 593 (35.2) | 555 (33.0) | 530 (31.5) | |
| High school or above | 454 (27.0) | 448 (26.6) | 440 (26.1) | 412 (24.5) | |
| **Annual Income, N (%)** | | | | | 0.003* |
| <5000 CNY | 450 (26.7) | 459 (27.3) | 432 (25.7) | 429 (25.5) | |
| 5000-9999 CNY | 245 (14.6) | 219 (13.0) | 186 (11.1) | 182 (10.8) | |
| 10000-19999 CNY | 236 (14.0) | 227 (13.5) | 235 (14.0) | 237 (14.1) | |
| ≥20000 CNY | 752 (44.7) | 778 (46.2) | 830 (49.3) | 835 (49.6) | |
| Medical history and risk factor, N (%) | | | | | |
| Current smoking | 446 (26.5) | 352 (20.9) | 339 (20.1) | 430 (25.5) | 0.431 |
| Alcohol consumption | 268 (15.9) | 220 (13.1) | 242 (14.4) | 303 (18.0) | 0.055 |
| Physical inactivity | 424 (25.2) | 424 (25.2) | 454 (27.0) | 565 (33.6) | <0.0001* |
| Hypertension | 966 (57.4) | 1035 (61.5) | 1147 (68.2) | 1193 (70.9) | <0.0001* |
| Diabetes | 750 (44.6) | 711 (42.2) | 687 (40.8) | 713 (42.4) | 0.137 |
| Dyslipidemia | 925 (55.0) | 1047 (62.2) | 1152 (68.4) | 1286 (76.4) | <0.0001* |
| Prior atrial fibrillation | 16 (1.0) | 12 (0.7) | 20 (1.2) | 20 (1.2) | 0.267 |
| Prior stroke | 71 (4.2) | 96 (5.7) | 96 (5.7) | 127 (7.5) | <0.0001* |
| Family history of stroke | 166 (9.9) | 197 (11.7) | 221 (13.1) | 219 (13.0) | 0.002* |
| General observation indexes | | | | | |
| SBP, mmHg | 136 (130-148) | 137 (130-149) | 139 (130-152) | 140 (130-154) | <0.0001* |
| DBP, mmHg | 82 (76-90) | 82 (76-90) | 83 (77-90) | 83 (76-90) | 0.290 |
| FBG, mmol/L | 5.99 (5.00-7.80) | 5.80 (4.90-7.70) | 5.70 (4.90-7.25) | 5.99 (5.04-7.59) | 0.790 |
| HbA1c, % | 5.60 (5.10-6.80) | 5.70 (5.20-6.60) | 5.60 (5.10-6.50) | 5.70 (5.20-6.70) | 0.096 |
| TG, mmol/L | 1.80 (1.22-2.25) | 1.99 (1.54-2.50) | 2.11 (1.70-2.91) | 2.34 (1.79-3.37) | <0.0001* |
| TC, mmol/L | 4.89 (4.07-5.59) | 5.01 (4.25-5.72) | 4.96 (4.25-5.66) | 4.97 (4.21-5.71) | 0.010* |
| LDL-C, mmol/L | 2.60 (2.06-3.20) | 2.77 (2.14-3.35) | 2.75 (2.13-3.34) | 2.70 (2.10-3.29) | 0.068 |
| HDL-C, mmol/L | 1.30 (1.01-1.69) | 1.20 (0.99-1.46) | 1.13 (0.96-1.37) | 1.06 (0.90-1.29) | <0.0001* |
| Indicators of adiposity | | | | | |
| BMI, $kg/m^2$ | 22.43 (20.95-23.87) | 23.82 (22.22-25.33) | 25.10 (23.44-26.87) | 27.33 (25.51-29.22) | <0.0001* |
| WC, cm | 78.0 (73.0-80.0) | 82.0 (78.0-85.0) | 87.0 (83.0-90.0) | 94.0 (89.0-99.0) | <0.0001* |

MetS, metabolic syndrome; CVAI, Chinese visceral adiposity index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin A 1c; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol; BMI, Body Mass Index, WC, waist circumferences. Statistical significance is considered at * $P < 0.05$.

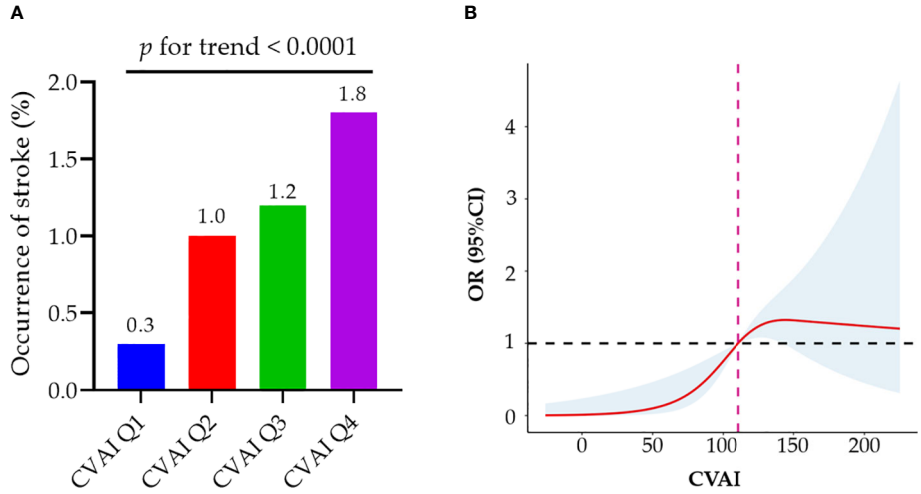


FIGURE 3
Associations of baseline CVAI with incident stroke among MetS patients. **(A)** MetS patients in the higher quartile of CVAI demonstrate a significantly elevated risk of stroke; **(B)** Dose–response relationship of CVAI and stroke risk. A reduced stroke risk was observed when the CVAI was either less than 110.91. MetS, metabolic syndrome; CVAI, Chinese Visceral Adiposity Index; OR, odds ratio; CI, confidence interval.

# 4 Discussion

The present study confirms the superiority of CVAI over BMI and WC in identifying individuals with MetS in a large Chinese population. Furthermore, this investigation is, to the best of our knowledge, the first to detect a robust positive correlation between incident stroke and CVAI in patients with MetS. Our findings suggest a strong association between elevated levels of CVAI and incident stroke in Chinese adults diagnosed with MetS and that reducing CVAI levels could help to mitigate the risk of stroke in patients with MetS.

Epidemiologic studies have demonstrated that the standardized prevalence of MetS is 31.1% among Chinese individuals aged ≥20 years (37). Furthermore, as the obese population continues to increase, so too does the incidence of MetS. The baseline prevalence of MetS in our sample population (35.5%) was consistent with statistics reported in previous epidemiological research (37). The excessive accumulation of abdominal visceral

TABLE 5 Associations of baseline CVAI with incident stroke in MetS patients.

| Variants | No. of case (%) | Crude | | Model 1 [a] | | Model 2 [b] | |
|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | p Value | OR (95% CI) | p Value | OR (95% CI) | p Value |
| **Per SD increase** | | 1.64 (1.30-2.06) | <0.0001* | 1.61 (1.26-2.04) | <0.0001* | 1.52 (1.18-1.95) | <0.0001* |
| Quartiles | | | | | | | |
| Quartile 1 (< 88.45) | 5/1683 (0.3) | Reference | | Reference | | Reference | |
| Quartile 2 (≥ 88.45 & < 110.79) | 16/1683 (1.0) | 3.22 (1.17-8.81) | 0.023* | 3.25 (1.18-8.96) | 0.023* | 3.08 (1.11-8.52) | 0.030* |
| Quartile 3 (≥ 110.79 & < 133.32) | 20/1683 (1.2) | 4.04 (1.51-10.78) | 0.005* | 4.12 (1.52-11.17) | 0.005* | 3.78 (1.38-10.32) | 0.010* |
| Quartile 4 (≥133.32) | 31/1683 (1.8) | 6.30 (2.44-16.24) | <0.0001* | 6.03 (2.29-15.90) | <0.0001* | 5.34 (1.99-14.32) | 0.001* |
| *p* for trend | | | <0.0001* | | <0.0001* | | 0.001* |
| Categories | | | | | | | |
| Quartile 1-2 (< 110.79) | 21/3366 (0.6) | Reference | | Reference | | Reference | |
| Quartile 3-4 (≥ 110.79) | 51/3366 (1.5) | 2.45 (1.47-4.08) | 0.001* | 2.35 (1.38-3.98) | 0.002* | 2.14 (1.25-3.69) | 0.006* |

CVAI, Chinese visceral adiposity index; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval; SD, standard deviation.
[a] Model 1 contained individual characteristics (age, sex, education, economic status). [b] Model 2 added lifestyle risk factors and medical history (smoking, alcohol drinking and physical activity, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, prior stroke, family medical history of stroke on the base of model 1. Statistical significance is considered at * P < 0.05.

fat is characteristic of MetS and clinically significant when assessing MetS in individuals of normal body weight (18). In the Chinese population, CVAI has been proposed as a valid, dependable indicator of visceral adiposity dysfunction (38). Our findings indicate that CVAI levels are significantly higher among those with MetS than those without it. Although previous studies have shown that CVAI has a favorable predictive performance for detecting MetS (39, 40), their findings were limited by having been derived from relatively small sample sizes. By contrast, our investigation demonstrates a significant positive association between CVAI levels and MetS in a large study population. CVAI exhibited superior performance in the diagnosis of MetS among Chinese adults, as evidenced by a higher AUC and greater overall discriminative ability than those of BMI and WC. This result is consistent with the findings of the previous research (39, 40), suggesting that CVAI, a quantitative index of visceral fat, can serve as a more reliable indicator of MetS than either BMI or WC.

The present study has also revealed that MetS patients in the higher quartile of CVAI were associated with lower levels of educational attainment. This finding may be attributed to the fact that individuals with higher levels of education are more inclined towards adopting healthier behaviors, which in turn may lead to a greater likelihood of remission from MetS (41). Moreover, it was noted that individuals diagnosed with MetS displayed a significant positive association between their income level and CVAI, signifying a rise in visceral adiposity with an increase in income

TABLE 6 Subgroup analysis between CVAI with stroke.

| Characteristics | Crude OR (95%CI) | p for interaction | Adjusted OR (95%CI) [a] | Adjusted p for interaction [a] |
|---|---|---|---|---|
| **Age, years** | | 0.274 | | 0.512 |
| <60 | 2.18 (0.86-5.53) | | 1.97 (0.73-5.33) | |
| ≥60 | 2.03 (1.08-3.80) | | 2.13 (1.10-4.13) | |
| **Sex** | | 0.703 | | 0.384 |
| Male | 2.72 (1.29-5.74) | | 2.49 (1.15-5.41) | |
| Female | 2.23 (1.11-4.49) | | 1.73 (0.79-3.76) | |
| **Diabetes** | | 0.846 | | 0.836 |
| Yes | 2.59 (1.28-5.25) | | 2.27 (1.06-4.87) | |
| No | 2.34 (1.12-4.91) | | 2.13 (0.98-4.65) | |
| **Hypertension** | | 0.341 | | 0.377 |
| Yes | 2.01 (1.16-3.51) | | 1.95 (1.08-3.53) | |
| No | 4.02 (1.09-14.88) | | 3.31 (0.82-13.29) | |
| **Dyslipidemia** | | 0.230 | | 0.319 |
| Yes | 3.19 (1.59-6.41) | | 2.73 (1.32-5.64) | |
| No | 1.65 (0.72-3.75) | | 1.46 (0.60-3.57) | |
| **Prior stroke** | | 0.386 | | 0.464 |
| Yes | 1.52 (0.51-4.54) | | 2.27 (0.64-8.13) | |
| No | 2.63 (1.47-4.70) | | 2.25 (1.22-4.16) | |
| **Current smoking** | | 0.375 | | 0.224 |
| Yes | 3.59 (1.32-9.77) | | 3.63 (1.28-10.27) | |
| No | 2.12 (1.17-3.84) | | 1.65 (0.87-3.16) | |
| **Alcohol consumption** | | 0.482 | | 0.558 |
| Yes | 4.08 (0.88-18.98) | | 2.91 (0.55-15.28) | |
| No | 2.27 (1.32-3.92) | | 2.10 (1.17-3.75) | |
| **Physical inactivity** | | 0.763 | | 0.636 |
| Yes | 2.16 (0.90-5.20) | | 2.01 (0.81-5.03) | |
| No | 2.55 (1.36-4.78) | | 2.25 (1.15-4.42) | |

CVAI, Chinese visceral adiposity index; OR, odds ratio; CI, confidence interval.
[a] Adjusted for all covariates except effect modifier. Statistical significance is considered at * $P < 0.05$.

(42–44). The observed trend is incongruent with the findings in developed nations, where individuals with lower incomes typically exhibit elevated rates of obesity and MetS. One plausible explanation for this disparity may be linked to the inclination of individuals with slightly higher incomes in developing countries to consume highly processed foods that lack nutritional value and contain "empty calories," which are additional to their daily diet (44). Future studies ought to explore the correlation between visceral adiposity and dietary patterns within developing country populations.

Patients diagnosed with MetS are considered at high-risk for stroke (8–10). The current study demonstrates that the incidence of stroke during 2-year follow-up in patients with MetS is 2.31 times higher than it is for their counterparts without MetS, underscoring the importance of preventing stroke incidence in MetS patients. Mendelian randomization studies have suggested that visceral adiposity exerts a more potent impact on stroke risk than does general adiposity (45). Furthermore, visceral adiposity has been causally linked to the occurrence of stroke (46). While research on the longitudinal associations between visceral adiposity and stroke risk in patients with MetS has been limited, the present large population-based prospective cohort study found a strong association between elevated CVAI and incident stroke in Chinese adults who experienced MetS—even after adjustment for potential confounders. Specifically, each 1 SD increase in CVAI was found to increase the risk of incident stroke by a factor of 1.52 after correction. These findings provide additional support for the potential of reducing CVAI as a strategy to lower the risk of incident stroke among individuals with MetS.

Previous research has indicated that individuals with MetS and a BMI indicative of general obesity are at an increased risk of developing CVD relative to those without general obesity [17]. In our study, participants with general obesity were also found to have a higher risk of incident stroke relative to their non-obese counterparts; however, this trend did not reach statistical significance. The restricted cubic spline analysis revealed a dose-dependent association between CVAI and an increased risk of incident stroke. However, as BMI increases, an inverted U-shaped dose-response relationship was observed. One possible explanation is that BMI is unable to distinguish between the accumulation of fat-free mass and adipose tissue, leading to misidentification of individuals with high muscle mass as overweight or obese. The aforementioned data suggests that CVAI reflects stroke risk better than does BMI. Thus, in the routine practice of stroke prevention, assessing excessive body weight should incorporate an indicator of visceral adiposity rather than BMI alone.

Multiple factors may account for the correlation between CVAI and stroke in patients with MetS. First, CVAI levels are influenced by dyslipidemia, a common vascular risk factor for stroke associated with MetS. Second, the relationship might be explained by a demonstrated correlation between CVAI and the early development of traditional risk factors for stroke: e.g., Han et al. demonstrated a positive correlation between elevated CVAI and heightened risks of diabetes (47), a well-documented risk factor for stroke. The association between elevated CVAI and an increased risk of developing hypertension provides further support for the connection between CVAI and stroke risk factors (48). Finally, visceral adipose tissue not only secretes elevated levels of pro-inflammatory cytokines (49, 50), but also fulfills endocrine functions and plays a pivotal role in the pathogenesis of insulin resistance (51). The pathophysiological alterations prompted by visceral adipose tissue may exacerbate the risk of atherosclerosis, a major contributor to ischemic stroke. Indeed, enhanced levels of CVAI are positively associated with an increased likelihood of carotid atherosclerotic plaque formation (28, 52). Subsequent investigations could further explore the correlation between CVAI and serum concentrations of pro-inflammatory cytokines.

Interestingly, the present investigation did not observe any significant association between CVAI and stroke in non-MetS patients. This finding is consistent with those of Mirzaei et al., who observed no significant elevation in the risk of CVD in either metabolically healthy normal weight and metabolically healthy obese (MHO) groups after a 12-year follow-up period (53). A 14-year population-based prospective study of 5,314 individuals aged ≥55 years in Rotterdam also found that MHO did not augment the risk of cardiovascular disease (54). One possible explanation for this finding is that the incidence of cardiovascular events may be more closely linked to progression towards metabolic syndrome than obesity in middle-aged and older individuals (55). Further investigations are warranted to examine the contribution of CVAI in MetS risk among individuals with metabolically healthy normal weight and MHO.

This study is, to the best of our knowledge, the first study to investigate a correlation between CVAI and incident stroke in a robust sample size of Chinese MetS patients. Specifically, a gradual increase in the risk of stroke was observed when the CVAI surpassed the threshold of 110.91. Therefore, it is recommended that individuals diagnosed with MetS undergo further medical examinations to determine their susceptibility to stroke when their CVAI score exceeds 110.91 and promptly implement preventive measures against stroke. While this study benefitted from meticulous data collection and rigorous adjustment for confounding factors, it is subject to the following limitations. The 2-year follow-up period allowed for only a limited number of events for analysis. For which reason, the logistic regression models did not meet the criterion of 10 events per variable (EPV) in analyzing stroke risk among MetS patients. Nonetheless, it has been recommended that sample sizes of 5 to 10 EPV included in a regression equation could yield fairly stable coefficients in logistic regression models [44,45]. Moreover, our results exhibited a degree of resemblance to analogous previous investigations. Hence, it is suggested that our results are robust to some extent. Additionally, a 2-year follow-up period remains a reasonable timeframe for identifying individuals with an elevated risk of stroke. In addition to long-term risk information, short-term stroke risk information may also be of interest and more persuasive for behavior modification. An additional limitation of this study pertains to its geographical scope, as it was solely carried out in Hunan Province. Therefore, further validation across other provinces or larger populations is necessary to substantiate the universality of the findings. Finally, the impact of diet and medication on incident stroke was not taken into account due to data limitations.

## 5 Conclusions

CVAI demonstrates an independent and positive correlation with MetS, outperforming BMI and WC in identifying individuals with MetS. These findings recommend CVAI as a superior screening tool for MetS. Furthermore, elevated levels of CVAI are strongly linked to incident stroke in Chinese adults diagnosed with MetS, suggesting that reducing CVAI levels can mitigate the risk of stroke in individuals with MetS.

## 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 studies involving human participants were reviewed and approved by Xiangya Hospital Ethics Committee. The protocol and informed consent for the study of the China Stroke High-risk Population Screening and Intervention Program were reviewed and approved by the Institutional Review Board at the Capital Medical University Xuanwu Hospital early. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

Conceptualization, JX and ZL. Methodology, QH, BD and ZL. Software, QH and XF. Validation, YD, FY and JF. Formal analysis, ZL and MW. Investigation, XF. Resources and data curation, JX. Writing—original draft preparation, ZL. Writing—review and editing, and project administration, JX. All authors have read and agreed to the published version of the manuscript.

## Funding

This research was supported by the National Key Research and Development Projects (2022YFC3602400, 2022YFC3602401), the National Natural Science Foundation of China (82271369), the Provincial Key Plan for Research and Development of Hunan (Grant No. 2020SK2067), the Natural Science Foundation of Hunan Province (Grant No. 2021JJ31109), and the supported by the Fundamental Research Funds for the Central Universities of Central South University (2022ZZTS0821).

## Acknowledgments

We thank all the patients, hospitals, and staff involved in the China Stroke High-risk Population Screening and Intervention Program.

## 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



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1218905/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Review
PUBLISHED 14 July 2023
DOI 10.3389/fendo.2023.1216708



OPEN ACCESS

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RECEIVED 04 May 2023
ACCEPTED 26 June 2023
PUBLISHED 14 July 2023

CITATION
Qiu L, Gao C, Wang H, Ren Y, Li J, Li M, Du X, Li W and Zhang J (2023) Effects of dietary polyphenol curcumin supplementation on metabolic, inflammatory, and oxidative stress indices in patients with metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Front. Endocrinol.* 14:1216708. doi: 10.3389/fendo.2023.1216708



# Effects of dietary polyphenol curcumin supplementation on metabolic, inflammatory, and oxidative stress indices in patients with metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials

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**Objective:** The aim was to conduct a systematic review and meta-analysis for assessing the effectiveness and safety of dietary polyphenol curcumin supplement on metabolic, inflammatory, and oxidative stress indices in patients with metabolic syndrome (MetS).

**Methods:** A comprehensive search for clinical trials was conducted in the following scientific databases: PubMed, SCOPUS, Cochrane Library, EMBASE, Web of Science, and China Biological Medicine. Randomized controlled trials (RCTs) evaluating the efficacy and safety of curcumin supplement for MetS were identified. A random-effects meta-analysis was performed using inverse variance, and efficacy was expressed as mean difference (MD) with 95% confidence interval (CI). The metabolic syndrome markers that were evaluated in the present study included waist circumference (WC), fasting blood sugar (FBS), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), tumor necrosis factor-a (TNF-a), interleukin 6 (IL-6), C-reactive protein (CRP), ultrasensitive c-reactive protein (hsCRP), and malondialdehyde (MDA). By employing the Cochrane tool, RCTs were assessed for bias risk.

**Results:** A total of 785 participants from 13 RCTs were included, with intervention durations ranging from 4 to 12 weeks. Compared with the control group, the curcumin group had positive effects on WC (MD = -2.16, 95% CI: -3.78 to -0.54, $p = 0.009$, seven studies), FBS (MD = -8.6, 95% CI: -15.45 to -1.75, $p = 0.01$, nine studies), DBP (MD = -2.8, 95% CI: -4.53 to - 1.06, $p = 0.002$, five studies), HDL-C (MD = 4.98, 95% CI: 2.58 to 7.38, $p < 0.0001$, eight studies), TNF-a (MD = -12.97, 95% CI: -18.37 to -7.57, $p < 0.00001$, two studies), CRP (MD = - 1.24, 95% CI: -1.71 to -0.77, $p < 0.00001$, two studies), and MDA (MD = -2.35, 95% CI: -4.47 to -0.24,

$p$ = 0.03, three studies). These improvements were statistically significant. Meanwhile, there was no significant improvement in SBP (MD = -4.82, 95% CI: -9.98 to 0.35, $p$ = 0.07, six studies), TG (MD = 1.28, 95% CI: -3.75 to 6.30, $p$ = 0.62, eight studies), IL-6 (MD = -1.5, 95% CI: -3.97 to 0.97, $p$ = 0.23, two studies), or hsCRP (MD = -1.10, 95% CI: -4.35 to 2.16, $p$ < 0.51, two studies). FBS, SBP, HDL-C, IL-6, CRP, hsCRP, and MDA had a relatively high heterogeneity.

**Conclusion:** Curcumin exhibited promising potential in enhancing markers associated with metabolic syndrome, including inflammation. However, additional studies are required to confirm such findings since the included evidence is limited and has a relatively high heterogeneity.

**Systematic review registration:** https://www.crd.york.ac.uk/prospero, identifier CRD42022362553.

KEYWORDS

curcumin, turmeric, metabolic syndrome, inflammation, meta-analysis

# 1 Introduction

Metabolic syndrome (MetS) is a metabolic disease. The National Cholesterol Education Program Adult Treatment Panel III (NCEP: ATPIII) and the International Diabetes Federation (IDF) are prominent organizations dedicated to addressing issues related to cholesterol and diabetes. At present, the two most extensively adopted definitions are those of the IDF and NCEP: ATP III (1). The criteria of both organizations for assessing MetS include waist circumference (WC), blood pressure (for assessing MetS BP), fasting blood sugar (FBS), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) (2). As a novel non-communicable disease, metabolic syndrome has emerged as a global problem. MetS, although challenging to measure epidemiologically, is estimated to be approximately three times more prevalent than diabetes. Therefore, it is believed to affect around one-fourth of the global population already (3). Moreover, MetS can lead to an increased risk of diabetes and coronary heart disease and is associated with a number of malignancies, including colon, liver, and pancreatic cancers (4, 5).

Abdominal adiposity is highly correlated to increased morbidity and mortality (6). Additionally, it serves as an indicator of "dysfunctional adipose tissue," which is a key factor in the clinical diagnosis of MetS (7). MetS is a growing global public health concern. To effectively manage the condition, new and efficient treatments with minimal adverse effects are urgently needed.

Curcumin, a natural plant-based dietary polyphenol, is an active ingredient derived from turmeric from the ginger family. Curcumin has anti-inflammatory, anti-oxidant, anti-diabetic, and anti-atherosclerotic properties (8–10), which can improve the metabolic parameters and symptoms of polycystic ovarian syndrome, MetS, non-alcoholic fatty liver, and cardiovascular disease (11). As suggested by a recent study, curcumin is a potential drug for dealing with MetS (12).

In previous research, curcumin supplementation has been reported to improve obesity-related indices, fasting glucose, and lipids in metabolic diseases such as obesity, fatty liver, and MetS (13–18). A previous meta-analysis also revealed that curcumin supplementation improved certain components of MetS, including FBS, TG, diastolic blood pressure (DBP), and HDL-C, but there were no significant changes in systolic blood pressure (SBP) and WC (19). Another study reported similar results (20). However, four (21–24) newly randomized controlled trials on metabolic indices were missed in the aforementioned meta-analysis. Notably, pro-inflammatory state and oxidative stress are significant factors of MetS and play an important role in the development process of MetS (25, 26). In a previous meta-analysis, it was found that curcumin did not have a significant effect in reducing inflammatory markers associated with chronic inflammatory diseases (27). However, a randomized controlled trial demonstrated that curcumin supplementation improved the indicators of inflammation and oxidative stress in patients with critical sepsis (28). Furthermore, in one study, oxidative stress and inflammatory markers in conditions such as obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD) were systematically reviewed (29). However, there has been no systematic review conducted specifically on inflammatory and oxidative stress markers in patients with metabolic syndrome (MetS). As such, the aim of the present study was to perform a meta-analysis of published randomized controlled clinical trials to further evaluate the effects of curcumin on metabolic, inflammatory, and oxidative stress markers in patients with MetS.

# 2 Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 (30) standards were followed in

the execution of the current meta-analysis, which was registered with PROSPERO under ID number CRD42022362553.

## 2.1 Literature search strategy

From the outset through June 2022, six electronic databases—PubMed, SCOPUS, Cochrane Library, EMBASE, Web of Science, and China Biological Medicine (CBM)—were thoroughly searched. The terms used included the following: "curcumin" or "turmeric yellow" or "yellow, turmeric" or "curcumin phytosome" or "curcuminoid" or "curcuma" or "curcuminoid supplement" or "curcumin extract" and "metabolic syndrome" or "metabolic syndromes" or "syndrome, metabolic" or "syndromes, metabolic" or "metabolic syndrome X" or "insulin resistance syndrome X" or "syndrome X, metabolic" or "syndrome X, insulin resistance" or "metabolic X syndrome" or "syndrome, metabolic X" or "X Syndrome, metabolic" or "dysmetabolic syndrome X" or "Reaven syndrome X" or "syndrome X, Reaven" or "metabolic cardiovascular syndrome" or "cardiovascular syndrome, metabolic" or "syndrome, metabolic cardiovascular" or "cardiometabolic syndrome" or "cardiometabolic syndromes" or "syndrome, cardiometabolic" or "insulin resistance syndrome x" or "insulin resistance" or "metabolic diseases" or "plurimetabolic syndrome" or "syndrome x plus", and "randomized controlled trial" or "randomized" or "placebo" or "RCTs". In order to include any relevant studies that may not have been captured in the initial database search, a thorough examination of the reference lists of potentially eligible literature was conducted.

## 2.2 Research selection

The studies included in the present analysis met the following inclusion criteria (1): participants of both genders aged 18 years or older, (2) diagnosed with metabolic syndrome according to either NCEP-ATP III or IDF guidelines (31), (3) evaluated the effects of curcumin on at least one metabolic, inflammatory, or oxidative stress marker, and (4) provided data on the baseline and endpoint measurements for both intervention and control groups or reported changes within each group. When there were numerous reports regarding the identical population under study, the most comprehensive dataset was examined. There were no exclusions based on the individuals' race or sexual orientation (Table 1).

The following exclusion criteria were applied: (1) trials without specific restrictions, (2) studies with a duration of less than 4 weeks, (3) participants taking antihypertensive, antidyslipidemic, or antidiabetic medications, (4) insufficient data reported in the included studies, and (5) participants with malignancies or other systemic or chronic diseases unrelated to diabetes.

## 2.3 Data extraction and quality assessment

After removing any duplicate entries, two reviewers individually evaluated the remaining records for qualification using the titles and abstracts. Subsequently, the reviewers individually selected potentially eligible literature in full text for inclusion in the present study. The title of the initial author, the publishing year, the location, the number of participants (in the intervention and placebo arms), the MetS diagnostic criteria, the participants' ages and genders, the intervention dose, the length of the study, the reported side effects, and the results were all extracted by two reviewers.

Using the method suggested by the Cochrane Handbook V.5.1.0 (32), two writers independently evaluated the included randomized controlled trials' (RCTs) risk of bias. Seven categories were considered during the evaluation, including the blinding of participants and staff, the blinding of the result evaluation, bad outcome data, selective reporting, and other biases. According to the recommendations in the Cochrane Handbook, each item was awarded a risk-of-bias score that ranged from moderate to high to unclear. In addition, STATA 15.1 software was used to plot funnel plots for determining the presence of publication bias.

## 2.4 Statistical analysis

Review Manager was used for every analysis (RevMan 5.4; Cochrane Collaboration, Copenhagen, Denmark) (33). In comparison to the controls, curcumin's effects on metabolic indices and inflammatory marker results were expressed as mean differences (MD) and reported with corresponding 95% confidence intervals (CI). For all data, a $p$-value less than 0.05 was regarded as statistically significant. The heterogeneity was assessed by inconsistency($I^2$) and chi-square tests. High heterogeneity between studies was considered when the heterogeneity $p$ <0.1 and $I^2 \geq 50\%$. Conversely, low heterogeneity was considered when

TABLE 1 Eligibility criteria.

| Inclusion criteria | |
|---|---|
| Participants | Patients with a diagnosis MetS |
| Interventions | The intervention group was given curcumin supplementation (unlimited dose, dosage form, or duration) |
| Comparisons | The control group was treated with placebo or blank |
| Outcomes | WC, FBS, SBP, DBP, TG, HDL-C, TNF-a, IL-6, CRP, hsCRP, and MDA |
| Study type | RCTs assessing the effects of curcumin supplementation on MetS |

these criteria were not met. By removing one study at a time and redoing the analysis, a sensitivity analysis was performed. Subgroup analyses were also conducted by sample size and intervention duration based on the features of the included studies.

# 3 Results

## 3.1 Selection of trials

The explicit research screening process is shown in Figure 1. The preliminary database retrieval and the additional retrieval yielded a total of 691 records, with 434 articles being excluded for duplicated records. A total of 241 items were eliminated after reading the titles and abstracts in accordance with the inclusion and exclusion criteria. After reading the full texts of 16 studies, two studies were excluded due to non-compliant outcome indicators, and one study had missing data. This resulted in the inclusion of 13 randomized controlled studies with 785 patients (21–24, 34–42).

## 3.2 Research characteristics

Table 2 provides an overview of the trials that were taken into consideration. All 13 studies included in the analysis were parallel RCTs conducted between 2014 and 2022. Iran ($n$ = 10) accounted for the majority of the trials, followed by Pakistan ($n$ = 1), China ($n$ = 1), and Italy (n = 1). The total sample size included 785 MetS participants (373/412, male/female). Two cohorts contained exclusively male (34, 36) participants, and two cohorts consisted of only female (24, 35) participants. The trials ranged in length from 4 to 12 weeks, with two lasting 4 weeks (21, 38), three lasting 6 weeks (24, 35, 41), four lasting 8 weeks (34, 36, 39, 40), and four lasting 12 weeks (22, 23, 37, 42).

## 3.3 Risk of bias

Figure 2 demonstrates that three studies were assigned a low risk of bias due to extensive reporting of information on each item, while 10 trials were given an uncertain risk of bias due to insufficient reporting. Among the included studies, 10 RCTs had insufficient information regarding the random sequence generation method (21, 22, 24, 34, 35, 38–42), and 10 RCTs had imperfect allocation concealment information (21, 22, 24, 34, 35, 38–42). The design and blinding implementation of three RCTs were not clear (21, 34, 38).

## 3.4 Results of the meta-analysis

### 3.4.1 Waist circumference

Seven trials (22–24, 34, 36, 38, 41) gave waist circumference data without heterogeneity ($p$ = 0.97, $I2$ = 0%); hence, a fixed-effects model

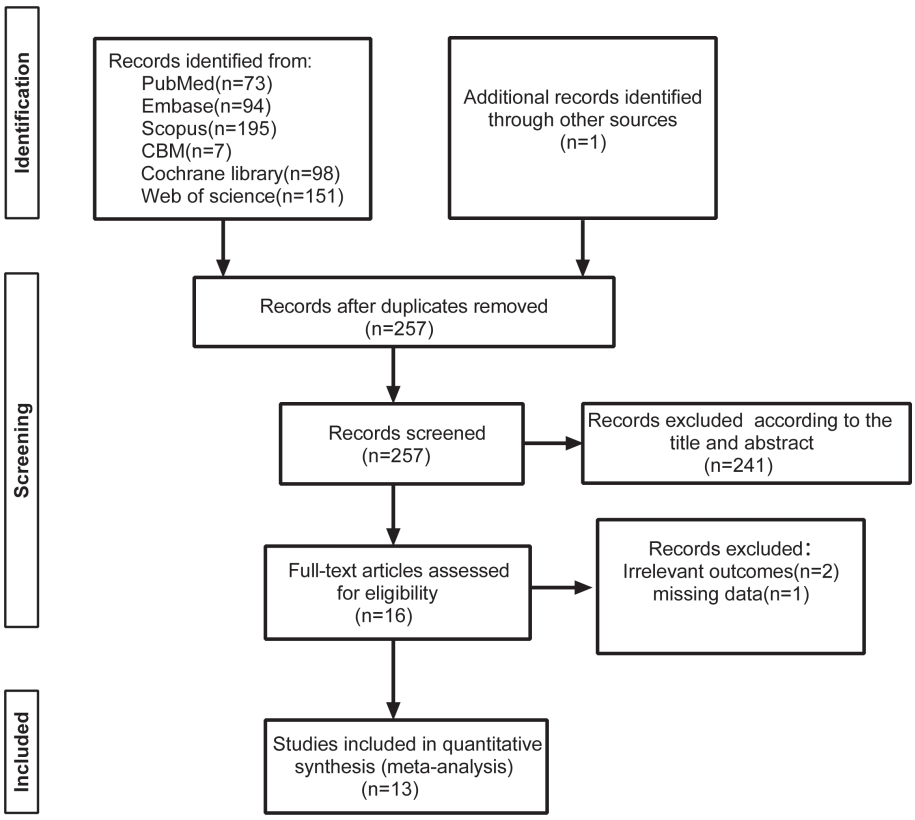


FIGURE 1
Flow diagram of the literature screening process and results.

TABLE 2 Characteristics of the trials included in the meta-analysis.

| Author, year | Location | MetS diagnostic criteria | Age (intervention/control) | No. of participant (intervention/control) | Sex (female/male) | Type of intervention/placebo | Dose of intervention (mg/day) | Duration of study (weeks) | Side effects | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| Salimi, 2017 | Iran | NCEP-ATP III | Mean age, 48 | 10/10 | 20/0 | Curcumin/placebo | 20 mg/kg | 8 | None | BMI, weight, WC, FBG, FAT%, BP, HDL-C, TG, TNF-α, |
| Alidadi, 2021 | Iran | IDF | 42.84 ± 6.25/44.43 ± 5.92 | 32/28 | 29/31 | Curcumin/placebo | 500 | 12 | None | BMI, WC, NC, FM, VFA, weight, FPG, TC, TG, HDL-C, LDL-C, SBP, DBP |
| Amin, 2015 | Pakistan | NCEP-ATP III | 42.4 ± 13.7/41.57 ± 12.8 | 56/52 | 108/0 | Supplement of turmeric powder/spaghula husk capsule | 2,400 | 8 | Dyspepsia | BMI, weight, WC, HC, SBP, DBP, FBG, LDL, HDL, TG, CRP |
| Bateni, 2021 | Iran | NCEP-ATP III | 50 ± 9/54 ± 7 | 22/21 | 10/33 | Nana-micelle curcumin/placebo | 80 | 12 | None | BMI, weight, WC, total body fat%, total body muscle%, SBP, DBP, FBS, HbA1c, Insulin, TG, TC, LDL-C, HDL-C |
| Pierro, 2015 | Italy | NCEP-ATP III | 39.10 ± 16.8/41.85 ± 15.91 | 22/22 | 17/27 | Curcumin supplement/phosphatidylserine | 800 | 4 | None | BMI, Weight, WC, HC, FAT% |
| Osali, 2020 | Iran | NCEP-ATP III | Mean age, 62.3 ± 1.23 | 11/11 | 0/22 | Nano-curcumin/placebo | 80 | 6 | None | BMI, Weight, WC, Glucose, SBP, TG, HDL, body fat%, MDA, CRP, IL-6, IL-10 |
| Panahi, 2015 | Iran | NCEP-ATP III | 44.80 ± 8.67/43.46 ± 9.7 | 50/50 | 50/50 | Curcuminoids–piperine/placebo | 1,000 | 8 | None | hsCRP, MDA, SBP, DBP, FBS, HbA1c |
| Saberi-Karimian,2018 | Iran | IDF | 37.52 ± 9.47/38.59 ± 10.28 | 36/36 | 11/61 | Curcumin/placebo | 1,000 | 6 | None | Weight, BMI, WC, FBG, hsCRP, FAT%, SBP, DBP, LDL-C, HDL-C, TC, TG, T-Chol, Apo A, Apo B |
| Yang, 2014 | Iran | NCEP-ATP III | 59.03 ± 10.1/59.61 ± 14.09 | 30/29 | 23/36 | Curcumin extract/placebo | 1,890 | 12 | Stomach pain, mild diarrhea, nausea | Weight, BMI, TG, T-Chol, FPG, HDL-C, LDL-C, T-Chol, VLDL, HbA1c |
| Bateni, 2022 | Iran | NCEP-ATP III | 50 ± 9/54 ± 7 | 22/21 | 10/33 | Nana-micelle curcumin/placebo | 80 | 12 | None | TAC, MDA, hsCRP, NF-kB |
| Panahi, 2016 | Iran | NCEP-ATP III | 44.80 ± 8.67/43.46 ± 9.7 | 50/50 | 50/50 | Curcuminoids–piperine/placebo | 1,000 | 8 | Gastrointestinal | TNF-α, IL-6, TGF-β, MCP-1 |
| Zhang, 2019 | China | NCEP-ATP III | 66.9 ± 14.1/68.1 ± 12.3 | 46/46 | 45/47 | Curcumin/control | 1,500 | 4 | None | TC, TG, FPG, LDL-C, HDL-C |
| Osali, 2018 | Iran | NCEP-ATP III | Mean age, 62.3 ± 1.23 | 11/11 | 0/22 | Nano-curcumin/placebo | 80 | 6 | None | TNF-α |

MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; FBG, fasting blood glucose; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; hsCRP, high-sensitivity C-reactive protein; Apo A, apolipoprotein A; Apo B, apolipoprotein B; VLDL, very-low-density lipoprotein; HbA1c, hemoglobin A1c; MDA, malondialdehyde; HC, hip circumference; NC, neck circumference; VFA, visceral fat area; TGF-β, transforming growth factor beta; MCP-1, chemoattractant protein-1.





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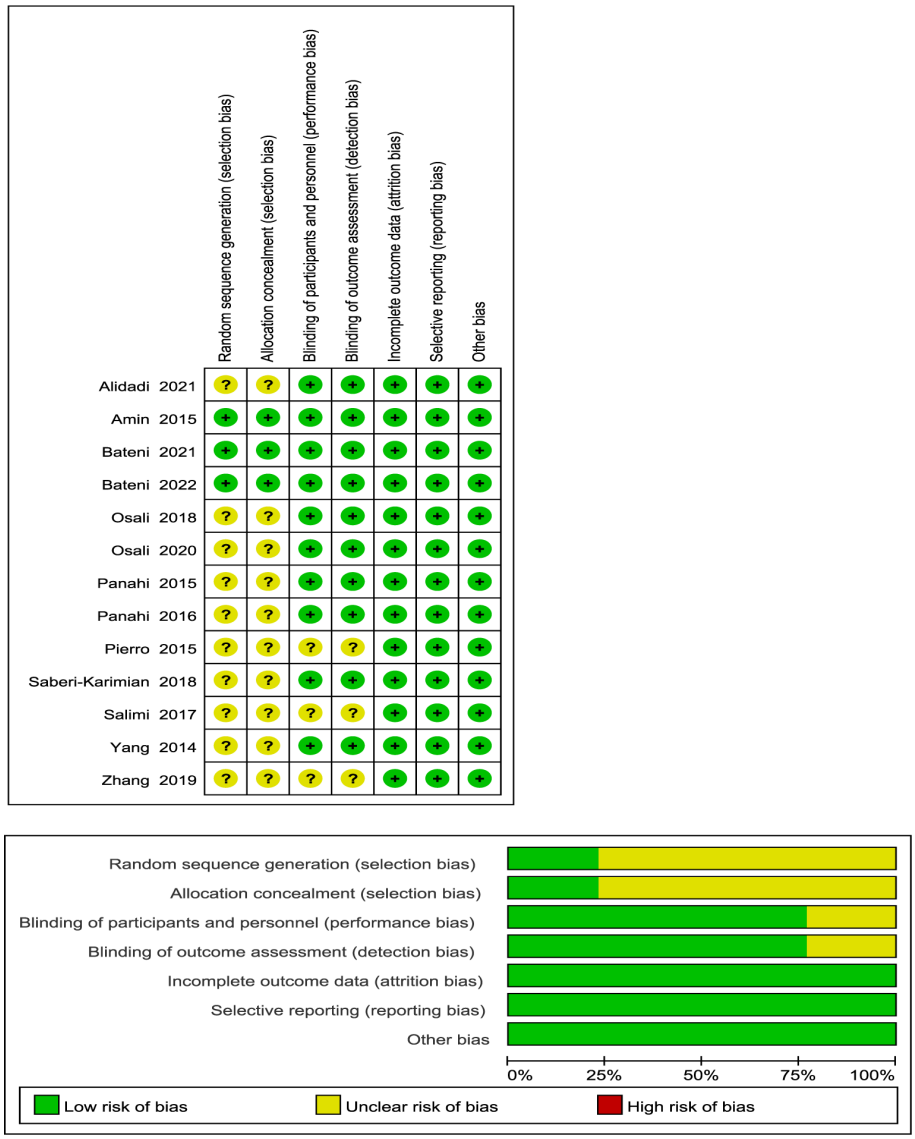


FIGURE 2
Risk assessment of the included studies.

was used. The outcomes demonstrated that, as a consequence of reducing WC, the intervention group surpassed the control group (MD = -2.16, 95% CI: -3.78 to -0.54, $p$ = 0.009) (Figure 3).

### 3.4.2 Fasting blood sugar

Nine trials (21–24, 34, 36, 39, 41, 42) showed statistically significant heterogeneity in fasting glucose outcomes ($p$ = 0.0005, $I2$ = 71%) and therefore used a random-effects model. The findings demonstrated that the experimental group fared better in decreasing the FBS than the placebo group (MD = -8.6, 95% CI: -15.45 to -1.75, $p$ = 0.01) (Figure 4).

### 3.4.3 Blood pressure

A fixed-effects model was used to analyze the results, which revealed that the intervention group outperformed the control group in lowering the diastolic blood pressure (MD = -2.8, 95% CI: -4.53 to -1.06, $p$ = 0.002) (Figure 5). A total of five studies (22, 23, 36, 39, 41) reported diastolic blood pressure outcomes without statistically significant homogeneity ($p$ = 0.16, $I2$ = 40%).

A total of six studies (22–24, 36, 39, 41) reported statistically significant heterogeneity in SBP outcomes ($p$ = 0.0004, $I2$ = 78%) and therefore used a random-effects model. According to the findings, curcumin had a negligible impact on SBP (MD = -4.82, 95% CI: -9.98 to 0.35, $p$ = 0.07) (Figure 6).

### 3.4.4 Triglycerides

Eight studies (21–24, 34, 36, 41, 42) showed triglyceride outcomes with no statistically significant heterogeneity ($p$ = 0.21, $I2$ = 27%). As such, the results of a fixed-effects model demonstrated that curcumin's influence did not significantly lower the TG (MD = 1.28, 95% CI: -3.75 to 6.30, $p$ = 0.62) (Figure 7).

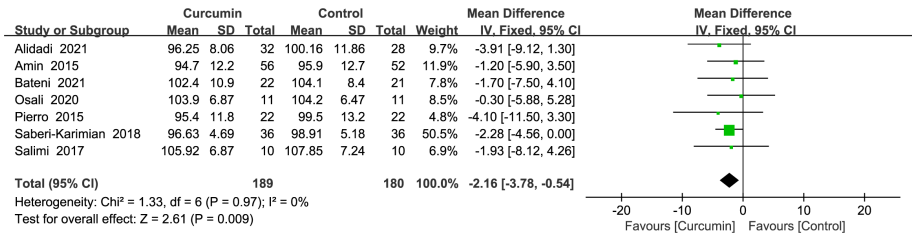


FIGURE 3
Effect of curcumin supplement on waist circumference.

### 3.4.5 High-density lipoprotein cholesterol

Eight trials (21–24, 34, 36, 41, 42) demonstrated significant heterogeneity in the outcomes related to HDL cholesterol ($p$ = 0.001, $I2$ = 71%). By employing a random-effects model, the data indicated that the intervention group had a more pronounced effect in increasing HDL cholesterol levels compared with the placebo group (MD = 4.98, 95% CI: 2.58 to 7.38, $p$ < 0.0001) (Figure 8).

### 3.4.6 Inflammation indicators

Two studies (24, 40) reported statistically significant heterogeneity in the results for interleukin 6 (IL-6) ($p$ = 0.02, I2 = 81%). Thus, the results of a model with random effects showed that curcumin had no discernible impact on IL-6 (MD = -1.5, 95% CI: -3.97 to 0.97, $p$ = 0.23) (Figure 9A).

The tumor necrosis factor-a (TNF-a) results from two trials (35, 40) reported high homogeneity ($p$ = 0.004, $I2$ = 88%). After employing a model with random effects, the outcomes revealed that the intervention group surpassed the control group in lowering the TNF-a (MD = -12.97, 95% CI: -18.37 to -7.57, $p$ < 0.00001) (Figure 9B).

Based on the results of two studies (24, 36), which did not show statistically significant heterogeneity for C-reactive protein (CRP) outcomes ($p$ = 0.58, $I2$ = 0%), a fixed-effects model was used. The findings indicated that the intervention group exhibited a greater reduction in CRP levels compared with the control group (MD = -1.24, 95% CI: -1.71 to -0.77, $p$ < 0.00001) (Figure 9C).

Two studies (37, 39) reported statistically significant homogeneity ($p$ < 0.00001, $I2$ = 98%) in the results for ultrasensitive C-reactive protein (hsCRP). After employing a model with random effects, the findings revealed that the effect of curcumin did not significantly alter the hsCRP (MD = -1.10, 95% CI: -4.35 to 2.16, $p$ = 0.51) (Figure 9D).

### 3.4.7 Oxidative stress marker

Three studies (24, 37, 39) reported statistically significant heterogeneity ($p$ < 0.00001, $I2$ = 92%) in the results for malondialdehyde (MDA). Using a random-effects model, the results showed that the intervention group was superior to the control group in reducing MDA (MD = -2.35, 95% CI: -4.47 to -0.24, $p$ = 0.03) (Figure 10).

## 3.5 Adverse events

A total of three studies (36, 40, 42) reported mild gastrointestinal and digestive adverse effects, mainly including diarrhea, nausea, and constipation, which could be attributed to the high daily dose of curcumin.

## 3.6 Publication bias

Publication bias was assessed for WC as an outcome indicator using a funnel plot. The Begg's test yielded a $p$-value of 0.548, and the Egger's test yielded a $p$-value of 0.946. The results suggest that there was no substantial publication bias among the included studies. The funnel plot is shown in Figure 11.

## 3.7 Sensitivity analysis

Significant heterogeneity was observed in studies reporting FBS, SBP, and HDL-C. As such, sensitivity analyses were performed to identify the potential causes. The sensitivity analysis indicated that

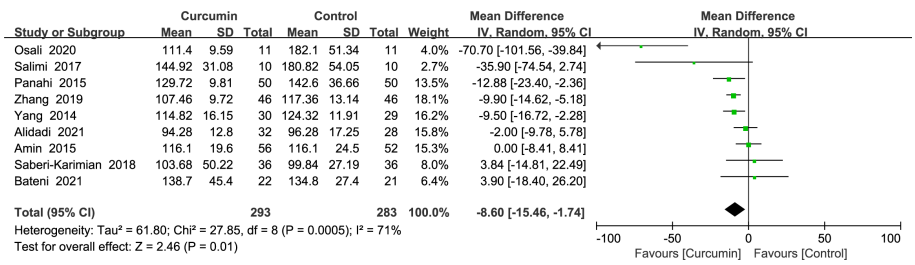


FIGURE 4
Effect of curcumin supplement on fasting blood sugar.

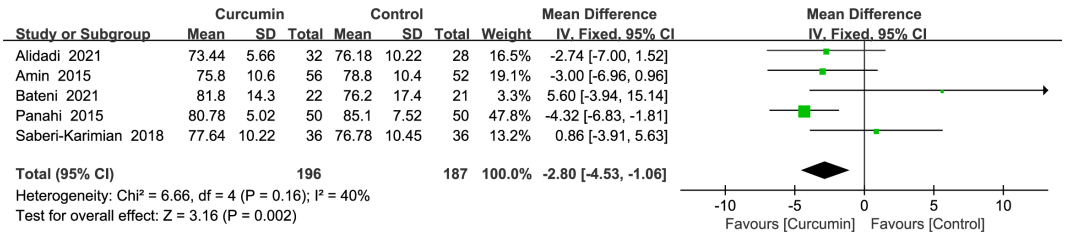


FIGURE 5
Effect of curcumin supplement on diastolic blood pressure.

the study by Osai et al. (2020) had a notable influence on the heterogeneity of the FBS and SBP outcomes. However, after removing the study from the analysis, the heterogeneity became non-significant (Supplementary Figures S1, S2). For the heterogeneous results of HDL-C, no single study interfered with the results when any single study was excluded (Supplementary Figure S3).

## 3.8 Subgroup analysis

The results of the subgroup analyses by sample size or duration did not differ from those of the overall analyses of FBS, SBP, DBP, TG, and HDL-C. (Supplementary Figures S4–S8). The only exception was a significant increase in HDL-C in trials with a duration less than or equal to 6 weeks compared with trials with a duration greater than 6 weeks (Supplementary Figure S8A). The subgroup analyses by duration or sample size showed differences from the overall analysis of WC, which did not change significantly in trials with durations greater than 6 weeks (Supplementary Figure 9A) or in trials with less than 60 patients (Supplementary Figure 9B).

## 3.9 GRADE assessment

The GRADE tool was used to rate the evidence for the 11 outcome indicators (WC, FBS, DBP, SBP, TG, HDL-C, IL-6, TNF-a, CRP, hsCRP, and MDA). The evidence was categorized as "moderate", "low", or "very low" based on specific reasons for downgrading, such as a high risk of bias, inconsistency, and imprecision. The detailed ratings and reasons for downgrading can be found in Table 3.

# 4 Discussion

The effects of curcumin supplementation on WC, FBS, BP, TG, and HDL levels and inflammatory markers (IL-6, TNF-a, CRP, and hsCRP) in MetS patients were assessed by analyzing 13 randomized controlled trials. The minimum duration of the studies was 4 weeks, and the maximum duration was 12 weeks. The results of the present study show significant improvements in WC, FBS, DBP, HDL, and inflammatory markers (TNF-a and CRP) levels. However, there were no significant changes observed in SBP, TG levels, IL-6, and hsCRP.

In comparison with a previous systematic evaluation (19), the present results differ in terms of waist circumference, and curcumin supplementation was found to significantly reduce waist circumference. The reason for such findings could be attributed to the inclusion of new studies to increase the sample size. As has been previously demonstrated, the pathophysiological mechanism of MetS involves systemic oxidative stress brought on by central obesity (43–45), and waist circumference is a significant indicator of abdominal obesity and a proxy for visceral adipose tissue (46). Waist circumference plays a crucial role in adult metabolic syndrome early detection and the prediction of insulin resistance (47). Studies have confirmed that WC, similar to body mass index (BMI), is associated with BP, insulin resistance, and blood lipids (48). According to epidemiological research, visceral adiposity is a substantial major risk for insulin resistance, cardiovascular disease, stroke, MetS, and mortality (49). Therefore, a reduction in waist circumference can help improve the metabolic index of metabolic syndrome and reduce mortality. Through inhibiting differentiation medium-induced β-catenin downregulation and downregulating the expression of peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT enhancer binding protein α(C/EBPα), the

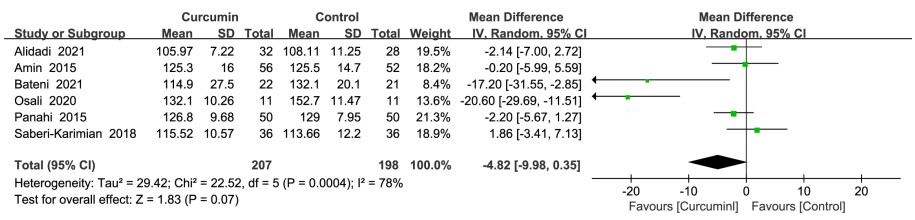


FIGURE 6
Effect of curcumin supplement on systolic blood pressure.

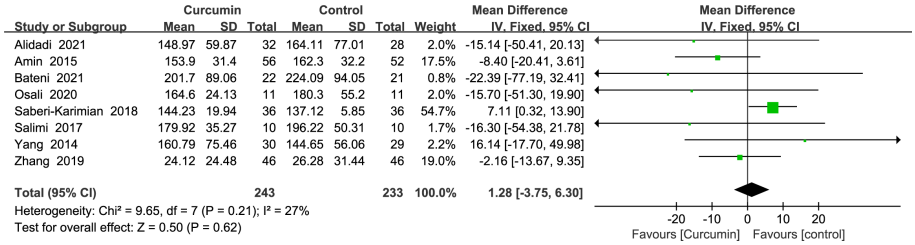


FIGURE 7
Effect of curcumin supplement on triglycerides.

process may contribute to reducing lipid accumulation in 3T3-L1 adipocytes (50).

Furthermore, the impact of curcumin administration on MetS inflammatory and oxidative stress biomarkers was thoroughly examined. A previous systematic review found that curcumin supplementation improved the inflammation and oxidative stress in obesity, diabetes, and NAFLD (29). However, no studies have been conducted to independently perform a meta-analysis on the co-occurrence of metabolic syndrome, inflammation, and oxidative stress. Notably, curcumin supplementation was found to significantly improve TNF-a, but not hsCRP. The two studies included in the analysis of hsCRP were found to differ in the dose of curcumin used and the duration of the intervention, with Bateni et al. (37) using 80 mg of nanocurcumin per day for 12 weeks and Pahahi et al. (2015) using 1,000 mg of curcumin per day for 8 weeks. One study found that a 10-week intervention with 1,500 mg of curcumin daily in type 2 diabetes significantly improved the hsCRP level (51), and another study showed that a 12-week intervention with nano-curcumin in patients with NAFLD significantly improved the hsCRP level (52). Based on such findings, the present authors believe that metabolic syndrome, as a complex metabolic disorder, may require larger doses of curcumin supplementation to achieve a significant improvement in hsCRP. In the present study, there was a significant improvement in TNF-a and CRP inflammatory indexes with curcumin supplementation. The present study encompasses all available research on the association between curcumin supplementation and inflammation as well as oxidative stress in individuals with MetS. Moreover, a broader range of clinical outcome measures related to curcumin supplementation in patients with metabolic syndrome was evaluated, thereby offering additional evidence-based insights.

Curcumin is significant for the improvement of inflammatory and oxidative stress indicators. While the exact pathophysiology of metabolic syndrome remains unclear, there are widely acknowledged potential pathways that contribute to its development. Such pathways include insulin resistance and the presence of chronic low-grade inflammation, which are commonly associated with central obesity (53, 54). Chronic inflammation also interacts with oxidative stress (55). The majority of MetS patients are asymptomatic, but according to the Framingham Risk Score (56), they have a 16% to 18% chance of experiencing their first coronary event within a 10-year timeframe, which raises their risk of cardiovascular disease by fivefold and their risk of type 2 diabetes by twofold (57). Inflammation can also produce insulin resistance directly or indirectly; therefore, various inflammatory markers are considered as reliable MetS biomarkers. The administration of curcumin, which leads to improvements in inflammatory and oxidative stress markers, not only enhances the overall condition of patients with MetS but also reduces the likelihood of developing cardiovascular disease.

In the obese state, adipocyte hypertrophy and overcrowding lead to the hypoxic necrosis of cells, and necrotic adipocytes attract mononuclear macrophages to cluster, and the number of macrophages in adipose tissue increases from 10%–15% to 40%–50%, leading to the infiltration of macrophages. Such infiltration induces the macrophages to polarize to M1-type pro-inflammatory phenotype and generate and emit inflammatory substances such TNF-a, IL-1, and nitric oxide synthase ($NOS_2$), among others, which, in turn, regulate local and systemic inflammation (58, 59). These inflammatory factors further activate the macrophages and impair insulin signaling in adipocytes, leading to systemic insulin resistance (60). According to epidemiology,

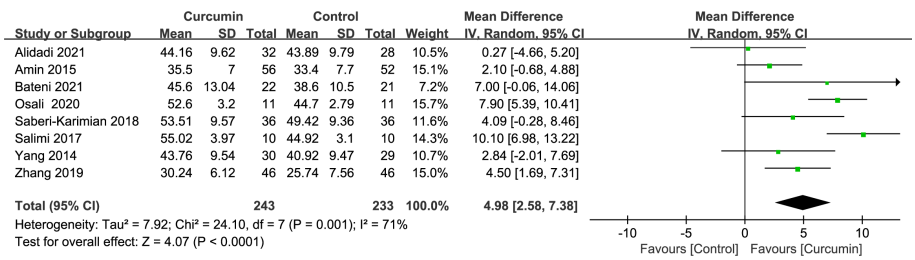


FIGURE 8
Effect of curcumin supplement on high-density lipoprotein cholesterol.

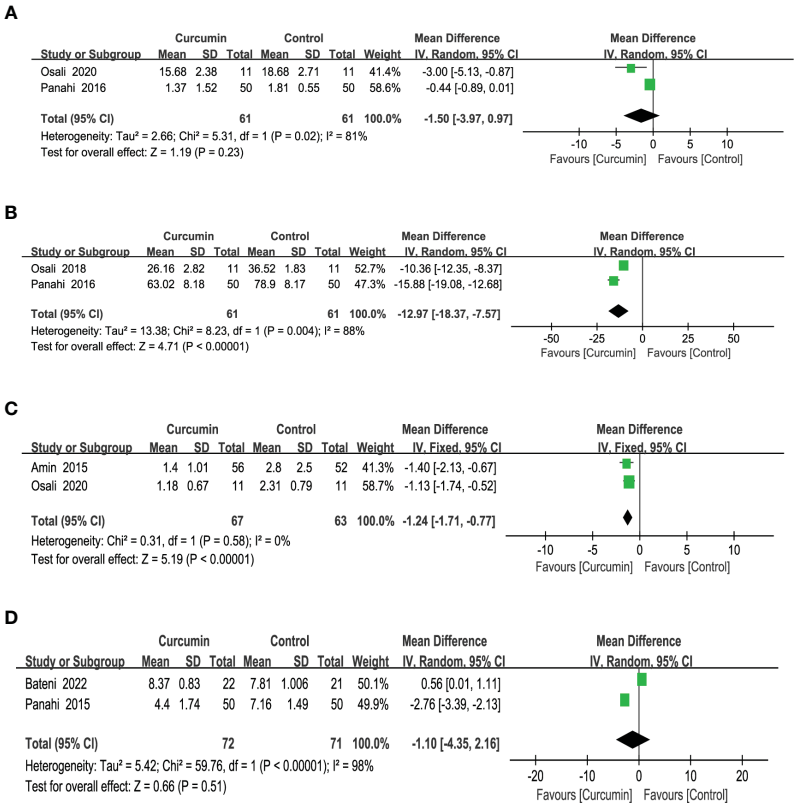


FIGURE 9
Effect of curcumin supplement on inflammation indicators: **(A)** IL-6, **(B)** TNF-a, **(C)** C-reactive protein, and **(D)** hsCRP.

patients with diabetes mellitus (DM), hypertension, atherosclerosis, and cardiovascular events had increased levels of IL-6 and TNF-a (45). Thus, an assumption could be made that the possible mechanism of curcumin treatment of MetS involves reducing chronic inflammation and oxidative stress by regulating macrophage polarization.

First, to our knowledge, the present research represents the first meta-analysis of curcumin's impact on inflammatory and oxidative stress markers in MetS. Second, in the present study, the sample size was expanded by including new studies on the basis of previous meta-analyses. Third, bias was decreased to a certain extent because only randomized controlled clinical trials were included. Fourth, the robustness of the findings was demonstrated through sensitivity analyses in which each study was omitted one at a time, indicating that the conclusions were reliable. Fifth, to evaluate the potential research characteristics of the association between curcumin supplementation and metabolic syndrome, subgroup analyses of intervention duration and the sample size were conducted.

However, the present study also has several limitations. First, although the present study was not restricted to language and region, 12 of the 13 included studies were from Asian countries, including as many as 10 studies from Iran. The generalizability of the results needs to be further verified. Second, despite being the first meta-analysis conducted on the impact of curcumin on inflammatory and oxidative stress markers in individuals with MetS, the credibility of the results was somewhat compromised due to the limited number of publications included in the study. Third, there was a higher risk of bias in the research since two of the included studies had only male participants and two studies had only female participants. Fourth, the use of products that favorably enhance the bioavailability of curcumin (including piperine or alkaloids) was not excluded. Fifth, the limited amount of research

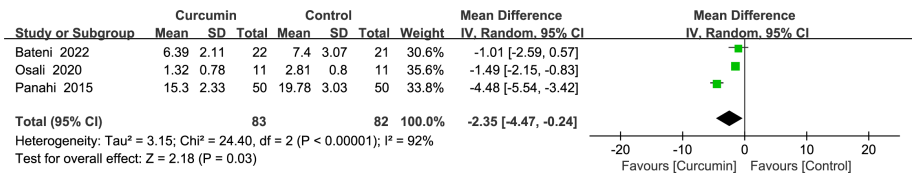


FIGURE 10
Effect of curcumin supplement on malondialdehyde.

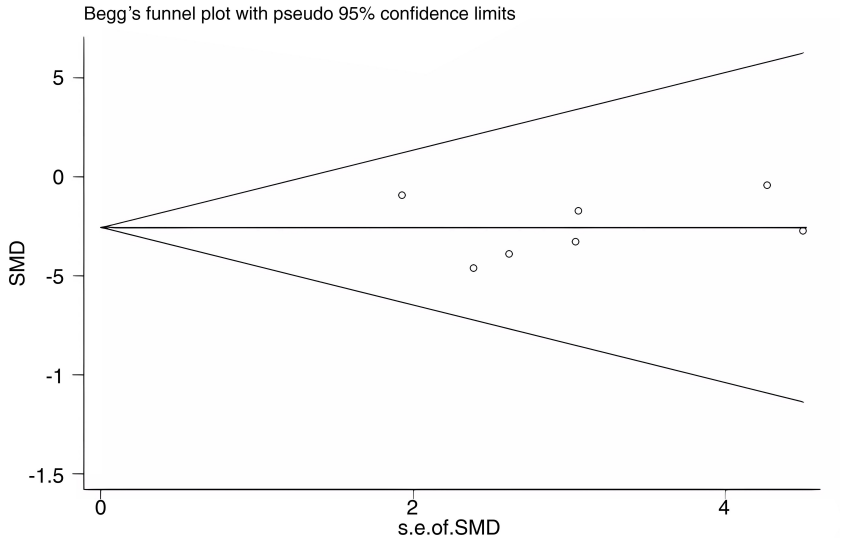


FIGURE 11
Publication bias.

TABLE 3 GRADE summary of outcomes for EG *versus* CG for patients with MetS.

| Outcomes | No. of participants (studies) | Anticipated absolute effects (95% CI) | | Relative effect (95% CI) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | | Risk with CG | Risk difference with EG | | |
| WC | 369 (7) | The mean WC ranged from 95.9 to 107.85 | The mean WC in the EG was 2.16 lower (3.78 to 0.54 lower) | – | ⊕⊕◯◯ LOW[a,b] |
| FBS | 576 (9) | The mean FBS ranged from 96.28 to 182.1 | The mean FBS in the EG was 8.6 lower (15.46 to 1.74 lower) | – | ⊕⊕◯◯ LOW[a,c] |
| DBP | 383 (5) | The mean DBP ranged from 76.18 to 85.1 | The mean DBP in the EG was 2.8 lower (4.53 to 1.06 lower) | – | ⊕⊕◯◯ LOW[a,b] |
| SBP | 405 (6) | The mean SBP ranged from 108.11 to 152.7 | The mean SBP in the EG was 4.82 lower (9.98 to 0.35 lower) | – | ⊕⊕◯ LOW[a,c] |
| TG | 476 (8) | The mean TG ranged from 26.28 to 224.09 | The mean TG in the EG was 1.28 higher (3.75 lower to 6.3 higher) | – | ⊕⊕⊕◯ MODERATE[a] |
| HDL-C | 476 (8) | The mean HDL-C ranged from 25.74 to 49.42 | The mean HDL-C in the EG was 1.28 higher (2.58 to 7.38 higher) | – | ⊕⊕◯◯ LOW[a,c] |
| IL-6 | 122 (2) | The mean IL-6 ranged from 1.81 to 18.68 | The mean IL-6 in the EG was 1.50 lower (3.97 lower to 0.97 higher) | – | ⊕◯◯◯VERY LOW[a,b,c] |
| TNF-a | 122 (2) | The mean TNF-a ranged from 36.52 to 78.9 | The mean TNF-a in the EG was 12.97 lower (18.37 to 7.57 lower) | – | ⊕◯◯◯ LOW[a,b] |
| CRP | 130 (2) | The mean CRP ranged from 2.31 to 2.8 | The mean CRP in the EG was 1.24 lower (1.71 to 0.77 lower) | – | ⊕⊕◯◯ LOW[a,b] |
| hsCRP | 143 (2) | The mean hsCRP ranged from 1.006 to 1.49 | The mean hsCRP in the EG was 1.10 lower (4.35 lower to 2.16 higher) | – | ⊕◯◯◯ VERY LOW[a,b,c] |
| MDA | 165 (3) | The mean MDA ranged from 2.81 to 19.78 | The mean MDA in the EG was 2.35 lower (4.47 to 0.24 lower) | – | ⊕◯◯◯ VERY LOW[a,b,c] |

CG, control group; CI, confidence interval; EG, experimental group.
[a]Poor methodology including the method of randomization, allocation concealment, and blinding.
[b]Small sample sizes.
[c]$I^2 \geq 50\%$ for heterogeneity.
⊕:Meets the quality of evidence rating. ◯:Does not meet the quality of evidence rating.

available did not allow for a breakdown of the dosage of curcumin utilized in the smaller groups. Sixth, one of the studies included in the analysis used a combination of curcumin and black seed extract. Nigella sativa seed extract had a beneficial effect on MetS, which may have caused a bias in the analysis.

## 5 Conclusion

The present meta-analysis demonstrates that curcumin supplementation has a positive impact on MetS patients. Future randomized controlled studies should focus on addressing the limitations identified in the present analysis. Future research should aim to include larger sample sizes that encompass diverse ethnic groups, consider gender differences, and explore various forms of curcumin supplements to ensure high bioavailability. In addition, more thorough research is required to determine how curcumin affects inflammatory and oxidative stress indicators in metabolic syndrome. Further exploration is needed to better understand the mechanisms by which curcumin may be effective in treating metabolic syndrome.

## Author contributions

LQ and JZ conceptualized the research question. CG and YR participated in drafting and writing the review. CG, HW, and YR participated in the formulation of retrieval strategies, data acquisition, data analysis, and quality assessment. JL and ML participated in the drawing of tables and figures. XD and WL participated in the critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

## Funding

This study was funded by the Science and Technology Innovation Project of the Chinese Academy of Traditional Chinese Medicine (CI2021A03005).

## 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



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1216708/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 27 July 2023
DOI 10.3389/fendo.2023.1230176



OPEN ACCESS

EDITED BY
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RECEIVED 28 May 2023
ACCEPTED 05 July 2023
PUBLISHED 27 July 2023

CITATION
Jung HS and Choi JW (2023) Association between COVID-19 and incidence of cardiovascular disease and all-cause mortality among patients with diabetes. *Front. Endocrinol.* 14:1230176. doi: 10.3389/fendo.2023.1230176



# Association between COVID-19 and incidence of cardiovascular disease and all-cause mortality among patients with diabetes

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**Introduction:** Although the risk of coronavirus disease 2019 (COVID-19) infection is higher in patients who are diagnosed with diabetes than in those who are not, research on the risk of cardiovascular disease (CVD) in COVID-19 infected patients diagnosed with diabetes compared to those who are not infected by COVID-19 is lacking. This study aimed to examine the association between COVID-19, incidence of CVD, and all-cause mortality in patients with diabetes.

**Methods:** This study used data from the Health Insurance Review and Assessment, and included 16,779 patients with COVID-19 and 16,779 matched controls between January 2017 and June 2021. The outcomes included cardiovascular disease (CVD), coronary heart disease, stroke, and all-cause mortality. Cox proportional hazards regression models were used to evaluate these associations.

**Results:** Patients with diabetes hospitalized because of COVID-19 had a significantly increased risk of CVD (adjusted hazard ratio [AHR], 2.12; 95% confidence interval [CI]: 1.97, 2.27) than those without COVID-19. The risks of coronary heart disease (AHR, 2.00; 95% CI: 1.85, 2.17) and stroke (AHR, 2.21; 95% CI: 1.90, 2.57) were higher in the intervention group than in the control group. In the case of all-cause mortality for middle-aged adults, we observed a higher risk in diabetes patients hospitalized due to COVID-19 than in patients without COVID-19 (AHR, 1.37; 95% CI: 1.18, 1.59).

**Conclusions:** This study showed that patients with diabetes hospitalized due to COVID-19 had an increased risk of CVD, coronary heart disease, stroke incidence, and mortality than those who were not COVID-19 infected, suggesting more careful prevention and management among patients with COVID-19.

KEYWORDS

**diabetes, COVID-19, cardiovascular disease, coronary heart disease, stroke, mortality**

# Introduction

The rapid spread of coronavirus disease 2019 started from its emergence in Wuhan, China, and has affected many countries around the world, causing various complications and death in severely infected patients. In January 2020, the first case of COVID-19 was observed in Korea, with approximately 30 million patients, accounting for more than half of the total population. This is still ongoing, and the number of cumulative deaths is 34,000 approximately. Generally, COVID-19 is accompanied by clinical symptoms, including cough, fever, sore throat, and muscle pain. However, some seriously infected patients experience severe symptoms such as dyspnoea, shock, and multiple organ dysfunction syndrome (1–3). Moreover, COVID-19 has had a major effect on the incidence of severe diseases related to the cardiovascular system, including stroke, heart failure, and death (4–8).

With the ongoing COVID-19 pandemic, many studies in various nations have reported factors that increase risk of severe COVID-19 infection (9, 10). In particular, patients who have comorbidities such as hypertension or diabetes suffered from severe COVID-19 symptoms (11–15). Furthermore, the risk of COVID-19 infection is higher in patients who were diagnosed with diabetes than those who were not (16–18). These infection risk and severity of symptoms are known to be related to several clinical mechanism including the viral load due to efficient virus entry and abnormal immune system with cytokine responses (16). Therefore, it is important to investigate the risk factors linked to COVID-19 in patients with diabetes to manage the prognosis after COVID-19 infection.

Although cardiovascular disease (CVD) is a typical complication in patients with diabetes, research on the risk of CVD in COVID-19 patients with diabetes is insufficient (19, 20). In Sweden, there was a study that compared COVID-19 and influenza on the risk of severe diseases and mortality in diabetes patients (21). The risk of death was significantly higher in COVID-19 patients than in influenza patients; however, there was no statistically significant difference in stroke events. Another study compared CVD complications in COVID-19 patients with and without diabetes; however, this study included a relatively small number of participants (n = 140) registered in the hospital's electronic medical records (22). This study showed that the risk of CVD incidence significantly increased in patients with diabetes; however, the estimation was unstable for several outcomes owing to the small sample size. However, none of these studies conducted a comparative analysis of COVID-19 uninfected patients. To understand the risk of COVID-19 infection in patients with diabetes, it is necessary to compare them with uninfected patients with diabetes as the control group.

Thus, in this study, we aimed to measure the risk of CVD incidence in COVID-19 infected diabetes patients compared with that in uninfected patients with diabetes. Furthermore, we conducted a subgroup analysis stratified by gender and age to investigate the relationship within each group.

# Methods

## Data and study sample

We designed cohort study to evaluate the risk of CVD incidence in COVID-19 infected diabetes compared with that in uninfected patients with diabetes. We used data from the Health Insurance Review and Assessment (HIRA) between January 2014 and May 2022 (23). The national health insurance system in Korea provides coverage for nearly 98% of the population, including a national medical aid program. The data includes visiting information on the medical facilities of individuals in the Korean population, such as sex, age, diagnosis, treatment, surgery, prescription, in-hospital death, and costs.

Among the 54,282,771 participants enrolled between January 2017 and June 2021, participants who did not receive a diabetes diagnosis were excluded from the study (n=46,013,518) and COVID-19 patients who were not hospitalized (n=28,232). We used the International Classification of Disease 10 (ICD-10) codes to define patients, and those who were diagnosed with diabetes (ICD-10 codes: E10-E14) more than twice within 6 months or prescribed hypoglycaemic agents were defined as patients with diabetes (n=8,268,253). Among these patients, those who were hospitalized because of COVID-19 infection were categorized as the case group (n=53,270).

For comparison, patients who had diabetes without COVID-19 infection were selected for the control group (n=8,186,751). To minimize selection bias, we performed 1:1 propensity score matching (PSM) for sex and age of individual participants. Sex and age, which were matching variables, were set based on the date of diabetes diagnosis. After completing PSM, the first date of COVID-19 infection for each individual in the case group was assigned as the index date of the matched control group. Participants were diagnosed with diabetes after the index date (n=10,223) or with CVD before the index date (n=38,016). We considered the wash-out period to be 3 years before the index date for the CVD outcome. After these exclusions, participants in the no-comparison group were excluded (n=24,843). Finally, this study enrolled 16,729 participants for each group (Figure 1).

## Measurements

The outcome of this study was the period from COVID-19 (ICD-10 codes: U07.1, U07.2, B34.2, and B97.2) infection to the diagnosis of CVD or date of death. We used ICD-10 codes for the diagnosis of CVD, including coronary heart disease (CHD) (ICD-10 codes: I20–I25) and stroke (ICD-10 codes: I60–I63). The period of outcomes started from the first date of COVID-19 infection between January 2017 and June 2021, which was defined as the index date. All participants were observed until May 2022 for CVD event and date of death. CVD diagnosis and death were defined as the first diagnosis or death date after the index date, respectively. For participants in whom events did not occur, period were measured by the last follow-up date.

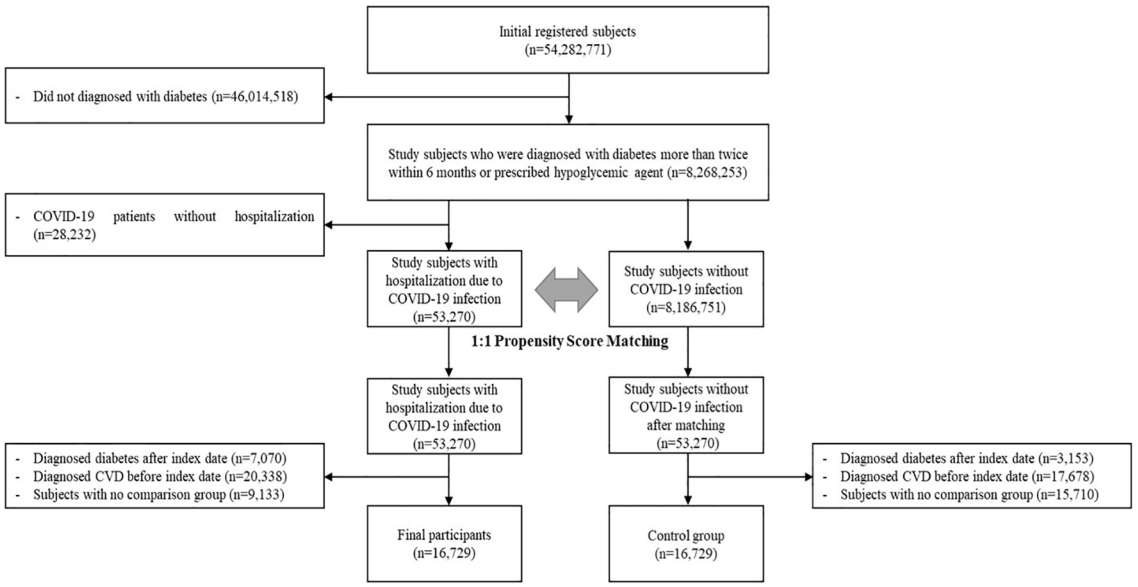


FIGURE 1
Flow chart of study participants.

In this study, the matched variables, sex and age, were measured based on the date of diabetes diagnosis, and the characteristics were defined as follows: the comorbidities were measured by the presence of medical history with heart failure (ICD-10 codes: I50, I11.0, I13.0, and I13.2), chronic kidney disease (ICD-10 codes: N17–N19, Z49, I12.0–I12.9, I13.1, I13.2, N08.3, E10.2, E11.2, E12.2, E13.2, E14.2, and Z99.2), peripheral artery disease (ICD-10 codes: G45, G46, I60–I69, I70.2, I73.9, I74.2–I74.9), chronic obstructive pulmonary disease (ICD-10 codes: J44), pneumonia (ICD-10 codes: J10–J18), obesity (ICD-10 codes: E66), rheumatologic disease (ICD-10 codes: M05–M14, M30–M36, and M79.0), atrial fibrillation (ICD-10 codes: I48), and cancer (ICD-10 codes: C00-C99). We observed comorbidities from the index date until 3 years ago.

## Statistical analysis

In Table 1, we have provided the details of demographic characteristics, such as sex and age, along with their comorbidities. All variables were compared between groups before and after matching. Number of participants and percentage are presented as categorical variables while mean ± standard deviations are presented as continuous variables. To examine the differences between groups,

TABLE 1 General characteristics of study participants.

| Variables | Pre-PSM | | | | | Post-PSM | | |
|---|---|---|---|---|---|---|---|---|
| | Diabetes patients with hospitalization due to COVID-19 infection | | Diabetes patients without COVID-19 infection | | p-value | Diabetes patients without COVID-19 infection | | p-value |
| | N, Mean | %, SD | N, Mean | %, SD | | N, Mean | %, SD | |
| Total | 16,729 | | 8,186,751 | | | 16,729 | | |
| Sex | | | | | <0.001 | | | 1.000 |
| Men | 8,413 | 50.3 | 4,250,051 | 51.9 | | 8,413 | 50.3 | |
| Women | 8,316 | 49.7 | 3,936,700 | 48.1 | | 8,316 | 49.7 | |
| Age (mean ± standard deviation) | 59.94 | 15.3 | 61.27 | 14.6 | <0.001 | 60.03 | 15.3 | 0.5894 |
| Comorbidities | | | | | | | | |
| Heart failure | 3,752 | 22.4 | 1,071,289 | 13.1 | <0.001 | 1,317 | 7.9 | <0.001 |
| CKD | 4,023 | 24.1 | 1,380,051 | 16.9 | <0.001 | 2,839 | 17.0 | <0.001 |

*(Continued)*

TABLE 1 Continued

| Variables | Pre-PSM | | | | | Post-PSM | | |
|---|---|---|---|---|---|---|---|---|
| | Diabetes patients with hospitalization due to COVID-19 infection | | Diabetes patients without COVID-19 infection | | p-value | Diabetes patients without COVID-19 infection | | p-value |
| | N, Mean | %, SD | N, Mean | %, SD | | N, Mean | %, SD | |
| Peripheral artery disease | 4,115 | 24.6 | 1,955,371 | 23.9 | 0.0306 | 3,814 | 22.8 | <0.001 |
| COPD | 1,172 | 7.0 | 493,835 | 6.0 | <0.001 | 731 | 4.4 | <0.001 |
| Pneumonia | 6,120 | 36.6 | 1,102,796 | 13.5 | <0.001 | 1,846 | 11.0 | <0.001 |
| Obesity | 134 | 0.8 | 41,672 | 0.5 | <0.001 | 113 | 0.7 | 0.1799 |
| Rheumatologic disease | 8,649 | 51.7 | 3,713,054 | 45.4 | <0.001 | 7,593 | 45.4 | <0.001 |
| Atrial fibrillation | 644 | 3.9 | 303,866 | 3.7 | 0.3459 | 308 | 1.8 | <0.001 |
| Cancer | 4,228 | 25.3 | 1,278,975 | 15.6 | <0.001 | 2,760 | 16.5 | <0.001 |
| CVD | 2,944 | 17.6 | – | – | – | 1,237 | 7.4 | <0.001 |
| Death | 1,723 | 10.3 | – | – | – | 919 | 5.5 | <0.001 |

PSM, propensity score matching; COVID-19, coronavirus disease 2019; SD, standard deviation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

statistical analysis was performed using Pearson's chi-square test and independent t-test for each type of variable.

For the two main outcomes, the association between hospitalization due to COVID-19 and the incidence of CVD or all-cause mortality was evaluated using Cox proportional hazards regression models. Adjusted hazard ratios (AHR) and 95% confidence intervals were calculated after adjusting for comorbidities. In addition, CVD events were separated into CHD and stroke events and evaluated for each event. First, our objective was to investigate the impact of COVID-19 hospitalization on the incidence of CVD and all-cause mortality in patients with diabetes. Second, we performed a subgroup analysis based on sex and age. Proportional hazard assumptions were assessed statistically and satisfied all the models. Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Institutional Review Board of Health Insurance Review and Assessment (Trial registration: 2023-018-001).

# Results

This study included 16,729 participants from the case and control groups. The average observation period was 439.0 days (standard deviation: 197.7 days). The demographic characteristics of the study participants are summarized in Table 1. Following 1:1 propensity score matching, there were an equal number of patients with diabetes hospitalized due to COVID-19 and in the control group (n=33,458). The mean age of the participants in each group was 59.94 years and 60.03 years, respectively, and approximately half of the participants were female (49.7%).

## Association between COVID-19 and incidence of CVD and all-cause mortality among patients with diabetes

Patients with diabetes hospitalized due to COVID-19 had a higher proportion across all categories of comorbidities. Among these comorbidities, statistically significant differences were observed between groups, except obesity. The differences were especially notable among patients with heart failure, CKD, and pneumonia. In the case group, 22.4% of participants had been diagnosed with heart failure, compared to only 7.9% in the control group. The incidences of CKD and pneumonia were 24.1% and 36.6% in the case group, and 17.0% and 11.0% in the control group, respectively.

The results of Cox proportional hazards model to examine the risk of CVD, CHD, stroke events, and all-cause mortality are summarized in Table 2, including the number of events, AHR, and 95% confidence interval (CI). Patients with diabetes who were hospitalized due to COVID-19 demonstrated a significantly increased risk of CVD (AHR, 2.12; 95% CI: 1.97, 2.27) than those without COVID-19. Regarding the incidence of CHD, the risk was higher in patients with diabetes who were hospitalized because of COVID-19 than in those without COVID-19 (AHR, 2.00; 95% CI: 1.85, 2.17). Furthermore, patients with diabetes who were hospitalized due to COVID-19 showed a higher risk of stroke incidence compared to those without COVID-19 (AHR, 2.21; 95% CI 1.90, 2.57). In the case of all-cause mortality, we observed a higher risk in patients with diabetes hospitalized because of COVID-19 than in patients without COVID-19 (AHR, 1.10; 95% CI: 1.01, 1.20).

TABLE 2 Association between COVID-19 and incidence of CVD and all-cause mortality among patients with diabetes .

| Variables | N | Events | adjusted HR | 95% CI | | p-value |
|---|---|---|---|---|---|---|
| CVD events | | | | | | |
| COVID-19 | | | | | | |
| No | 16,729 | 1,237 | 1.00 | | | |
| Yes | 16,729 | 2,944 | 2.12 | 1.97 | 2.27 | <0.001 |
| CHD events | | | | | | |
| COVID-19 | | | | | | |
| No | 16,729 | 971 | 1.00 | | | |
| Yes | 16,729 | 2,256 | 2.00 | 1.85 | 2.17 | <0.001 |
| Stroke events | | | | | | |
| COVID-19 | | | | | | |
| No | 16,729 | 266 | 1.00 | | | |
| Yes | 16,729 | 688 | 2.21 | 1.90 | 2.57 | <0.001 |
| All-cause mortality | | | | | | |
| COVID-19 | | | | | | |
| No | 16,729 | 919 | 1.00 | | | |
| Yes | 16,729 | 1,723 | 1.10 | 1.01 | 1.20 | 0.030 |

COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; CHD, coronary heart disease.

## Association between COVID-19 and incidence of CVD and all-cause mortality by sex and age

Figure 2 shows the results of subgroup analysis according to sex and age. For all categories of sex and age, which were men, women, middle-aged adults, and older adults, patients with diabetes hospitalized due to COVID-19 showed a significantly higher risk of CVD incidence than uninfected patients with diabetes, especially in older adults (AHR, 2.45; 95% CI: 2.20, 2.73). In terms of sex, both men (AHR, 2.12; 95% CI: 1.92, 2.34) and women (AHR, 2.11; 95% CI: 1.92, 2.33) with diabetes who were hospitalized due to COVID-19 had an increased risk for CVD incidence. For middle-aged adults with diabetes who were hospitalized due to COVID-19 had a significantly higher risk of all-cause mortality compared to those who were not infected (AHR, 1.37; 95% CI: 1.18, 1.59). There were no significant differences among the other categories.

# Discussion

In this study, we discovered that patients with diabetes who were hospitalized because of COVID-19 had an increased risk of CVD incidence and all-cause mortality, as compared to those without COVID-19. Depending on the CVD subtype, CHD incidence and stroke incidence were significantly higher in patients hospitalized due to COVID-19 infection as well. From the results of subgroup analysis according to sex and age, patients with diabetes hospitalized due to COVID-19 showed a significantly higher risk of CVD and all-cause mortality than uninfected patients for all categories of subgroups, including men, women, middle-aged adults, and older adults. The risk of all-cause mortality in the middle-aged adults was significantly higher in patients with diabetes hospitalized because of COVID-19 than uninfected patients and there was no difference in case of older adults. While the risk of death from COVID-19 infection is known to be higher in older adults, our study considered all-cause mortality due to the structure of the data. Despite adjusting for comorbidities, the risk of death from other factors remains which may explain no difference between COVID-19 infected group and uninfected group. In middle-aged adults, the risk of all-cause mortality including COVID-19 infection could be higher in COVID-19 infected group compared to uninfected group because of the risk of death from other factors is relatively low.

In a previous study, the results indicated that there was no statistically significant difference in risk of stroke and ischemic heart disease between influenza-infected patients with diabetes and patients with diabetes hospitalized due to COVID-19 for both diabetes types 1 and 2; however, the risk of death was significantly higher in patients hospitalized for COVID-19 (21). We defined the control group as patients with diabetes but without COVID-19, and we showed that the risk of CVD incidence, including CHD and stroke, was increased in patients with diabetes hospitalized due to COVID-19. These results regarding the incidence of CVD could be due to differences in the definition of the control group.

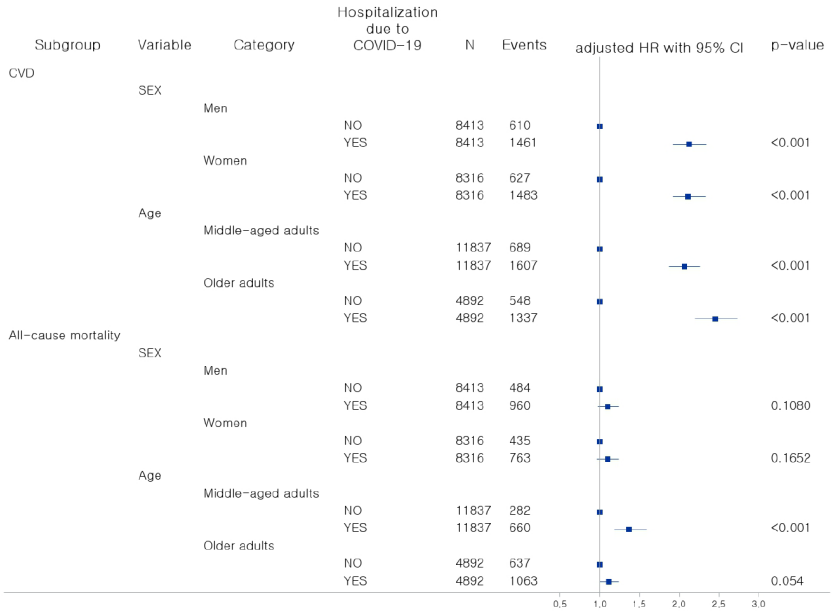


FIGURE 2
Association between COVID-19 and incidence of CVD and all-cause mortality by sex and age. COVID-19, coronavirus disease-19; HR, hazard ratio; CI, Confidence interval; CVD, cardiovascular disease.

Several previous studies have examined the association between diabetes and CVD, along with the relationship between COVID-19 and CVD. In a previous study, the risk of stroke increased in COVID-19 patients, and a link between severe COVID-19 and stroke incidence was reported (4–8). These results suggest that the risk of stroke could be increased in patients with severe COVID-19 compared to uninfected individuals, especially those with known risk factors such as diabetes, which we discussed in this study. Another study that investigated the association between COVID-19 and CVD showed an increased risk of CVD, such as cerebrovascular disorders, myocarditis, and heart failure, 30 days after COVID-19 infection, indicating that follow-up management should be conducted in COVID-19 patients with cardiovascular disease (8). There are several clinical mechanism that infection of COVID-19 increase CVD disease. First, the endothelium performs various functions, including coagulation and inflammatory responses. The coronavirus can invade endothelial cells, causing direct damage to the cell membrane and thus directly impacting endothelial dysfunction. Inflammation and coagulation due to endothelial dysfunction can increase cardiovascular disease and cytokine responses due to an abnormal immune system can cause brain damage (24, 25). Second, the renin-angiotensin system, which is related to the regulation of the kidney, heart, and vascular physiology, is downregulated due to COVID-19, which can cause abnormalities in the function of organs such as the heart and brain (4–8). Third, COVID-19 infection can affect lipid metabolism. It can lead to increased levels of cholesterol and triglycerides in patients, which can induce inflammation of the vascular endothelium and increase the risk of cardiovascular disease (26).

Diabetes is known to be a risk factor for mortality in COVID-19 patients, and our study observed an increased risk of all-cause mortality among patients with diabetes who were hospitalized due to COVID-19, as compared to those who were not infected COVID-19 (11–15). This could be due to reasons such as a weakened immune system, inflammation, and control of blood sugar (11–15). From this perspective, our findings indicate that COVID-19 prevention and management are necessary to reduce mortality and CVD incidence in patients with diabetes.

This study had some limitations. First, although our data have no information on some parameters that could affect the incidence of CVD and mortality, such as body mass index (BMI), this study used the diagnosis information for obesity to adjust the effect of BMI on results (27, 28). Second, we could not control for the vaccination effect, which affects the severity of the COVID-19 infection. Although we defined the control group as hospitalized patients with COVID-19 to reflect the severity of the COVID-19 infection, the vaccination status of every study participant was unknown and this may have affected the analysis results. Third, our database was limited to the Korean population. Further studies are needed to examine our findings in other countries and ethnic groups.

## Conclusion

This study is the first to investigate the association between COVID-19 and the incidence of CVD in patients with diabetes compared to diabetes patients without COVID-19. We found that patients with diabetes hospitalized with COVID-19 had an increased risk of CVD incidence and mortality compared to those who were not COVID-19 infected. Our results indicate that careful prevention and management are needed for patients with COVID-19 diagnosed with diabetes. Further studies are required to investigate the association between COVID-19 and other severe diseases in patients with diabetes.

## Data availability statement

The datasets presented in this article are not readily available because of privacy or ethical restrictions. Requests to access the datasets should be directed to the corresponding author.

## Ethics statement

This study was approved by the Institutional Review Board of Health Insurance Review and Assessment (Trial registration: 2023-018-001).

## Author contributions

HJ and JC designed the study. HJ and JC performed the literature review and interpretation for data analysis. HJ and JC analyzed the data. HJ and JC wrote the draft. All authors contributed to the article and approved the submitted version.

## 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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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 05 September 2023
DOI 10.3389/fendo.2023.1241307



OPEN ACCESS

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RECEIVED 16 June 2023
ACCEPTED 14 August 2023
PUBLISHED 05 September 2023

CITATION
Cao W, Deng Y, Lv L, Liu X, Luo A, Yin L and Li Z (2023) Assessment of left ventricular function in patients with type 2 diabetes mellitus by non-invasive myocardial work.
*Front. Endocrinol.* 14:1241307.
doi: 10.3389/fendo.2023.1241307



# Assessment of left ventricular function in patients with type 2 diabetes mellitus by non-invasive myocardial work

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**Background:** Diabetes mellitus (DM) is a chronic disease that poses a serious risk of cardiovascular diseases. Therefore, early detection of impaired cardiac function with non-invasive myocardial imaging is critical for improving the prognosis of patients with DM.

**Purpose:** This study aimed to assess the left ventricular (LV) function in patients with type 2 diabetes mellitus (T2DM) by non-invasive myocardial work technique.

**Materials and methods:** In all, 67 patients with T2DM and 28 healthy controls were included and divided into a DM group and a control group. Two-dimensional dynamic images of apical three-chamber view, apical two-chamber view, and apical four-chamber view were collected from all subjects, consisting of at least three cardiac cycles. LV myocardial strain parameters, including global longitudinal strain (GLS) and peak strain dispersion (PSD), as well as myocardial work parameters, including global constructive work (GCW), global wasted work (GWW), global work index (GWI), and global work efficiency (GWE), were obtained and analyzed.

**Results:** A total of 15 subjects were randomly selected to assess intra-observer and inter-observer consistency of myocardial work parameters and strain parameters, which showed excellent results (intra-class correlation coefficients: 0.856 - 0.983, $P<0.001$). Compared with the control group, the DM group showed significantly higher PSD (37.59 ± 17.18 ms *vs.* 27.72 ± 13.52 ms, $P<0.05$) and GWW (63.98 ± 43.63 mmHg% *vs.* 39.28 ± 25.67 mmHg%, $P<0.05$), and lower GWE (96.38 ± 2.02% *vs.* 97.72 ± 0.98%, $P<0.001$). Furthermore, the PSD was positively correlated with GWW ($r = 0.565$, $P<0.001$) and negatively correlated with GWE ($r = -0.569$, $P<0.001$).

**Conclusion:** Uncoordinated LV myocardial strain, higher GWW, and lower GWE in patients with T2DM may serve as indicators for the early assessment of cardiac impairment in T2DM.

KEYWORDS

**myocardial work, type 2 diabetes mellitus, left ventricle, function, non-invasive**

## Highlights

- Uncoordinated LV myocardial strain, higher GWW, and lower GWE may be considered indicators of the early assessment of cardiac impairment in T2DM.
- Uncoordinated LV myocardial strain might be one of the reasons for increased GWW and decreased GWE.

## Introduction

The GBD Diabetes Collaborators have recently reported that the global burden of diabetes remains a significant public health challenge. In 2021, it was estimated that 529 million individuals were living with diabetes worldwide, with a global age-standardized total diabetes prevalence of 6.1%. By the year 2050, 89 out of 204 countries and territories will have an age-standardized rate of diabetes prevalence greater than 10% (1). Patients with type 2 diabetes mellitus (T2DM) have an increased incidence of cardiovascular diseases and are at high risk of experiencing sudden cardiac death (2, 3). Cardiac function impairment can occur at an early stage, even though the clinical manifestations of heart failure may not be obvious at this stage (4).

Early detection of impaired cardiac function is of great value for early treatment and improved prognosis. Cardiac magnetic resonance (CMR) is considered a precise non-invasive technique available for assessing cardiac structure and function. However, it possesses lower temporal resolution than echocardiography (5). Moreover, due to its expensive cost, time-consuming nature, and susceptibility to respiratory and arrhythmic artifacts, the clinical application of CMR remains somewhat restricted. In contrast, echocardiography, including tissue Doppler imaging, speckle tracking imaging, and non-invasive myocardial work, offers the advantages of convenience, affordability, and lack of ionizing radiation. Echocardiography is widely utilized in clinical settings. Non-invasive myocardial work is a new technique for evaluating myocardial function that provides a quantitative assessment of left ventricle function (6, 7). To date, only a limited number of studies have applied non-invasive myocardial work to explore the changes in myocardial function in patients with T2DM. However, some problems remain unsolved. First, the potential confounding effects of other coexisting conditions, including but not limited to hyperlipidemia and hypertension, on cardiac function injury have not been adequately addressed. Second, conventional ultrasound parameters have not been comprehensively evaluated in comparative studies (8–10). Finally, the results of some studies are controversial. Wang (8) and Yan (9) have suggested that individuals with T2DM exhibit increased global wasted work (GWW) and decreased global work efficiency (GWE) compared to the general population. However, Wang et al. found no statistically significant differences in GWW and GWE between the two groups (10). In the present study, we used a non-invasive myocardial work technique to obtain myocardial work parameters and compared them with conventional ultrasound parameters after excluding potential confounding factors. The findings of this study may provide evidence for the early diagnosis of impaired cardiac function in patients with T2DM.

## Materials and methods

### Study population

The DM group in this study consisted of 67 patients with T2DM who received treatment at Sichuan Provincial People's Hospital between November 2018 to February 2019. Patients were required to meet the World Health Organization (WHO) standards (11), have no history of heart disease, and have normal physical examination and electrocardiogram (ECG) results. The inclusion criteria were as follows: (1) the presence of classic symptoms of hyperglycemia, including thirst, polyuria, weight loss, and blurry vision, along with a random blood glucose value of 200 mg/dL (11.1 mmol/L) or higher; (2) absence of classic symptoms of hyperglycemia, but the presence of any of the following criteria: fasting plasma glucose (FPG) values ≥ 126 mg/dL (7.0 mmol/L) (fasting defined as no caloric intake for at least 8 hours), two-hour plasma glucose values of ≥ 200 mg/dL (11.1 mmol/L) during a 75 g oral glucose tolerance test, and a glycosylated hemoglobin A1c (HbA1c) value ≥ 6.5% (48 mmol/mol). The diagnosis of diabetes was confirmed on a subsequent day by repeating the same test for confirmation or through two different tests that were concordant with the diagnosis of diabetes (12). The exclusion criteria were as follows: patients with type 1 DM, coronary atherosclerotic heart disease, congenital heart disease, cerebral infarction, peripheral arterial occlusive disease, valvular stenosis, valvular moderate or severe regurgitation, clinical diagnosis of heart failure, as well as those patients whose ultrasound examination revealed a left ventricular ejection fraction (LVEF) < 50%, intracardiac thrombus, intracardiac tumor, familial hypercholesterolemia, atrial fibrillation and other severe arrhythmias, Takayasu arteritis and other autoimmune diseases, liver or renal dysfunction, and poor ultrasound imaging quality of the heart. The control group consisted of 28 healthy volunteers who had no history of physical and laboratory evidence of DM, hypertension, hypercholesterolemia, or cardiovascular, cerebrovascular, or peripheral vascular diseases. These volunteers were matched to the patients in the DM group based on age and sex. The exclusion criteria of healthy controls were the same as the DM group. The study protocol was approved by the ethics committee of our hospital, and written informed consent was obtained from all participants.

### Demographic characteristics

Data including age, sex, and body mass index (BMI) were collected from all participants. Additionally, serum levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), FPG, and glycosylated HbA1c were measured at the clinical laboratory department of our hospital. Measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were obtained from enrolled patients and healthy controls at the time of the acquisition of the apical views.

## Traditional LV function examination

All participants were subjected to a left lateral position for echocardiographic examination, and electrodes were connected to record the ECG. A GE Vivid E9 ultrasound machine (GE Inc., Boston, USA), equipped with an M5S phased array probe (1.5-4.6 MHz) (GE Inc., Boston, USA) was used to scan the heart while participants held their breath. After all the images were collected directly by an associate chief physician, a chief physician evaluated the image quality and the standard of the section, and selected graphics were recognized by both doctors for follow-up analysis. When there was a dispute, another chief physician was asked to evaluate or collect images again.

Pulsed Doppler was used to measure peak early-diastolic mitral velocity (E) and peak late-diastolic mitral velocity (A), while tissue Doppler imaging was used to measure the peak early-diastolic velocity (e') of the lateral and septal mitral annulus. The average e' was then calculated as (lateral e'+ septal e')/2, while the Tei index was calculated as (time interval between the end of wave a and the start of wave e in the next cardiac cycle - time interval between the start and end of wave s)/time interval between the start and end of wave s. The endocardial boundary was delineated at the end-systolic and end-diastolic periods of the apical two-chamber and four-chamber views. This allowed for the automatic calculation of left ventricular end-systolic volume (ESV), end-diastolic volume (EDV), stroke volume (SV), and ejection fraction (EF).

## LV myocardial strain and myocardial work parameters acquisition

The two-dimensional dynamic images (at least three cardiac cycles) of the apical three-chamber view, apical two-chamber view, and apical four-chamber view, and the pulsed-wave Doppler images of the aortic valve and mitral valve were imported into EchoPAC workstation (GE Inc., Boston, USA) for analysis. The opening and closing nodes of the aortic and mitral valves were recorded by analyzing the blood flow spectra. A software program was utilized in conjunction with electrocardiography to identify dynamic images of three cardiac sections. Additionally, the left ventricular intima was auto-traced and manually corrected. Furthermore, blood pressure data was collected from the subjects and analyzed using the non-invasive myocardial work mode. Finally, the myocardial strain and myocardial work parameters of the left ventricle were obtained, including global longitudinal strain (GLS), peak strain dispersion (PSD), global constructive work (GCW), global wasted work (GWW), global work index (GWI), and global work efficiency (GWE).

## Repeatability of measurements

In all, the images of 15 subjects were randomly selected, and their myocardial strain parameters and myocardial work parameters were independently measured by Li Z (12 years of work experience) and Cao W (1 year of work experience). Two weeks later, Li Z reanalyzed the images.

## Statistical analysis

Statistical analysis was conducted using SPSS 22.0 (IBM Corp., Armonk, NY, USA). The measurement data were expressed as mean ± standard deviation (SD). To compare the two groups, the Student's t-test and Wilcoxon rank sum test were used based on the normality and homogeneity of the variance of the data. Categorical data were expressed as n (%), and the $\chi^2$ test was used for between-group comparisons. Bivariate correlation was assessed using Pearson correlation analysis. Inter-group and intra-group consistency tests were performed by intra-class correlation coefficients (ICCs). $P < 0.05$ was considered statistically significant.

# Results

A total of 67 patients were enrolled in the DM group, with an average age of 59.85 ± 12.17 years, including 38 men. The control group consisted of 28 subjects with an average age of 57.63 ± 12.72 years, including 12 men.

## Demographic characteristics

Compared with the control group, patients with T2DM had significantly higher serum levels of FPG (10.59 ± 4.96 mmol/L vs. 4.98 ± 0.60 mmol/L, P<0.001) and higher levels of HbA1c (9.70 ± 3.70% vs. 5.11 ± 0.68%, P<0.001) (Table 1). No significant differences were observed in other baseline demographic characteristics between the two groups (P>0.05) (Table 1).

## Differences in conventional ultrasound parameters between the DM and the control groups

Compared with the control group, the DM group showed slower lateral e' (9.11 ± 2.70 cm/s *vs.* 10.88 ± 3.99 cm/s, *P*<0.05) and septal e' (7.35 ± 2.25 cm/s *vs.* 8.85 ± 2.70 cm/s, *P*<0.01) (Table 2). However, there were no significant differences in ESV, EDV, SV, EF, E/A, E/average e', and Tei index between the two groups (P>0.05) (Table 2).

## Differences in strain parameters and myocardial work parameters between the DM and the control groups

Although there was no statistically significant difference in GLS between the two groups, the proportion of patients with GLS > -20% was significantly higher in the DM group than in the control group (36

TABLE 1 Demographic characteristics.

| | DM group (n=67) | Control group (n=28) | P-value |
|---|---|---|---|
| Age, years | 59.85 ± 12.17 | 57.63 ± 12.72 | 0.433 |
| Male, n (%) | 38 (56.7%) | 12 (42.9%) | 0.157 |
| BMI, kg/m$^2$ | 25.21 ± 3.49 | 23.75 ± 2.24 | 0.144 |
| SBP, mm Hg | 131 ± 19 | 123 ± 18 | 0.073 |
| DBP, mm Hg | 76 ± 12 | 74 ± 9 | 0.353 |
| HR, bpm | 76 ± 12 | 74 ± 14 | 0.389 |
| TG, mmol/L | 2.44 ± 2.70 | 1.35 ± 0.55 | 0.095 |
| TC, mmol/L | 4.64 ± 1.24 | 4.56 ± 0.92 | 0.803 |
| LDL-C, mmol/L | 2.56 ± 0.97 | 2.90 ± 0.71 | 0.185 |
| HDL-C, mmol/L | 1.12 ± 0.35 | 1.26 ± 0.24 | 0.121 |
| FPG, mmol/L | 10.59 ± 4.96 | 4.98 ± 0.60 | 0.000 |
| HbA1c, % | 9.70 ± 3.70 | 5.11 ± 0.68 | 0.000 |

Values are expressed as mean ± standard deviation or number (%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin A1c.

(53.7%) *vs.* 8 (28.6%), respectively, P<0.05) (Table 3). Furthermore, compared with the control group, the DM group exhibited increased PSD (PSD: 37.59 ± 17.18 ms *vs.* 27.72 ± 13.52 ms, P<0.05) and GWW (63.98 ± 43.63 mmHg% *vs.* 39.28 ± 25.67 mmHg%, P<0.05), and decreased GWE (96.38 ± 2.02% *vs.* 97.72 ± 0.98%, P<0.001, P<0.001) (Figure 1, Table 3). However, there was no significant difference in GWI and GCW between the two groups (P>0.05) (Table 3).

## Correlations of strain parameters and myocardial work parameters

The correlation analysis revealed a positive correlation between PSD and GWW (r = 0.565, P<0.001) and a negative correlation between PSD and GWE (r = -0.569, P<0.001) (Figure 2, Table 4).

TABLE 2 Conventional LV function parameters.

| | DM group (n=67) | Control group (n=28) | P-value |
|---|---|---|---|
| E, cm/s | 71.67 ± 17.10 | 68.52 ± 12.16 | 0.358 |
| A, cm/s | 78.90 ± 16.36 | 73.93 ± 18.88 | 0.236 |
| E/A | 0.94 ± 0.25 | 0.96 ± 0.22 | 0.621 |
| Lateral e', cm/s | 9.11 ± 2.70 | 10.88 ± 3.99 | 0.046 |
| Septal e', cm/s | 7.35 ± 2.25 | 8.85 ± 2.70 | 0.009 |
| E/average e' | 8.47 ± 2.52 | 8.01 ± 3.37 | 0.539 |
| EDV, ml | 70.69 ± 20.04 | 64.93 ± 17.07 | 0.200 |
| ESV, ml | 22.79 ± 8.30 | 21.56 ± 7.06 | 0.505 |
| SV, ml | 47.93 ± 13.97 | 43.41 ± 12.07 | 0.151 |
| EF, % | 68.04 ± 6.76 | 66.79 ± 6.53 | 0.426 |
| Tei index | 0.52 ± 0.16 | 0.49 ± 0.76 | 0.315 |

Values are expressed as mean ± standard deviation.
E, peak early-diastolic mitral velocity; A, peak late-diastolic mitral velocity; e', mitral annular peak early-diastolic velocity; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; EF, ejection fraction.

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TABLE 3 Myocardial work parameters and strain parameters.

| | DM group (n=67) | Control group (n=28) | P-value |
|---|---|---|---|
| GLS, % | -18.94 ± 2.99 | -19.68 ± 1.75 | 0.153 |
| GLS > -20%, n (%) | 36 (53.7%) | 8 (28.6%) | 0.025 |
| PSD, ms | 37.59 ± 17.18 | 27.72 ± 13.52 | 0.012 |
| GWI, mmHg% | 2026.35 ± 533.68 | 1959.36 ± 353.61 | 0.565 |
| GCW, mmHg% | 2297.16 ± 537.51 | 2259.52 ± 373.12 | 0.710 |
| GWW, mmHg% | 63.98 ± 43.63 | 39.28 ± 25.67 | 0.010 |
| GWE, % | 96.38 ± 2.02 | 97.72 ± 0.98 | 0.000 |

Values are expressed as mean ± standard deviation or number (%).
GLS, global longitudinal strain; PSD, peak strain dispersion; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global constructive efficiency.

## Repeatability of measurements

The ICCs values of GLS, PSD, GWI, GWE, GCW, and GWW were all greater than 0.75 (P<0.001) (Table 5), indicating good reproducibility and reliability of the tests.

# Discussion

In 1972, Rubler and his colleagues first proposed the concept of diabetic cardiomyopathy, which suggested that DM is an independent causative factor of cardiovascular disease (13). Diabetic cardiomyopathy can cause myocardial hypertrophy and fibrosis due to metabolic disorders and other mechanisms, eventually leading to impaired diastolic and systolic functions. Cardiac diastolic dysfunction is more common and occurs earlier than systolic dysfunction (14–17). Echocardiography is a simple, non-invasive, and inexpensive method that can be used to diagnose heart failure, and evaluate prognosis and is considered the preferred imaging technique for clinical staff to evaluate myocardial function (18). Non-invasive myocardial work combines LV pressure with GLS to address the influence of afterload on LV deformation. This method allows for a more comprehensive and accurate evaluation of both local and global myocardial function (19–21). In this study, we found that a few LV diastolic function parameters were changed in patients with T2DM. Specifically, the lateral e' and septal e' were decreased, while the LV systolic function parameters, such as EF and Tei index, remained normal. Moreover, GWE was reduced,

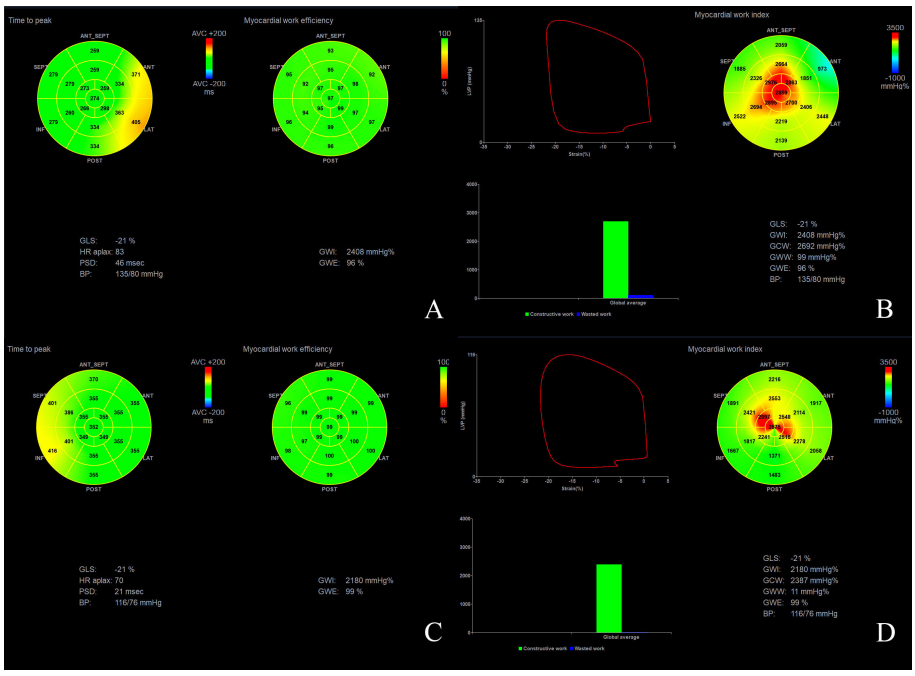


FIGURE 1
Myocardial work assessment of a patient with DM **(A, B)**, and a healthy subject **(C, D)**.

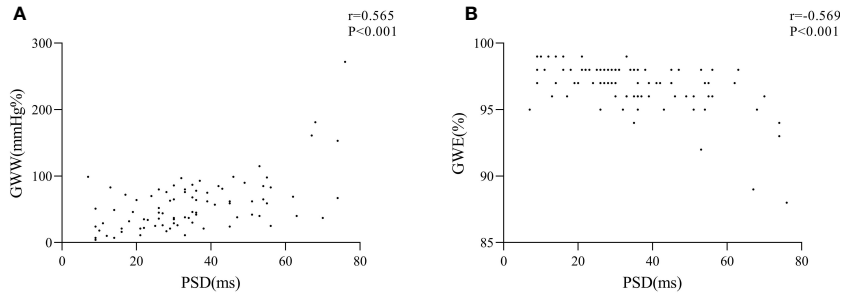


FIGURE 2
Correlation analysis of PSD and GWW **(A)** and GWE **(B)**.

while PSD and GWW were increased in patients with T2DM compared with the controls. Therefore, PSD, GWW, and GWE may have potential value in evaluating early LV dysfunction in patients with T2DM.

## Assessment of LV diastolic function in patients with T2DM

To evaluate LV diastolic function, commonly used parameters include E/A, e', E/average e', etc. E and A reflect the pressure gradient between the left atrium and the LV in the early and late diastolic periods, respectively, and the ratio can be used to reflect the type of LV filling (including normal, abnormal, or pseudo-normalized) and evaluate LV diastolic function. The lateral e' < 10cm/s and septal e'< 7cm/s are considered two indicators of abnormal LV diastolic function. E/average e' can also be used to reflect LV filling pressure. E/average e' < 8 usually indicates normal LV filling pressure, and E/average e' > 14 is highly specific to increased LV filling pressure (14, 22). In this study, we found that compared with the control group, the amplitude of the motion of the mitral annulus in the DM group was reduced, suggesting that diastolic dysfunction may have existed in patients with T2DM.

## Evaluation parameters of LV systolic function in patients with T2DM

EF is the most used parameter for the clinical evaluation of LV systolic function. It reflects the proportion of blood ejected from the left ventricle into the systemic circulation during each cardiac cycle. Although GLS is less commonly used in clinical practice compared to EF, it is a more stable, repeatable, and suitable measure for evaluating subclinical cardiac dysfunction in patients (17). GLS reflects the shortening of the LV myocardium in the direction of the long axis during the systolic period, and a GLS value > -20% is suggested to indicate abnormal LV systolic function. A smaller absolute value indicates worse systolic function. PSD reflects the difference in time when the peak strain reaches each segment of the LV and is used to evaluate the synchronicity of LV myocardial deformation. In this study, the EF values of the two groups were similar and within the normal range. However, the PSD value and the number of patients with GLS>-20% were significantly higher in the DM group compared with the control group. This suggests that in patients with T2DM, LV myocardial deformation displays asynchrony and the longitudinal myocardial strain has been damaged to varying degrees, despite a normal EF.

TABLE 4 Pearson correlation analysis.

| | PSD | |
|---|---|---|
| | r value | P-value |
| GWW | 0.565 | 0.000 |
| GWE | -0.569 | 0.000 |

PSD, peak strain dispersion; GWW, global wasted work; GWE, global constructive efficiency.

## Evaluation of LV global function in patients with T2DM

LV non-invasive pressure-strain loop is generated through two-dimensional speckle tracking technology combined with the LV pressure curve, and it reflects the myocardial work (14). GWI reflects the total LV myocardial work from the mitral valve closure to its opening. GCW reflects the LV myocardial work done to facilitate ventricular ejection and relaxation by making myocardial shortening during systole and lengthening during diastole. Conversely, GWW reflects the LV myocardial work done to hinder ventricular ejection and relaxation by making myocardial lengthening during systole and shortening during diastole. GWE can be calculated as GCW/(GCW+GWW) (10, 23). The Tei index is the ratio of the sum of isovolumic contraction time and isovolumic relaxation time to the ejection time, and it reflects the overall systolic and diastolic function of the LV. An increase in the Tei index indicates a decrease in cardiac function. In this study, GWI, GCW, and Tei index were almost the same in the DM group compared to the control group, but GWW showed a significant increase and GWE was apparently reduced. In the early stage of diabetes, compensation may help maintain normal GWI, GCW, and Tei index. However, due to the increased PSD, some segments of the LV myocardium may reach the peak strain before the end of systole and begin to relax during systole, while some segments may not reach the peak strain at the end of systole, and continue to

TABLE 5 Repeatability of measurements.

| | $ICC_1$(n=15) | P value | 95%CI | $ICC_2$(n=15) | P-value | 95%CI |
|---|---|---|---|---|---|---|
| GLS | 0.915 | 0.000 | 0.769-0.971 | 0.912 | 0.000 | 0.699-0.972 |
| PSD | 0.915 | 0.000 | 0.771-0.970 | 0.933 | 0.000 | 0.951-0.994 |
| GWI | 0.983 | 0.000 | 0.951-0.994 | 0.933 | 0.000 | 0.812-0.977 |
| GCW | 0.973 | 0.000 | 0.922-0.991 | 0.940 | 0.000 | 0.830-0.979 |
| GWW | 0.856 | 0.000 | 0.633-0.949 | 0.925 | 0.000 | 0.796-0.974 |
| GWE | 0.882 | 0.000 | 0.691-0.959 | 0.964 | 0.000 | 0.897-0.988 |

$ICC_1$, Intra-group correlation coefficient; $ICC_2$, Inter-group correlation coefficient. GLS, global longitudinal strain; PSD, peak strain dispersion; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global constructive efficiency.

contract during diastole, leading to an increased GWW and a decreased GWE. Our study showed that PSD was positively correlated with GWW and negatively correlated with GWE, suggesting that uncoordinated LV myocardial strain might be one of the reasons for increased GWW and decreased GWE. Wang et al. found that LV GWW was increased, and the GWE was decreased in patients with T2DM, but their study showed a decrease in EF (5). In our study, the EF and Tei index of patients with T2DM was still normal, suggesting that the changes of LV GWW and GWE occurred earlier than changes in EF and Tei index, which would indicate that GWW and GWE might be more sensitive in detecting cardiac dysfunction in patients with T2DM.

## Limitations

We utilized a non-invasive cardiac ultrasound imaging technique to measure LV myocardial strain and myocardial work parameters. This method is safe, painless, and radiation-free. Moreover, we have provided a novel non-invasive technique for evaluating cardiac function in patients with T2DM. Our findings demonstrate that this technique can identify early signs of cardiac damage in these patients, providing important evidence and possibilities for early intervention and management. The present study has limitations that need to be acknowledged. First, the small sample size in this study limits the ability to perform deep subgroup analysis. Second, the potential influence of hypertension and dyslipidemia in patients with T2DM cannot be completely excluded. However, there was no statistically significant difference in the prevalence of hypertension and dyslipidemia between the two groups, suggesting that their influence might be relatively low. Finally, the history of medication use in T2DM patients was not discussed in this study.

# Conclusion

When only a few diastolic function parameters changed and EF and Tei index remain normal in patients with T2DM, PSD, GWW, and GWE seem to be more sensitive to subclinical LV dysfunction. Uncoordinated LV myocardial strain might be one of the reasons for the increased GWW and decreased GWE. Myocardial strain and myocardial work parameters have good reproducibility and may have potential value in detecting early LV dysfunction in patients with T2DM.

# 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 studies involving humans were approved by the ethics committees of Sichuan Provincial People's hospital. 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.

# Author contributions

ZL and LY designed the research. ZL and YD collected the ultrasound images. ZL, WC, and LL analyzed the ultrasound images. WC, ZL, and LY wrote the main manuscript text. XL and YD finished statistic analysis and prepared Tables 1–5. AL prepared Figures 1 and 2. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

# Funding

The study was supported by the Sichuan Provincial Department of Science and Technology Project (No.2022YFS0247) and the grant from Sichuan Provincial Science and Technology Activities for Overseas Students (No. 2022JY0649).

# 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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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 20 September 2023
DOI 10.3389/fendo.2023.1211954



OPEN ACCESS

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RECEIVED 25 April 2023
ACCEPTED 31 August 2023
PUBLISHED 20 September 2023

CITATION
Yang CD, Chen JW, Quan JW, Shu XY, Feng S, Aihemaiti M, Ding FH, Shen WF, Lu L, Zhang RY and Wang XQ (2023) Long-term glycemic variability predicts compromised development of heart failure with improved ejection fraction: a cohort study. *Front. Endocrinol.* 14:1211954. doi: 10.3389/fendo.2023.1211954



# Long-term glycemic variability predicts compromised development of heart failure with improved ejection fraction: a cohort study

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**Background:** A substantial portion of heart failure (HF) patients adherent to guideline-directed medical therapies have experienced improved ejection fraction (EF), termed HFimpEF. Glycemic variability (GV) has emerged as a critical cardiometabolic factor. However, the relation between long-term GV and the incidence of HFimpEF is still unclear.

**Methods:** A total of 591 hospitalized HF patients with reduced EF (HFrEF, EF≤ 40%) admitted from January 2013 to December 2020 were consecutively enrolled. Repeat echocardiograms were performed at baseline and after around 12 months. The incidence of HFimpEF, defined as (1) an absolute EF improvement ≥10% and (2) a second EF > 40% and its association with long-term fasting plasma glucose (FPG) variability were analyzed.

**Results:** During a mean follow-up of 12.2 ± 0.6 months, 218 (42.0%) patients developed HFimpEF. Multivariate analysis showed FPG variability was independently associated with the incidence of HFimpEF after adjustment for baseline HbA1c, mean FPG during follow-up and other traditional risk factors (odds ratio [OR] for highest vs. lowest quartile of CV of FPG: 0.487 [95% CI 0.257~0.910]). Evaluation of GV by alternative measures yielded similar results. Subgroup analysis revealed that long-term GV was associated with HFimpEF irrespective of glycemic levels and diabetic conditions.

**Conclusions:** This study reveals that greater FPG variability is associated with compromised development of HFimpEF. A more stable control of glycemic levels might provide favorable effects on myocardial functional recovery in HF patients even without diabetes.

KEYWORDS

**glycemic variability, heart failure with improved ejection fraction, heart failure with reduced ejection fraction, myocardial recovery, fasting plasma glucose**

# Introduction

Heart failure (HF) is a prevalent clinical syndrome with high mortality and morbidity. With the development of guideline-directed medical treatment and device therapy, a substantial proportion of HF patients with reduced ejection fraction (EF, HFrEF) have experienced improved left ventricular (LV) EF, thereafter termed HF with recovered or improved EF (HFimpEF) (1–5). Compared with other types of HF, HFimpEF possesses distinct pathophysiological characteristics, clinical manifestations, and better prognosis (4–7). In the 2022 AHA/ACC/HFSA Guideline for the Management of HF (8), HFimpEF was thus proposed as a new classification of HF. The process of myocardial functional improvement is coordinately driven by adaptive molecular change, metabolic profile alteration, improved cardiomyocyte contractility and LV geometric restoration (7, 9, 10). However, the predisposing factors for HFimpEF are still under investigation.

Glycemic variability (GV) refers to fluctuations in glucose levels within-days or over months to years. GV has been recognized as a critical risk factor for diabetic macrovascular and microvascular complications (11–14), and adverse cardiovascular events even in patients without diabetes (15–21). In the setting of acute HF, elevated in-hospital GV confers higher risk of both short-term and long-term mortality in addition to classic glucose metrics (22, 23). The adverse impact of long-term glucose fluctuations on clinical outcomes has also been confirmed in chronic HF patients (24, 25). Nevertheless, the impact of GV on myocardial recovery in failing hearts is still unclear. In the present study, we analyzed the relationship between long-term GV and the incidence of HFimpEF.

# Methods

## Study population

We consecutively enrolled 951 patients diagnosed with HFrEF (EF ≤ 40%) on hospitalization between January 2013 and December 2020 in Shanghai Ruijin Hospital. A total of 78 patients comorbid with renal failure requiring hemodialysis (n=32), diseases requiring steroid therapy (n=13), malignant tumor (n=9), heart transplantation (n=1) and in-hospital death (n=23) were excluded. The enrolled patients were routinely followed up and underwent repeat echocardiograms at around 12-month ( ± 1 month). During follow-up, there were 49 patients who died for any reason within 13 months from the index admission date and thus were excluded. Another 74 subjects were also excluded due to loss to echocardiogram follow-up for any other reason. Given that the development of HFimpEF was the primary endpoint, patients who received the follow-up echocardiogram at around 12-month but died thereafter were not excluded from the analysis. For calculation of long-term GV, subjects (n=231) without at least three fasting plasma glucose (FPG) measurements with ≥3 months apart were further excluded (Figure 1).

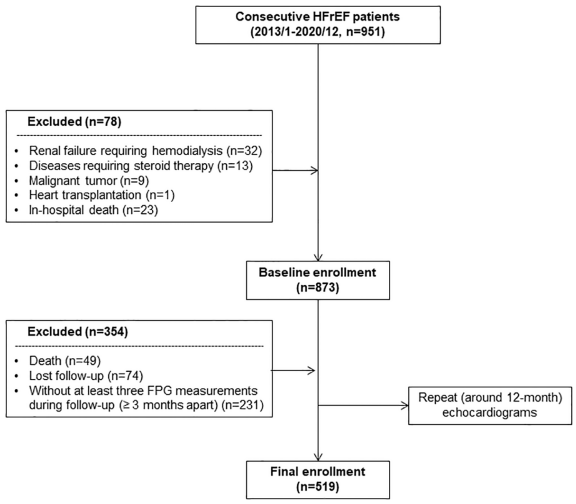


FIGURE 1
Flowchart of patient enrollment. FPG, fasting plasma glucose; HFrEF, heart failure with reduced ejection fraction.

The primary outcome was the development of HFimpEF, which was diagnosed based on follow-up echocardiogram according to the universal HFimpEF definition (26): (1) an absolute EF improvement ≥10% and (2) a second EF > 40%.

This study complies with the Declaration of Helsinki. The study protocol was approved by Shanghai Ruijin Hospital ethics committee, and written informed consent was obtained from all participants.

## Clinical and biochemical assessments

Detailed information of medical history and lifestyle was obtained using a standard questionnaire by trained physicians on admission. Body mass index (BMI) was calculated as weight/height$^2$ (kilograms per square meter). Body surface area (BSA) was calculated by Stevenson's formula: 0.0061 × height + 0.0128 × weight - 0.1529 (27). Hypertension was diagnosed according to the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (BP; JNC 7) (28). The diagnosis of diabetes was made according to the criteria of American Diabetes Association (29). Ischemic etiology was diagnosed based on medical history survey, examination by coronary computed tomography angiography (CTA) or coronary angiogram.

All the blood samples were drawn after overnight fasting. Plasma glucose, insulin, liver and renal function, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed (HITACHI 912 Analyzer, Roche Diagnostics, Germany). The estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation (30). Blood HbA1c was measured using ion-exchange high performance liquid

chromatography with Bio-rad Variant Hemoglobin Testing System (Bio-Rad Laboratories, USA).

## Echocardiographic examination

Comprehensive transthoracic echocardiography was performed using a commercially available system (Vivid-I, GE Healthcare, Milwaukee, WI). The sonographers were blinded to this study. Two-dimensional echocardiography and Doppler flow imaging were recorded from standard parasternal and apical transducer positions.

EF was calculated using the modified Simpson's biplane technique. The LV length was measured in an apical 4-chamber view. To facilitate application of clinical normality cut points, LV end-diastolic volume (EDV) and end-systolic volume (ESV) were indexed by BSA calculated at the study time point. LV mass was estimated from M-mode measurements by the formula: LV mass = $0.8 \times 1.04 \times [(EDD + IVST + PWT)^3 - EDD^3] + 0.6$, and was indexed by BSA, where EDD is LV end-diastolic diameter, IVST is interventricular septal thickness, PWT is LV posterior wall thickness.

## GV measurement

Long-term GV was measured during follow-up period for ≥ 3 times with at least 3-month intervals. The mean and variability of FPG were calculated. FPG variability was primarily defined as intraindividual coefficient of variation (CV) of FPG across visits, which was calculated as the standard deviation (SD) divided by the mean value. The alternative variability of FPG includes: 1) average successive variability (ASV), which was defined as the average absolute difference between successive values and 2) the variability independent of the mean (VIM), which was calculated by the equation as previously reported (19): $VIM=100\times SD/mean^{\beta}$, where β is the regression coefficient based on natural logarithm of SD on natural logarithm of mean of the study population. FPG variability was calculated both as continuous and categorical variables grouped by quartiles of CV, ASV or VIM.

## Nested case-control study

A case-control study was nested into the HF cohort to examine the association between GV and the development of HFimpEF. Each case (HFimpEF) was matched by 1 control (persistent HFrEF) randomly sampled from the cohort members based on sex, age ( ± 2 years) and duration of echocardiogram follow-up. Meanwhile, GV was treated as a dichotomized variable by fusing the original quartile 1~2 as stable glycemic control and quartile 3~4 as unstable glycemic control of all the 3 GV measures (CV, ASV, VIM). A total of 200 case-control pairs were matched for the final analysis.

## Statistical analysis

Continuous variables were presented as median (interquartile range [IQR]) or mean ± SD, and categorical data were summarized as frequencies (percentages). Normal distribution of continuous variables was evaluated by Shapiro-Wilk test. For normally distributed variables, differences in quartiles of FPG variability and subgroup analysis were performed by one-way analysis of variance (ANOVA) followed by *post hoc* Bonferroni correction. For non-normally distributed continuous variables, differences were analyzed by Mann-Whitney U test or Kruskal-Wallis test. Differences in categorical variables were analyzed by $\chi^2$ test. Univariate logistic regression analysis was performed to identify predictors for HFimpEF. Afterwards, multivariate regression models were constructed to interrogate the association between FPG variability and HFimpEF. In model 1, age and sex were adjusted. In model 2, additional adjustment was performed with HF etiology, BP, BMI, and history of diabetes. In model 3, we further adjusted HbA1c, renal function, mean FPG levels during follow-up and baseline EDV index. In model 4, cardiac resynchronizing therapy (CRT) and medical therapies including beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), spironolactones as well as sodium-glucose cotransporter 2 (SGLT2) inhibitors were additionally adjusted. FPG variability was analyzed both as continuous and categorical variables in univariate and multivariate regression models. The association between GV and HFimpEF in the nested case-control study was analyzed by conditional logistic regression.

All statistical analyses were performed using the R statistical package v.4.0.3 (R Project for Statistical Computing, Vienna, Austria). A 2-tailed $P<0.05$ was considered statistically significant.

# Results

## Baseline characteristics of the study population

A total of 519 HFrEF patients were finally enrolled in this study. The mean age was 61.3 ± 12.7 years with 80.3% male patients. Among these subjects, 30.1% were with diabetes (n=156). There were 53.2% of HFrEF patients with an ischemic etiology, and 83.3% of them were diagnosed based on coronary CTA or angiogram during the index admission. The mean number of intrapersonal FPG tests was 5.34 ± 2.47 times. The mean FPG level during follow-up was 6.61 ± 1.99 mmol/L, and CV, ASV, VIM of FPG during follow-up were 0.162 [IQR 0.093~0.268], 1.190 [IQR 0.568~2.235] and 0.641 [IQR 0.408~0.968], respectively. Correlation analyses showed that GV indices such as CV and ASV of FPG were positively correlated to mean FPG levels (CV: Pearson's r = 0.56, $P<0.001$; ASV: Pearson's r= 0.73, $P<0.001$), whereas no correlation was found between VIM of FPG and mean FPG levels (Pearson's r= -0.04, $P=0.348$).

After dividing these patients into 4 groups based on quartiles of CV of FPG, we found subjects with higher GV tended to be elder, more frequently with diabetes and ischemic HF etiology, and with higher levels of baseline HbA1c, FPG as well as NT-proBNP. Subjects in the highest quartile were more frequently on anti-platelet therapy. There was no significant difference in sex, BMI, smoking habits, history of hypertension, atrial fibrillation, New York Heart Association (NYHA) grades, lipid profiles, renal function, CRT implantation and other therapies between the 4 quartiles (Table 1).

In addition, documented hypoglycemic event defined as FPG< 2.8 mmol/L during follow-up was compared. In our study, 3.3% of the subjects suffered hypoglycemic episodes, which was more frequent in higher quartiles of CV of FPG (0 vs. 0 vs. 2.3% vs. 10.8%, $P<0.003$).

## Changes in LV geometry and function

LV geometric and functional parameters at baseline and around 12-month follow-up were compared in subjects with different

TABLE 1 Baseline demographic and clinical characteristics.

| Quartiles of CV of FPG | Q1<0.093 | Q2 0.094~0.162 | Q3 0.163~0.268 | Q4 ≥0.269 | *P*-value |
|---|---|---|---|---|---|
| n | 130 | 130 | 129 | 130 | |
| **Demographic characteristics and clinical assessments** | | | | | |
| Male sex | 112 (86.2) | 98 (75.4) | 104 (80.6) | 103 (79.2) | 0.178 |
| Age, years | 59.75 ± 13.31 | 60.28 ± 13.05 | 61.22 ± 12.00 | 64.06 ± 12.15 | 0.030 |
| Diabetes | 20 (15.4) | 19 (14.6) | 45 (34.9) | 72 (55.4) | <0.001 |
| Hypertension | 65 (50.0) | 62 (47.7) | 71 (55.0) | 77 (59.2) | 0.243 |
| Atrial fibrillation | 16 (12.3) | 20 (15.4) | 14 (10.9) | 10 (7.7) | 0.273 |
| Dyslipidemia | 80 (61.5) | 70 (53.8) | 78 (60.5) | 85 (65.4) | 0.290 |
| Smoking habits | 60 (46.2) | 50 (38.5) | 45 (34.9) | 54 (41.5) | 0.297 |
| BMI, $kg/m^2$ | 24.77 ± 3.43 | 24.79 ± 3.87 | 24.90 ± 3.74 | 24.42 ± 3.54 | 0.754 |
| Systolic BP, mmHg | 120.56 ± 20.44 | 127.67 ± 24.79 | 125.16 ± 19.97 | 123.83 ± 21.21 | 0.074 |
| Diastolic BP, mmHg | 71.81 ± 13.34 | 77.97 ± 18.40 | 76.16 ± 14.19 | 75.68 ± 15.08 | 0.015 |
| Ischemic etiology | 60 (46.2) | 58 (44.6) | 73 (56.6) | 85 (65.4) | 0.002 |
| NYHA grades (II/III/IV) | 27 (20.8)/ 80 (61.5)/ 23 (17.7) | 26 (20.0)/ 88 (67.7)/ 16 (12.3) | 21 (16.3)/ 85 (65.9)/ 23 (17.8) | 27 (20.8)/ 85 (65.4)/ 18 (13.8) | 0.775 |
| **Laboratory measurements** | | | | | |
| HbA1c, % | 6.02 ± 0.80 | 6.13 ± 0.84 | 6.48 ± 1.15 | .24 ± 1.55 | <0.001 |
| FPG, mmol/L | 5.31 (4.87~5.92) | 5.26 (4.77~6.06) | 5.78 (4.90~7.31) | 6.59 (5.14~9.61) | <0.001 |
| Triglyceride, mmol/L | 1.35 (0.99~1.90) | 1.30 (0.94~1.63) | 1.27 (0.95~1.66) | 1.27 (0.94~1.69) | 0.446 |
| Total cholesterol, mmol/L | 4.14 ± 1.08 | 4.00 ± 1.04 | 4.02 ± 1.22 | 3.98 ± 1.11 | 0.644 |
| HDL cholesterol, mmol/L | 1.08 ± 0.26 | 1.07 ± 0.28 | 1.02 ± 0.27 | 1.01 ± 0.28 | 0.052 |
| LDL cholesterol, mmol/L | 2.51 ± 0.86 | 2.46 ± 0.88 | 2.44 ± 0.97 | 2.42 ± 0.93 | 0.879 |
| eGFR, $mL/min/1.732m^2$ | 90.75 ± 16.97 | 87.96 ± 16.99 | 87.75 ± 24.01 | 84.81 ± 22.32 | 0.136 |
| NT-proBNP, pg/mL | 1674.0 (714.3~3237.0) | 2166.0 (588.9~4190.5) | 2866.0 (1360.0~5075.0) | 3598.5 (1695.5~7174.8) | <0.001 |
| **CRT implantation** | | | | | |
| CRT | 16 (12.3) | 22 (16.9) | 13 (10.1) | 12 (9.2) | 0.227 |
| **Medication** | | | | | |
| Aspirin | 70 (53.8) | 67 (51.5) | 73 (56.6) | 71 (54.6) | 0.877 |

*(Continued)*

TABLE 1 Continued

| Quartiles of CV of FPG | Q1<0.093 | Q2 0.094~0.162 | Q3 0.163~0.268 | Q4 ≥0.269 | *P*-value |
|---|---|---|---|---|---|
| n | 130 | 130 | 129 | 130 | |
| $P_2Y_{12}$ inhibitors | 48 (36.9) | 53 (40.8) | 64 (49.6) | 77 (59.2) | 0.001 |
| Beta-blockers | 119 (91.5) | 111 (85.4) | 117 (90.7) | 106 (81.5) | 0.051 |
| ACEI/ARB | 61 (46.9) | 71 (54.6) | 61 (47.3) | 71 (54.6) | 0.402 |
| ARNI | 45 (34.6) | 36 (27.7) | 36 (27.9) | 25 (19.2) | 0.051 |
| SGLT2 inhibitors | 7 (5.4) | 9 (6.9) | 10 (7.8) | 6 (4.6) | 0.713 |
| Spironolactones | 104 (80.0) | 94 (72.3) | 86 (66.7) | 86 (66.2) | 0.048 |
| Diuretics | 82 (63.1) | 82 (63.1) | 86 (66.7) | 83 (63.8) | 0.921 |
| Statins | 64 (49.2) | 69 (53.1) | 72 (55.8) | 76 (58.5) | 0.485 |

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin-receptor neprilysin inhibitors; BMI, body mass index; BP, blood pressure; CRT, cardiac resynchronizing therapy; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2.

quartiles of CV of long-term FPG (Table 2). At baseline, there was no significant difference in LV function and volumes. During the follow-up, EF was improved from 32.38% ± 5.28% to 42.12% ± 10.17% ($P$<0.001) and LV volumes were restored in the overall population. However, the trend towards EF improvement was markedly impaired with increasing FPG variability ($P$=0.003). LV reverse remodeling was also attenuated in patients with high FPG variability (ΔEDV index: $P$=0.004; ΔESV index: $P$<0.001).

## Association between FPG variability and HFimpEF

After 12.2 ± 0.6 months, 218 (42.0%) patients developed HFimpEF and another 301 (58.0%) patients remained HFrEF.

Univariate regression analysis (Supplementary Table 1) revealed that predictors for HFimpEF were younger age, non-diabetes, non-ischemic etiology, higher BP, lower HbA1c levels, lower EDV index and use of SGLT2 inhibitors. The 3 measures of FPG variability (CV, ASV and VIM) were all inversely associated with HFimpEF either when treated as continuous or categorical variables.

Multivariate regression analysis (Table 3) showed that different measures of FPG variability were persistently associated with the development of HFimpEF after adjustment for age and sex (Model 1), clinical characteristics (Model 2), renal function, baseline HbA1c, mean FPG control levels, LV volumes (Model 3) and treatment regimens (Model 4). In the full adjustment model (Model 4), patients with highest quartile of CV of FPG corresponded to a 51.3% (OR: 0.487 [95% CI 0.257~0.910]) decreased likelihood of HFimpEF as compared to the lowest quartile. Similar findings were also observed when these measures of FPG variability were treated as continuous variables (Supplementary Table 2).

Furthermore, subgroup analysis (Figure 2) demonstrated interaction terms were non-significant across subgroups of sex, age, BMI, FPG levels, the presence of diabetes and ischemic etiology, indicating the associations between FPG variability and HFimpEF were similar among these subgroups. Especially, the association kept significant irrespective of diabetic conditions and mean FPG levels.

## Sensitivity analyses

Given that diabetic patients, especially those with poor glycemic control, usually have greater glycemic fluctuations, the association between GV and HFimpEF was verified by excluding patients with baseline HbA1c > 8% or on insulin treatment (Supplementary Table 3). We found CV and VIM of FPG persisted to significantly associate with HFimpEF in both models after multivariable adjustment, suggesting that GV was associated with HFimpEF even when patients with poor glycemic control were excluded. Furthermore, a nested case-control study was conducted by matching HFimpEF and persistent HFrEF patients in the cohort at 1:1 ratio (Supplementary Table 4). Consistently, we found patients with high GV (quartile 3~4 had significantly lower probability of HFimpEF than those with low GV (quartile 1~2) assessed by 3 different GV measures (Supplementary Table 5).

# Discussion

The major findings of the present study are that HF patients with higher long-term GV are less likely to experience LV functional improvement. Long-term GV is an independent risk factor for the development of HFimpEF.

Hyperglycemia increases risk of physical impairment (31), coronary heart disease (32), heart failure (33), peripheral artery disease (34) and stroke (35), irrespective of diabetic conditions. Long-term poor glycemic control marked by high HbA1c was associated with higher risk of all-cause mortality and hospitalization for patients with cardiovascular disease (36–39). Recent studies also found that acute hyperglycemic status reflected

10.3389/fendo.2023.1211954

TABLE 2 Left ventricular geometric and functional changes during follow-up.

| Quartiles of CV of FPG | | Q1<0.093 | Q2 0.094~0.162 | Q3 0.163~0.268 | Q4 ≥0.269 | *P*-value |
|---|---|---|---|---|---|---|
| EDV index, mL/m$^2$ | B | 125.93 ± 31.87 | 123.05 ± 29.95 | 120.49 ± 31.84 | 116.79 ± 33.44 | 0.140 |
| | F | 107.60 ± 30.91 | 104.09 ± 29.03 | 109.33 ± 35.64 | 108.14 ± 33.07 | 0.608 |
| | Δ | -18.33 ± 25.44 | -18.96 ± 25.29 | -11.16 ± 23.22 | -8.65 ± 32.39 | 0.004 |
| ESV index, mL/m$^2$ | B | 83.50 ± 24.59 | 81.67 ± 24.37 | 78.26 ± 26.16 | 76.12 ± 30.84 | 0.125 |
| | F | 60.56 ± 26.86 | 58.70 ± 25.22 | 64.31 ± 31.43 | 64.44 ± 28.76 | 0.285 |
| | Δ | -22.94 ± 23.50 | -22.97 ± 23.37 | -13.95 ± 22.36 | -11.68 ± 31.12 | <0.001 |
| EDD, mm | B | 65.61 ± 7.62 | 64.92 ± 6.99 | 64.02 ± 8.11 | 62.65 ± 7.44 | 0.011 |
| | F | 61.04 ± 8.16 | 60.18 ± 7.30 | 61.49 ± 8.96 | 60.33 ± 8.03 | 0.529 |
| | Δ | -4.57 ± 6.17 | -4.75 ± 6.20 | -2.53 ± 5.66 | -2.32 ± 7.36 | 0.001 |
| ESD, mm | B | 54.45 ± 7.57 | 53.95 ± 7.00 | 52.65 ± 8.54 | 51.51 ± 7.84 | 0.010 |
| | F | 47.14 ± 9.26 | 46.33 ± 8.41 | 48.30 ± 10.14 | 47.61 ± 9.12 | 0.376 |
| | Δ | -7.32 ± 7.68 | -7.62 ± 7.77 | -4.35 ± 7.71 | -3.90 ± 9.29 | <0.001 |
| IVST, mm | B | 9.28 ± 1.62 | 9.32 ± 1.46 | 9.27 ± 1.48 | 9.35 ± 1.78 | 0.971 |
| | F | 9.58 ± 1.57 | 9.62 ± 1.48 | 9.48 ± 1.42 | 9.70 ± 1.82 | 0.730 |
| | Δ | 0.31 ± 1.29 | 0.30 ± 1.21 | 0.21 ± 1.36 | 0.35 ± 1.54 | 0.871 |
| PWT, mm | B | 9.00 ± 1.36 | 9.05 ± 1.47 | 8.99 ± 1.22 | 9.02 ± 1.43 | 0.985 |
| | F | 9.07 ± 1.19 | 9.29 ± 1.34 | 9.00 ± 1.27 | 9.05 ± 1.27 | 0.260 |
| | Δ | 0.07 ± 1.32 | 0.24 ± 1.29 | 0.01 ± 1.20 | 0.04 ± 1.37 | 0.482 |
| LV mass index, g/m$^2$ | B | 146.24 ± 38.55 | 143.71 ± 33.51 | 140.19 ± 34.72 | 138.69 ± 37.64 | 0.349 |
| | F | 131.37 ± 31.32 | 130.59 ± 29.89 | 132.64 ± 37.01 | 132.72 ± 35.28 | 0.950 |
| | Δ | -14.86 ± 31.17 | -13.12 ± 29.65 | -7.55 ± 29.34 | -5.96 ± 27.14 | 0.050 |
| EF, % | B | 32.26 ± 4.94 | 32.23 ± 5.01 | 32.20 ± 5.48 | 32.83 ± 5.70 | 0.739 |
| | F | 43.48 ± 9.73 | 43.76 ± 10.03 | 40.74 ± 10.10 | 40.47 ± 10.49 | 0.009 |
| | Δ | 11.22 ± 9.36 | 11.53 ± 10.21 | 8.53 ± 9.54 | 7.64 ± 11.47 | 0.003 |

B, baseline; F, follow-up; Δ, changes in corresponding parameters; CV, coefficient of variation; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; ESD, end-systolic diameter; ESV, end-systolic volume; FPG, fasting plasma glucose; IVST, interventricular septal thickness; LV, left ventricle; PWT, posterior wall thickness.

by stress hyperglycemia ratio predicted adverse outcomes in patients with nonobstructive coronary arteries (40), coronary chronic total occlusion (41) and acute coronary syndrome (42).

Apart from mean glycemic levels, existing evidence reveals that GV, no matter short-term or long-term, is an independent risk factor for the incidence of HF. Of note, both FPG variability and HbA1c variability represent variability of glycemic control levels but comprise different aspects of dysregulated glycemic homeostasis. On one hand, HbA1c, representing a weighted mean glucose level over the preceding 2-3 months, is usually more stable than FPG and thus has less variability (43). On the other hand, HbA1c is an integrated assessment reflecting both FPG and postprandial plasma glucose (PPG) levels (44). A Korean nationwide population-based study revealed that over a median follow-up of 5.3 years, the risk of HF increased by 15% (HR: 1.15 [95% CI 1.10~1.20]) in subjects with the highest quartile of FPG variability compared to those with the lowest quartile (45). A number of diabetic cohort studies demonstrated that higher long-term HbA1c variability valued by different measures was independently associated with increased risk of HF (46–48). In non-diabetic patients, GV accessed by mean amplitude of glycemic excursions (MAGE) was also related to incident HF after myocardial infarction (49). Furthermore, GV has been recognized as a significant predictor for major adverse cardiovascular events (MACE) independent of mean glycemic control levels and conventional risk factors both in diabetic and non-diabetic HF patients (22–25, 50).

Attributed to advanced guideline-directed medical and device therapies, 10%~52% of HF patients have experienced myocardial recovery and developed HFimpEF (1–5). Of note, the specific definition of HFimpEF varies according to different guidelines or clinical studies. The proposed universal definition of HFimpEF (51) put forward a requirement of ≥10-point increase from baseline EF in addition to the criteria of a baseline EF ≤40% and a follow-up measurement > 40% as stated in the 2022 AHA/ACC/HFSA

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TABLE 3 Multivariate regression analysis for development of HFimpEF.

| | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| CV of FPG | | 0.007* | | 0.014* | | 0.007* | | 0.011* |
| Q1 (<0.093) | Reference | – | Reference | – | Reference | – | Reference | – |
| Q2 (0.093~0.162) | 1.114 (0.678~1.831) | 0.670 | 0.994 (0.598~1.651) | 0.981 | 0.960 (0.571~1.610) | 0.876 | 0.931 (0.550~1.573) | 0.788 |
| Q3 (0.163~0.268) | 0.656 (0.395~1.082) | 0.100 | 0.628 (0.373~1.052) | 0.078 | 0.578 (0.337~0.985) | 0.045 | 0.589 (0.341~1.011) | 0.056 |
| Q4 (≥0.269) | 0.565 (0.337~0.940) | 0.029 | 0.558 (0.321~0.962) | 0.037 | 0.478 (0.256~0.883) | 0.019 | 0.487 (0.257~0.910) | 0.025 |
| ASV of FPG | | 0.020* | | 0.044* | | 0.017* | | 0.015* |
| Q1 (<0.568) | Reference | – | Reference | – | Reference | – | Reference | – |
| Q2 (0.568~1.190) | 0.715 (0.434~1.174) | 0.185 | 0.627 (0.375~1.042) | 0.073 | 0.614 (0.363~1.033) | 0.067 | 0.618 (0.362~1.048) | 0.075 |
| Q3 (1.191~2.240) | 0.618 (0.372~1.022) | 0.062 | 0.604 (0.356~1.021) | 0.061 | 0.565 (0.324~0.980) | 0.043 | 0.541 (0.308~0.946) | 0.032 |
| Q4 (≥2.241) | 0.557 (0.334~0.921) | 0.023 | 0.561 (0.321~0.976) | 0.041 | 0.446 (0.224~0.875) | 0.020 | 0.442 (0.219~0.881) | 0.021 |
| VIM of FPG | | 0.011* | | 0.015* | | 0.013* | | 0.018* |
| Q1 (<0.408) | Reference | – | Reference | – | Reference | – | Reference | – |
| Q2 (0.408~0.641) | 0.673 (0.408~1.107) | 0.120 | 0.635 (0.381~1.054) | 0.080 | 0.622 (0.369~1.043) | 0.073 | 0.633 (0.373~1.069) | 0.088 |
| Q3 (0.642~0.968) | 0.679 (0.412~1.115) | 0.127 | 0.667 (0.401~1.107) | 0.119 | 0.637 (0.378~1.067) | 0.088 | 0.660 (0.388~1.116) | 0.122 |
| Q4 (≥0.969) | 0.497 (0.297~0.825) | 0.007 | 0.500 (0.296~0.837) | 0.009 | 0.487 (0.283~0.829) | 0.009 | 0.496 (0.287~0.851) | 0.011 |

Model 1, adjustment for age and sex.
Model 2, additional adjustment for HF etiology, systolic and diastolic blood pressure, body mass index and history of diabetes.
Model 3, additional adjustment for HbA1c, renal function, mean fasting glucose levels during follow-up, and baseline left ventricular end-diastolic volume index.
Model 4, additional adjustment for CRT, use of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, spironolactones, sodium-glucose cotransporter 2 inhibitors.
ASV, average successive variability; CI, confidence interval; CRT, cardiac resynchronizing therapy; CV, coefficient of variation; FPG, fasting plasma glucose; HF, heart failure; HFimpEF, heart failure with improved ejection fraction; OR, odds ratio; VIM, variability independent of the mean.
*P for trend.

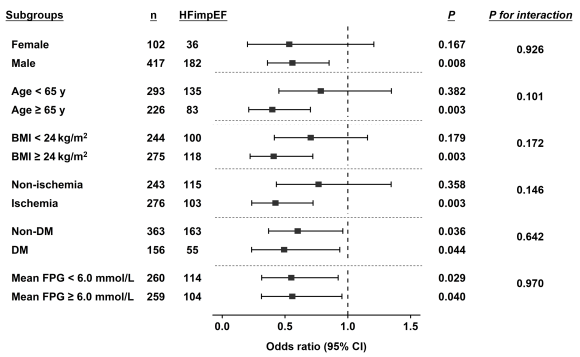


FIGURE 2
Subgroup analysis by forest plot. Forest plot shows the association between VIM of long-term FPG and incidence of HFimpEF in different subgroups and the significance of the corresponding interaction terms. The dashed reference line indicates odds ratio of 1.0. BMI, body mass index; DM, diabetes mellitus; FPG, fasting plasma glucose; HFimpEF, heart failure with improved ejection fraction; VIM, variability independent of the mean.

guideline (8). In this study, we adopted the universal definition since a 10-point increase in EF guarantees actual myocardial functional improvement and minimizes the impact by interobserver and intraobserver measurement variabilities.

We recently showed that glucose metabolic disorders reflected by hyperglycemia or insulin resistance are associated with compromised development of HFimpEF (52, 53). However, to our knowledge, the relationship between GV and HFimpEF remains unknown. In accordance with previous reports, 42.0% of hospitalized HF patients in this study developed HFimpEF during 12-month follow-up. Besides, we for the first time demonstrated that LV functional improvement accompanied by reverse remodeling was prominently compromised with increasing long-term FPG variability. Multivariate regression analysis showed that long-term FPG variability was independently associated with the incidence of HFimpEF, even after adjustment for baseline HbA1c as well as mean FPG levels during follow-up. These findings were also confirmed by the nested case-control study. Furthermore, subgroup analysis revealed the association between FPG variability and

HFimpEF persisted significant irrespective of the presence of diabetes and mean FPG control levels. In addition, we assessed FPG variability by different measures including CV, ASV and VIM. CV and ASV are relatively simple and more feasible in clinical practice, whereas VIM is calculated based on logarithmic curve fitting to eliminate its correlation with mean FPG. We revealed that all these measures of FPG variability yielded similar findings. These data jointly support the notion that GV *per se* plays a negative role in the development of HFimpEF through mechanisms independent of glycemic levels.

Noteworthy, although only a small proportion of patients were on SGLT2 inhibitors (n=32, 6.2%) since the medication has not been introduced to our center until the second half of 2019, the univariate analysis exhibited a positive association between the use of SGLT2 inhibitors and HFimpEF. SGLT2 inhibitors have pleiotropic cardio-protective effects through modulating renin-angiotensin-aldosterone system, shifting energy substrate, and attenuating systemic inflammatory status (54, 55). Given the promising results from DAPA-HF (56) and EMPEROR-Reduced trials (57), SGLT2 inhibitors have become a cornerstone of HFrEF treatment. Resent trails revealed that SGLT2 inhibitors also improve outcomes of patients with HF with preserved EF, no matter with or without diabetes (58–60). Existing evidence suggested that SGLT2 inhibitors facilitate LV reverse remodeling and diastolic function (61–64). Our results further implied that SGLT2 inhibitors may exert favorable effects on myocardial functional recovery, which certainly awaits further confirmation in prospectively designed clinical studies.

Based on existing clinical and basic studies, several potential mechanisms might account for the negative impact of GV on myocardial recovery. First, dramatic glycemic oscillation promotes oxidative stress in the myocardium, thereby leading to mitochondrial damage, endothelial dysfunction, inflammatory response and finally myocardial fibrosis (65–68). Second, greater GV is presumably associated with more hypoglycemic episodes. In our study, 3.3% of the subjects suffered hypoglycemic event, which was only observed in patients with higher GV. Established evidence has displayed that hypoglycemia stimulates sympathetic nervous system, thus increasing cardiac preload, arrhythmia, inflammation and thereby posing deleterious effects on myocardium (69–71). Third, patients with marked glycemic oscillation tend to have poor compliance to medical treatments, thus attenuating the beneficial effects of pharmacological therapies on myocardial recovery.

## Limitations

Our findings should be interpreted in the context of the following limitations. First, this study is a retrospective analysis based on prospectively collected data from a single center, and the result is potentially subject to selection bias. Second, hypoglycemic episodes were not analyzed and adjusted in the multivariate analysis since they were only documented from long-term FPG values owing to the study design and thus probably underestimated. Third, hospitalization for HF is associated with worsening of EF, which may to some extent affect our findings. Finally, prospective studies are warranted to analyze the causal link between GV and occurrence of HFimpEF.

# Conclusions

In conclusion, our findings suggest that greater long-term GV is associated with compromised development of HFimpEF. A more stable control of glycemic levels might provide favorable effects on myocardial recovery in HF patients even without diabetes.

# 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 studies involving humans were approved by Ruijin Hospital, Shanghai Jiao-Tong University School of Medicine. 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

CY, JC and XW performed study design, data analysis and data interpretation. CY and XW performed manuscript writing. CY, JC, JQ, XS, SF, MA and XW performed data collection. CY, JQ, FD, WS, LL, RZ and XW performed manuscript revision. All authors contributed to the article and approved the submitted version.

# Funding

This work was supported by National Natural Science Foundation of China (Grant No. 81870179, 82000369, 82170423), Shanghai Municipal Commission of Health and Family Planning (Grant No. 20194Y0042), Technology Transfer Project of Shanghai Jiao Tong University School of Medicine (Grant No. ZT202103).

# 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.2023.1211954/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 27 October 2023
DOI 10.3389/fendo.2023.1276789



OPEN ACCESS

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RECEIVED 13 August 2023
ACCEPTED 13 October 2023
PUBLISHED 27 October 2023

CITATION
Guo XL, Wang JW, Tu M and Wang W (2023) Perirenal fat thickness as a superior obesity-related marker of subclinical carotid atherosclerosis in type 2 diabetes mellitus. *Front. Endocrinol.* 14:1276789. doi: 10.3389/fendo.2023.1276789



# Perirenal fat thickness as a superior obesity-related marker of subclinical carotid atherosclerosis in type 2 diabetes mellitus

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**Objective:** Emerging evidence highlighted that perirenal adipose tissue might regulate the cardiovascular and metabolism system through several pathways. This study aimed to assess the association between perirenal fat thickness (PrFT) and subclinical carotid atherosclerosis (SCCA) in type 2 diabetes mellitus (T2DM).

**Method:** A total of 670 participants with complete data were included in this study. The trained reviewer collected demographic and anthropometric information. Laboratory assessments were determined by standard methods. PrFT and SCCA were evaluated by computed tomography and ultrasound. Binomial logistic regression analysis was conducted to assess the association between PrFT and SCCA. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the identifying value of PrFT for SCCA.

**Results:** Overall, the prevalence of SCCA was 61.8% in T2DM. PrFT was significantly increased in the SCCA group. Growing trends were observed in the prevalence of hypertension, carotid intima-media thickness (cIMT) > 1, plaque, and SCCA across the PrFT quartiles. Spearman correlation analysis revealed that PrFT was positively associated with cIMT ($r$ = 0.401, $p$ < 0.001). This correlation remained significant after adjustment for visceral fat area (VFA), subcutaneous fat area (SFA), and traditional metabolic risk factors ($\beta$ = 0.184, $p$ < 0.001). Meanwhile, PrFT was independently correlated with plaque, cIMT > 1 mm, and SCCA. The ORs (95% CI) were 1.072 (1.014–1.135), 1.319 (1.195–1.455), and 1.216 (1.119–1.322). Furthermore, PrFT remained correlated considerably with SCCA in subgroup analysis after stratification for age, sex, smoking, hypertension, and body mass index. From the ROC curve analysis, the AUCs (95% CI) of PrFT, VFA, and SFA identifying SCCA were 0.794 (0.760–0.828), 0.760 (0.724–0.796), and 0.697 (0.656–0.737), respectively. The AUC of PrFT was significantly higher than VFA ($p$ = 0.028) and SFA ($p$ < 0.001). The optimal cutoff values of PrFT were 14.0 mm, with a sensitivity of 66.7% and a specificity of 76.2%.

**Conclusion:** PrFT was independently associated with cIMT, plaque, cIMT > 1 mm, and SCCA as a superior obesity-related marker of SCCA in T2DM.

**Clinical trial registration:** Clinical Trials.Gov, identifier ChiCTR2100052032.

KEYWORDS

obesity, perirenal fat thickness, sub-clinical carotid atherosclerosis, carotid intima-to-media thickness, type 2 diabetes mellitus

# Introduction

Subclinical carotid atherosclerosis (SCCA) is a chronic inflammatory disease occurring in the carotid artery wall, which manifests as increased carotid intima-to-media thickness (cIMT) and plaque formation without any symptoms (1). Evidence from meta-analysis demonstrated SCCA (2). Type 2 diabetes mellitus (T2DM) is closely associated with CVD, contributing to being an independent risk factor for CVD. Despite the incidence of CVD, cardiovascular mortality in T2DM has decreased over the past decades due to the advances in CVD prevention (3, 4). The latest epidemiological surveys also revealed that CVD was the major cause of death in T2DM (5). Notably, the current practice guidelines for managing CVD in T2DM are shifting from glucose-centric strategies to a more personalized patient-centered approach. Developing effective strategies to prevent SCCA progression to CVD is essential. Identifying risk factors is the priority in developing effective prevention strategies.

Obesity is the major risk factor linked to SCCA with T2DM, and its rapidly increased prevalence drives the increase of SCCA in T2DM. Meanwhile, obesity can lead to dyslipidemia, hyperglycemia, increased oxidative stress, insulin resistance, and systemic inflammation (6), which also accelerates the development of SCCA in T2DM. Excessive accumulation of subcutaneous and visceral fat is the main manifestation of obesity. Compared to subcutaneous adipose tissue, visceral adipose tissue (VAT) plays more functional roles in the pathogenesis of CVD, metabolic syndrome (MetS), and T2DM (7, 8). Owing to more visceral fat accumulation, T2DM appeared to have more obesity-related consequences like CVD, stroke, and metabolic disorders (9). The association between VAT and SCCA has been explored in previous studies. Clinical studies observed that VAT volume and epicardial fat thickness (EFT) were independently associated with SCCA after adjustment for traditional cardiometabolic risk factors (10, 11). In addition to the conventional VAT and epicardial fat, emerging evidence highlighted that perirenal adipose tissue might play essential roles in regulating the cardiovascular system and has the potency to be a new target for CVD prevention (12).

Perirenal adipose tissue (PAT) is a kind of measurable VAT located in the retroperitoneal space. Compared with other VATs, PAT has a complete vascular supply and lymphatic system, which provide the structural basis for regulating the cardiovascular and metabolism systems (13, 14). Favre et al. found that perirenal fat thickness (PrFT) measured with computed tomography (CT) is a reliable estimate of PAT mass (15). As a marker of SCCA, several clinical studies revealed that PrFT was positively associated with cIMT in children and HIV-1-infected patients receiving highly active antiretroviral therapy (16, 17). Furthermore, the clinical study also found that the visceral fat area (VFA) had a good diagnostic value for SCCA in Japanese patients (18). Based on these findings, we can assume that PrFT may also have a good identifying value for SCCA as VFA. In addition, work completed on data showed that the association between PrFT and SCCA remained uncertain. Hence, this study aimed to explore the association between PrFT and SCCA to identify this novel risk factor for CVD. At the same time, this study would further compare the value of PrFT and VFA in identifying SCCA.

# Materials and methods

## Study population

This cross-sectional study consecutively recruited T2DM admitted to the metabolic management center at Longyan First Affiliated Hospital of Fujian Medical University from December 2022 to June 2023. The study exclusion criteria were as follows: (1) with a special type of diabetes (e.g., monogenic diabetes syndromes, diseases of the exocrine pancreas, and drug- or chemical-induced diabetes), type 1 diabetes mellitus, and gestational diabetes mellitus; (2) with a history of previous CVD; (3) with renal structure abnormalities (e.g., a history of renal region surgery, presence of renal tumors and cysts, or perirenal inflammation exudates); (4) with special conditions preventing completion of CT or ultrasound examination (e.g., pregnancy, severe spinal curvature, or allergic to ultrasound coupling agents); and (5) with incomplete data. Previous studies reported that the prevalence of SCAA is approximately 50% to 60% in T2DM (19). Hence, this study planned a sample size of 600–700 T2DM according to a multiple binomial logistic regression model requirement to evaluate the association between PrFT and SCCA by SASS software statistics. Overall, this study screened 702 participants. The final analysis included 670 participants, meeting the inclusion and exclusion criteria. The flowchart of excluded and included participants is presented in Figure 1. This study was approved by the Ethical Committee of Longyan First Affiliated Hospital of Fujian Medical University (LY-2020069) and registered

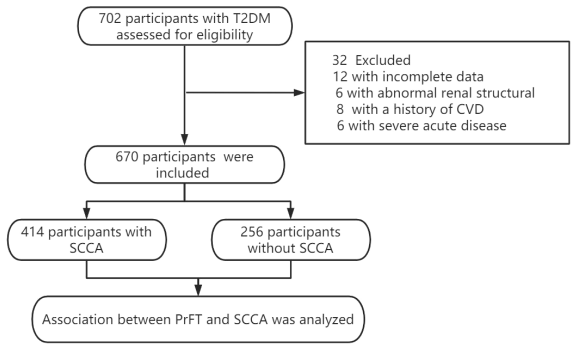


FIGURE 1
Flow diagram of the participants excluded and included in this study.

in Clinical Trials. Gov (ChiCTR2100052032). Study procedures were conducted in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants.

## Clinical and laboratory assessments

The demographic data about medical history and lifestyle, including smoking, history of diseases or surgery, age, and gender, were collected by trained interviewers using a standard questionnaire and reviewing medical records. The current smoking status was defined as participants who continually smoked seven cigarettes a week for over 6 months. Anthropometric information, including height, weight, and blood pressure (BP), was measured by trained nurses using standardized methods. During height and weight measurements, participants wore hospital gowns and were barefoot. An electronic height and weight measuring device measured weight and height. Body mass index (BMI) was calculated as the weight divided by the square of height ($kg/m^2$). On three occasions, an electronic sphygmomanometer measured systolic BP (SBP) and diastolic BP (DBP) with an appropriate cuff size. The mean of three readings was calculated as the final BP.

Laboratory assessments were determined by standardized methods using fasting venous blood samples. The measurement of fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein (HDL-c), uric acid (UA), creatinine, and alanine aminotransferase was determined by an auto-biochemical analyzer (Roche Diagnostics Corporation). Glycosylated hemoglobin A1c (HbA1c) was measured by high-performance liquid chromatography with a D10 set (Bio-Rad). Insulin resistance was evaluated by the homeostasis model assessment (HOMA-IR): fasting serum insulin (μU/mL) × FBG (mmol/L)/22.5.

## Measurement of PrFT

Participants underwent CT scanning via Revolution VCT 128 (General Electric, Milwaukee, USA) to obtain renal structure images while in a supine position. The CT scanning area was covered between the pubic symphysis and the 10th thoracic vertebra. Experienced radiologists reconstructed the images using Advantage Windows 4.4 software (GE, Milwaukee, USA) to obtain 1.25-mm-thick consecutive slices. PrFT was measured using the method first proposed by the Mayo Clinic, which is widely used to measure PrFT. The detailed measurement was as follows (20): (1) The window center is set at −100 HU, and widths range from −50 to −200 HU. (2) PAT was differentiated from other tissues at the renal venous plane (*) by density (21). (3) The average maximal distance (blue arrow line) between the kidney's posterior wall and the abdominal wall's inner limit on the left and right side was measured as PrFT (Supplementary Figure 1). Two radiologists blinded to clinical findings were involved in measuring PrFT to reduce inter-operator variability. The inter-operator agreement between the two radiologists is 0.89. Furthermore, the average maximal distance of renal length at the coronal plane on both kidneys was measured as renal diameters.

## Measurement of VFA

Participants were performed with the abdominal bioelectrical impedance analysis method (DUALSCAN HDS-2000, Omron, Japan) to measure VFA and subcutaneous fat area (SFA) in a supine position. Experienced operators conducted the measurement according to the instrument operating manual: (1) current 1 (500 μA, 50 kHz) was applied to four pairs of electrodes fixed bilaterally between the hand and foot, and the voltage was measured axially on the abdomen; (2) a constant current (500 μA, 50 kHz) was applied to the eight electrodes placed around the trunk at the umbilical level; and (3) lean body mass was calculated by abdominal axis impedance. The mean voltage between abdominal surface electrodes calculated SFA. VFA was calculated by the two impedance data sets combined with abdominal shape parameters.

## Assessment of SCCA

Participants were performed with high-resolution B-mode carotid ultrasonography (EPIQ 5, Philips, Andover, MA) with an L12-5 MHz ultrasonic probe to measure the carotid arteries (common carotid artery, internal carotid artery, and external carotid artery) according to the standardized protocol (21). Participants were examined supine with slight neck hyper-extension towards the contralateral side. Common carotid arteries with the regular lumen–intima interface parallel to the adventitia on both sides were captured for further measurements. The average intima-media thickness (IMT) of the far vessel wall at a site approximately 1 cm proximal to the carotid bulb was calculated as cIMT. Carotid plaque was defined as a focal structure that protruded at least 0.5 mm into the arterial lumen, vascular lumen thickness greater than 50% of the surrounding IMT, or IMT > 1.5 mm. All operations were performed by experienced ultrasonologists who were blind to clinical information. The inter-operator agreement

between the two ultrasonologists is 0.93. SCCA was defined as participants with cIMT > 1.0 mm or (and) carotid plaque (22).

## Statistical analysis

Statistical analysis was performed using SPSS 23.0 software (SPSS Inc. IBM). Descriptive data are expressed as means ± standard deviation (SD). Discrete variables were summarized in frequency tables (*N*, %). The difference in baseline characteristics between SCCA and non-SCCA groups was analyzed by the independent samples *t*-test or Kruskal–Wallis test. Furthermore, a one-way analysis of variance followed by the Tukey test for multiple comparisons was conducted to investigate the difference in metabolic risk factors among PrFT quartiles. The chi-squared ($\chi^2$) test or Fisher exact test was used to compare categorical variables. The relationship between PrFT and cIMT was assessed using Spearman correlation analysis. Multiple regression analysis was used to estimate the independent correlation of PrFT with cIMT. Binomial logistic regression analysis was used to estimate the independent variable of PrFT for SCCA. The receiver operating characteristic curves were used to compare the identifying value of SCCA between PrFT and VFA. A two-tailed value of $p < 0.05$ was considered statistically significant.

# Results

## Baseline characteristics of the study population

Overall, the mean age of participants was 53.1 ± 8.3 years old, with a mean diabetic duration of 5.1 ± 3.2 years. The mean PrFT was 12.7 ± 4.7 mm. Table 1 summarizes the baseline characteristics of participants in the SCCA and non-SCCA groups. In the SCCA group, the cardiometabolic risk factors like age, BMI, WC, SBP, DBP, TG, TC, LDL-c, UA, HOMA-IR, SFA, and VFA were statistically higher than the non-SCCA group ($p < 0.05$). Meanwhile, the SCCA group was more hypertensive and smoked more than the non-SCCA group ($p < 0.05$). In contrast, the HDL-c

TABLE 1 Baseline characteristics of participants in SCCA and non-SCCA groups.

| Variable | Total (*n* = 670) | SCCA (*n* = 414) | Non-SCCA (*n* = 256) | *p* |
|---|---|---|---|---|
| Age (years) | 53.1 ± 8.3 | 54.9 ± 8.4 | 50.1 ± 7.2 | <0.001 |
| Men, *n* (%) | 352 (52.5) | 217 (52.4) | 135 (52.7) | 0.488 |
| Duration (years) | 5.1 ± 3.2 | 5.5 ± 3.2 | 4.5 ± 3.1 | <0.001 |
| BMI (kg/m$^2$) | 24.5 ± 2.9 | 25.4 ± 2.9 | 23.0 ± 2.1 | <0.001 |
| WC (cm) | 85.8 ± 6.9 | 87.8 ± 7.2 | 82.3 ± 4.8 | <0.001 |
| SBP (mmHg) | 133.7 ± 17.6 | 139.5 ± 17.2 | 124.5 ± 14.1 | <0.001 |
| DBP (mmHg) | 81.7 ± 9.7 | 83.5 ± 8.6 | 78.2 ± 10.4 | <0.001 |
| HbA1c (%) | 8.7 ± 1.1 | 8.8 ± 1.2 | 8.6 ± 0.9 | 0.071 |
| TG (mmol/L) | 2.14 ± 1.33 | 2.58 ± 1.45 | 1.44 ± 0.68 | <0.001 |
| TC (mmol/L) | 5.17 ± 1.20 | 5.27 ± 1.23 | 5.02 ± 1.02 | <0.001 |
| HDL-c (mmol/L) | 1.10 ± 0.25 | 1.04 ± 0.24 | 1.20 ± 0.22 | <0.001 |
| LDL-c (mmol/L) | 3.55 ± 0.96 | 3.59 ± 0.99 | 3.41 ± 0.90 | 0.048 |
| UA (μmol/L) | 364.5 ± 85.3 | 383.7 ± 87.6 | 333.5 ± 75.1 | <0.001 |
| Creatinine (μmol/L) | 70.3 ± 13.1 | 70.3 ± 12.9 | 70.4 ± 13.6 | 0.924 |
| ALT (IU/L) | 33.9 ± 8.7 | 34.7 ± 8.8 | 33.4 ± 8.6 | 0.067 |
| HOMA-IR | 3.19 ± 1.74 | 6.27 ± 3.02 | 4.38 ± 2.72 | <0.001 |
| PrFT (mm) | 12.7 ± 4.8 | 14.6 ± 4.0 | 9.7 ± 4.2 | <0.001 |
| VFA (cm$^2$) | 89.1 ± 17.3 | 91.6 ± 17.1 | 85.2 ± 14.7 | <0.001 |
| SFA (cm$^2$) | 167.2 ± 27.7 | 171.3 ± 27.6 | 160.5 ± 25.9 | <0.001 |
| Renal diameter (cm) | 11.4 ± 1.6 | 11.4 ± 1.5 | 11.3 ± 1.8 | 0.862 |
| Hypertension, *n* (%) | 244 (36.0) | 205 (49.5) | 39 (15.2) | <0.001 |
| Smoking, *n* (%) | 256 (38.2) | 182 (44.0) | 69 (27.0) | <0.001 |

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; UA, uric acid; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment insulin resistance; VFA, visceral fat area; SFA, subcutaneous fat area; PrFT, perirenal fat thickness; SCCA, subclinical carotid atherosclerosis.

was decreased in the SCCA group ($p < 0.05$). As expected, the PrFT was also increased in the SCCA group compared with the non-SCCA group (12.7 ± 4.7 mm vs. 9.7 ± 4.2 mm, $p < 0.05$).

## Cardiometabolic risk factors and cIMT based on PrFT quartiles

Table 2 presents the cardiometabolic risk factors and cIMT based on the quartiles of PrFT (Q1: <8.60; Q2: 8.60–14.0; Q3: 14.01–16.10; Q4: >16.10). The results revealed significant differences in BMI, WC, SBP, DBP, TG, TC, LDL-c, HDL-c, UA, HOMA-IR, SFA, and VFA among the four quartiles ($p < 0.05$). Meanwhile, increasing trends were observed in the BMI, WC, SBP, DBP, TG, HOMA-IR, SFA, and VFA across the PrFT quartiles. A decreasing trend was also observed in HDL-c across the PrFT quartiles. Figure 2 illustrates the prevalence of hypertension, cIMT > 1, plaque, and SCCA across the PrFT quartiles. The prevalence of hypertension, cIMT > 1, plaque, and SCCA were 36.4%, 41.5%, 42.8%, and 61.8% in T2DM, respectively. There were significant differences in the prevalence of hypertension, cIMT > 1, plaque, and SCCA among the four quartiles ($p < 0.05$). Furthermore, increasing trends were observed in the prevalence of hypertension, cIMT > 1, plaque, and SCCA across the PrFT quartiles.

## Correlation of PrFT with cIMT

Spearman correlation analysis was conducted to assess the correlation of PrFT with cIMT. As shown in Figure 3, PrFT was positively associated with cIMT ($r = 0.401$, $p < 0.001$). Multiple linear regression analysis was conducted to evaluate the correlation between PrFT and cIMT after adjustment for cardiometabolic risk factors. In Model 1, after adjustment for age, sex, BMI, WC, SBP, DBP, diabetic duration, and smoking, PrFT was significantly correlated with cIMT ($\beta = 0.317$, $p < 0.001$). In Model 2, after adjustment for TG, TC, LDL-c, HDL-c, HbA1c, UA, and HOMA-IR, PrFT was also significantly correlated with cIMT ($\beta = 0.235$, $p < 0.001$). Furthermore, PrFT maintained a significant correlation with cIMT ($\beta = 0.184$, $p < 0.001$) after additional adjustment for renal diameters, SFA, and VFA (Model 3).

## Correlation of PrFT with plaque, cIMT > 1 mm, and SCCA

Binomial logistic regression analysis was conducted to evaluate the correlations of PrFT with plaque, cIMT > 1 mm, and SCCA. As illustrated in Figure 4, PrFT was independently correlated with plaque, cIMT > 1 mm, and SCCA after adjustment for age, sex, BMI, WC, SBP, DBP, diabetic duration, smoking (Model 1), TG, TC, LDL-c, HDL-c, HbA1c, UA, and HOMA-IR (Model 2). After additional adjustment for renal diameters, SFA, and VFA (Model 3), PrFT remained significantly correlated with plaque, cIMT > 1 mm, and SCCA. The ORs (95% CI) were 1.072 (1.014–1.135), 1.319 (1.195–1.455), and 1.216 (1.119–1.322).

Figure 5 presents the subgroup analysis of the association between PrFT and SCCA after stratification for age, sex, smoking, hypertension, and BMI. The results revealed no significant additive interactions between PrFT and SCCA in sex, age, hypertension, smoking, and BMI subgroups ($p$ for interaction > 0.05). PrFT was

TABLE 2 Cardiometabolic risk factors and cIMT based on PrFT quartiles.

| Variable | Q1 ($n$ = 169) | Q2 ($n$ = 164) | Q3 ($n$ = 172) | Q4 ($n$ = 165) | $p$ |
|---|---|---|---|---|---|
| Age (years) | 52.6 ± 8.9 | 53.8 ± 7.8 | 52.9 ± 8.0 | 53.0 ± 8.2 | 0.359 |
| BMI (kg/m$^2$) | 21.6 ± 2.0 | 23.7 ± 1.7 | 25.5 ± 1.9 | 27.2 ± 2.7 | <0.001 |
| WC (cm) | 79.5 ± 3.4 | 83.4 ± 3.7 | 87.9 ± 5.4 | 92.3 ± 6.7 | <0.001 |
| SBP (mmHg) | 116.3 ± 10.8 | 130.1 ± 13.3 | 142.1 ± 8.5 | 146.5 ± 18.3 | <0.001 |
| DBP (mmHg) | 81.7 ± 9.7 | 83.5 ± 8.6 | 81.7 ± 9.7 | 78.2 ± 10.4 | <0.001 |
| HbA1c (%) | 8.6 ± 0.9 | 8.7 ± 1.0 | 8.9 ± 1.4 | 8.7 ± 0.9 | 0.141 |
| TG (mmol/L) | 1.05 ± 0.72 | 1.81 ± 0.77 | 2.24 ± 0.68 | 3.49 ± 1.58 | <0.001 |
| TC (mmol/L) | 4.82 ± 1.16 | 5.25 ± 1.10 | 5.23 ± 1.30 | 5.40 ± 1.14 | <0.001 |
| HDL-c (mmol/L) | 1.33 ± 0.21 | 1.13 ± 0.19 | 1.01 ± 0.14 | 0.94 ± 0.23 | <0.001 |
| LDL-c (mmol/L) | 3.24 ± 0.92 | 3.59 ± 0.77 | 3.72 ± 1.10 | 3.62 ± 0.94 | 0.048 |
| UA (μmol/L) | 285.5 ± 60.9 | 339.9 ± 65.9 | 385.9 ± 72.0 | 406.8 ± 90.2 | <0.001 |
| HOMA-IR | 2.89 ± 1.64 | 4.97 ± 2.37 | 6.39 ± 2.10 | 7.95 ± 3.32 | <0.001 |
| cIMT (mm) | 0.74 ± 0.09 | 0.93 ± 0.12 | 1.04 ± 0.10 | 1.12 ± 0.11 | <0.001 |
| VFA (cm$^2$) | 82.6 ± 13.3 | 86.7 ± 13.9 | 91.6 ± 15.8 | 95.7 ± 17.2 | <0.001 |
| SFA (cm$^2$) | 151.8 ± 21.9 | 163.3 ± 24.1 | 173.9 ± 26.7 | 179.8 ± 23.4 | <0.001 |

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin A1c; TG, triglyceride; TC, total cholesterol; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; UA, uric acid; ALT, alanine aminotransferase; HOMA-IR, homeostasis model assessment insulin resistance; VFA, visceral fat area; SFA, subcutaneous fat area; cIMT, carotid intima-to-media thickness; PrFT, perirenal fat thickness; SCCA, subclinical carotid atherosclerosis.

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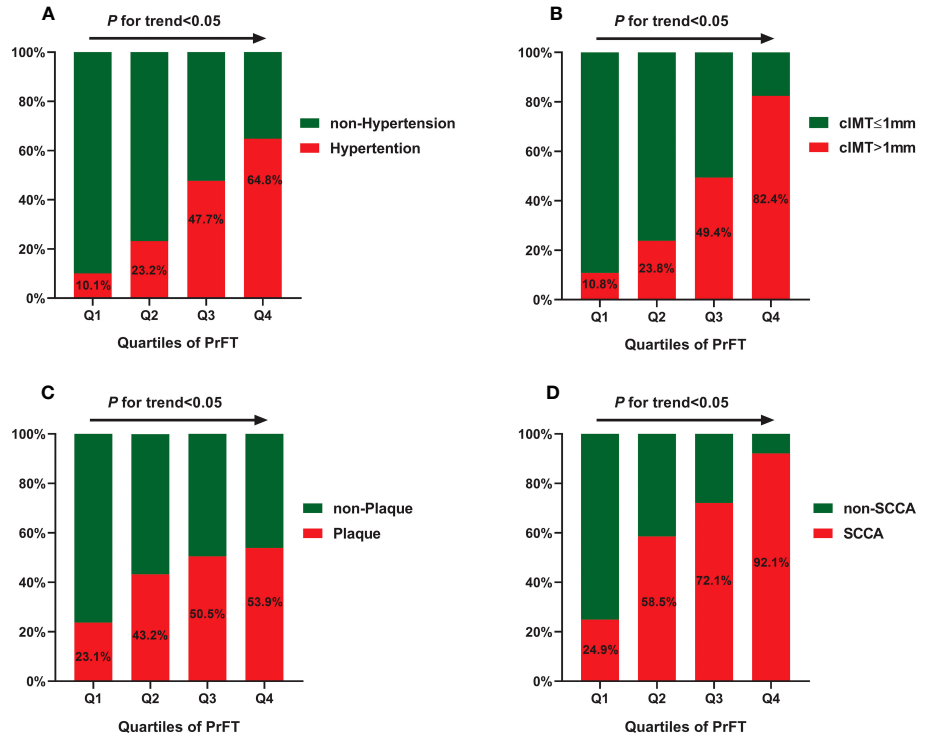


FIGURE 2
The prevalence of hypertension **(A)**, cIMT > 1 mm **(B)**, plaque **(C)**, and SCCA **(D)** across the PrFT quartiles. cIMT, carotid intima-to-media thickness; PrFT, perirenal fat thickness; SCCA, subclinical carotid atherosclerosis.

also significantly correlated with SCCA in any subgroups of age, sex, BMI, smoking, and hypertension after Model 3, except for the variables used for stratification.

## Values of PrFT in identifying SCCA

Figure 6 shows the performance for evaluating the value of PrFT, VFA, and SFA for identifying SCCA. The AUCs (95% CI) of PrFT, VFA, and SFA were 0.794 (0.760–0.828), 0.760 (0.724–0.796), and 0.697 (0.656–0.737), respectively. The AUC of PrFT was significantly higher than VFA ($p$ = 0.028) and SFA ($p$ < 0.001). The optimal cutoff values of PrFT were 14.0 mm, with a sensitivity of 66.7% and a specificity of 76.2% (Table 3).

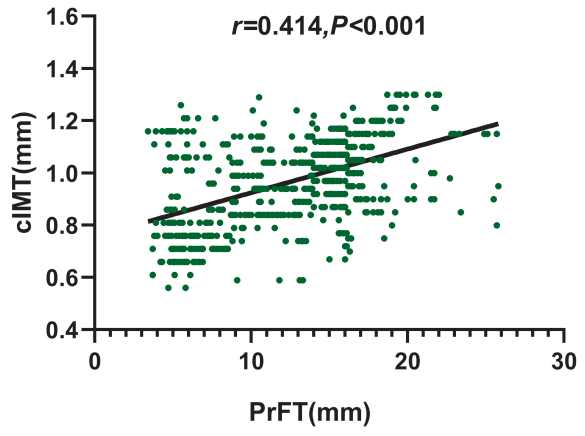


FIGURE 3
Correlation of PrFT with cIMT in T2DM analyzed by Spearman correlation analysis. cIMT, carotid intima-to-media thickness; PrFT, perirenal fat thickness.

# Discussion

Emerging studies highlighted that PAT might functionally regulate the cardiovascular system and potentially be a target for CVD prevention (12, 23). SCCA was well-recognized as an independent predictor of future CVD events. Work completed on data showed that the association between PrFT and SCCA remained uncertain. Therefore, this study assessed the association between PrFT and SCCA. Meanwhile, we further compared the value of PrFT and VFA in identifying SCCA. The results revealed that PrFT was significantly increased in participants with SCCA. Meanwhile, PrFT was independently correlated with cIMT, plaque, cIMT > 1 mm, and SCCA after adjustment for cardiometabolic risk factors. Moreover, PrFT remained significantly associated with SCCA in subgroup analysis of age, sex, BMI, smoking, and hypertension. Furthermore, PrFT was superior to VFA and SFA in identifying SCCA.

T2DM is closely associated with SCCA. The prevalence of SCCA was relatively high (61.8%) in our study. Obesity involves excessive accumulation of adipose tissue, which is thought to be a leading risk factor for CVD and T2DM. VAT is most important in adipose

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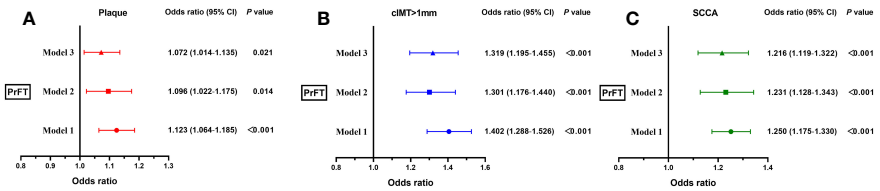


FIGURE 4
Binomial logistic regression analysis of the association between PrFT and plaque **(A)**, cIMT > 1 mm **(B)**, and SCCA **(C)**. Model 1: adjusted for age, sex, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, diabetic duration, and smoking. Model 2: additional adjustment for triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein, uric acid, glycosylated hemoglobin A1c, and homeostasis model assessment insulin resistance. Model 3: further adjustment for renal diameters, and subcutaneous and visceral fat areas. PrFT, perirenal fat thickness; cIMT, carotid intima-to-media thickness; SCCA, subclinical carotid atherosclerosis.

biology categories based on fat depots' anatomical and physiological characteristics. VAT is active in releasing bio-active factors such as leptin, adiponectin, tumor necrosis factor-α, interleukin-6, interleukin-8, and MCP-1 that are involved in the pathogenesis of CVD, metabolic disorders, and T2DM (24, 25). Recent studies have shown that the CVD risk associated with obesity is particularly relevant for VAT. Increased accumulation of VAT not only drives the increased prevalence of T2DM and SCCA but also accelerates the development of SCCA in T2DM (26). Atherosclerosis was previously considered a lipid-storage disease. In comparison, emerging evidence has demonstrated that it was a subacute inflammatory condition of the vessel wall characterized by infiltration of macrophages and T cells. Metabolic disorders can trigger chronic low-grade inflammation at almost every step of the atherogenic process, which plays a major role in developing atherosclerosis (27, 28). Hence, we can observe that the cardiometabolic risk factors like BMI, WC, SBP, DBP, TC, LDL-c, UA, HOMA-IR, SFA, and VFA were significantly increased in the SCCA group. Hypertension, insulin resistance, and dyslipidemia are the main cardiometabolic risk factors that can accelerate the development of atherosclerosis. Previous studies suggested that excessive PAT increases the risk of hypertension, insulin resistance, and dyslipidemia. De Pergola et al. observed that increased PrFT was positively associated with increased mean 24-h BP levels in overweight and obese subjects (29). Maria et al. also found that decreased anti-hypertensive medications and SBP levels were significantly associated with decreased PrFT in hypertensive obese subjects after sleeve-gastrectomy surgery (30). Meanwhile, increased PrFT was also associated with reduced HDL-c and increased insulin resistance in overweight and obese subjects (31). The results of our study were consistent with the previous studies. Increasing trends were observed in the SBP, DBP, TG, and HOMA-IR across the PrFT quartiles. A decreasing trend was also observed in HDL-c.

Increased cIMT and plaque are validated markers of atherosclerosis. Previous studies found that increased PAT was associated with increased cIMT. Bassols et al. observed that PAT

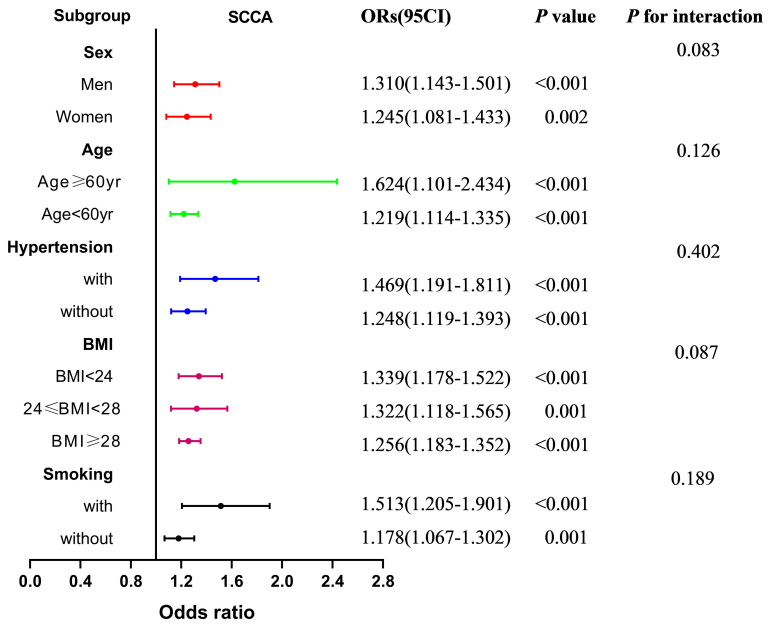


FIGURE 5
Subgroup analysis of the association between PrFT and SCCA after stratification for age, sex, smoking, hypertension, and body mass index. PrFT, perirenal fat thickness; SCCA, subclinical carotid atherosclerosis.

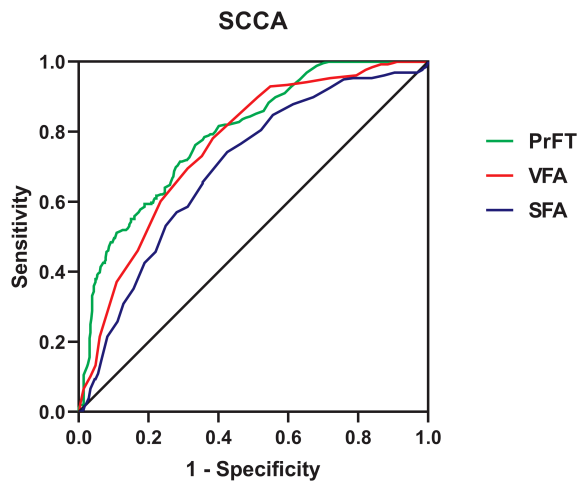


FIGURE 6
Receiver operating characteristic curves for the cutoff value of PrFT, SFA, and VFA identifying SCCA. PrFT, perirenal fat thickness; SCCA, subclinical carotid atherosclerosis; VFA, visceral fat area; SFA, subcutaneous fat area.

was independently associated with cIMT after adjusting for BMI, gender, age, and metabolic parameters in 142 overweight ($\beta = 0.250$) and 142 obese ($\beta = 0.254$) children (16). Okeahialam et al. found that PrFT measured by ultrasound was positively correlated with cIMT ($\beta = 0.195$) in 221 overweight or obese subjects (32). Consistent with the above studies, our studies revealed that PrFT was independently associated with cIMT ($\beta = 0.184$) after adjustment for cardiometabolic risk factors, SFA, and VFA in 670 participants with T2DM. The correlation of SCCA with VAT volume and EFT has been evaluated in previous studies. Several clinical studies observed that VAT volume and EFT were independent predictors of SCCA and plaque (10, 11, 33–35). As VAT volume and EFT, this study also found that PrFT was significantly correlated with plaque, cIMT > 1 mm, and SCCA independent of cardiometabolic risk factors, SFA, and VFA. Moreover, PrFT remained correlated considerably with SCCA in subgroup analysis after stratification for age, sex, smoking, hypertension, and BMI. Ohashi et al. found that VFA was significantly associated with the presence and extent of CAC as a marker of subclinical atherosclerosis in Japanese patients (18). As expected, our study also revealed that PrFT had a good identifying value for SCCA. Furthermore, the AUC of PrFT was significantly higher than VFA and SFA. These findings indicated that PrFT might be a better marker of SCCA in T2DM.

Among the underlying mechanisms that attempt to explain the association between PrFT and SCCA, PAT's unique structure and biology may play critical roles. PAT shares the same developmental origin as typical VAT and thus has the same roles as VAT in cardiovascular and metabolism systems. However, there are some differences between typical VAT and PAT in histology, physiology, and functions. PAT has a complete blood supply system, lymph fluid drainage, and innervation, making it more like an organ than connective tissue (14). Furthermore, the unique morphological basis ensures that perirenal fat plays more functional roles in energy metabolism and adipokine bio-transformation than typical VAT (36). Intracellular lipid accumulation by foam cells, vascular smooth muscle cells, and T lymphocytes characterize the atherosclerotic lesion. This can increase the intima-media thickness and progress to atherosclerotic lesions due to chronic endothelium injury. The chronic inflammatory response was considered the critical factor of atherosclerosis and started from the earliest stages of pathology initiation. Emerging evidence highlighted that perirenal fat could regulate the cardiovascular system via neural reflexes, adipokine secretion, adipocyte interactions, and paracrine substances (37, 38). PAT is highly active in cytokine synthesis by local immune cells like T lymphocytes and monocytes/macrophages (39), which may play essential roles in triggering the inflammatory response in the endothelium. In addition, increasing evidence demonstrated that inflammatory factors like tumor necrosis factor-α, interleukin-6, and interleukin-8 can also be released from PAT, which is involved in the pathogenesis of atherosclerosis (40).

## Strength and limitation

This study adjusted several potential confounding variables and included enough population to evaluate the association between PrFT and SCCA. Several limitations need to be mentioned in this study. First, this study was designed as a cross-sectional study based on prospectively collected data from a single center in the Chinese population without follow-up. Second, the PrFT was measured by CT. The radiation may limit its use in some conditions, such as pregnancy. Third, the measurement of PrFT may vary under different detection methods. The optimal cutoff values of PrFT for SCCA may not apply to participants who underwent ultrasound examinations.

# Conclusion

It is well-acknowledged that participants can benefit from intensive primary prevention strategies at an earlier stage of

TABLE 3 ROC curve analysis of PrFT, VFA, and SFA in identifying SCCA.

| Variables | AUC (95% CI) | Cutoff value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| PrFT (mm) | 0.794 (0.760–0.828) | 14.0 | 66.7 | 76.2 |
| VFA ($cm^2$) | 0.760 (0.724–0.796) | 89.0 | 61.6 | 78.1 |
| SFA ($cm^2$) | 0.697 (0.656–0.737) | 168.0 | 57.5 | 74.2 |

PrFT, perirenal fat thickness; VFA, visceral fat area; SFA, subcutaneous fat area; SCCA, subclinical carotid atherosclerosis.

atherosclerosis. Our study found a novel risk factor and promising target for SCCA. PrFT was independently associated with cIMT, plaque, cIMT > 1 mm, and SCCA and had a good identifying value for SCCA than VFA and SFA. These findings indicated that PrFT might be a superior obesity-related marker of SCCA in T2DM. More attention should be paid on T2DM with excessive accumulation of PAT.

## 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 Ethical Committee of Longyan First Affiliated Hospital of Fujian 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

XG: Data curation, Formal Analysis, Investigation, Methodology, Software, Writing – original draft. JW: Data curation, Investigation, Methodology, Software, Writing – original draft. MT: Data curation, Investigation, Writing – original draft. WW: Data curation, Investigation, Methodology, Writing – review & editing, Formal Analysis, Writing – original draft.

## Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

## 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.2023.1276789/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Perirenal adipose tissue was differentiated from other tissues at the renal venous plane (*) by density. The average maximal distance (blue arrow line) between the kidney's posterior wall and the abdominal wall's inner limit on the left and right side was measured as perirenal fat thickness.

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 03 November 2023
DOI 10.3389/fendo.2023.1294909



OPEN ACCESS

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RECEIVED 15 September 2023
ACCEPTED 16 October 2023
PUBLISHED 03 November 2023

CITATION
Yang S, Shi X, Liu W, Wang Z, Li R, Xu X, Wang C, Li L, Wang R and Xu T (2023) Association between triglyceride glucose-body mass index and heart failure in subjects with diabetes mellitus or prediabetes mellitus: a cross-sectional study. *Front. Endocrinol.* 14:1294909. doi: 10.3389/fendo.2023.1294909



# Association between triglyceride glucose-body mass index and heart failure in subjects with diabetes mellitus or prediabetes mellitus: a cross-sectional study

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**Background:** The triglyceride glucose-body mass index (TyG-BMI) is a surrogate indicator of insulin resistance. However, the association of TyG-BMI with heart failure (HF) in individuals with diabetes mellitus or prediabetes mellitus is unknown.

**Methods:** This study included 7,472 participants aged 20–80 years old with prediabetes or diabetes from the National Health and Nutrition Examination Survey (2007–2018). The TyG-BMI was calculated as Ln [triglyceride (mg/dL) × fasting blood glucose (mg/dL)/2] × BMI, and individuals were categorized into tertiles based on TyG-BMI levels. The relationship of TyG-BMI with HF was analyzed using multiple logistic regression models. Subgroup analyses were stratified by gender, age, hypertension, and diabetes mellitus status.

**Results:** This cross-sectional study had 7,472 participants (weighted n = 111,808,357), including 329 HF participants. Participants with a high TyG-BMI were prone to HF. The highest tertile group with a fully adjusted model was more likely to have HF compared to the lowest tertile group (odds ratio [OR], 2.645; 95% CI, 1.529–4.576). Restricted cubic spline analysis showed a significant dose-response relationship between TyG-BMI and HF ($P < 0.001$). In subgroup analyses, similar results were seen in terms of age (≥50 years old), gender, hypertension, and diabetes mellitus status.

**Conclusion:** A high TyG-BMI is significantly associated with HF risk in participants with diabetes mellitus or prediabetes mellitus.

KEYWORDS

**triglyceride glucose-body mass index, heart failure, diabetes mellitus, prediabetes mellitus, insulin resistance, NHANES**

# Introduction

Heart failure (HF) is a systemic disease caused by multiple factors (1). The main features are damage to the structure and function of the heart and alterations in neurohormonal regulation (2). The mortality rate of hospitalized patients with HF is approximately 4% (3, 4), and the mortality rate of these patients within one month of discharge is 10% (5). One in five individuals older than 40 years will develop HF (6). This creates health hazards and adds pressure to the economy. Thus, early identification and intervention in individuals at high risk of developing HF are essential.

Many studies have shown that the incidence of HF is very high in the diabetes mellitus population (7), and diabetics with HF have a greater risk of death (8). Diabetic women have five times the risk of developing HF as non-diabetic women (9, 10). Prediabetes mellitus is the intermediate stage between normal blood glucose and diabetes mellitus, and it is characterized by impaired glucose metabolism (11). In a related study, prediabetes mellitus also increased the risk of HF, and prediabetic patients were more likely to develop ejection-preserved HF and have worse clinical prognosis (12). A high risk of HF in patients with diabetes mellitus or prediabetes mellitus may be related to insulin resistance (IR), but no study has examined the mechanism of action (13, 14).

The hyperinsulinemic euglycemia clamp technique is the gold standard for measuring IR (15). Because of economic cost and ethical issues, the application of the technique in clinical practice is difficult (15). Recently, the triglyceride glucose (TyG) index was found to be similarly sensitive and specific in predicting IR (16, 17), with triglyceride glucose-body mass index (TyG-BMI) predicting IR better than the TyG index. Therefore, our study explores the association of TyG-BMI with HF in patients with diabetes mellitus or prediabetes mellitus.

# Materials and methods

## Participants and study design

The participants were selected from the National Health and Nutrition Examination Survey (NHANES) from 2007–2018. The National Center for Health Statistics, the heart of the Centers for Disease Control and Prevention, comprises NHANES, which is a study investigating the nutritional and health status of adults and children in the United States. A total of 12,745 individuals with fasting blood glucose (FBG) and hemoglobin A1c (HbA1c) data, as well as complete history of diabetes mellitus from 2007–2018 were included in the study. We excluded 5,273 participants for the following reasons: (1) participants without HF questionnaire data; (2) participants without BMI, TG, and/or FBG data; and (3) participants without other covariates. Figure 1 shows the flow chart of the systematic selection process.

Diabetes mellitus and prediabetes mellitus were defined as follows: for diabetes mellitus, patients were informed by a doctor to have diabetes mellitus, or patients had FBG ≥126 mg/dl or HbA1c ≥6.5%. For prediabetes mellitus, patients had FBG 100–125 mg/dl or HbA1c 5.7%–6.4% (18). Finally, 7,472 participants were selected for analysis. The public database provided the data for this study, and written informed consent was obtained from the participants by NHANES.

## Assessment of HF

The NHANES questionnaire asks: "Has a doctor or other health professional ever told you that you have been diagnosed with HF?". The participants who answered "yes" were considered to have HF.

## Data collection and measurements

Demographic data included age, gender, and race. Race included non-Hispanic White, Mexican American, other Hispanic, non-Hispanic Black, and other races. Questionnaire data included drinking status, smoking status, disease status (hypertension, coronary artery disease, and stroke), and medication status (ACE inhibitors, beta blocker, statin, and diuretics). Smoking was defined as smoking more than one hundred cigarettes in the past year (19). Drinking consumption was defined as having had 12 glasses of wine in the past year (20). The history of diseases was given to patients by a doctor. Measured data included BMI, systolic blood pressure (SBP), and diastolic

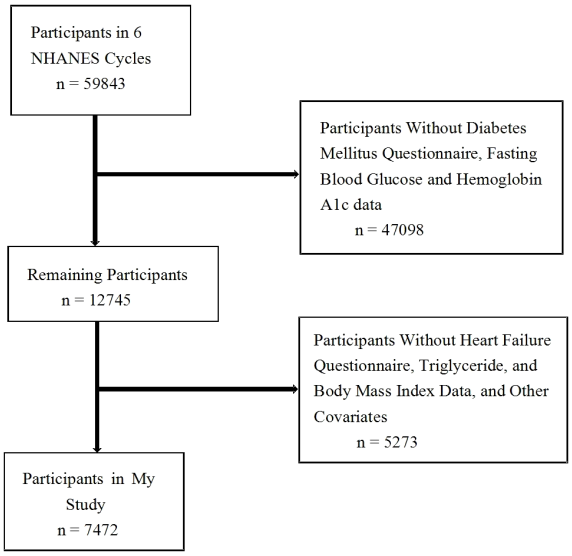


FIGURE 1
The flow chart of the systematic selection process.

**Abbreviations:** HF, heart failure; TyG-BMI, triglyceride glucose-body mass index; NHANES, National Health and Nutritional Examination Survey; IR, insulin resistance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; FBG, fasting blood glucose; HbA1c, hemoglobin A1c.

blood pressure (DBP). Laboratory data collection was performed using fasting blood samples, including FBG, creatinine, HbA1c, estimated glomerular filtration rate (eGFR), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC).

## Definition of index

The formulas for calculating the indexes were as follows.

TyG index = Ln [TG (mg/dL) × FBG (mg/dL)/2

BMI = weight (kg)/height $(m)^2$

TyG-BMI = TyG index × BMI

## Statistical analyses

Qualitative variables were expressed as numbers (n) and percentages (%), and continuous variables were expressed as mean ± standard deviation. Participants were categorized into tertiles based on TyG-BMI. The chi-square test or Kruskal–Wallis H-test was used for analysis. Assessment of the nonlinear association between TyG-BMI and HF used restricted cubic spline curves. We used multiple logistic regression models to explore the correlation between TyG-BMI and HF. Model 1 was non-adjusted; model 2 was adjusted for age, gender, race, smoking status, and drinking consumption; model 3 was adjusted for model 2, LDL-C, eGFR, hypertension, coronary artery disease, ACE inhibitors, Beta blocker, stain, and diuretics.

In subgroups analyses, we stratified the analysis by hypertension (yes or no), gender (male or female) and age (< 50 or ≥ 50 years old), and diabetes mellitus status (diabetes mellitus or prediabetes mellitus) and assessed interactions by likelihood ratio tests. All analyses were performed using R version 3.6.1 (https://www.r-project.org/). Statistical tests were significant at $P < 0.05$.

# Results

## Baseline characteristics

In our study, our final analysis included 7,472 NHANES participants (weighted n = 111,808,357). The baseline characteristics of the patients according to the TyG-BMI tertiles: tertile 1 (TyG-BMI <232.72), tertile 2 (232.72 ≤ TyG-BMI < 286.33), and tertile 3 (TyG-BMI ≥286.33) are shown in Table 1. This study included 1,547 diabetes mellitus patients and 5,925 prediabetes patients, of which 329 (3.6%) had HF. The mean age of all individuals was 54.69 ± 16.10 years, with 46.2% males and 53.8% females. Participants of the T3 group showed higher total cholesterol, BMI, FBG, SBP, DBP, HbA1c, and TG than participants of the T1 group.

## The association of TyG-BMI with HF

As shown in Table 2, logistic regression models showed the association of TyG-BMI with HF. When TyG-BMI was analyzed as a continuous variable, patients were more likely to have HF (OR, 1.009; 95% CI, 1.006–1.012). T3-group patients had higher odds of developing HF than T1-group patients in the fully adjusted model (odds ratio [OR], 2.645; 95% CI, 1.529–4.576). When TyG-BMI was converted to a categorical variable, the P for trend was also significant in unadjusted (P for trend, <0.001) or adjusted (P for trend, <0.001) models. In Figure 2, using a multiple logistic regression model with cubic spline functions, we observed a dose-response relationship of TyG-BMI with HF (non-linear $P < 0.05$), and a higher TyG-BMI (>258.26) was associated with an increased HF risk.

## Subgroup analyses

The results of the subgroup analyses are shown in Table 3 and Figure 3. For participants aged ≥50 years, TyG-BMI was significantly associated with a higher HF prevalence. Subgroup analyses of gender and hypertension showed significant associations between TyG-BMI and HF prevalence. Finally, a higher TyG-BMI associated with a greater HF prevalence in diabetes mellitus (OR, 1.008; 95% CI, 1.003–1.012) and prediabetes mellitus (OR, 1.009; 95% CI, 1.005–1.012) patients. No obvious interactions between TyG-BMI and HF in all subgroup analyses (P for interaction, >0.05) were noted.

# Discussion

This cross-sectional study explored the association of TyG-BMI with HF in diabetic and prediabetic populations from NHANES 2007–2018. Our study confirmed that diabetic or prediabetic participants with high TyG-BMI were more likely to have HF. When the index was used as a categorical or continuous variable, TyG-BMI was significantly associated with increased HF risk. Restricted cubic spline analysis indicated that high TyG-BMI had a dose-response relationship with HF development. The risk is higher when the index is greater than 258.26.

Previous studies have confirmed that the TyG index is a surrogate marker for IR (16, 21). BMI is the simplest measure to assess body fat and metabolism (22). TyG-BMI is the multiplication of the TyG index and BMI. Er et al. indicated that TyG-BMI was better than the TyG index, BMI, conventional lipid levels, visceral obesity index, lipid accumulation products, and adipokine and lipid ratios in predicting IR (23). Liu et al. reported a significantly increased incidence of atherosclerotic cardiovascular disease in Taiwanese adults with increasing TyG-BMI (24). In another study, a linear relationship of TyG-BMI with ischemic stroke in the general population was demonstrated (25). A cross-sectional

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TABLE 1 Characteristics of participants in the study.

| | Overall | Tertile 1 | Tertile 2 | Tertile 3 | P value |
|---|---|---|---|---|---|
| N | 7472 | 2491 | 2490 | 2491 | |
| TyG-BMI | 268.62(70.48) | 201.31(23.16) | 258.23(15.34) | 346.32(56.10) | <0.001 |
| Age (years) | 54.69(16.10) | 55.48(17.38) | 55.48(15.86) | 53.11(14.96) | <0.001 |
| < 50 | 2761(41.90) | 886(40.70) | 881(40.50) | 994(44.40) | |
| ≥ 50 | 4711(58.10) | 1605(59.30) | 1609(59.50) | 1497(55.60) | 0.001 |
| Male (n, %) | 3962(53.80) | 1416(56.10) | 1409(56.50) | 1137(49.00) | <0.001 |
| Race (n, %) | | | | | <0.001 |
| Mexican American | 1214(9.30) | 263(6.40) | 471(10.80) | 480(10.80) | |
| Other Hispanic | 827(5.80) | 238(5.20) | 300(6.50) | 289(5.90) | |
| Non-Hispanic White | 2854(64.50) | 943(64.30) | 919(63.30) | 992(65.70) | |
| Non-Hispanic Black | 1554(11.60) | 494(10.90) | 483(10.90) | 577(12.80) | |
| Other Race | 1023(8.80) | 553(13.20) | 317(8.50) | 153(4.80) | |
| Current smoker (n, %) | 3448(47.10) | 1121(46.80) | 1158(47.40) | 1169(47.00) | <0.001 |
| Drinking consumption (n, %) | 3806(75.40) | 1266(76.40) | 1314(77.10) | 1226(72.90) | 0.373 |
| BMI (Kg/m2) | 30.51(7.20) | 24.04(2.65) | 29.41(2.32) | 38.09(6.38) | <0.001 |
| HbA1c (%) | 6.12(1.11) | 5.81(0.72) | 6.06(0.99) | 6.5(1.39) | |
| FBG (mmol/L) | 6.67(1.97) | 6.08(1.10) | 6.53(1.73) | 7.39(2.56) | <0.001 |
| SBP (mmHg) | 127.66(17.37) | 126.84(18.58) | 127.71(16.66) | 128.45(16.64) | 0.015 |
| DBP (mmHg) | 70.67(12.68) | 69.20(12.57) | 70.74(11.93) | 72.08(13.29) | <0.001 |
| TC (mmol/L) | 4.99(1.10) | 4.90(1.06) | 5.05(1.13) | 5.01(1.09) | <0.001 |
| TG (mmol/L) | 1.61(1.52) | 1.09(0.53) | 1.60(0.93) | 2.16(2.24) | <0.001 |
| HDL (mmol/L) | 1.36(0.39) | 1.41(0.41) | 1.35(0.38) | 1.33(0.39) | <0.001 |
| LDL (mmol/L) | 2.83(0.95) | 2.84(0.92) | 2.83(0.96) | 2.83(0.98) | 0.992 |
| eGFR | 113.88(50.85) | 88.88(32.57) | 107.42(37.31) | 145.30(58.53) | <0.001 |
| Creatinine (umol/L) | 80.80(38.56) | 80.76(36.33) | 81.7(34.90) | 79.93(43.59) | 0.364 |
| Heart failure (n, %) | 329(3.60) | 76(2.50) | 97(3.00) | 156(5.10) | <0.001 |
| Diabetes mellitus status (n, %) | | | | | <0.001 |
| Prediabetes mellitus | 5925(83.00) | 2214(92.10) | 2026(85.60) | 1685(71.80) | |
| Diabetes mellitus | 1547(17.00) | 277(7.90) | 464(14.40) | 806(28.20) | |
| Hypertension (n, %) | 3443(42.40) | 877(30.40) | 1169(42.80) | 1397(53.50) | <0.001 |
| Coronary artery disease | 400(4.80) | 136(4.80) | 122(4.40) | 142(5.30) | 0.424 |
| Stroke (n, %) | 329(3.70) | 101(3.60) | 108(3.30) | 120(4.20) | 0.416 |
| ACE inhibitors (n, %) | 1901(27.00) | 644(26.60) | 595(27.40) | 662(26.80) | 0.080 |
| Beta blocker (n, %) | 1049(14.50) | 372(14.90) | 354(14.80) | 323(13.80) | 0.129 |
| Statin (n, %) | 2015(28.40) | 677(27.70) | 663(28.90) | 675(28.60) | 0.894 |
| Diuretics (n, %) | 1309(18.40) | 435(18.70) | 431(18.80) | 443(17.70) | 0.904 |

TyG-BMI, triglyceride glucose-body mass index; BMI, body mass index; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

TABLE 2 Relationship between TyG-BMI and heart failure.

| Exposure | Model 1 | Model 2 | Model 3 |
|---|---|---|---|
| TyG-BMI | 1.005(1.003,1.007) <0.001 | 1.007(1.005,1.010) <0.001 | 1.009(1.006,1.012) <0.001 |
| TyG-BMI tertile | | | |
| T1 | 1.0 | 1.0 | 1.0 |
| T2 | 1.218(0.728,2.036) 0.448 | 1.286(0.759,2.178) 0.346 | 1.247(0.743,2.092) 0.399 |
| T3 | 2.121(1.339,3.358) 0.002 | 2.712(1.625,4.525) <0.001 | 2.645(1.529,4.576) <0.001 |
| P for trend | <0.001 | <0.001 | <0.001 |

Data are presented as odds ratios, 95% confidence intervals, and P-value.
Model 1 was non-adjusted; model 2 was adjusted for gender, age, race, smoking status, and drinking consumption; model 3 was adjusted for model 2, LDL-C, eGFR, hypertension, coronary artery disease, ACE inhibitors, Beta blocker, stain, and diuretics.

study has indicated that individuals with a high TyG-BMI are more likely to have prehypertension (26), whereas a prospective study using data from Hong Kong and Taiwan found that individuals with a high TyG index were more likely to have HF (27). Xu et al. also reported that the TyG index was significantly associated with the prevalence of HF (28). The differences between our study and these two studies may be related to the fact that TyG-BMI predicted IR better than the TyG index, and previous cohorts were from the general population. Our study included diabetic and prediabetic patients.

In our subgroup analyses, fully-adjusted models showed a positive relationship between TyG-BMI and HF in individuals aged ≥50 years but not in those aged <50 years, which is probably due to the fact that fewer individuals aged <50 years developed HF than those aged ≥50 years in our study. Meanwhile, our study indicated that males with elevated TyG-BMI had a higher risk of

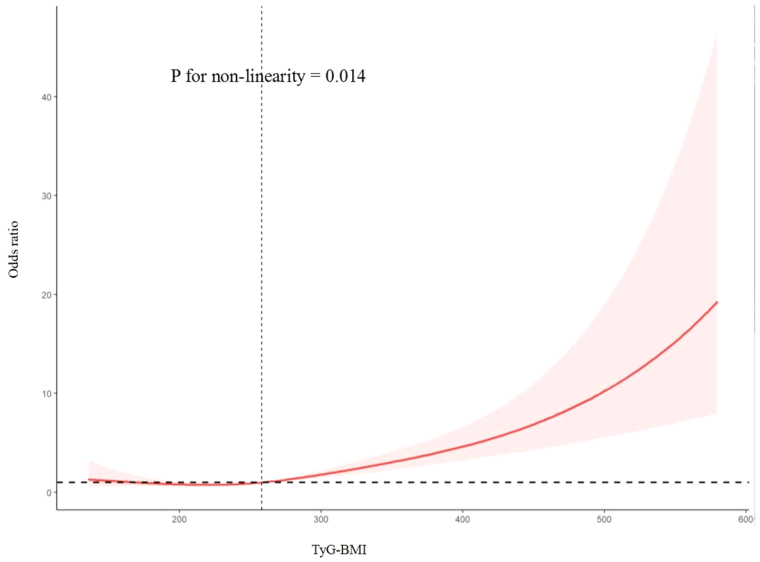


FIGURE 2
Restricted cubic spline curve for the association between TyG-BMI with heart faliure.

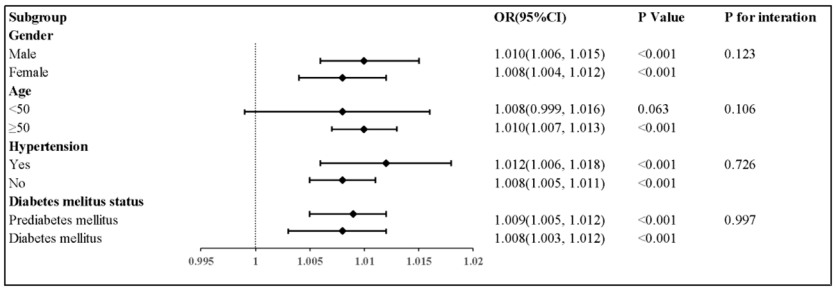


FIGURE 3
Subgroup analyses for the association between TyG-BMI with heart faliure. Adjusted for gender, age, race, smoking status, and drinking consumption, LDL-C, eGFR, hypertension, coronary artery disease, ACE inhibitors, Beta blocker, stain, and diuretics.

TABLE 3 Subgroup analyses for the association between TyG-BMI index and heart faliure.

| Subgroup | OR(95%CI) | P Value | P for interation |
|---|---|---|---|
| Gender | | | |
| Male | 1.010(1.006, 1.015) | <0.001 | 0.123 |
| Female | 1.008(1.004, 1.012) | <0.001 | |
| Age | | | |
| <50 | 1.008(0.999, 1.016) | 0.063 | 0.106 |
| ≥50 | 1.010(1.007, 1.013) | <0.001 | |
| Hypertension | | | |
| Yes | 1.012(1.006, 1.018) | <0.001 | 0.726 |
| No | 1.008(1.005, 1.011) | <0.001 | |
| Diabetes mellitus status | | | |
| Prediabetes mellitus | 1.009(1.005, 1.012) | <0.001 | 0.997 |
| Diabetes mellitus | 1.008(1.003, 1.012) | <0.001 | |

Adjusted for sex, gender, race, smoking status, and drinking consumption, LDL-C, eGFR, hypertension, coronary artery disease, ACE inhibitors, Beta blocker, stain, and diuretics.

developing HF than females. Although females are less likely to develop IR than males (29), HF due to high BMI and diabetes mellitus is more common in females (30), and diabetic females are more likely to develop coronary heart disease than males (31, 32). In summary, our findings are inconsistent with previous studies.

The TyG-BMI was associated with increased HF risk in diabetes mellitus status subgroup analysis, and the P for interaction was not significant, indicating TyG-BMI can be used to reflect HF risk of prediabetic and diabetic populations. In prediabetic and diabetic populations, HF occurrence was more likely to be induced by IR. Currently, the association between IR and HF can be explained by several mechanisms. Firstly, IR leads to cardiac pressure overload or ischemia susceptibility, which is possibly caused by impaired glucose utilization and subsequent increased free fatty acid oxidation (33, 34). Secondly, IR leads to adverse activation of the sympathetic nervous system, with chronic hyperinsulinemia increasing angiotensinogen release from adipose tissues and angiotensin II receptor expression, ultimately leading to aberrant cardiac remodeling and cardiac dysfunction (35). However, the mechanism of action between IR and HF requires further study.

The current study has several limitations. Firstly, our study is a cross-sectional observational study. Further prospective cohort studies, which include a control group, are likely to provide more real-world evidence in the future. Secondly, the diagnosis of HF may have been under- or over-reported by individuals in the questionnaire. Thirdly, the impact of the oral glucose tolerance test results on the diagnosis of prediabetes or diabetes was not considered.

## Conclusions

In conclusion, a high TyG-BMI was significantly associated with an increased HF risk in patients with diabetes mellitus or prediabetes mellitus. Treatments aimed at reducing TyG-BMI for HF prevention are urgently required.

## 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://www.cdc.gov/nchs/nhanes.

## Ethics statement

The present study received approval from the National Center for Health Statistics and database obtained consent from the participants. 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

SY: Data curation, Methodology, Writing – original draft. XS: Data curation, Methodology, Writing – original draft. WL: Data curation, Methodology, Writing – review & editing. ZW: Data curation, Methodology, Writing – review & editing. RL: Data curation, Writing – original draft. XX: Data curation, Writing – original draft. CW: Data curation, Writing – original draft. LL: Writing – review & editing. RW: Writing – review & editing. TX: Writing – review & editing.

## Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Jiangsu Provincial Health Commission Project Fund (Grant number: M2020015), Jiangsu Provincial Science and Technology Department Social Development Fund (Grant number: BE2019639), Jiangsu Traditional Chinese Medicine Science and Technology Development Plan Project (Grant number: YB201988), Xuzhou Innovative plan to Promote Science Technology (Grant number: KC21192), and Xuzhou Practical Innovation Program for University Students (Grant number: SJCX23_1389).

## Acknowledgments

We would like to thank the NHANES database for providing data for the study and express our gratitude to all members of this study,

including the study sponsors, and all participants. We also thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

## 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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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 22 December 2023
DOI 10.3389/fendo.2023.1259062



OPEN ACCESS

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RECEIVED 15 July 2023
ACCEPTED 06 December 2023
PUBLISHED 22 December 2023

CITATION
Wang S, Zhang X, Keerman M, Guo H, He J, Maimaitijiang R, Wang X, Ma R and Guo S (2023) Impact of the baseline insulin resistance surrogates and their longitudinal trajectories on cardiovascular disease (coronary heart disease and stroke): a prospective cohort study in rural China. *Front. Endocrinol.* 14:1259062. doi: 10.3389/fendo.2023.1259062



# Impact of the baseline insulin resistance surrogates and their longitudinal trajectories on cardiovascular disease (coronary heart disease and stroke): a prospective cohort study in rural China

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**Background:** This study aimed to assess the association of baseline insulin resistance (IR) surrogates and their longitudinal trajectories with cardiovascular diseases (CVD) to provide a useful reference for preventing CVD.

**Methods:** This study was a prospective cohort study conducted in the 51st Regiment of the Third Division of Xinjiang Corps. A total of 6362 participants were recruited in 2016 to conduct the baseline survey, and the follow-up surveys in 2019, 2020, 2021, and 2022. The Kaplan–Meier method was used to estimate the cumulative incidence of CVD according to the baseline IR surrogates of metabolic insulin resistance score (METS-IR) and triglyceride-glucose (TyG) index. Cox regression models were used to assess the association between the baseline IR surrogates and CVD. The impact of the longitudinal trajectories of the IR surrogates on CVD was analyzed after excluding those with IR surrogate data measured ≤2 times. Based on the group-based trajectory model (GBTM), the trajectory patterns of IR surrogates were determined. The Kaplan-Meier method was used to estimate the cumulative incidence of CVD in each trajectory group of METS-IR and TyG index. Cox regression models were used to analyze the association between different trajectory groups of each index and CVD. In addition, the Framingham model was utilized to evaluate whether the addition of the baseline IR surrogates increased the predictive potential of the model.

**Results:** Baseline data analysis included 4712 participants. During a median follow-up of 5.66 years, 572 CVD events were recorded (mean age, 39.42 ± 13.67 years; males, 42.9%). The cumulative CVD incidence increased with the

ascending baseline METS-IR and TyG index quartiles (Q1–Q4). The hazard ratio and 95% confidence interval for CVD risk in Q4 of the METS-IR and TyG index were 1.79 (1.25, 2.58) and 1.66 (1.28, 2.17), respectively, when compared with Q1. 4343 participants were included in the trajectory analysis, based on the longitudinal change patterns of the METS-IR and TyG index, the following three trajectory groups were identified: low-increasing, moderate-stable, and elevated-increasing groups. Multivariate Cox regression revealed that the hazard ratio (95% confidence interval) for CVD risk in the elevated-increasing trajectory group of the METS-IR and TyG index was 2.13 (1.48, 3.06) and 2.63 (1.68, 4.13), respectively, when compared with the low-rising group. The C-index, integrated discrimination improvement value, and net reclassification improvement value were enhanced after adding the baseline METS-IR and TyG index values to the Framingham model ($P$<0.05).

**Conclusions:** Elevated baseline IR surrogates and their higher long-term trajectories were strongly associated with a high risk of CVD incidence in Xinjiang's rural areas. Regular METS-IR and TyG index monitoring can aid in the early detection of CVD-risk groups.

KEYWORDS

**cardiovascular disease, cohort study, metabolic score for insulin resistance, triglyceride-glucose index, trajectory analysis**

# 1 Introduction

Cardiovascular diseases (CVD) are associated with high morbidity and mortality rates. Approximately one-third of deaths worldwide are attributable to CVD, which ranks first among chronic non-communicable diseases in terms of fatalities (1). With approximately 330 million people afflicted, the incidence of CVD is rising in China, as is the illness burden associated with CVD (2). Therefore, early detection of persons at risk for CVD through effective screening measures and the development of preventative and treatment strategies are critical.

Insulin resistance (IR) represents one of the key pathogenic mechanisms of CVD, which promotes CVD development through numerous physiological and biochemical pathways that accelerate and exacerbate the CVD processes (3). The homeostasis model assessment of insulin resistance (HOMA-IR) is a common approach for assessing IR; however, its practical application is restricted because insulin is not a conventional measure, and the test is expensive (4). The recently introduced metabolic score for insulin resistance (METS-IR) and triglyceride-glucose (TyG) index has the advantages of being less expensive and simpler than HOMA-IR and has been proven to be useful in assessing IR (5, 6). The correlations of METS-IR and TyG index with CVD risk have been validated in various cohorts (7–9). However, most of the previous studies analyzed the association of METS-IR and TyG index with CVD using single measurement data, neglecting the influence of their dynamic changes on CVD during the follow-up period.

Although the prevalence of CVD is substantial in the rural areas of Xinjiang, investigations involving IR surrogates in this population are limited (10). To provide a reference and theoretical foundation for CVD risk prediction and targeted prevention and control, this study used a prospective cohort to assess the relationship between the baseline and trajectories of IR surrogates with CVD.

# 2 Materials and methods

## 2.1 Study population

The 51st Regiment of the Third Division of Xinjiang Corps was chosen as the survey location using a typical sampling method. In total, 6567 adult residents of the 51st Regiment's five squadrons for over a year were chosen as survey participants using a stratified cluster random sampling method. The baseline survey was conducted in 2016, and the follow-up surveys in 2019, 2020, 2021, and 2022. The contents of the follow-up survey were consistent with those of the baseline survey. At baseline, 6362 participants were surveyed after excluding the floating population, pregnant women, those unable to participate in the survey (n=158), and those with incomplete basic information (n=47). During the follow-up period, 414 participants were lost to follow-up (follow-up rate: 93.5%). After excluding baseline CVD participants (n=574), baseline METS-IR and TyG data incomplete participants (n=346),

and baseline covariate information missing participants (n=316), 4712 participants were included in the study to look into the association between the baseline IR surrogates and CVD. To examine the impact of the longitudinal trajectories of the IR surrogates on CVD, 4343 participants were included after excluding those with METS-IR and TyG index data measured ≤2 times (n=369) (Figure 1).

## 2.2 Data collection

### 2.2.1 General information collection

Professionally trained personnel administered the questionnaire and conducted physical examinations for the participants. The face-to-face survey using a questionnaire was conducted to collect demographic information, lifestyle habits (including exercise frequency, smoking habits, and drinking habits), and family and personal medical histories. Physical examination was conducted using standard methods to measure height, weight, waist circumference (WC), and other health indicators. Height and weight measuring instrument was used to measure height and weight and the body mass index (BMI) was calculated. The participants in the measurement stood straight, leaned on the column, removed their shoes and bulky apparel, and fixed their gaze ahead while keeping both eyes flat. The WC was measured by a flexible ruler at the horizontal position of the axillary line between the lower edge of the costal arch and the midpoint of the iliac crest. The blood pressure was measured twice in the seated position at an interval of 5 mins using an electronic sphygmomanometer (OMRON HEM-7051, Omron, Dalian Co., Ltd.), and the average result was recorded.

### 2.2.2 Laboratory examination

Venous blood samples (5 mL) were collected from the anterior aspect of the participants' elbows while they were fasting on the day of the physical examination. Biochemical indicators such as fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density

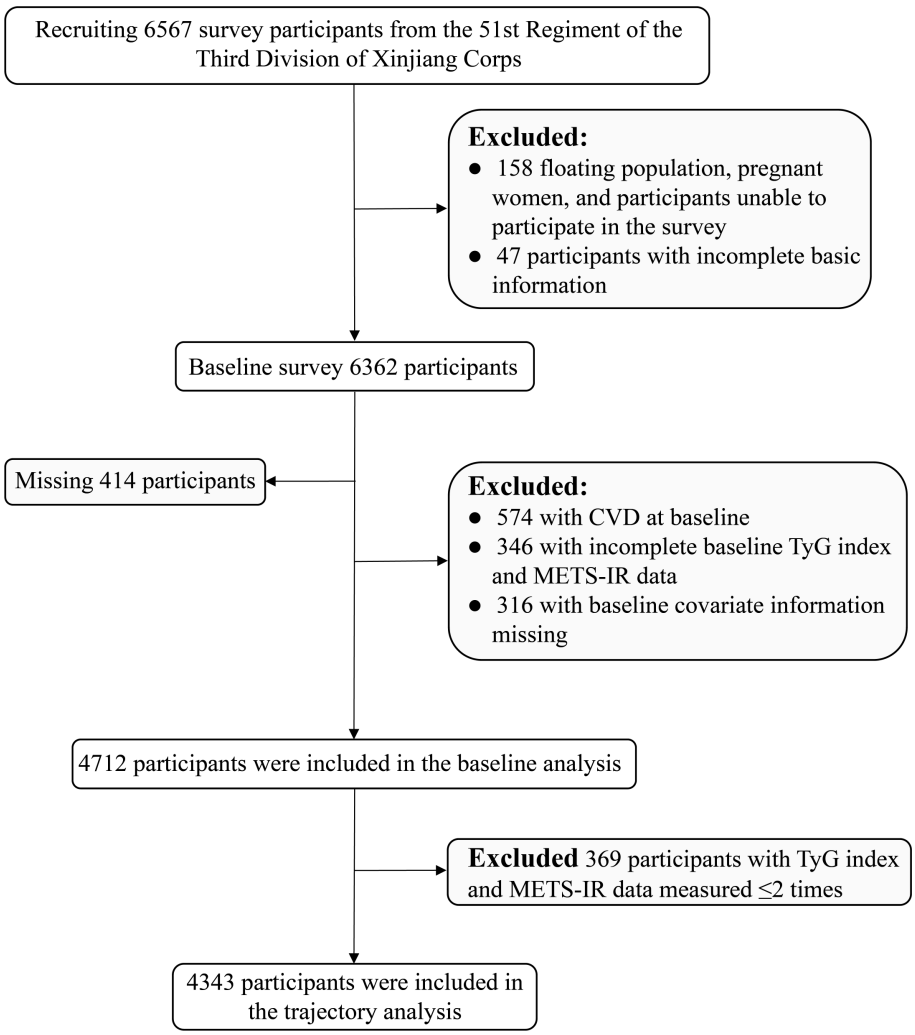


FIGURE 1
Flow chart of the inclusion and exclusion criteria of the rural Xinjiang population. (*CVD*, cardiovascular diseases; *TyG* index, triglyceride-glucose index; *METS-IR*, metabolic insulin resistance score).

lipoprotein cholesterol (HDL-C) were measured using the OLYMPUS 2007 automatic biochemical analyzer. The METS-IR was calculated as "Ln [(2×FPG (mg/dL))+TG (mg/dL)]×BMI/Ln [HDL-C (mg/dL)]" (6); the TyG index was calculated as "Ln [TG (mg/dL)×FPG (mg/dL)/2]" (5).

## 2.3 Relevant definitions

(1) Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, self-reported hypertension, or self-reported use of antihypertensive medications within 2 weeks (11);

(2) Prediabetes and diabetes: prediabetes was defined as 5.6 mmol/L≤FPG≤ 7.0 mmol/L; diabetes was defined as FPG ≥7.0 mmol/L or history of diabetes (12);

(3) Smoking: continuous or cumulative smoking for ≥6 months (13);

(4) Drinking: ≥2 times/month for >6 months (14);

(5) Exercise frequency: regular exercise (≥3 times/week, exercise time: ≥30 min/session); occasional exercise (<3 times/week, exercise time: <30 min/session); and almost no exercise (<1 time/week) (15).

## 2.4 Diagnostic criteria for cardiovascular disease

The study outcome events were new-onset coronary heart disease (International Classification of Diseases, Tenth Revision [ICD-10]: I20–I25) or stroke (ICD-10: I60–I64 and I69) during the follow-up period (16). Data on the outcome events were obtained from questionnaires, public primary hospital case files, and social security information. The time of the first outcome event was chosen as the end event if several outcome events occurred in the same participant. Those who self-reported the outcome events had to present documentation of the clinical diagnosis made at a county-level hospital or higher.

## 2.5 Statistical analysis

### 2.5.1 Descriptive analysis

Continuous variables are presented as means ± standard deviations, and the independent samples t-test was used for inter-group comparisons. Categorical variables are presented as frequencies and composition ratios, and the $\chi^2$-test was used for inter-group comparisons.

### 2.5.2 Analysis of the association between baseline IR surrogates and CVD

The Kaplan–Meier method was used to estimate the cumulative incidence of CVD in the quartile groups of the baseline METS-IR and TyG index, and the log-rank test was performed to determine any difference in the cumulative incidence of CVD in the quartile groups. Cox regression models were used to analyze the association between the quartile groups of each index and CVD onset. The covariates of the multivariate Cox regression model included age, sex, education level, exercise frequency, WC, smoking, drinking, family history of CVD, hypertension, HDL-C, and LDL-C. Subgroup analyses were for the following variables: sex, age (<45 and ≥45 years), BMI (<28 and ≥28 kg/m$^2$), and hypertension (yes and no). The interaction between the subgroups was evaluated using the likelihood ratio test. Sensitivity analysis was performed to verify the consistency of the results. Initially, to reduce the possibility of reverse causality, the participants who experienced an outcome event within the first year of the follow-up were excluded. Secondly, the Cox regression analysis was repeated after excluding the population with hypertension, considering that this population might affect the findings. Third, sensitivity analysis was performed after excluding the population with dyslipidemia. Finally, a sensitivity analysis was conducted, excluding individuals with prediabetes and diabetes. The Framingham CVD risk score model (17) was used to evaluate the incremental predictive value of the baseline METS-IR and TyG index and to assess whether their addition could improve the predictive power of the model based on the C-index, net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

### 2.5.3 Analysis of the association between IR surrogates' trajectories and CVD

The group-based trajectory model (GBTM) (18) identifies population subgroups with similar development trends over time in the cohort based on multiple repeated measurement data and depicts the longitudinal development trajectory curve of each subgroup. In this study, the trajectory patterns of the METS-IR and TyG index of the participants were determined using the above model. We repeatedly tested models with groups ranging from 2 to 5 until the ideal group of trajectories was identified. Following this, the variation order of each trajectory (linear, quadratic, and cubic) was modified for repeated testing so that the estimated values of each parameter reached the significance level; this allowed for the determination of the curve shape of each trajectory group in the final model. The following criteria were used to determine which trajectory-fitting model was the best: (1) absolute Bayesian information criterion minimization; (2) average posterior probabilities of each trajectory subgroup >0.70; and (3) followed the explanation of the expert theory. The METS-IR and TyG index trajectories were subsequently divided into the following three groups based on the results of numerous iterations of the fit: low-rising group, moderate-stable group, and elevated-increasing group. This has been presented in the additional table files (Supplementary Table 1). To assess the effect of the METS-IR and TyG index trajectory groups on CVD, the Kaplan–Meier method was used to calculate the cumulative incidence of CVD in each trajectory group. The log-rank test was used for comparison between the groups, and the Cox regression model was used to examine the impact of the different trajectory groups of the METS-IR and TyG index on CVD. The sensitivity analysis method

for the different trajectory groups of the METS-IR and TyG index was the same as that used for the baseline data analysis.

All data were analyzed using SPSS 26.0, Stata 17.0, and R 4.1.2; *P*-values <0.05 were considered statistically significant for all analyses.

# 3 Results

## 3.1 Baseline characteristics

Among the 4712 participants in this study, 42.9% were male, and the average age was 39.42 ± 13.02 years. The FPG, TG, TC, HDL-C, LDL-C, BMI, and WC differed significantly between the CVD and non-CVD groups ($P<0.05$). Smoking habits, family history of CVD, and hypertension were reported in 17.1%, 19.4%, and 40.9% of the participants in the CVD group, respectively, which were significantly higher than those reported in the non-CVD group participants ($P<0.05$). The percentage of the CVD group participants with no formal education and almost no exercise was higher than that of the whole population (Table 1).

## 3.2 Association between baseline IR surrogates and CVD

The cohort had a cumulative CVD incidence of 12.1% during a median follow-up period of 5.66 years. In total, 572 participants had their first CVD event during 23,614.71 person-years of follow-up (24.22/1000 person-years). With the ascending baseline METS-IR and TyG index quartiles, the cumulative incidence of CVD increased

TABLE 1 Baseline characteristics of Xinjiang's rural population according to the incidence of cardiovascular diseases.

| Variables | CVD group (n=572) | Non-CVD group (n=4140) | Total (n=4712) | t/$\chi^2$ value | *P* value |
|---|---|---|---|---|---|
| Male (%) | 205 (35.8) | 1816 (43.9) | 2021 (42.9) | 13.215 | <0.001 |
| Age (years) | 49.79 ± 12.93 | 37.98 ± 12.36 | 39.42 ± 13.02 | 20.581 | <0.001 |
| Education level | | | | 33.749 | <0.001 |
| Illiterate/semi-illiterate (%) | 284 (49.7) | 1564 (37.8) | 1848 (39.2) | | |
| Junior high school and below (%) | 242 (42.3) | 2278 (55.0) | 2520 (53.5) | | |
| High School and above (%) | 46 (8.0) | 298 (7.2) | 344 (7.3) | | |
| Exercise frequency | | | | 16.816 | <0.001 |
| Regular exercise (%) | 171 (29.9) | 1449 (35.0) | 1620 (34.3) | | |
| Occasional exercise (%) | 28 (4.9) | 338 (8.2) | 366 (7.8) | | |
| Almost no exercise (%) | 373 (65.2) | 2353 (56.8) | 2726 (57.9) | | |
| Systolic blood pressure (mmHg) | 137.86 ± 24.59 | 126.37 ± 19.16 | 127.77 ± 20.24 | 10.736 | <0.001 |
| Diastolic blood pressure(mmHg) | 80.96 ± 15.55 | 74.98 ± 11.82 | 75.71 ± 12.49 | 8.844 | <0.001 |
| FPG (mmol/L) | 4.97 ± 1.27 | 4.68 ± 0.98 | 4.72 ± 1.03 | 5.105 | <0.001 |
| TG (mmol/L) | 1.59 ± 0.63 | 1.38 ± 0.64 | 1.41 ± 0.64 | 7.207 | <0.001 |
| TC (mmol/L) | 4.76 ± 1.06 | 4.62 ± 1.04 | 4.64 ± 1.04 | 3.044 | 0.002 |
| HDL-C (mmol/L) | 1.34 ± 0.36 | 1.42 ± 0.38 | 1.41 ± 0.38 | -5.078 | <0.001 |
| LDL-C (mmol/L) | 2.74 ± 0.89 | 2.57 ± 0.89 | 2.59 ± 0.90 | 4.250 | <0.001 |
| BMI ($kg/m^2$) | 28.30 ± 4.14 | 26.46 ± 4.18 | 26.69 ± 4.22 | 9.842 | <0.001 |
| WC (cm) | 95.57 ± 10.33 | 90.67 ± 11.30 | 91.27 ± 11.30 | 10.499 | <0.001 |
| TyG index | 8.65 ± 0.46 | 8.43 ± 0.53 | 8.46 ± 0.52 | 10.379 | <0.001 |
| METS-IR | 41.67 ± 7.14 | 37.83 ± 7.15 | 38.30 ± 7.26 | 12.021 | <0.001 |
| Smoking (%) | 98 (17.1) | 571 (13.8) | 669 (14.2) | 4.604 | 0.032 |
| Drinking (%) | 27 (4.7) | 156 (3.8) | 183 (3.9) | 1.221 | 0.269 |
| Hypertension (%) | 234 (40.9) | 869 (21.0) | 1103 (23.4) | 111.215 | <0.001 |
| Family history of CVD (%) | 111 (19.4) | 478 (11.5) | 589 (12.5) | 28.385 | <0.001 |

(CVD, cardiovascular diseases; FPG, fasting plasma glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index, WC, waist circumference; METS-IR, metabolic insulin resistance score; TyG index, triglyceride-glucose index).

considerably and peaked in the Q4 group (Figure 2). After controlling for the baseline age, sex, education level, exercise frequency, WC, smoking, drinking, family history of CVD, hypertension, HDL-C, and LDL-C, the METS-IR and TyG index were found to be associated with an increased risk of CVD. Compared to Q1, the hazard ratio (HR) (95% confidence intervals [CI]) for the risk of CVD in Q4 of the METS-IR and TyG index was 1.79 (1.25, 2.58) and 1.66 (1.28, 2.17), respectively (Table 2).

The results of the sensitivity analyses were unchanged substantially after excluding those with an outcome event within the first year of follow-up, those with hypertension, those with dyslipidemia, and those with pre-diabetes and diabetes, in that order. This suggests that the results of this study are robust (Figure 3). The subgroup analysis indicated that the relationship between METS-IR and CVD was consistent with the main results, with an interaction elucidated between sex and METS-IR ($P<0.05$), males have a higher risk of CVD than females. The TyG index showed a positive association with the CVD risk in the subgroups of sex, age (<45 and ≥45 years), BMI (<28 and ≥28 kg/m$^2$), and non-hypertensive population; however, in the hypertensive population, no connection between the TyG index and CVD was found to be statistically significant, as shown in an additional table file (Supplementary Table 2).

## 3.3 Characterization of the IR surrogates' trajectories

The trajectory analysis included 4343 participants, of which 1871 (43.1%) were male, and the average age was 39.09 ± 12.85 years, as shown in an additional table file (Supplementary Table 3). Based on the change trajectory patterns of METS-IR and TyG index from 2016 to 2022, this study revealed three distinct trajectories (Figure 4). According to the best-fitting trajectory model, the trajectory of METS-IR can be classified into the low-rising trajectory group (n=1985, 45.7%), moderate-stable trajectory group (n=2114, 48.7%), and elevated-increasing trajectory group (n=244, 5.6%). The trajectory of the TyG index can be classified into the low-rising trajectory group (n=556, 12.8%), moderate-stable trajectory group (n=3579, 82.4%), and elevated-increasing trajectory group (n=208, 4.8%). The average values of the observations at each time point for the different trajectory groups of the METS-IR and TyG index are shown in an additional table file (Supplementary Table 4).

## 3.4 Relationship between the IR surrogates' trajectories and CVD

The cumulative CVD incidence in the low-rising group of the METS-IR and TyG index was 5.9% and 5.6% respectively. The cumulative CVD incidence was 16.7% and 12.4% in the moderate-stable group and 25.8% and 27.4% in the elevated-increasing group of the METS-IR and TyG index, respectively. The elevated-increasing group had a greater cumulative incidence of CVD than the other trajectory groups according to the Kaplan–Meier curves (Figure 5). Using the low-rising group as a reference, the multifactorial analysis revealed that the HR (95% CI) for CVD risk in the moderate-stable group of the METS-IR and TyG index trajectories was 1.65 (1.30, 2.08) and 1.62 (1.12, 2.34), respectively. Moreover, the HR (95% CI) for CVD risk in the elevated-increasing group of the METS-IR and TyG index trajectories was 2.13 (1.48, 3.06) and 2.63 (1.68, 4.13), respectively (Table 3).

Sensitivity analyses proved that on excluding individuals who experienced a CVD event within the first year of follow-up, those with hypertension, those with dyslipidemia, and those with pre-diabetes and diabetes, in that order, the relationship between the TyG index trajectory and CVD remained consistent with the primary results. The relationship between the METS-IR trajectory and CVD did not significantly change after excluding individuals experiencing a CVD event within the first year of follow-up and those with dyslipidemia. After excluding those with hypertension, no significant correlation was observed between the METS-IR trajectory and CVD incidence in the elevated-increasing group (Figure 6).

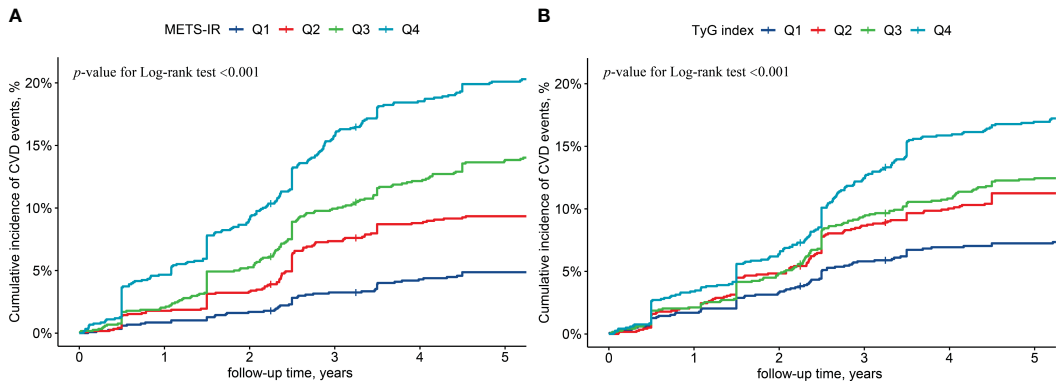


FIGURE 2
Cumulative cardiovascular diseases incidence by baseline metabolic insulin resistance score **(A)** and triglyceride-glucose index **(B)**. (*METS-IR*, metabolic insulin resistance score; *TyG* index, triglyceride-glucose index; *CVD*, cardiovascular disease; *Q1*, Quartile 1; *Q2*, Quartile 2; *Q3*, Quartile 3; *Q4*, Quartile 4).

TABLE 2 Risk of cardiovascular diseases by baseline insulin resistance surrogates in Xinjiang's rural population.

| Variables | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| METS-IR | | | | | | |
| Continuous (per unit) | 1.06 (1.05, 1.07) | <0.001 | 1.03 (1.02, 1.04) | <0.001 | 1.02 (1.01, 1.04) | 0.005 |
| Q1 (≤33.24) | Reference | | Reference | | Reference | |
| Q2 (33.25~) | 2.16 (1.57, 2.98) | <0.001 | 1.58 (1.14, 2.18) | 0.005 | 1.46 (1.05, 2.03) | 0.026 |
| Q3 (37.83~) | 3.11 (2.29, 4.22) | <0.001 | 1.94 (1.42, 2.64) | <0.001 | 1.71 (1.23, 2.39) | 0.002 |
| Q4 (≥42.40) | 4.77 (3.56, 6.40) | <0.001 | 2.24 (1.65, 3.04) | <0.001 | 1.79 (1.25, 2.58) | 0.002 |
| *P* for trend | | <0.001 | | <0.001 | | 0.004 |
| TyG index | | | | | | |
| Continuous (per unit) | 2.12 (1.81, 2.48) | <0.001 | 1.70 (1.44, 2.01) | <0.001 | 1.64 (1.38, 1.94) | <0.001 |
| Q1 (≤8.13) | Reference | | Reference | | Reference | |
| Q2 (8.14~) | 1.60 (1.22, 2.11) | 0.001 | 1.47 (1.12, 1.93) | 0.006 | 1.49 (1.13, 1.96) | 0.004 |
| Q3 (8.50~) | 1.77 (1.35, 2.31) | <0.001 | 1.42 (1.09, 1.86) | 0.010 | 1.40 (1.06, 1.83) | 0.016 |
| Q4 (≥8.81) | 2.47 (1.91, 3.18) | <0.001 | 1.79 (1.38, 2.31) | <0.001 | 1.66 (1.28, 2.17) | <0.001 |
| *P* for trend | | <0.001 | | <0.001 | | <0.001 |

Model 1: non-adjusted model.
Model 2: adjusted by baseline age and sex.
Model 3: adjusted by Model 2 and the baseline education level, exercise frequency, waist circumference, smoking, drinking, family history of cardiovascular disease, hypertension, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.
Q1, Q2, Q3, and Q4 represent the four quartiles.
(HR, hazard ratio; CI, confidence interval; METS-IR, metabolic insulin resistance score; TyG index, triglyceride-glucose index).

## 3.5 Predicting the CVD risk according to the baseline IR surrogates

The inclusion of the baseline METS-IR and TyG index to the Framingham model significantly increased its prediction potential. In the diverse sex populations, the addition of METS-IR and the TyG index enhanced the C-index. In the male population, the addition of the METS-IR and TyG index increased the NRI by 10.7% and 14.6%, respectively, and the IDI by 10.8% and 10.8%, respectively. In the female population, the addition of the METS-IR and TyG index increased the NRI by 18.1% and 22.7%, respectively, and the IDI by 0.9% and 1.3%, respectively (Table 4).

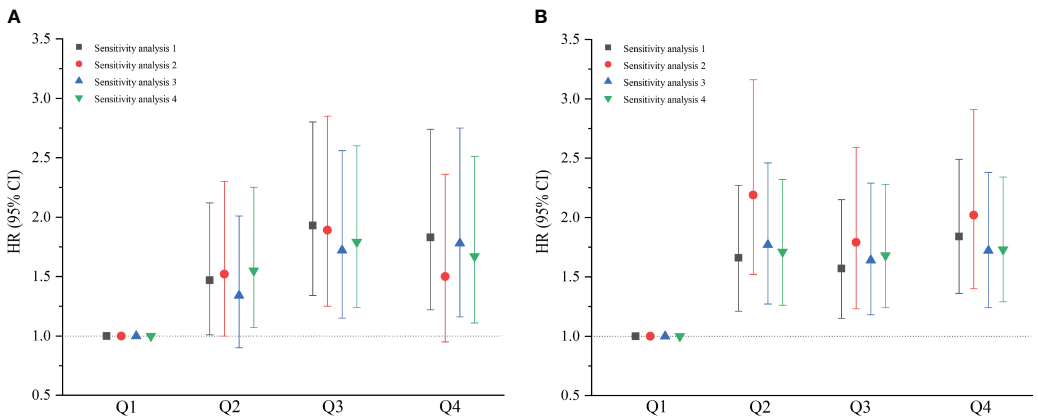


FIGURE 3
Sensitivity analyses of baseline metabolic insulin resistance score **(A)** and triglyceride-glucose index **(B)**. Sensitivity analysis 1 excluded the participants who experienced an outcome event within the first year of the follow-up (n=4602); Sensitivity analysis 2 excluded the population with hypertension (n=3609); Sensitivity analysis 3 excluded the population with dyslipidemia (n=3624); Sensitivity analysis 4 excluded the population with pre-diabetes and diabetes (n=4130). (*HR*, hazard ratio; *CI*, confidence interval; *Q1*, Quartile 1; *Q2*, Quartile 2; *Q3*, Quartile 3; *Q4*, Quartile 4).

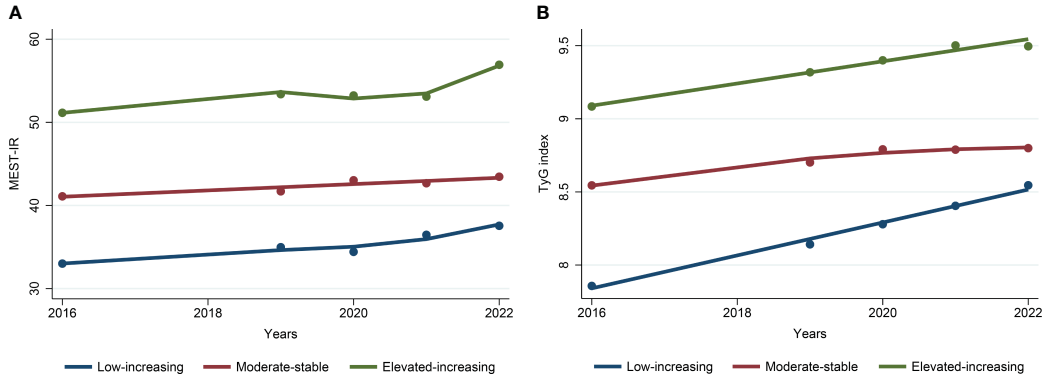


FIGURE 4
Trajectories of metabolic insulin resistance score **(A)** and triglyceride-glucose index **(B)** from 2016 to 2022. (*METS-IR*, metabolic insulin resistance score; *TyG* index, triglyceride-glucose index).

# 4 Discussion

This study investigated the association of the baseline IR surrogates and their longitudinal trajectories with the risk of CVD in this regional population based on the prospective cohort study conducted in the rural districts of Xinjiang. The primary results of this study are described below. First, IR surrogates (METS-IR and TyG index) are predictors of the likelihood of CVD incidence, independent of the traditional risk factors. The risk of CVD increased with the ascending quartiles of the baseline IR surrogates. Second, the IR surrogate trajectories were classified into low-rising, moderate-stable, and elevated-increasing groups. For the METS-IR and TyG index, the potential risk of CVD was higher in the group with an elevated-increasing trajectory and lower in the group with a low-rising trajectory. Third, the addition of the baseline METS-IR and TyG index to the Framingham model increased the predictive value of CVD events.

A complex combination of genetic, metabolic, and environmental factors contributes to CVD. IR is a critical risk factor for CVD, and the formation of atherosclerotic plaque as well as anomalies of ventricular hypertrophy and diastolic function produced by IR can hasten the progression of CVD (19). The METS-IR and TyG index, recently introduced as alternatives to IR, have garnered interest in epidemiological studies for their simplicity of measurement and cost-effectiveness. The METS-IR is based on routine biochemical tests and BMI calculations, and it can be used to screen insulin sensitivity and assess the cardiometabolic risk for the early detection of healthy and high-risk populations (6). The TyG index, derived from fasting glucose and TG levels, is also being used as a simple alternative to IR because it has higher sensitivity and specificity than the IR gold standard method and HOMA-IR (5, 20–22). In several populations, the TyG index has been proven as a CVD predictor (23–28). Currently, research associating the IR surrogates with new-onset CVD at a single time point is commonly available; however, the studies are restricted in their ability to adequately reflect the impact of the longitudinal temporal changes in the IR surrogates on the development of CVD. The group-based trajectory model proposed by Nagin et al. (18) provides a thorough overview of IR development over time in the study population, identifies population subgroups with comparable

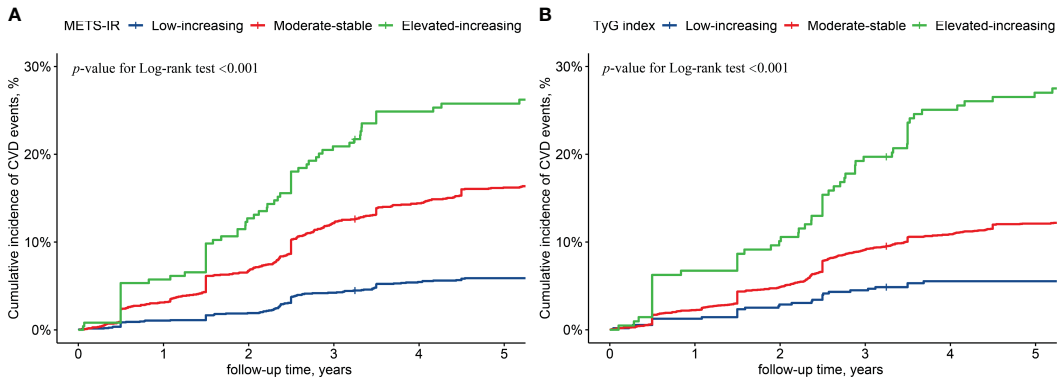


FIGURE 5
Cumulative cardiovascular diseases incidence by metabolic insulin resistance score **(A)** and triglyceride-glucose index **(B)** trajectories. (*METS-IR*, metabolic insulin resistance score; *TyG* index, triglyceride-glucose index; *CVD*, cardiovascular diseases).

TABLE 3 Risk of incident cardiovascular diseases by the trajectory groups of the insulin resistance surrogates.

| Variables | Case/Total | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|
| | | HR (95% CI) | *P* value | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| METS-IR | | | | | | | |
| Low-increasing | 118/1985 | Reference | | Reference | | Reference | |
| Moderate-stable | 352/2114 | 2.97 (2.41, 3.66) | <0.001 | 1.80 (1.45, 2.24) | <0.001 | 1.65 (1.30, 2.08) | <0.001 |
| Elevated-increasing | 63/244 | 4.95 (3.64, 6.72) | <0.001 | 2.55 (1.86, 3.49) | <0.001 | 2.13 (1.48, 3.06) | <0.001 |
| TyG index | | | | | | | |
| Low-increasing | 31/556 | Reference | | Reference | | Reference | |
| Moderate-stable | 445/3579 | 2.21 (1.54, 3.19) | <0.001 | 1.75 (1.22, 2.53) | 0.003 | 1.62 (1.12, 2.34) | 0.011 |
| Elevated-increasing | 57/208 | 5.23 (3.38, 8.10) | <0.001 | 2.85 (1.83, 4.45) | <0.001 | 2.63 (1.68, 4.13) | <0.001 |

Model 1: non-adjusted model.
Model 2: adjusted by baseline age and sex.
Model 3: adjusted by Model 2 and the baseline education level, exercise frequency, waist circumference, smoking, drinking, family history of cardiovascular disease, hypertension, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.
(HR, hazard ratio; CI, confidence interval; METS-IR, metabolic insulin resistance score; TyG index, triglyceride-glucose index).

patterns across time, and facilitates the identification of groups with a greater risk of CVD. Therefore, this study examined the relationship between baseline IR surrogates and CVD as well as the impact of the longitudinal trajectories of the IR surrogates on CVD.

## 4.1 IR surrogates were independent predictors of CVD

This study demonstrated that the baseline IR surrogates were independent risk factors for CVD and that higher IR surrogate values substantially enhanced the cumulative incidence of CVD. After multifactor adjustment, the HR (95% CI) for the risk of CVD in Q4 of the METS-IR and TyG index was 1.79 (1.25, 2.58) and 1.66 (1.28, 2.17), respectively, when compared with Q1. The subgroup analysis by sex revealed a statistically significant difference in the interaction between sex and METS-IR ($P<0.05$). The higher likelihood of CVD in males with high METS-IR than in their female counterparts was mostly related to the variations in the IR, lipid metabolism, and obesity levels between them. First, visceral fat is closely associated with IR. Males have a higher tendency to accumulate visceral fat, which is more harmful to human health than other areas of fat accumulation (29). Second, the decline of male gonadal activity increases with increased visceral fat and IR, which ultimately disturbs fat metabolism (30). Furthermore, no substantial changes were observed in the results of the sensitivity analyses after consecutively excluding those who had a CVD outcome event within the first year of follow-up, those with hypertension, those with dyslipidemia, and those with pre-diabetes and diabetes indicating that the findings of this study were relatively robust.

According to the literature on the Eastern Chinese population, a 1-unit elevation in the METS-IR can outcome in a 17% increase in

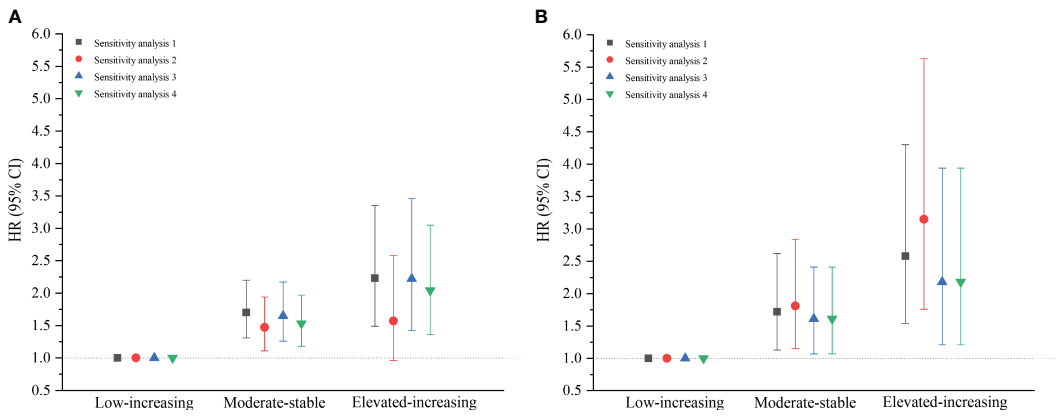


FIGURE 6
Sensitivity analyses of the metabolic insulin resistance score **(A)** and triglyceride-glucose index **(B)** trajectory groups. Sensitivity analysis 1 excluded the participants who experienced an outcome event within the first year of the follow-up (n=4242); Sensitivity analysis 2 excluded the population with hypertension (n=3334); Sensitivity analysis 3 excluded the population with dyslipidemia (n=3359); Sensitivity analysis 4 excluded the population with pre-diabetes and diabetes (n=3814). (*HR*, hazard ratio; *CI*, confidence interval).

TABLE 4 Predictive value of baseline insulin resistance surrogates for cardiovascular diseases in Xinjiang's rural population.

| Model | C-index (95% CI) | *P* value | NRI (95% CI) | *P* value | IDI (95% CI)) | *P* value |
|---|---|---|---|---|---|---|
| Male | | | | | | |
| Framingham | 0.782 (0.750, 0.814) | – | – | – | – | – |
| Framingham + METS-IR | 0.811 (0.781, 0.841) | <0.001 | 0.107 (0.032, 0.183) | 0.005 | 0.108 (0.087, 0.128) | <0.001 |
| Framingham + TyG index | 0.817 (0.788, 0.846) | <0.001 | 0.146 (0.072, 0.220) | <0.001 | 0.108 (0.089, 0.128) | <0.001 |
| Female | | | | | | |
| Framingham | 0.729 (0.701, 0.757) | – | – | – | – | – |
| Framingham + METS-IR | 0.740 (0.713, 0.767) | 0.020 | 0.181 (0.129, 0.233) | <0.001 | 0.009 (0.006, 0.012) | <0.001 |
| Framingham + TyG index | 0.751 (0.724, 0.777) | <0.001 | 0.227 (0.170, 0.284) | <0.001 | 0.013 (0.009, 0.016) | <0.001 |

(NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval; METS-IR, metabolic insulin resistance score; TyG index, triglyceride-glucose index).

the risk of CVD (31). Numerous studies examining the connection between IR surrogates and coronary artery calcification have reached the same conclusion that METS-IR has the strongest predictive value (32, 33). The overall HRs (95% CIs) for CVD risk in Q2, Q3, and Q4 of the TyG index were 1.05 (1.00, 1.10), 1.05 (1.00, 1.10), and 1.19 (1.14, 1.25), respectively, when compared with Q1, according to the UK Biobank cohort study with a sample size of over 4,00,000 (34). The TyG index had a substantial correlation with the onset of CVD, which was an independent predictor of CVD risk in the Caucasian population, according to the findings of the VMCUN cohort (35). Although the average age of the participants in our study was lesser than that in the aforementioned studies, both METS-IR and TyG index were equally established as independent risk factors for CVD. The METS-IR and TyG index can be regarded as essential reference indicators to indicate the CVD risk in the rural areas of Xinjiang, but we should carefully implement them within clinical practice, and clinical factors, such as blood glucose and blood lipid indicators, should also be considered in the use process. Furthermore, CVD is a disease with a multitude of pathogenic factors, which should be considered in conjunction with factors such as obesity, blood glucose, and blood lipid when stratifying the management of at-risk populations.

## 4.2 Long-term trajectories of elevated IR surrogates were associated with a high risk of CVD

The trajectory characteristics for each subgroup of the IR surrogates in this population were determined for the first time in this study, and the trajectories of METS-IR and TyG index were classified into the low-rising, moderate-stable, and elevated-increasing groups. These three trajectory groups of the METS-IR had a cumulative CVD incidence of 5.9%, 16.7%, and 25.8%, respectively, while those of the TyG index had a cumulative CVD incidence of 5.6%, 12.4%, and 27.4%, respectively. According to the Kaplan–Meier curves, the elevated-increasing group had a higher cumulative incidence of CVD than the other trajectory groups. Based on the multifactorial Cox model results, the CVD risk was 1.65 and 2.13 times greater in the moderate-stable and elevated-increasing groups than in the low-rising group of the METS-IR, respectively. The risk of CVD was 1.62 and 2.63 times greater in the moderate-stable and elevated-increasing groups than in the low-rising group of the TyG index, respectively. The Hanzhong adolescent hypertension cohort study revealed three TyG index trajectories and concluded that long-term trajectories of elevated TyG index were independently related to increased arterial stiffness (36). The same conclusion was confirmed that continuously increasing TyG index trajectories are associated with a noticeably higher risk of CVD in populations with normal weight, hypertension, and diabetes (37–39). For the early detection of CVD in the rural population of Xinjiang, it is essential to complete relevant biochemical indicator measurements and conduct long-term follow-ups. Individuals with elevated immediate levels of METS-IR and TyG index, along with those with elevated longitudinal trajectory levels should be actively followed.

## 4.3 IR surrogates had predictive value for the risk of CVD

Based on the Framingham risk score model, the predictive power of the baseline IR surrogates for CVD risk was evaluated in this study. After including the baseline METS-IR and TyG index in the Framingham model, significant improvements were observed in the new models of C-index, NRI, and IDI ($P<0.05$). The C-index increased by 0.009 in the investigation of METS-IR and coronary artery calcification in asymptomatic adults when the METS-IR was introduced to the prior model ($P<0.001$) (32). According to research on the population without diabetes in the East China region, the TyG index considerably enhanced the predictive value of CVD in the new model, when it was included in one that previously comprised only the traditional risk variables (40). Wang et al. (41) proved that the addition of the TyG index to a model with conventional risk factors could enhance its predictive ability of the risk of CVD. The results of this study corroborate the findings of the aforementioned studies.

## 5 Benefits and limitations

The primary strengths of this study are based on the aspects described below. The prospective cohort study approach showed high strength for causal justifications. It was representative of the general situation of the population of rural Xinjiang. It considered the implications of the dynamic changes in the METS-IR and TyG index on CVD during follow-up and revealed the regularity of the development of the METS-IR and TyG index in this study population. Multiple confounding factor adjustments were made regarding the association of the baseline METS-IR and TyG index along with their longitudinal trajectories with new-onset CVD. Moreover, sensitivity analyses were conducted to validate the study results.

This study has some limitations. First, with the characteristics of a long onset, complex course, lifelong nature, and uncertainty, CVD should be followed up over an extended period to validate the study findings. Second, there were some potential residual confounders, and the effects of economic income and nutritional intake on the study were not considered. Third, since fasting insulin levels in the study population were not evaluated, the effects of the IR surrogates on CVD risk could not be compared to those of HOMA-IR. Finally, since this study was limited to the population of the rural areas of Xinjiang, the generalization of its findings to other groups should be conducted cautiously.

## 6 Conclusion

Elevated baseline METS-IR and TyG index values were independent risk factors for new-onset CVD in the Xinjiang rural population. Furthermore, METS-IR and TyG index trajectory patterns were intimately linked to an increased risk of CVD. Glucose metabolism status can be assessed by utilizing METS-IR and TyG index in large-scale epidemiological surveys for identifying individuals at a high risk of CVD, considering its user-friendly assessment, simplicity of calculation, and low cost.

## 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 studies involving humans were approved by The Institutional Ethics Review Board of the First Affiliated Hospital of Shihezi University Medical College. 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

SW: Investigation, Conceptualization, Data curation, Methodology, Software, Visualization, Writing – original draft. XZ: Conceptualization, Data curation, Investigation, Writing – original draft. MK: Conceptualization, Data curation, Investigation, Writing – review & editing. HG: Data curation, Investigation, Project administration, Resources, Writing – review & editing. JH: Investigation, Methodology, Resources, Writing – review & editing. ReM: Conceptualization, Data curation, Investigation, Writing – review & editing. XW: Conceptualization, Data curation, Investigation, Writing – review & editing. RuM: Investigation, Supervision, Writing – review & editing. SG: Funding acquisition, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

## Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the Science and Technology Project of Xinjiang Production and Construction Corps (NO. 2021AB030) and the Shihezi University Innovation Outstanding Young Talents Program (Natural Science) (NO. CXPY202004).

## Acknowledgments

We sincerely thank the participants from rural areas who participated in this study for their willingness to participate in this study.

## 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



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1259062/full#supplementary-material

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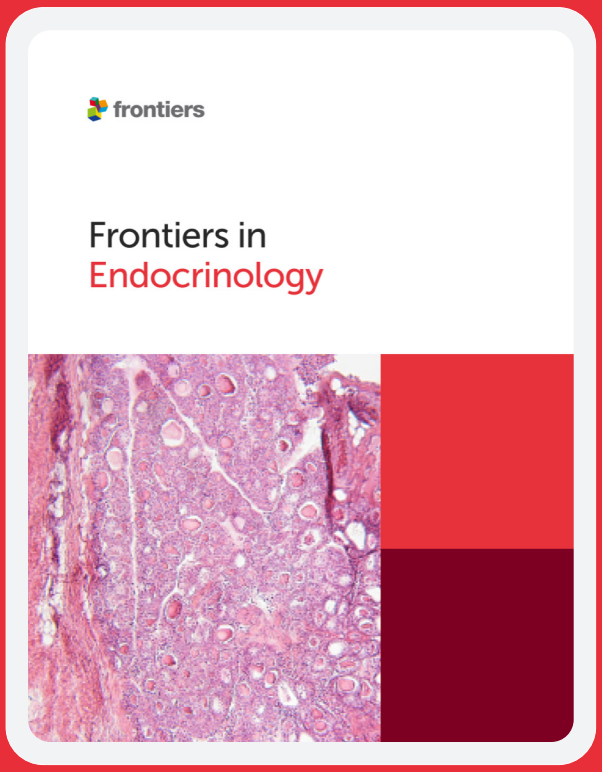


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