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ORIGINAL RESEARCH

The Relationship Between Insulin Resistance Indicated by Triglyceride and Glucose Index and Left Ventricular Hypertrophy and Decreased Left Ventricular Diastolic Function with Preserved Ejection Fraction

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Aim: The evidence on the association between insulin resistance (IR) and the prevalence or incidence of cardiac dysfunction has been controversial, and the relationship between pre-diabetic IR and cardiac function is lacking. Large sample studies in the Chinese general population are urgently needed to explore the association between IR and the risk of left ventricular hypertrophy (LVH) and decreased left ventricular diastolic function with preserved ejection fraction (LVDFpEF).

Methods: Based on a National Health Check-up database in China, we conducted a multicenter cross-sectional retrospective study in 344,420 individuals. Furthermore, at a single center, we performed two retrospective longitudinal studies encompassing 8270 and 5827 individuals to investigate the association between IR and the development of new-onset LVH and LVDFpEF, respectively. The median follow-up duration exceeded 2.5 years. The triglyceride and glucose (TyG) index, known for its high sensitivity in detecting IR, serves as a reliable alternative marker of IR. The logistic and cox proportional hazard regression models were used to determine the relationships.

Results: In the cross-sectional study, IR showed a positive association with the prevalence of LVH and decreased LVDFpEF after adjusting for confounders. In the longitudinal cohort, IR was also correlated with the new onset of LVH and decreased LVDFpEF, with hazard ratios (HR) of 1.986 (95% CI: 1.307, 3.017) and 1.386 (95% CI: 1.167, 1.647) in the fourth quartile of TyG levels compared to the lowest quartile, respectively, after adjusting for confounders. The subgroup analysis in non-hypertensive or non-diabetic people and the sensitivity analysis in the population with homeostasis model assessment of insulin resistance (HOMA-IR) further verified the above-mentioned results.

Conclusion: IR was associated with LVH and decreased LVDFpEF. Effective management of IR may prevent or delay the development of adverse LVH and decreased LVDFpEF.

Keywords: insulin resistance, triglyceride and glucose index, left ventricular hypertrophy, left ventricular diastolic function

Introduction

Insulin resistance (IR) is physiologically defined as a state of diminished response of insulin-targeted tissues to high physiological insulin levels, occurring in response to dysregulation of insulin signaling pathways, ectopic lipid

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accumulation in the liver and skeletal muscle, endoplasmic reticulum stress, inflammation and defects in HMGA1 gene.[1,2] In a state of insulin resistance or hyperinsulinemia, cardiac myocytes experience a series of changes in energy metabolism; for example, reduced glucose intake favors a shift in substrate towards increased oxidation of free fatty acids, leading to reduced cardiac efficiency.[3] Excessive accumulation of fatty acids in cardiac tissue and associated lipotoxicity impair insulin signaling and reduce normal physiological autophagy, leading to morphological and structural alterations and impaired myocardial performance.[4]

Left ventricular hypertrophy (LVH) and decreased left ventricular diastolic function with preserved ejection fraction (LVDFpEF) are marked predictors of adverse cardiovascular outcomes, such as diastolic heart failure.[5–7] Substantial evidence suggests that LVH and decreased LVDFpEF are an elaborate combination of a series of pathophysiological processes not limited to hypertension.[8–10] For example, a case-control study indicated that IR appears to be the primary predictor of LVH in black sub-Saharan African hypertensive patients.[11] A cross-sectional study from China proved that IR had a significant correlation with LVH in patients with early-stage chronic kidney disease.[12] Another cross-sectional study clarified that IR is independently associated with left ventricular diastolic dysfunction in subjects without overt diabetes mellitus type 2.[6] However, controversially, other studies have found a negative relationship between IR and LVH in adults.[13,14] These results are inconclusive, and most of them have been performed in specific subgroups. In addition, although there is relatively sufficient evidence of myocardial dysfunction in diabetic patients, the relationship between pre-diabetic insulin resistance and cardiac function is lacking.[4] However, it is worth noting that pre-diabetic insulin resistance may indeed play an essential role in the development of cardiac dysfunction.[4] There is a pressing need to carry out a large sample study in the Chinese general population to explore the role of pre-diabetic insulin resistance in the context of LVH and decreased LVDFpEF.

Therefore, we conducted a multicenter cross-sectional study and a single center cohort study based on a National Health Check-up database in China. The cross-sectional study offered valuable insights into the prevalence and potential risk factors associated with LVH and decreased LVDFpEF. Meantime, the cohort study enabled a deeper understanding of the possible role between IR and the evolution of LVH and decreased LVDFpEF in a more controlled setting. The finding will provide further evidence for the prevention and management of left ventricular hypertrophy and diastolic dysfunction.

Materials and Methods

Study Population

The cross-sectional study initially included a total of 363,386 participants from 16 health management centers from 8 provinces throughout the south and north (from 28.2 to 41.8°N latitude) in mainland China between January 2009 and December 2017. The participants who attended check-ups were a mixed population from nearby urban and rural areas. The population mainly consisted of adults with very diverse socioeconomic and occupational backgrounds, including public service employees, doctors, workers, farmers, and self-employed people. Participation in the health examinations was on a voluntary basis, and some examinations were provided free of charge under the encouragement of the employer or the government. All participants had fasting serum triglyceride (TG), fasting blood glucose (FBG), and transthoracic pulsed wave Doppler echocardiography measured. Participants who 1) were younger than 18 years old; 2) had structure heart disease (including valve stenosis, congenital heart disease, rheumatic heart disease, moderate and above or undetermined degree regurgitation, hypertrophic cardiomyopathy, and other rare structural abnormalities), coronary artery disease or myocardial infarction, or a history of cardiac surgery, hyperthyreosis, hypoglycemic drugs, or lipid-lowering drugs; 3) had an ejection fraction < 50% were excluded. Finally, 344,420 individuals were included in the cross-sectional study of the relationship between IR and LVH/decreased LVDFpEF.

The retrospective cohort study initially included 10,058 individuals who had undergone follow-up at a health check-up center in Beijing, China. After excluding participants who 1) were younger than 18 years old; 2) had structure heart disease (including valve stenosis, congenital heart disease, rheumatic heart disease, moderate and above or undetermined degree regurgitation, hypertrophic cardiomyopathy, and other rare structural abnormalities), coronary artery disease or myocardial infarction, or a history of cardiac surgery, hyperthyreosis, hypoglycemic drugs, or lipid-lowering drugs; 3)

had an ejection fraction < 50%, 9783 participants remained. Among these participants, 8818 individuals who had at least 1 year of follow-up and repeated measurements of TG, FBG, and transthoracic pulsed wave Doppler echocardiography were considered part of a longitudinal cohort. To explore the association between IR and the subsequent new onset of LVH, we excluded participants with LVH at baseline to constitute Cohort 1, including 8270 individuals. Similarly, to investigate the association between the IR and the subsequent decreased LVDFpEF, we excluded individuals with decreased LVDFpEF at baseline to form Cohort 2, including 5827 individuals. The flow chart for participant selection is shown in Figure 1A and B.

This study was approved by the central ethics board of Renmin Hospital of Wuhan University, followed by acceptance by the ethics center in each collaborating hospital. Ethics committees granted a waiver of the requirement for documentation of informed consent for just analyzing existing data after anonymization without individual identification.

Diagnostic Criteria

We collected parametric information about cardiac structure by transthoracic pulsed wave Doppler echocardiography, including the end-diastolic thickness of the interventricular septum (IVS) and left ventricular posterior wall (LVPW), the peak velocity of the early diastolic filling wave (E wave) and atrial filling (A wave), and the E to A ratio (E/A). Experienced sonographers at all health check-up centers examined participants and followed the same guidelines for diagnosing LVH and decreased LVDFpEF. The diagnostic criteria for LVH was that the end-diastolic thickness of IVS or/and LVPW was greater than 11 mm.[15] The diagnostic criteria for LVDFpEF was a ratio of E/A < 1.0.[16] The triglyceride and glucose (TyG) index, a novel parameter for IR, has been shown to be highly sensitive for the identification of IR.[17–19] The TyG index was calculated according to the following formulas: $TyG = Ln[TG(mg/dL) * FBG(mg/dL)/2]$.[19]

In the sensitivity analysis, we further used homeostatic model assessment of insulin resistance (HOMA-IR) as an indicator of IR, which was defined as HOMA-IR ≥ 2.5.[20] HOMA-IR = FBG (mmol/L) * fasting insulin level (μU/mL)/22.5. Hypertension was defined as personal medical history, use of antihypertensive drugs, and/or systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg.[21] Diabetes was defined as FBG ≥ 7.0 mmol/L, 2 h postprandial glucose ≥ 11.1 mmol/L, personal history or use of hypoglycemic drugs.[22]

Anthropometric and Laboratory Data

All participants underwent comprehensive anthropometric and clinical examinations by professional and experienced medical teams at each hospital. Anthropometric measurements, including height, weight, and waist circumference (WC), were measured in subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2). After sitting for at least 5 minutes, participants' SBP and DBP were measured with a mercury sphygmomanometer or electronic sphygmomanometer. A history of illness and medication use is recorded after detailed questioning by the practitioner. Routine blood tests and biochemical tests were performed under fasted conditions according to standard protocols and guidelines of accredited laboratories, and all test results were obtained by automated biochemical analyzers. These laboratory data include FBG, total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), uric acid (UA), and serum creatinine (SCR) concentrations.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. Non-normally distributed continuous variables were expressed as median and interquartile range (IQR) values. When comparing differences between groups, the Kruskal–Wallis test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables. The non-parameter imputation method missForest was conducted to process the missing data less than 20%. Logistic progression models were applied to examine the association between IR and LVH and decreased LVDFpEF. Cox proportional hazards models were used to evaluate the association between IR and the incidence of LVH or the association between IR and the subsequent incidence of decreased LVDFpEF. The odds ratio (OR) and hazard ratio (HR) with 95% confidence intervals (CI) were reported. Statistical significance was considered as two-sided $P < 0.05$. All

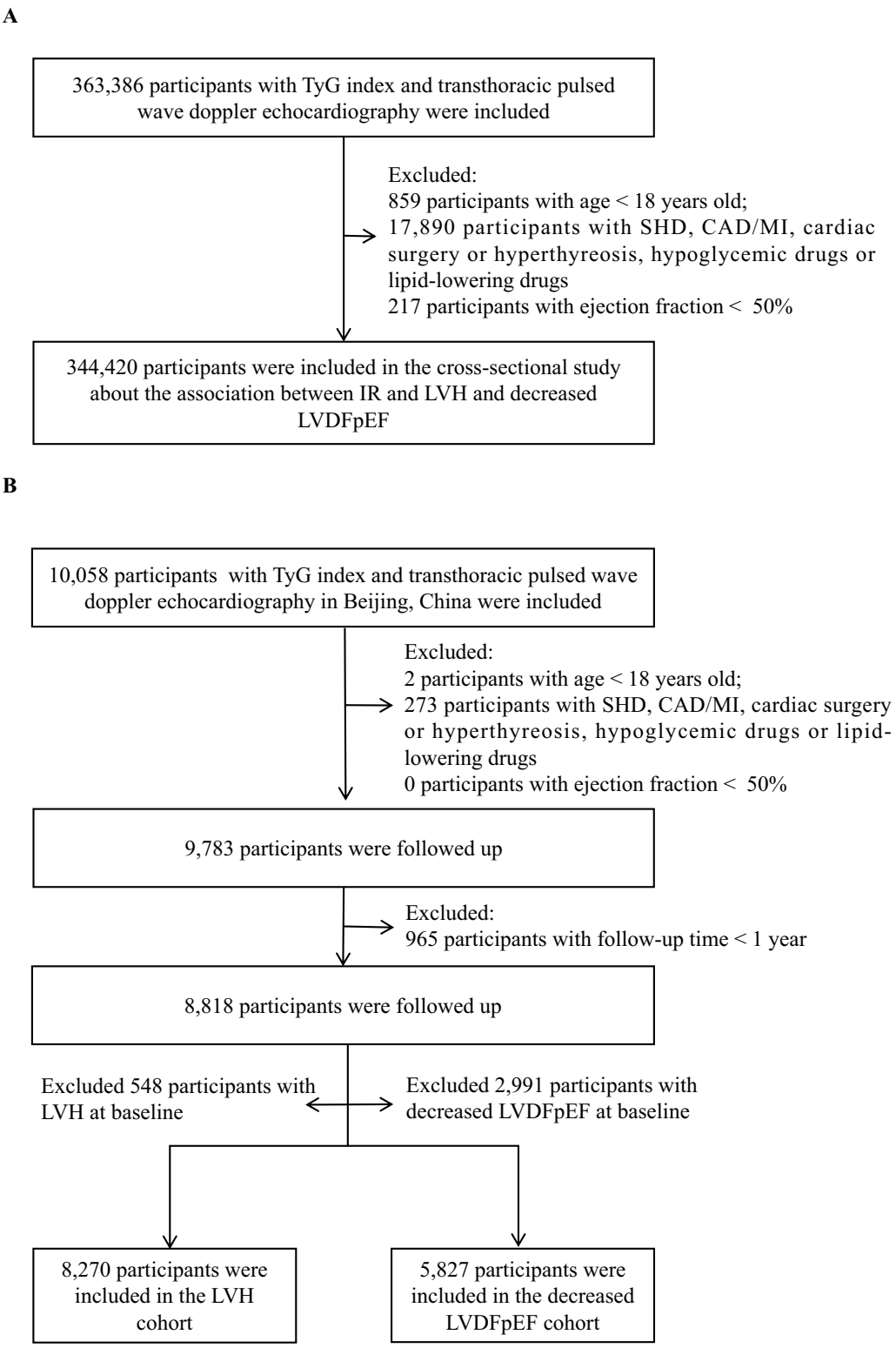

Figure 1 Flow chart for participant selection in cross-sectional (**A**) and longitudinal (**B**) studies on the association between IR and LVH and decreased LVDFpEF.
Abbreviations: TyG, triglyceride and glucose; SHD, structure heart disease; CAD, coronary artery disease; MI, myocardial infarction; IR, insulin resistance; LVH, left ventricular hypertrophy; LVDFpEF, left ventricular diastolic function with preserved ejection fraction.

data were analyzed using R-4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics (version 25.0, IBM, Armonk, NY, USA).

Subgroup Analysis

To further exclude the influence of hypertension and diabetes on the relationship between IR and the incidence of LVH and decreased LVDFpEF, we performed four subgroup analyses in non-diabetic and non-hypertensive populations.

Sensitivity Analysis

In order to test the stability of the results, we further conducted another cohort study using HOMA-IR as an indicator of IR in participants who had measured FBG and fasting insulin at a health check-up center in Beijing, China.

Results

Anthropometric and Laboratory Characteristics of Subjects in the Cross-Sectional Study

In the cross-sectional study, 344,420 participants were included to examine the relationship of IR with LVH and decreased LVDFpEF. The median age was 50.00 years (IQR, 43.00, 57.00) and males accounted for 61.71% in the cross-sectional dataset. According to the results of echocardiography, 3.08% of participants had LVH and 25.53% of participants had decreased LVDFpEF. 32.73% of individuals had hypertension, and 11.07% of participants had type 2 diabetes. When grouping participants into TyG quartiles, the prevalence of LVH was 1.34%, 2.54%, 3.31%, and 5.17%, respectively, from the lowest quartile to the highest quartile. Similarly, the higher TyG group had a higher prevalence of impaired LVDFpEF. Meantime, compared to the group with the lowest TyG index (TyG ≤ 8.29), the higher TyG groups were older in age and higher in levels of BMI, WC, SBP, DBP, FBG, TC, TG, LDL-C, ALT, AST, BUN, SCR, UA and lower level of HDL-C. The detailed baseline characteristics of individuals are shown in Table 1.

Association Between IR and the Prevalence of LVH and Impaired LVDFpEF in the Cross-Sectional Analysis

We applied logistic regression analysis to identify the association of IR with the prevalence of LVH and impaired LVDFpEF. In the unadjusted model, IR was significantly associated with the existence of LVH, with an OR of 1.919 (95% CI: 1.786, 2.061) ($P < 0.001$) in the 8.29 < TyG ≤ 8.70 group, 2.524 (95% CI: 2.356, 2.704) ($P < 0.001$) in the 8.70 < TyG ≤ 9.14 group, 4.019 (95% CI: 3.766, 4.290) ($P < 0.001$) in the TyG > 9.14 group. After adjusting for age, sex, LDL-C, BMI, ALT, hypertension, BUN and UA, the relationship between IR and LVH remained statistically significant, with an OR of 1.307 (95% CI: 1.215, 1.406) ($P < 0.001$) in the 8.29 <TyG ≤8.70 group, 1.399 (95% CI: 1.302, 1.502) ($P < 0.001$) in the 8.70 < TyG ≤ 9.14 group, and 1.914 (95% CI: 1.786, 2.051) ($P < 0.001$) in the TyG > 9.14 group (Table 2).

The logistic regression analysis revealed that the association between IR and decreased LVDFpEF was similar to the results between IR and LVH. In the unadjusted model, IR was significantly associated with decreased LVDFpEF, with an OR of 1.557 (95% CI: 1.521, 1.594) ($P < 0.001$) in the 8.29 < TyG ≤ 8.70 group, 1.870 (95% CI: 1.827, 1.913) ($P < 0.001$) in the 8.70 < TyG ≤ 9.14 group, and 2.168 (95% CI: 2.120, 2.218) ($P < 0.001$) in the TyG > 9.14 group. After adjusting for age, sex, LDL-C, BMI, ALT, hypertension, BUN and UA, the relationship between IR and decreased LVDFpEF remained statistically significant, with an OR of 1.274 (95% CI: 1.242, 1.307) ($P < 0.001$) in the 8.29 <TyG ≤8.70 group, 1.459 (95% CI: 1.421, 1.497) ($P < 0.001$) in the 8.70 < TyG ≤ 9.14 group, and 1.763 (95% CI: 1.717, 1.810) ($P < 0.001$) in the TyG > 9.14 group (Table 3).

Anthropometric and Laboratory Characteristics of Subjects in the Longitudinal Cohort Study

To further explore whether IR contributes to the new-onset of LVH and impaired LVDFpEF, we implemented two longitudinal cohort studies. In the new-onset LVH cohort study, there were 336 participants developed LVH among 8270

Table 1 Baseline Characteristics of 344,420 Participants Grouped by TyG Quartile in the Cross-Sectional Study

Characteristics	Total (n=344,420)	TyG≤8.29 (n=87,339)	8.29<TyG≤8.70 (n=86,954)	8.70<TyG≤9.14 (n=85,314)	TyG>9.14 (n=84,813)	*P* value[a]
Age (year, median (IQR))	50.00 [43.00, 57.00]	47.00 [40.00, 55.00]	50.00 [44.00, 58.00]	51.00 [44.00, 58.00]	50.00 [44.00, 56.00]	<0.001
Gender, male (%)	212,532 (61.71)	40,914 (46.85)	51,604 (59.35)	56,994 (66.80)	63,020 (74.30)	<0.001
BMI (kg/m^2, median (IQR))	24.98 [22.80, 27.22]	22.83 [20.82, 24.92]	24.62 [22.66, 26.71]	25.70 [23.82, 27.74]	26.56 [24.70, 28.58]	<0.001
WC (cm, median (IQR))	88.00 [81.00, 95.00]	80.00 [73.00, 87.00]	87.00 [80.00, 93.00]	90.00 [84.00, 96.00]	93.00 [88.00, 99.00]	<0.001
SBP (mmHg, median (IQR))	125.00 [113.00, 138.00]	117.00 [107.00, 130.00]	124.00 [113.00, 137.00]	128.00 [117.00, 140.00]	130.00 [120.00, 143.00]	<0.001
DBP (mmHg, median (IQR))	79.00 [71.00, 87.00]	74.00 [67.00, 81.00]	78.00 [70.00, 86.00]	80.00 [73.00, 89.00]	83.00 [76.00, 91.00]	<0.001
FBG (mmol/L, median (IQR))	5.25 [4.86, 5.75]	4.92 [4.61, 5.25]	5.16 [4.82, 5.53]	5.35 [4.98, 5.82]	5.79 [5.25, 6.86]	<0.001
TC (mmol/L, median (IQR))	4.83 [4.24, 5.47]	4.43 [3.92, 4.99]	4.76 [4.22, 5.35]	4.97 [4.40, 5.58]	5.20 [4.58, 5.87]	<0.001
TG (mmol/L, median (IQR))	1.40 [0.97, 2.07]	0.77 [0.64, 0.89]	1.20 [1.07, 1.33]	1.72 [1.53, 1.94]	2.82 [2.34, 3.70]	<0.001
LDL-c (mmol/L, median (IQR))	2.92 [2.39, 3.46]	2.59 [2.14, 3.08]	2.97 [2.49, 3.45]	3.13 [2.63, 3.68]	3.01 [2.42, 3.62]	<0.001
HDL-c (mmol/L, median (IQR))	1.27 [1.08, 1.51]	1.48 [1.27, 1.72]	1.32 [1.14, 1.54]	1.21 [1.05, 1.41]	1.10 [0.94, 1.29]	<0.001
ALT (IU/L, median (IQR))	19.63 [14.00, 28.39]	15.00 [11.19, 20.80]	18.10 [13.80, 25.41]	21.30 [15.90, 30.30]	25.70 [18.50, 37.00]	<0.001
AST (IU/L, median (IQR))	19.90 [16.40, 24.20]	18.10 [15.40, 22.00]	19.10 [16.10, 23.50]	20.00 [17.00, 25.00]	21.50 [17.80, 27.00]	<0.001
SCR (μmol/L, median (IQR))	70.80 [61.90, 81.00]	67.10 [57.40, 78.00]	70.40 [61.10, 81.00]	72.40 [63.20, 82.00]	73.00 [64.00, 82.40]	<0.001
UA (μmol/L, median (IQR))	328.10 [268.50, 390.00]	278.90 [231.40, 335.20]	319.00 [264.90, 374.70]	346.00 [291.00, 402.00]	372.10 [315.00, 432.70]	<0.001
BUN (mmol/L, median (IQR))	4.89 [4.10, 5.75]	4.73 [3.95, 5.66]	4.85 [4.10, 5.71]	4.90 [4.16, 5.76]	5.00 [4.23, 5.86]	<0.001
TyG index (median (IQR))	8.70 [8.29, 9.14]	8.03 [7.83, 8.17]	8.51 [8.40, 8.61]	8.91 [8.80, 9.02]	9.49 [9.29, 9.81]	<0.001
Type 2 diabetes (%)	38,144.00 (11.07)	1794.00 (2.05)	4215.00 (4.85)	8723.00 (10.22)	23,412.00 (27.60)	<0.001
Hypertension (%)	104,345.00 (32.73)	15,387.00 (19.02)	23,960.00 (29.77)	29,641.00 (37.53)	35,357.00 (45.09)	<0.001
Decreased LVDFpEF (%)	87,943.00 (25.53)	15,308.00 (17.53)	21,622.00 (24.87)	24,258.00 (28.43)	26,755.00 (31.55)	<0.001
LVH (%)	10,594.00 (3.08)	1170.00 (1.34)	2208.00 (2.54)	2827.00 (3.31)	4389.00 (5.17)	<0.001

Note: [a]*P* values were calculated by Kruskal–Wallis test for continuous variables and Fisher's exact test or χ^2 test for categorical variables.

Abbreviations: TyG index, triglyceride and glucose index; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate transaminase; SCR, serum creatinine; UA, uric acid; BUN, blood urea nitrogen; IQR, interquartile range; LVDFpEF, left ventricular diastolic function with preserved ejection fraction; LVH, left ventricular hypertrophy.

Table 2 Association of TyG Index and Left Ventricular Hypertrophy in the Cross-Sectional Study

TyG Groups	Crude		Model 1[a]		Model 2[b]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Q1	Ref		Ref		Ref	
Q2	1.919 (1.786, 2.061)	<0.001	1.642 (1.528, 1.764)	<0.001	1.307 (1.215, 1.406)	<0.001
Q3	2.524 (2.356, 2.704)	<0.001	2.064 (1.926, 2.212)	<0.001	1.399 (1.302, 1.502)	<0.001
Q4	4.019 (3.766, 4.290)	<0.001	3.274 (3.065, 3.497)	<0.001	1.914 (1.786, 2.051)	<0.001

Notes: [a]In the Model 1, the adjustment factors included age and sex. [b]In the Model 2, the adjustment factors included age, sex, low-density lipoprotein cholesterol (LDL-c), body mass index (BMI), alanine transaminase (ALT), hypertension, blood urea nitrogen (BUN), uric acid (UA). *P* values were calculated by logistic progression model.
Abbreviations: TyG, triglyceride and glucose, OR, odds ratio; CI, confidence interval.

Table 3 Association of TyG Index and Decreased Left Ventricular Diastolic Function with Preserved Ejection Fraction in the Cross-Sectional Study

TyG Groups	Crude		Model 1[a]		Model 2[b]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Q1	Ref		Ref		Ref	
Q2	1.557 (1.521, 1.594)	<0.001	1.344 (1.311, 1.378)	<0.001	1.274 (1.242, 1.307)	<0.001
Q3	1.870 (1.827, 1.913)	<0.001	1.616 (1.576, 1.656)	<0.001	1.459 (1.421, 1.497)	<0.001
Q4	2.168 (2.120, 2.218)	<0.001	2.055 (2.004, 2.106)	<0.001	1.763 (1.717, 1.810)	<0.001

Notes: [a]In the Model 1, the adjustment factors included age and sex. [b]In the Model 2, the adjustment factors included age, sex, low-density lipoprotein cholesterol (LDL-c), body mass index (BMI), alanine transaminase (ALT), hypertension, blood urea nitrogen (BUN), uric acid (UA). *P* values were calculated by logistic progression model.
Abbreviations: TyG, triglyceride and glucose, OR, odds ratio; CI, confidence interval.

participants without LVH at baseline. The median follow-up time was 2.53 (IQR, 1.70, 3.83) years. The baseline characteristics of individuals in this cohort were described in Table 4. The median age of the population who developed LVH was 49.00 years old (IQR, 45.00, 55.00), which was older than that of the non-LVH group, with a median age of 47.00 years old (IQR, 43.00, 52.00). The population that developed LVH had a greater proportion of males than those who did not develop LVH (89.88% vs 67.61%, $P < 0.001$). The population that developed LVH also had higher proportions of hypertension and diabetes and had higher levels of BMI, WC, SBP, DBP, FBG, TG, ALT, AST, fasting serum insulin, BUN and UA, but lower HDL-C levels. Notably, a significantly higher level of TyG index was observed in the subjects who developed LVH than in the non-LVH group (9.07 vs 8.76, $P < 0.001$).

In the cohort to explore the association between IR and new-onset impaired LVDFpEF, 25.59% of participants (n = 1491) developed decreased LVDFpEF among 5827 participants without decreased LVDFpEF at baseline. The median follow-up time was 2.55 (IQR, 1.70, 3.89) years. The baseline characteristics were shown in Table 5. Individuals who developed decreased LVDFpEF were older than those who did not develop decreased LVDFpEF, with median ages of 49.00 years old (IQR, 46.00, 53.00) and 44.00 years old (IQR, 40.00, 48.00), respectively. Males accounted for a considerably higher proportion in the group that developed decreased LVDFpEF than in the non-decreased LVDFpEF group (72.50% vs 65.66%, $P < 0.001$). The decreased LVDFpEF group also had higher levels of BMI, WC, SBP, DBP, FBG, TC, LDL-C, AST, BUN, and fasting serum insulin, but lower HDL-C levels. Notably, the level of TyG index in the group with impaired LVDFpEF was significantly greater than that in the non-decreased LVDFpEF group (8.85 vs 8.66, $P < 0.001$).

Association Between IR and the Occurrence of LVH and Impaired LVDFpEF in the Longitudinal Cohort

We applied Cox regression analysis to identify the association of IR with the occurrence of LVH and decreased LVDFpEF. In the crude model, compared with those in the lowest quartile of TyG levels, higher TyG levels increased

Table 4 Baseline Characteristics of 8270 Participants Grouped by Left Ventricular Hypertrophy in the Longitudinal Cohort Study

Characteristics	Total (n=8270)	Non-Left Ventricular Hypertrophy (n=7934)	Left Ventricular Hypertrophy (n=336)	*P* value[a]
Age (year, median (IQR))	48.00 [43.00, 52.00]	47.00 [43.00, 52.00]	49.00 [45.00, 55.00]	<0.001
Gender, male (%)	5666.00 (68.51)	5364.00 (67.61)	302.00 (89.88)	<0.001
BMI (kg/m^2, median (IQR))	25.16 [23.07, 27.22]	25.05 [22.99, 27.14]	26.97 [25.27, 28.81]	<0.001
WC (cm, median (IQR))	89.00 [81.00, 95.00]	89.00 [81.00, 95.00]	95.00 [90.00, 101.00]	<0.001
SBP (mmHg, median (IQR))	119.00 [108.00, 130.00]	118.00 [107.00, 130.00]	131.00 [120.00, 143.00]	<0.001
DBP (mmHg, median (IQR))	77.00 [70.00, 85.00]	77.00 [70.00, 84.00]	84.00 [77.75, 90.00]	<0.001
FBG (mmol/L, median (IQR))	5.33 [4.95, 5.82]	5.31 [4.95, 5.79]	5.69 [5.26, 6.48]	<0.001
TC (mmol/L, median (IQR))	4.82 [4.25, 5.44]	4.82 [4.24, 5.44]	4.91 [4.40, 5.53]	0.102
TG (mmol/L, median (IQR))	1.48 [1.02, 2.20]	1.46 [1.01, 2.18]	1.77 [1.34, 2.65]	<0.001
LDL-c (mmol/L, median (IQR))	3.08 [2.56, 3.61]	3.08 [2.56, 3.61]	3.12 [2.62, 3.67]	0.779
HDL-c (mmol/L, median (IQR))	1.18 [0.99, 1.42]	1.18 [0.99, 1.42]	1.07 [0.92, 1.25]	<0.001
ALT (IU/L, median (IQR))	20.70 [14.60, 30.70]	20.60 [14.50, 30.50]	24.80 [17.58, 34.25]	<0.001
AST (IU/L, median (IQR))	18.90 [15.90, 23.30]	18.90 [15.80, 23.20]	20.15 [17.15, 24.52]	<0.001
SCR (μmol/L, median (IQR))	69.00 [58.30, 78.00]	68.90 [58.00, 78.00]	73.00 [64.90, 81.00]	<0.001
UA (μmol/L, median (IQR))	343.00 [280.35, 405.00]	342.00 [278.00, 403.00]	386.00 [332.00, 439.00]	<0.001
BUN (mmol/L, median (IQR))	5.00 [4.30, 5.90]	5.00 [4.30, 5.90]	5.32 [4.60, 6.45]	<0.001
TyG index (median (IQR))	8.77 [8.36, 9.21]	8.76 [8.35, 9.20]	9.07 [8.69, 9.48]	<0.001
Fasting serum insulin (μU/mL, median (IQR))	9.12 [6.29, 13.18]	9.04 [6.25, 13.06]	11.71 [7.79, 15.71]	<0.001
Type 2 diabetes (%)	995.00 (12.03)	921.00 (11.61)	74 0.00 (22.02)	<0.001
Hypertension (%)	1476.00 (17.85)	1334.00 (16.81)	142.00 (42.26)	<0.001
Left ventricular hypertrophy (%)	336 0.00 (4.06)	0.00 (0.00)	336.00 (100.00)	<0.001

Note: [a]*P* values were calculated by Kruskal–Wallis test for continuous variables and Fisher's exact test or χ^2 test for categorical variables.
Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate transaminase; SCR, serum creatinine; UA, uric acid; BUN, blood urea nitrogen; TyG index, triglyceride and glucose index; IQR, interquartile range.

the risk of the subsequent incidence of LVH, with an HR of 2.339 (95% CI: 1.524, 3.591) in the second quartile of TyG levels, 3.405 (95% CI: 2.267, 5.114) in the third quartile of TyG levels, and 4.419 (95% CI: 2.974, 6.565) in the fourth quartile of TyG levels. After adjusting for age, sex, LDL-C, BMI, ALT, hypertension, BUN and UA, higher TyG levels were still significantly associated with the incidence of LVH, with an HR of 1.797 (95% CI: 1.179, 2.738) in the third quartile of TyG levels, and 1.986 (95% CI: 1.307, 3.017) in the fourth quartile of TyG levels (Table 6).

In the analysis of the association between IR and the later occurrence of decreased LVDFpEF, the crude model indicated that higher TyG levels were also significantly associated with the occurrence of decreased LVDFpEF when compared with those in the lowest quartile of TyG levels, with an HR of 1.373 (95% CI: 1.172, 1.609) in the second quartile of TyG levels, 1.551 (95% CI: 1.330,1.808) in the third quartile of TyG levels, and 1.695 (95% CI:1.457, 1.972) in the fourth quartile of TyG levels. The association remained significant after adjusting for confounding variables as mentioned above, with an HR of 1.213 (95% CI: 1.025, 1.434) in the third quartile of TyG levels, 1.386 (95% CI: 1.167, 1.647) in the fourth quartile of TyG levels (Table 7).

Subgroup Analysis

For the association between IR and the occurrence of LVH, we found that compared with those in the lowest quartile of TyG levels, the third and fourth quartiles of TyG levels were also significantly associated with the occurrence of LVH in non-hypertensive or non-diabetic people after adjusting for confounding variables. But for the association between IR and the occurrence of decreased LVDFpEF, only the fourth quartile of TyG levels were significantly associated with the occurrence of decreased LVDFpEF compared with those in the lowest quartile of TyG levels in non-hypertensive or non-diabetic people after adjusting for confounding variables. See the attached Tables S1–4 for a more detailed result.

Table 5 Baseline Characteristics of 5827 Participants Grouped by Decreased Left Ventricular Diastolic Function with Preserved Ejection Fraction in the Longitudinal Cohort Study

Characteristics	Total (n=5827)	Non-Decreased Diastolic Function (n=4336)	Decreased Diastolic Function (n=1491)	*P* value[a]
Age (year, median (IQR))	46.00 [41.00, 50.00]	44.00 [40.00, 48.00]	49.00 [46.00, 53.00]	<0.001
Gender, male (%)	3928.00 (67.41)	2847.00 (65.66)	1081.00 (72.50)	<0.001
BMI (kg/m^2, median (IQR))	24.82 [22.68, 26.98]	24.54 [22.31, 26.77]	25.57 [23.59, 27.47]	<0.001
WC (cm, median (IQR))	88.00 [80.00, 94.00]	86.00 [79.00, 93.00]	90.00 [84.00, 96.00]	<0.001
SBP (mmHg, median (IQR))	116.00 [106.00, 127.00]	115.00 [104.00, 126.00]	120.00 [111.00, 132.00]	<0.001
DBP (mmHg, median (IQR))	76.00 [69.00, 83.00]	75.00 [68.00, 82.00]	79.00 [72.00, 86.00]	<0.001
FBG (mmol/L, median (IQR))	5.25 [4.91, 5.70]	5.21 [4.88, 5.61]	5.42 [5.03, 5.96]	<0.001
TC (mmol/L, median (IQR))	4.79 [4.22, 5.40]	4.77 [4.20, 5.37]	4.88 [4.25, 5.46]	0.003
TG (mmol/L, median (IQR))	1.42 [0.98, 2.15]	1.38 [0.95, 2.10]	1.56 [1.09, 2.25]	<0.001
LDL-c (mmol/L, median (IQR))	3.04 [2.53, 3.56]	3.03 [2.52, 3.54]	3.07 [2.56, 3.64]	0.018
HDL-c (mmol/L, median (IQR))	1.19 [1.00, 1.44]	1.20 [1.00, 1.46]	1.15 [0.97, 1.38]	<0.001
ALT (IU/L, median (IQR))	20.30 [14.10, 30.50]	20.00 [13.80, 30.30]	21.10 [15.00, 30.90]	0.001
AST (IU/L, median (IQR))	18.70 [15.70, 23.00]	18.65 [15.50, 22.80]	19.00 [16.00, 23.30]	0.008
SCR (μmol/L, median (IQR))	69.00 [58.10, 78.00]	68.00 [58.00, 78.00]	70.00 [59.75, 78.00]	0.026
UA (μmol/L, median (IQR))	341.00 [275.00, 403.00]	338.00 [271.00, 400.00]	349.00 [286.00, 408.95]	<0.001
BUN (mmol/L, median (IQR))	5.00 [4.20, 5.90]	5.00 [4.20, 5.80]	5.10 [4.40, 6.00]	<0.001
TyG index (median (IQR))	8.71 [8.30, 9.16]	8.66 [8.24, 9.12]	8.85 [8.44, 9.26]	<0.001
Fasting serum insulin (μU/mL, median (IQR))	8.71 [6.02, 12.68]	8.50 [5.87, 12.41]	9.43 [6.66, 13.32]	<0.001
Type 2 diabetes (%)	530.00 (9.10)	306.00 (7.06)	224.00 (15.02)	<0.001
Hypertension (%)	822.00 (14.12)	519.00 (11.98)	303.00 (20.34)	<0.001
LVDFpEF (%)	1491.00 (25.59)	0.00 (0.00)	1491.00 (100.00)	<0.001

Note: [a]*P* values were calculated by Kruskal–Wallis test for continuous variables and Fisher's exact test or χ^2 test for categorical variables.
Abbreviations: BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate transaminase; SCR, serum creatinine; UA, uric acid; BUN, blood urea nitrogen; TyG index, triglyceride and glucose index; IQR, interquartile range; LVDFpEF, left ventricular diastolic function with preserved ejection fraction.

Table 6 Association of Baseline TyG Index and the Incidence of Left Ventricular Hypertrophy in the Longitudinal Cohort Study

TyG Groups	Crude		Model 1[a]		Model 2[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Q1	Ref		Ref		Ref	
Q2	2.339 (1.524, 3.591)	<0.001	1.706 (1.108, 2.627)	0.015	1.422 (0.920, 2.199)	0.113
Q3	3.405 (2.267, 5.114)	<0.001	2.333 (1.545, 3.523)	<0.001	1.797 (1.179, 2.738)	0.006
Q4	4.419 (2.974, 6.565)	<0.001	2.963 (1.978, 4.440)	<0.001	1.986 (1.307, 3.017)	0.001

Notes: [a]In the Model 1, the adjustment factors included age and sex. [b]In the Model 2, the adjustment factors included age, sex, low-density lipoprotein cholesterol (LDL-c), body mass index (BMI), alanine transaminase (ALT), hypertension, blood urea nitrogen (BUN), uric acid (UA). *P* values were calculated by cox proportional hazards model.
Abbreviations: TyG, triglyceride and glucose, HR, hazard ratio; CI, confidence interval.

Sensitivity Analysis

In the sensitivity analysis which used HOMA-IR as an indicator of IR, we found that the group with elevated HOMA-IR had an increased risk of LVH and decreased LVDFpEF compared to the group with normal HOMA-IR. The results also suggested IR was associated with the incidence of LVH and decreased LVDFpEF. See the attached Tables S5 and 6 for a more detailed result.

Table 7 Association of Baseline TyG Index and the Incidence of Decreased Left Ventricular Diastolic Function with Preserved Ejection Fraction in the Longitudinal Cohort Study

TyG Groups	Crude		Model 1[a]		Model 2[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Q1	Ref		Ref		Ref	
Q2	1.373 (1.172, 1.609)	<0.001	1.232 (1.049, 1.446)	0.011	1.169 (0.992, 1.377)	0.063
Q3	1.551 (1.330, 1.808)	<0.001	1.333 (1.138, 1.562)	<0.001	1.213 (1.025, 1.434)	0.024
Q4	1.695 (1.457, 1.972)	<0.001	1.581 (1.347, 1.855)	<0.001	1.386 (1.167, 1.647)	<0.001

Notes: [a]In the Model 1, the adjustment factors included age and sex. [b]In the Model 2, the adjustment factors included age, sex, low-density lipoprotein cholesterol (LDL-c), body mass index (BMI), alanine transaminase (ALT), hypertension, blood urea nitrogen (BUN), uric acid (UA). *P* values were calculated by cox proportional hazards model.
Abbreviations: TyG, triglyceride and glucose, HR, hazard ratio; CI, confidence interval.

Discussion

Our study provides evidence of the impact of IR on LVH and impaired LVDFpEF evaluated by echocardiography based on a large-sample population from health check-up centers in China. First, we executed a multi-centered cross-sectional study based on population from health check-up centers and found that IR was closely related to the prevalence of LVH and decreased LVDFpEF. Second, the results of the longitudinal LVH cohort study revealed that IR was associated with a new occurrence of LVH. Similarly, IR was also related to the incidence of decreased LVDFpEF in the longitudinal cohort. Meantime, subgroup analysis and sensitivity analysis further confirmed the relationship between IR and LVH and decreased LVDFpEF, indicating that IR may play an important role in the development of LVH and decreased LVDFpEF.

Better understanding and management of risk factors for subclinical left ventricular (LV) systolic and diastolic dysfunction years to decades preceding heart failure symptoms are highlighted in heart failure guidelines.[23] In fact, the myocardium underwent structural and metabolic changes in the presence of cardiovascular risk factors in the years to decades prior to the onset of symptomatic heart failure.[24] In this context, IR and other cardiovascular factors may play an important role in the occurrence and progression of cardiac remodeling and dysfunction. Conflicting information exists regarding IR involvement in the development of LVH or decreased LVDFpEF. Consistent with our study, a case control study including 88 participants with LVH and 132 participants without LVH found a significant relationship between IR (estimated with HOMA-IR) and LVH (estimated with left ventricular mass index) in hypertensive patients.[11] Another longitudinal, community-based study found that a higher level of serum insulin at baseline and its increase during follow-up independently predicted an increase in left ventricular mass index and worsening in LV systolic and diastolic function over time.[24] The CARDIA (Coronary Artery Risk Development in Young Adults) study (n = 3179) found the effects of high IR might constitute an important lifetime risk for the development of adverse LV remodeling and LV dysfunction among young adults.[25] However, controversially, another cross-sectional study did not find any relationship between IR (estimated with HOMA-IR) and LVH (estimated with Penn left ventricular mass index) in 275 subjects, regardless of univariate and multivariate regression analysis.[14] Galvan et al also found that IR (measured by the insulin-clamp technique) was not an independent determinant of LVH in a small sample of 50 Italian non-diabetic subjects after adjusting for blood pressure and BMI.[13]

These differences may be explained by differences in study population profiles, sample sizes, and methods used to diagnose IR and LVH. Our study is based on a national health check-up database in China with the pioneering large-scale populations. LVH was diagnosed by transthoracic pulsed wave Doppler echocardiography. IR was diagnosed by the TyG index, which has been shown to be highly sensitive for the identification of IR.[17–19] It is precisely due to the superiority of the TyG index to predict IR, as well as its convenience and economic efficiency, that the TyG index was widely used as a substitute index of IR to explore the predictive effects of diabetes and cardiovascular diseases.[26–28] Additionally, the reliability of our results was further confirmed by the results of subgroup analyses in non-diabetic and non-hypertensive populations and by sensitivity analyses using the HOMA-IR to reflect IR.

The mechanisms of cardiac hypertrophy involve many factors, such as tumor necrosis factor receptor-associated factor 3 and IκB kinase ε (IKKε), which promote cardiac hypertrophy, and E3 ligase tripartite motif-containing protein 16

(TRIM16), which attenuates cardiac hypertrophy, as confirmed by our previous studies.[29–33] IR is another important factor that may contribute to myocardial remodeling and diastolic dysfunction through the following mechanisms: The normal stress-free heart relies mainly on the oxidation of free fatty acids for energy production but can be converted to a more energy-efficient glycolysis under stress, ischemia, or injury.[24] IR-induced down-regulation of glucose transporter-4 expression results in reduced transmembrane transport and mitochondrial glucose oxidation, which reduces the rate of glycolysis.[34,35] The heart responds by increasing free fatty acid metabolism, which in turn leads to increased oxygen consumption, reduced cardiac efficiency, and lipotoxicity.[36] In addition, increased IR and fatty acid mitochondrial influx lead to excessive production of superoxide ions, which are involved in LVH and fibrosis.[24] Besides, the nutritional effects of insulin on myocardial tissue have been demonstrated in cell cultures and animal models.[37,38] Insulin can bind to and activate the insulin-like growth factor-1 receptor, leading to increased DNA and protein synthesis and cell proliferation. In particular, insulin has been shown to stimulate vascular smooth muscle proliferation and induce LVH by increasing mRNA levels and stimulating protein synthesis of muscle-specific genes (myosin light chain, O-actin, and troponin I).[8] Moreover, it has been suggested that hyperinsulinemia stimulates the activity of the sympathetic nervous system, which may directly affect ventricular structure due to growth-stimulating effects or indirectly by promoting increased heart rate and blood pressure levels.[8]

The increasing prevalence of heart failure with preserved ejection fraction, which is about to surpass that of heart failure with reduced ejection fraction,[39] has been of interest to researchers, but there are currently no much available disease-modifying therapies,[40] and so far only sodium-glucose co-transporter 2 (SLGT2) inhibitors have been found to improve the prognosis of this hypotype of heart failure.[41,42] Many mechanistic studies have shown that SLGT2 inhibitors improve heart failure prognosis by improving IR and regulating cardiac energy metabolism.[43] Clarification of the relationship between IR and decreased LVDFpEF could help provide a comprehensive development of drug targets for improving IR in the treatment of heart failure. So we further executed the study regarding the relationship between IR and the incidence of decreased LVDFpEF and identified IR as an important correlate of the occurrence of decreased LVDFpEF. Previous studies are consistent with our findings. For example, a study showed that IR was significantly related to left ventricular diastolic dysfunction in hypertensive patients.[5] Another study indicated that mildly elevated blood glucose (mildly impaired glucose metabolism) may worsen left ventricular diastolic dysfunction, even if anti-hypertensive therapy can control elevated blood pressure and the progression of hypertrophy.[44] Similarly, in animal models with abnormal glucose tolerance, sclerosis in the myocardial matrix and left ventricular sclerosis without LVH have been noted, which may provide some insight into the basis of the relationship between IR and left ventricular diastolic dysfunction.[45] The possible mechanism may be the accumulation of advanced glycation end products (including collagen, elastin, and other connective tissue proteins) in the myocardial interstitium, leading to reduced myocardial compliance in hyperglycemia.[44] Further clinical and basic studies are needed to confirm the relationship between IR and LVH and decreased LVDFpEF.

Limitations

The study has certain limitations that merit attention. First, our retrospective study is inherently limited in analyzing causality between IR and LVH and decreased LVDFpEF, and more definitive validation in prospective studies is needed. Second, the original images cannot be independently reviewed by the investigator, and therefore, differences between observers may lead to increased bias in the diagnosis of LVH and LVDFpEF. Third, the median follow-up time is shorter, which may neglect some people who will progress to LVH or decreased LVDFpEF. Fourth, a pseudo normalization (E/A>1) would be observed when the degree of decreased ventricular diastolic function was severe, which may result in a subset of participants with severe decreased LVDFpEF being neglected. Fifth, multilayer global longitudinal strain evaluation of myocardial deformation may provide more information on IR-related left ventricular dysfunction, unfortunately, our lack of myocardial strain parameters prevented correlation analyses.[46,47] Sixth, since our data are not derived from stratified sampling, the conclusions need to be generalized with caution to a broad population.

Conclusion

Our study found that IR was significantly associated with the prevalence and incidence of LVH and decreased LVDFpEF. The subgroup analysis further confirmed the conclusions after excluding the effects of hypertension and diabetes. Effective management of IR may prevent or delay the development of adverse LVH and decreased LVDFpEF.

Abbreviations

IR, insulin resistance; LVH, left ventricular hypertrophy; LVDFpEF, left ventricular diastolic function with preserved ejection fraction; TG, triglyceride; FBG, fasting blood glucose; TyG, triglyceride and glucose; IVS, interventricular septum; LVPW, left ventricular posterior wall; E wave, the peak velocity of the early diastolic filling wave; A wave, the peak velocity of the early atrial filling; HOMA-IR, homeostatic model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; UA, uric acid; SCR, serum creatinine; IQR, interquartile range; OR, odds ratio; HR, hazard ratio; CI, confidence intervals.

Ethics

The study has been confirmed to comply with the Declaration of Helsinki.

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Disclosure

The authors declare that there are no conflicts of interest in this work.

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