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# Adiposity modifies the association between heart failure risk and glucose metabolic disorder in older individuals: a community-based prospective cohort study

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## Abstract

**Background** Glucose metabolic disorder is associated with the risk of heart failure (HF). Adiposity is a comorbidity that is inextricably linked with abnormal glucose metabolism in older individuals. However, the effect of adiposity on the association between glucose metabolic disorder and HF risk, and the underlying mechanism remain unclear.

**Methods** A total of 13,251 participants aged ≥ 60 years from a cohort study were categorized into euglycemia, prediabetes, uncontrolled diabetes, and well-controlled diabetes. Adiposity was assessed using body mass index (BMI), waist-to-hip ratio (WHR), and visceral fat area (VFA). Adiposity-associated metabolic activities were evaluated using adiponectin-to-leptin ratio (ALR), homeostatic model assessment of insulin resistance (HOMA-IR), and triglyceride-glucose index (TyG). The first occurrence of HF served as the outcome during the follow-up period.

**Results** A total of 1,138 participants developed HF over the course of an average follow-up period of 10.9 years. The rate of incident HF occurrence was higher in prediabetes, uncontrolled diabetes, and well-controlled diabetes participants compared to that in euglycemia participants. However, the high rates were significantly attenuated by BMI, VFA, and WHR. For WHR in particular, the hazard ratio for incident HF was 1.18 (95% confidence interval (CI): 1.03, 1.35, $P_{adj.}$=0.017) in prediabetes, 1.59 (95% CI: 1.34, 1.90, $P_{adj.}$<0.001) in uncontrolled diabetes, and 1.10 (95% CI: 0.85, 1.43, $P_{adj.}$=0.466) in well-controlled diabetes. The population attributable risk percentage for central obesity classified by WHR for incident HF was 30.3% in euglycemia, 50.0% in prediabetes, 48.5% in uncontrolled diabetes, and 54.4% in well-controlled diabetes. Adiposity measures, especially WHR, showed a significant interaction with glucose metabolic disorder in incident HF (all $P_{adj.}$<0.001). ALR was negatively associated and HOMA-IR and TyG were positively

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associated with BMI, WHR, VFA, and incident HF (all $P_{adj.}$<0.05). ALR, HOMA-IR, and TyG mediated the associations for BMI, WHR and VFA with incident HF (all $P_{adj.}$<0.05).

**Conclusions** Adiposity attenuated the association of glucose metabolic disorder with incident HF. The results also showed that WHR may be an appropriate indicator for evaluating adiposity in older individuals. Adiposity-associated metabolic activities may have a bridging role in the process of adiposity attenuating the association between glucose metabolic disorder and incident HF.

**Trial registration** retrospectively registered number: ChiCTR-EOC-17,013,598.

**Keywords** Adiposity, Glucose metabolic disorder, Heart failure, Metabolic activity, Moderating effect, Mediating effect

## Introduction

Heart failure (HF) is a common final stage of heart diseases. It has been identified as a global pandemic in 2017, with a current prevalence of over 64 million cases worldwide [1–5]. Over 30% of patients with HF die within one year and >60% die within five years of diagnosis [3–9]. HF represents a significant burden on individuals and the social healthcare system. Currently, HF remains associated with poor outcomes despite the dramatic advances in therapeutic and management strategies [2, 3, 5, 8–13]. Fully elucidating the risk factors for HF and their interactions may be beneficial and effective for HF prevention and intervention.

Glucose metabolic disorder is a major contributor to the occurrence and development of HF among numerous modifiable risk factors [3, 14–16]. Epidemiological studies have confirmed a substantially increased risk of HF in patients with diabetes [3, 16–21]. The risk of HF caused by diabetes is approximately two-fold the level in male patients without diabetes and up to five-fold the level in female patients [3, 16–21]. Diabetes produces an additional 44% increase in HF risk in females compared to males [21–23]. However, the causes of these differences have not been fully elucidated.

Adiposity is an important HF risk factor that is inextricably linked with abnormal glucose metabolism [3, 24–28]. Subcutaneous and visceral fat accumulation are the two main forms of adiposity. Sex differences in the distribution and accumulation of body fat are well documented [29–31]. Female patients have a greater body fat mass and preferential gluteofemoral area accumulation, whereas male patients are more prone to abdominal fat deposition [29, 32–34]. Gluteofemoral adipose tissue is characterized by low metabolic activity, act as a metabolic sink for lipid storage and offer protection against cardiometabolic diseases, while abdominal fat shows high activity, releasing metabolites such as free fatty acids, adipokine, inflammatory molecules, and neurohormones directly to the cardiovascular system, causing endothelial dysfunction and cardiometabolic diseases [29, 32–34]. It is an important reason for the differences in HF risk between men and women. Thus, the present study hypothesized that adipose accumulation in different body areas may modify the association between glucose metabolic disorder and HF risk.

Body mass index (BMI) has been used to evaluate and identify obesity in many studies. However, the reliability and accuracy of BMI, particularly when used to determine the association between obesity and HF, are challenged by waist circumference (WC), visceral adipose tissue, and WC-to-hip-circumference ratio (WHR) [28, 35–37]. Khan et al. [35] suggested that WHR is the most appropriate indicator for evaluating adiposity distribution among obesity measures.

The primary objective of the preset study was to investigate the effect of adiposity modulation on the association between glucose metabolic disorder and HF in older adults using a community-based prospective cohort study. In addition, the role of adiposity-associated metabolic activities in the association between adiposity and HF was explored.

## Materials and methods

### Study population and design

The participants in the present study were community-dwelling older adults aged 60 years and over from Shandong, China (Retrospectively Registered: ChiCTR-EOC-17013598) [38–40]. The original study aims to explore multiple and potential risk factors of chronic diseases, as described elsewhere [38–40]. The cohort was expanded to more than 20,000 individuals aged 15 years and older between April 2007 to November 2011. For this current study, a total of 13,251 older individuals were eligible and enrolled based on the following exclusion criteria: congestive heart failure, myocardial infarction, stroke, thyroid and parathyroid disease, Cushing's syndrome, dementia, psychosis, liver dysfunction, renal dysfunction, dialysis treatment, acute and chronic infectious diseases, malignancy, autoimmune diseases, connective tissue diseases, alcohol and drug abuse, contraindications to bioelectrical impedance analyzer (BIA), and unwillingness to provide informed consent. Individuals who planned to leave the study area within five years and failed to complete the baseline evaluation were also excluded from the study. Participants were visited between three and four,

six and seven, and eight and nine years after baseline visit to acquire clinical characteristics.

The present research was conducted in compliance with the Declaration of Helsinki and the study protocol was approved by the Research Ethics Committee of the Institute of Basic Medicine, Shandong Academy of Medical Sciences, Jinan, China. Written informed consent was obtained from all participants.

#### Glucose metabolic status assessment and classification

Blood samples from each participant were collected by experienced nurses in the morning after overnight fasting. Plasma and serum were separated and stored at -80℃ for subsequent analyses. The concentration of fasting plasma glucose (FPG) was measured using a routine enzymatic method with a Hitachi 7600 (Hitachi, Ltd., Tokyo, Japan) automated biochemical analyzer. Hemoglobin A1c (HbA1c) was measured using ion-exchange high-performance liquid chromatography.

Glucose metabolic status was divided into the following categories: euglycemia (FPG < 100 mg/dL, HbA1c < 5.7%, no diagnosed diabetes, no use of antihyperglycemic medication), prediabetes (FPG 100–125 mg/dL and/or HbA1c 5.7–6.4%, no diagnosed diabetes, and no use of antihyperglycemic medication), uncontrolled diabetes (FPG ≥ 126 mg/dL and/or HbA1c ≥ 6.5%, diagnosed diabetes, and use of antihyperglycemic medication), and well-controlled diabetes (FPG < 126 mg/dL and HbA1c < 6.5%, diagnosed diabetes, and use of antihyperglycemic medication) [41, 42].

#### Anthropometric and body composition assessments

Body weight, height, WC, hip circumference, and visceral fat area (VFA) were assessed in a quiet, bright, and warm room (22–24℃) by trained nurses who were blinded to the clinical data for participants. Participants were asked to fast for 3 h, empty their bladder, and wear a minimal amount of clothing and no shoes. Body weight was measured to the nearest 0.1 kg using a segmental multifrequency BIA (InBody720, Biospace Co., Seoul, Korea). Height was determined to the nearest 0.1 cm using a wall-mounted stadiometer. BMI was calculated as body weight (kg)/body height (m) squared. WC and hip circumference were measured using inelastic tape to the nearest 0.1 cm at the midpoint between the iliac crest and the lower rib margins and at the level of the great trochanter. WHR was calculated as WC (cm)/hip circumference (cm). VFA ($cm^2$) was evaluated using a BIA (InBody720, Biospace Co., Seoul, Korea) according to the manufacturer's protocol. VFA ($cm^2$) of 30 male and 30 female randomly selected patients measured using magnetic resonance imaging (MRI; 3.0-Tesla scanner, Signa Horizon LX, GE Medical Systems, Pittsburgh, PA, USA) according to a turbo spin echo imaging protocol was used to correct the BIA device's measurements. There was a good consistency between the VFAs determined using MRI and using BIA with correlation coefficient of 0.81.

In the present study, participants were classified into non-general vs. general obesity groups depending on their BMI (< 28.0 $kg/m^2$ vs. ≥ 28.0 $kg/m^2$), non-central vs. central obesity groups depending on their WHR (≤ 0.8 vs. > 0.8 for female participants and ≤ 0.9 vs. > 0.9 for male participants) [43, 44], and low vs. high VFA groups depending on the VFA quintile (sex-specific three low quintiles vs. two high quintiles).

#### Plasma lipid, serum creatinine, and hemoglobin assessment

Plasma concentrations of triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol and serum concentration of creatinine were determined using a routine enzymatic method with a Hitachi 7600 (Hitachi, Ltd., Tokyo, Japan) automated biochemical analyzer. Hemoglobin was detected using a hemoglobin colorimetric assay kit (Beyotime, Shanghai, China).

#### Adiposity-associated metabolic activity assessment

In the present study, homeostatic model assessment of insulin resistance (HOMA-IR), adiponectin-to-leptin ratio (ALR), and triglyceride-glucose index (TyG) were used to assess adiposity-associated metabolic activities. HOMA-IR was calculated using the following formula: HOMA-IR = FPG (mmol/L) × insulin (mU/L)/22.5 [45, 46]. A landmark for investigating adipose-mediated tissue crosstalk, ALR [47, 48] was calculated by dividing adiponectin by leptin. TyG was determined using the following formula: TyG = ln [TG (mg/dL) × FPG (mg/dL)/2] [49, 50].

Plasma concentrations of insulin, leptin, and adiponectin were detected using enzyme-linked immunosorbent assay kits (Beyotime, Shanghai, China) following the manufacturer's instructions. The minimum detectable concentrations were 1.54 mU/L for insulin, 26.6 pg/mL for leptin, and 56 pg/mL for adiponectin. Intra- and inter-assay coefficients of variations were both < 10% for insulin, leptin, and adiponectin.

#### Covariates

Age, smoking status, alcohol consumption, exercise, history of hypertension, history of dyslipidemia, history of atrial fibrillation, use of antihypertension, lipid-lowering, anticoagulation, and anti-atrial fibrillation medications, systolic blood pressure (SBP), diastolic blood pressure (DBP), heartbeat, and plasma lipid levels were included as covariates. The plasma concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) was detected using obtained plasma with a recombinant

human NT-pro-BNP kit (Beyotime, Shanghai, China). In addition, since renal dysfunction and anemia are significantly associated with HF [10, 51], estimated glomerular filtration rate (eGFR) and hemoglobin level were also included as covariates in the present study. The eGFR was estimated according to the formula provided by the Chronic Kidney Disease Epidemiology Collaboration using serum creatinine level on the basis of age, sex, and ethnicity [40, 52]. Common carotid artery intima-media thickness and plaque were detected using high-resolution ultrasound with a 7.5-MHz linear array transducer (Vivid *i*, GE Medical Systems Ultrasound Israel Ltd). Carotid artery plaque was defined as a IMT ≥ 1.5 mm [53, 54].

#### Outcomes of interest

First HF occurrence at hospitalization and specialized outpatient visit during the follow-up period were the primary outcomes of interest in the present study. HF was determined according to the International Classification of Diseases 10th Revision code I50 and adjudicated by a committee based on the review of medical records, including clinical signs and symptoms, echocardiogram recording, NT-proBNP level, and medication use.

#### Statistical analysis

Continuous data were represented as the mean with standard deviation (SD) or median with interquartile range (IQR, 25th to 75th percentiles), depending on the normality determined by the Kolmogorov-Smirnov test. Categorical data were represented as frequencies with percentages. Cumulative incidence values for HF were assessed among participants stratified by glucose metabolic status (euglycemia vs. prediabetes, uncontrolled diabetes, and well-controlled diabetes) and adiposity (non-general vs. general obesity, non-central vs. central obesity, and low vs. high VFA) using Fine-Gray models accounting for competing risk of death. Multiplicative interactions were included in the models to evaluate the effect of adiposity modulation on the associations between incident HF and glucose metabolic status [each continuous and categorical variable of adiposity (BMI, WHR, and VFA and general obesity, central obesity, and high VFA)*glucose metabolic status]. The confounders included in separate models were as follows: Model 1 for none; Model 2 for age, smoking status, alcohol consumption, regular physical activity, plasma lipid level; Model 3 for confounders in Model 2 plus BMI; Model 4 for confounders in Model 2 plus WHR; and Model 5 for confounders in Model 2 plus VFA. Restricted cubic splines method was used to assess the associations of BMI, WHR, VFA, HOMA-IR, TyG, and ALR with incident HF and to adjust for confounders in Model 2.

The population attributable risk percentage (PARp) for incident HF across the categories of adiposity was assessed using the following formula: PARp = 1-[(1-S0($t$))/(1-S($t$))], where S0($t$) is the counterfactual survival function and S($t$) is the factual survival function [37].

Multiple linear regression models were generated to assess the associations of HOMA-IR, ALR, and TyG with BMI, WHR, and VFA adjusted for confounders in Model 2. Mediating effect analysis was carried out to assess the roles of HOMA-IR, ALR, and TyG in the association between adiposity and HF adjusted for confounders in Model 2.

For sensitivity analyses, diabetes patients were divided into uncontrolled and well-controlled diabetes groups to assess the association between diabetes and HF. The adiposity characteristics were used as categorical and continuous variables to evaluate the association with HF. In addition, the differences of the changes in adiposity and metabolic indicators were compared using linear mixed models between groups classified by glucose metabolic status during follow-up period.

R (version 4.3.2, R Foundation for Statistical Computing) and SPSS (version 26.0, IBM Corp., Armonk, NY, USA) software packages were used to perform all statistical analyses. GraphPad Prism (version 9.1.0, GraphPad Prism Software Inc., San Diego, CA, USA) and R (version 3.6.3, R Foundation for Statistical Computing) software packages were used to generate graphs. Two-tailed *P*-value of < 0.05 was considered statistically significant.

## Results

#### Baseline characteristics

Among the 13,251 participants (age: 60.0–95.0 years), there were 6,803 (51.3%) female participants. In addition, 6,249 (47.2%) participants had euglycemia, 4,793 (36.2%) had prediabetes, 1,356 (10.2%) had uncontrolled diabetes, and 853 (6.4%) had well-controlled diabetes. The median value was 24.21 kg/m$^2$ for BMI (IQR: 21.73, 26.54), 0.86 for WHR (IQR: 0.79, 0.93), and 160.95 cm$^2$ for VFA (IQR: 148.24, 173.68). Figure 1 shows the study flowchart and Table 1 details the baseline demographic and clinical characteristics.

#### Adiposity modifies the association between glucose metabolic disorder and incident HF

Over an average of 10.9 years (IQR: 10.1, 11.6) of follow-up, 1,138 older adults developed HF, representing an incidence of 7.89 per 1,000 person-years. Among them, 413 participants (6.02 per 1,000 person-years) had euglycemia, 441 (8.47 per 1,000 person-years) had prediabetes, 216 (14.93 per 1,000 person-years) had uncontrolled diabetes, and 68 (7.48 per 1,000 person-years) had well-controlled diabetes. Clinical characteristics of participants with new-onset HF are presented in **Supplementary Table 1**. The occurrence rate of incident HF in prediabetes, uncontrolled diabetes, and well-controlled diabetes

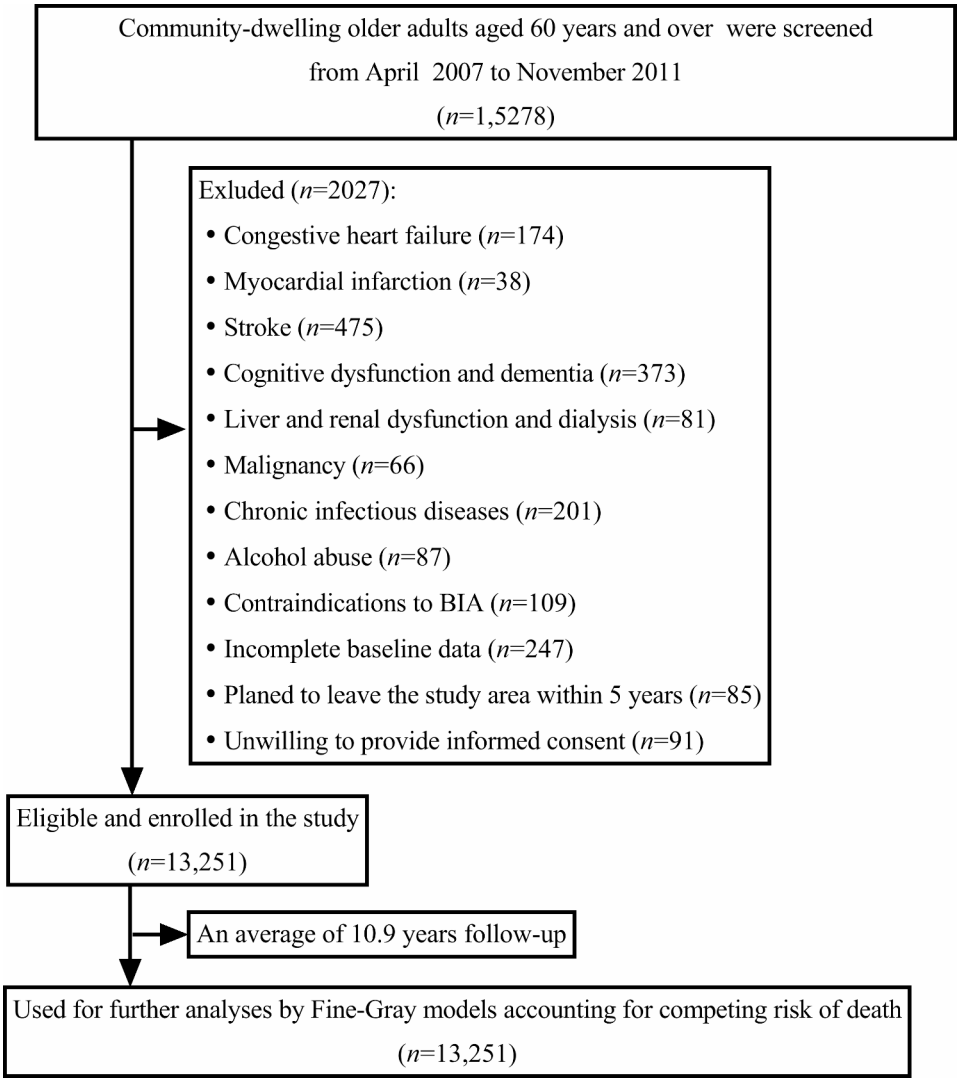


**Fig. 1** Flowchart depicting the recruitment of participants

participants was significantly higher compared to that in euglycemia participants after adjustment for confounders excluding BMI, VFA, and WHR (all $P<0.05$, Fig. 2). Interestingly, the higher risks were markedly blunted after BMI, VFA, and WHR were separately included as confounders in the adjustment analysis models. In particular, the risk of HF was not any more statistically significant in well-controlled diabetes participants after adjustment for WHR and VFA (Fig. 2**and Supplementary Table 2**). Similar results were found after participants were stratified by sex (**Supplementary Fig. 1 and Supplementary Table 2**).

### Adiposity and incident HF

The occurrence of incident HF in participants with general obesity, central obesity, or high VFA was significantly higher than in those with non-general obesity, non-central obesity, or low VFA, respectively (all $P_{adj.}<0.001$, Fig. 3). With each one-SD increment in BMI, WHR, and VFA, the occurrence of incident HF increased 0.44-, 0.81- and 0.48-fold, respectively (all $P_{adj.}<0.001$, Table 2). The restricted cubic splines results showed U-shaped associations between HF risk and BMI (cutoff: 24.2 kg/m$^2$) and VFA (cutoff: 160.9 cm$^2$), and an approximately linear association between WHR and HF risk (cutoff: 0.8, Fig. 3). Similar results were noted in male and female participants (**Supplementary Figs. 2 and 3 and Supplementary Table 3**).

### Interaction between glucose metabolic disorder and adiposity in incident HF

Table 3 describes the interaction between adiposity and glucose metabolic disorder in incident HF during the follow-up period. The WHR interaction, used as either category or continuous measure, with glucose metabolic disorder in incident HF was greater than the BMI

**Table 1** Baseline demographic and clinical characteristics of the study participants grouped by glucose metabolic status

| Characteristics | Overall (*n* = 13,251) | Euglycemia (*n* = 6,249) | Prediabetes (*n* = 4,793) | Uncontrolled diabetes (*n* = 1,356) | Well-controlled diabetes (*n* = 853) | *P* value |
|---|---|---|---|---|---|---|
| Age, years | 68.36 ± 6.16 | 67.98 ± 5.93 | 68.52 ± 6.36* | 69.08 ± 6.33*,† | 69.13 ± 6.22*,† | < 0.001 |
| Female, *n* (%) | 6,803 (51.30) | 3,064 (49.00) | 2,499 (52.10)* | 705 (52.00)* | 535 (62.70)*,†,‡ | < 0.001 |
| Smoking, *n* (%) | 3,506 (26.50) | 1,864 (29.80) | 1,199 (25.00)* | 288 (21.10)*,† | 155 (18.20)*,† | < 0.001 |
| Drinking, *n* (%) | 4,335 (32.70) | 2,184 (34.90) | 1,534 (32.00)* | 430 (31.70)* | 187 (21.90)*,†,‡ | < 0.001 |
| Regular physical activity, *n* (%) | 7,723 (58.30) | 3,715 (59.40) | 2,651 (55.30)* | 811 (59.80)† | 546 (64.00)*,†,‡ | < 0.001 |
| Hypertension, *n* (%) | 10,092 (76.20) | 4,705 (75.30) | 3,652 (76.20) | 1,051 (77.50) | 684 (80.20)*,† | 0.009 |
| Dyslipidemia, *n* (%) | 5,291 (39.90) | 2,339 (37.40) | 1,923 (40.10)* | 636 (46.90)*,† | 393 (46.10)*,† | < 0.001 |
| Antihypertensive medication, *n* (%) | 7,479 (56.40) | 3,408 (54.50) | 2,760 (57.60)* | 815 (60.10)* | 496 (58.10)* | < 0.001 |
| Lipid-lowering medication, *n* (%) | 1,376(10.40) | 642 (10.30) | 438 (9.10)* | 217 (16.00)*,† | 79 (9.30)‡ | < 0.001 |
| BMI, kg/m$^2$ | 24.25 ± 3.59 | 23.67 ± 3.48 | 24.46 ± 3.56* | 25.94 ± 3.68*,† | 24.51 ± 3.59*,‡ | < 0.001 |
| WHR | 0.82 ± 0.10 | 0.80 ± 0.09 | 0.83 ± 0.10* | 0.88 ± 0.11*,† | 0.83 ± 0.11*,‡ | < 0.001 |
| VFA, cm$^2$ | 161.73 ± 19.76 | 157.55 ± 18.80 | 162.69 ± 19.74* | 171.99 ± 19.30*,† | 160.73 ± 20.03*,†,‡ | < 0.001 |
| SBP, mm Hg | 147.36 ± 18.82 | 146.92 ± 18.89 | 147.60 ± 18.61 | 148.64 ± 18.68* | 147.27 ± 19.58 | 0.015 |
| DBP, mm Hg | 71.01 ± 9.19 | 70.90 ± 9.27 | 71.28 ± 9.00 | 71.18 ± 9.49 | 70.04 ± 9.23†,‡ | 0.002 |
| Heart rate, bpm | 73.93 ± 9.39 | 73.76 ± 9.36 | 73.83 ± 9.13 | 74.91 ± 10.23*,† | 74.15 ± 9.59 | < 0.001 |
| TCHO, mmol/L | 5.00 ± 0.87 | 4.94 ± 0.85 | 5.04 ± 0.86* | 5.14 ± 0.93*,† | 5.07 ± 0.86* | < 0.001 |
| TG, mmol/L | 1.70 ± 0.63 | 1.64 ± 0.60 | 1.72 ± 0.62* | 1.85 ± 0.74*,† | 1.78 ± 0.63*,† | < 0.001 |
| HDL-C,, mmol/L | 1.27 ± 0.42 | 1.27 ± 0.42 | 1.27 ± 0.41 | 1.25 ± 0.42 | 1.28 ± 0.42 | 0.169 |
| LDL-C, mmol/L | 2.96 ± 0.76 | 2.92 ± 0.75 | 2.99 ± 0.76* | 3.05 ± 0.80* | 2.98 ± 0.78 | < 0.001 |
| FPG, mg/dL | 106.07 ± 24.84 | 88.37 ± 7.53 | 112.82 ± 7.755* | 159.31 ± 31.41*,† | 113.17 ± 12.51*,‡ | < 0.001 |
| HbA1c, % | 5.76 ± 0.97 | 5.10 ± 0.43 | 6.08 ± 0.21* | 7.88 ± 1.10*,† | 5.47 ± 0.48*,†,‡ | < 0.001 |
| CCA-IMT, mm | 1.68 (1.35, 2.00) | 1.64 (1.32, 1.93) | 1.68 (1.35, 2.01)* | 1.79 (1.48, 2.20)*,† | 1.70 (1.40, 2.10)*,‡ | < 0.001 |
| CCA-plaque, *n* (%) | 8,686 (65.55) | 3,955 (63.29) | 3,139 (65.49)* | 1,008 (74.34)*,† | 584 (68.46)*,‡ | < 0.001 |
| Hemoglobin, g/L | 12.12 ± 1.03 | 12.48 ± 0.91 | 11.98 ± 0.95* | 11.09 ± 0.92*,† | 11.90 ± 1.04*,‡ | < 0.001 |
| NT-pro-BNP, pg/mL | 155.61 (150.49, 159.71) | 153.18 (147.50, 156.44) | 157.04 (152.98, 160.26)* | 165.10 (161.04, 169.72)*,† | 157.48 (150.73, 161.60)*,‡ | < 0.001 |
| TyG index | 8.89 ± 0.43 | 8.71 ± 0.37 | 8.95 ± 0.36* | 9.38 ± 0.44*,† | 9.11 ± 0.41*,†,‡ | < 0.001 |
| Insulin, mU/L | 12.01 ± 2.19 | 13.40 ± 1.66 | 11.43 ± 1.43* | 8.79 ± 1.51*,† | 10.30 ± 1.97*,†,‡ | < 0.001 |
| HOMA-IR | 3.01 ± 0.30 | 2.92 ± 0.27 | 3.03 ± 0.27* | 3.33 ± 0.31*,† | 3.03 ± 0.28*,‡ | < 0.001 |
| Leptin, ng/mL | 9.50 ± 1.38 | 9.26 ± 1.32 | 9.59 ± 1.39* | 10.25 ± 1.38*,† | 9.61 ± 1.34*,‡ | < 0.001 |
| Adiponectin, μg/mL | 19.21 (16.12, 23.48) | 20.12 (16.99, 25.40) | 18.87 (15.96, 22.80)* | 15.95 (13.14, 19.45)*,† | 19.28 (16.05, 24.75)*,†,‡ | < 0.001 |
| ALR | 1.99 (1.69, 2.41) | 2.12 (1.83, 2.60) | 1.94 (1.66, 2.30)* | 1.58 (1.32, 1.86)*,† | 1.94 (1.65, 2.48)*,†,‡ | < 0.001 |
| eGFR, ml/min/1.73 m$^2$ | 93.34 (89.13, 97.94) | 95.07 (90.73, 99.42) | 91.94 (88.09, 96.43)* | 90.06 (84.37, 95.38)*,† | 93.50 (90.84, 97.43)*,†,‡ | < 0.001 |

Results are medians with interquartile range (IQR, 25th to 75th percentiles) or numbers and percentages. BMI; body mass index; WC, Waist circumference; HC, Hip circumference; WHR, Waist-to-hip ratio; VFA, Visceral fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TCHO, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; CCA, common carotid artery; IMT, intima-media thickness; TyG, Triglyceride-glucose; NT-pro-BNP, N-terminal fragment brain natriuretic peptides; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; ALR, Adiponectin-to-leptin ratio; eGFR, evaluate glomerular filtration rate. *$P < 0.05$, compared with euglycemia; †$P < 0.05$, compared with prediabetes; ‡$P < 0.05$, compared with uncontrolled diabetes

and VFA interactions [1.59 (95% confidence interval (CI): 1.52, 1.66) vs. 1.40 (95% CI: 1.34, 1.46) and 1.42 (95% CI: 1.34, 1.49) for category measure, 1.27 (95% CI: 1.24, 1.31) vs. 1.19 (95% CI: 1.15, 1.22) and 1.18 (95% CI: 1.16, 1.20) for continuous measure]. The glucose metabolic disorder interactions with adiposity in incident HF in male and female participants are presented in **Supplementary Table 4**.

### Population attributable risk percentage of adiposity measures for incident HF

The PARps for general obesity, central obesity, and high VFA for incident HF were 15.3%, 45.9%, and 32.9% in overall, 13.6%, 30.3%, and 22.7% in euglycemia, 17.4%, 50.0%, and 34.8% in prediabetes, 18.9%, 48.5%, and 33.1% in uncontrolled diabetes, and 22.8%, 54.4%, and 45.6% in well-controlled diabetes groups, respectively. Compared to euglycemia, the PARps for general obesity, central obesity, and high VFA were higher in prediabetes,

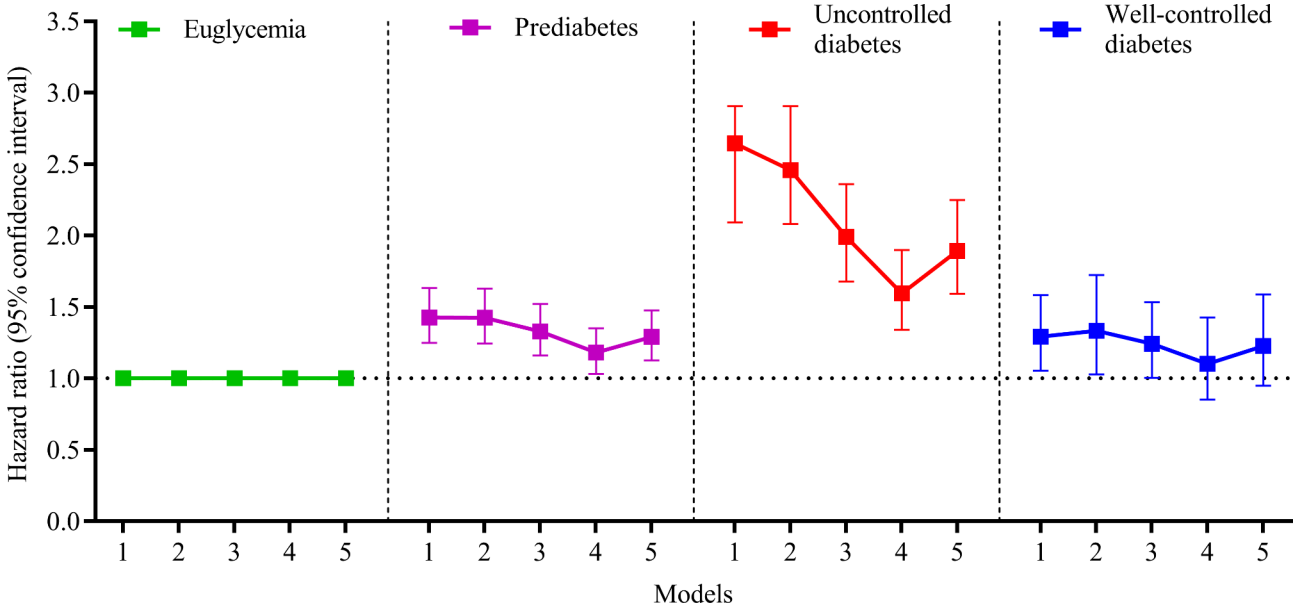


**Fig. 2** HF hazard ratio changes in different adjustment analysis models. Model 1 was not adjusted for any factors; Model 2 was adjusted for adjusted for age, smoking, alcohol consumption, regular physical activity, and plasma lipids; Model 3 was adjusted for confounders in Model 2 plus BMI; Model 4 was adjusted for confounders in Model 2 plus WHR, and Model 5 was adjusted for confounders in Model 2 plus VFA

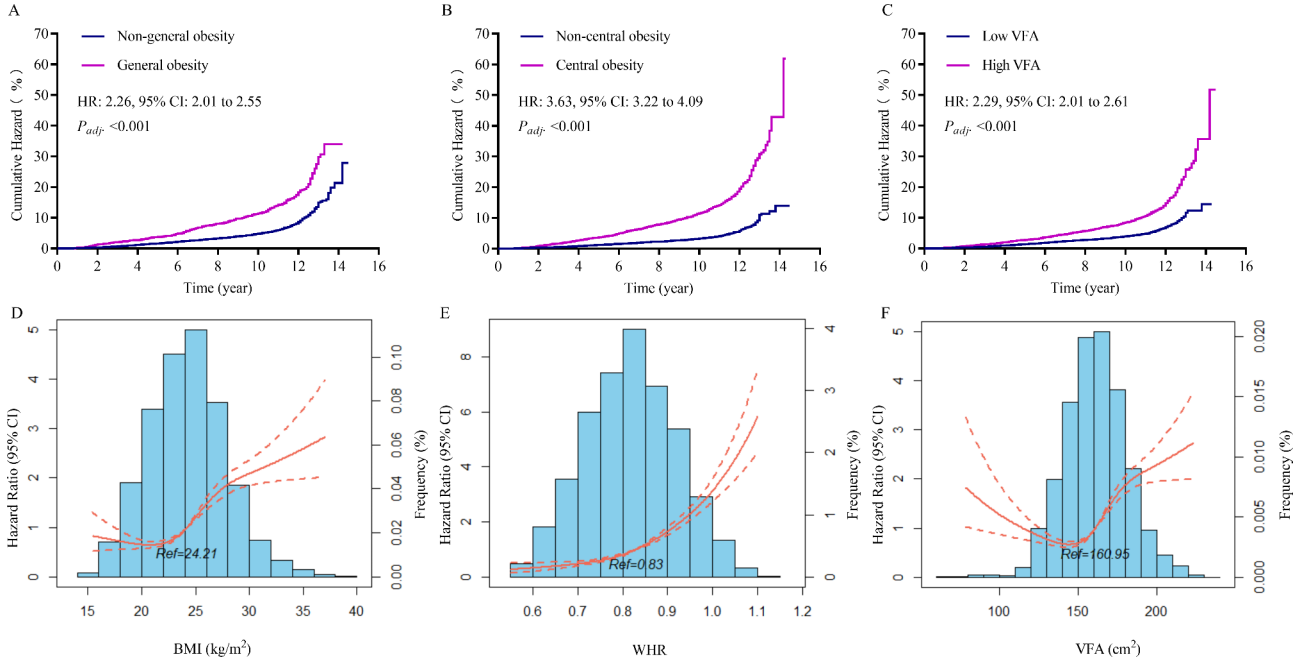


**Fig. 3** Association for body fat distribution and accumulation with HF risk. (**A**) Cumulative hazard for HF in participants (**A**) with and without general obesity, (**B**) with and without central obesity, and (**C**) with low and high VFA. The association between (**D**) BMI, (**E**) WHR, and (**F**) VFA and HF risk analyzed using restricted cubic splines. Models are adjusted for adjusted for age, smoking, alcohol consumption, regular physical activity, and plasma lipids. BMI, body mass index; WHR, waist-to-hip circumference ratio; VFA, visceral fat area

**Table 2** Association of one-SD increment BMI, WHR, and VFA with incident HF

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| One-SD increment BMI | 1.45 (1.37, 1.54) | < 0.001 | 1.44 (1.36, 1.53) | < 0.001 |
| One-SD increment WHR | 1.81 (1.70, 1.92) | < 0.001 | 1.81 (1.70, 1.92) | < 0.001 |
| One-SD increment VFA | 1.51 (1.42, 1.59) | < 0.001 | 1.48 (1.40, 1.57) | < 0.001 |

Model 1 adjusted for none. Model 2 adjusted for adjusted for age, smoking, alcohol consumption, regular physical activity, and plasma lipids. BMI, body mass index; WHR, waist-to-hip circumference ratio; VFA, visceral fat area

**Table 3** Interaction between adiposity and glucose metabolic disorder on incident HF

| | Glucose metabolic status*categories of obesity | | | | | Glucose metabolic status*continuous measures of adiposity | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Model 1 | | Model 2 | | | Model 1 | | Model 2 | |
| | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| *Obesity categorized by BMI | 1.40 (1.34, 1.46) | < 0.001 | 1.40 (1.34, 1.46) | < 0.001 | *BMI | 1.19 (1.16, 1.22) | < 0.001 | 1.19 (1.15, 1.22) | < 0.001 |
| *Obesity categorized by WHR | 1.60 (1.53, 1.67) | < 0.001 | 1.59 (1.52, 1.66) | < 0.001 | *WHR | 1.28 (1.25, 1.31) | < 0.001 | 1.27 (1.24, 1.31) | < 0.001 |
| *High VFA categorized by VFA | 1.42 (1.34, 1.49) | < 0.001 | 1.42 (1.34, 1.49) | < 0.001 | *VFA | 1.18 (1.15, 1.21) | < 0.001 | 1.18 (1.16, 1.20) | < 0.001 |

Model 1 adjusted for none. Model 2 adjusted for adjusted for age, smoking, alcohol consumption, regular physical activity, and plasma lipids. BMI, body mass index; WHR, waist-to-hip circumference ratio; VFA, visceral fat area

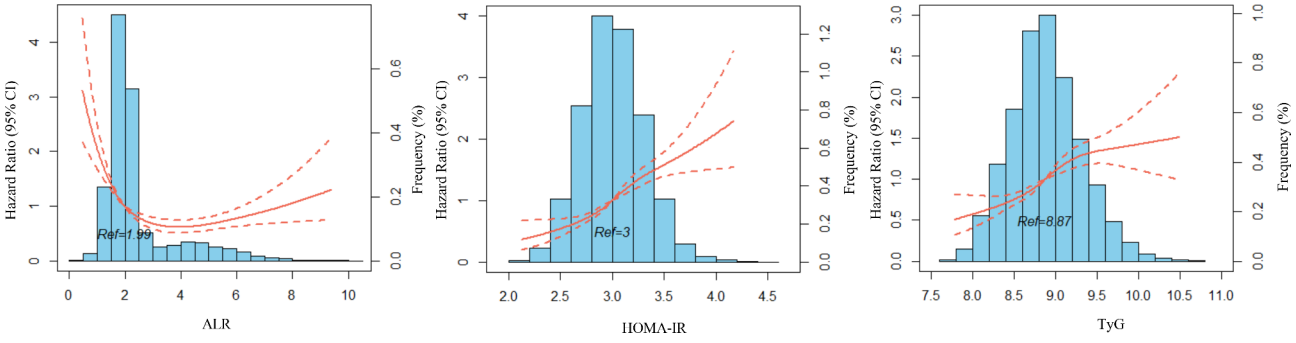


**Fig. 4** Association between metabolic activity and HF risk analyzed using restricted cubic splines. The association between (**A**) ALR, (**B**) HOMA-IR, and (**C**) TyG and HF risk. Models are adjusted for adjusted for age, smoking, alcohol consumption, regular physical activity, and plasma lipids. ALR, adiponectin-to-leptin ratio; HOMA-IR, homeostatic model assessment of insulin resistance; TyG, triglyceride-glucose index

**Table 4** Cumulative hazard of incident HF with one-SD increment HOMA-IR, ALR, FAR, and TyG

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| One-SD increment ALR | 0.79 (0.74, 0.85) | < 0.001 | 0.81 (0.75, 0.88) | < 0.001 |
| One-SD increment HOMA-IR | 1.27 (1.20, 1.34) | < 0.001 | 1.25 (1.18, 1.33) | < 0.001 |
| One-SD increment TyG | 1.54 (1.39, 1.71) | < 0.001 | 1.31 (1.26, 1.37) | < 0.001 |

Model 1 adjusted for none. Model 2 adjusted for adjusted for age, smoking, alcohol consumption, regular physical activity, and plasma lipids. ALR, adiponectin-to-leptin ratio; HOMA-IR, homeostatic model assessment of insulin resistance; TyG, triglyceride-glucose index

uncontrolled diabetes, and well-controlled diabetes groups. The PARp for central obesity was higher than that for general obesity and high VFA.

### Associations between adipose-related metabolic activities and incident HF

HOMA-IR and TyG were significantly and positively associated, while ALR was negatively associated with incident HF analyzed using restricted cubic splines (Fig. 4). The cutoff was 2.0 for ALR, 3.0 for HOMA-IR, and 8.9 for TyG. The HF risk increased 0.25- and 0.31-fold with one-SD increment in HOMA-IR and TyG, respectively (all $P_{adj.}$<0.001, Table 4). On the contrary, the risk decreased 0.19-fold with one-SD increment in ALR ($P_{adj.}$<0.001, Table 4). Significant associations were still present after participants were stratified by sex (**Supplementary Fig. 4 and Supplementary Table 5**).

### Associations between adiposity and metabolic activities

After adjustment for confounders, BMI, WHR, and VFA were significantly and positively associated with HOMA-IR and TyG and negatively associated with ALR (all $P_{adj.}$<0.001, Table 5).

**Table 5** Associations between adiposity and adipose-associated-metabolic activity

| | ALR | | HOMA-IR | | TyG | |
|---|---|---|---|---|---|---|
| | **Beta (95% CI)** | ***P* value** | **Beta (95% CI)** | ***P* value** | **Beta (95% CI)** | ***P* value** |
| BMI (kg/m$^2$) | -0.12 (-0.13, -0.12) | < 0.001 | 0.027 (0.026, 0.029) | < 0.001 | 0.012 (0.011, 0.013) | < 0.001 |
| WHR | -6.83 (-7.02, -6.64) | < 0.001 | 1.14 (1.09, 1.18) | < 0.001 | 0.50 (0.46, 0.53) | < 0.001 |
| VFA (cm$^2$) | -0.05 (-0.05, -0.04) | < 0.001 | 0.007 (0.007, 0.007) | < 0.001 | 0.002 (0.002, 0.003) | < 0.001 |

Models adjusted for adjusted for age, smoking, alcohol consumption, regular physical activity, and plasma lipids in the analysis models. BMI, body mass index; WHR, waist-to-hip circumference ratio; VFA, visceral fat area; ALR, adiponectin-to-leptin ratio; HOMA-IR, homeostatic model assessment of insulin resistance; TyG, triglyceride-glucose index

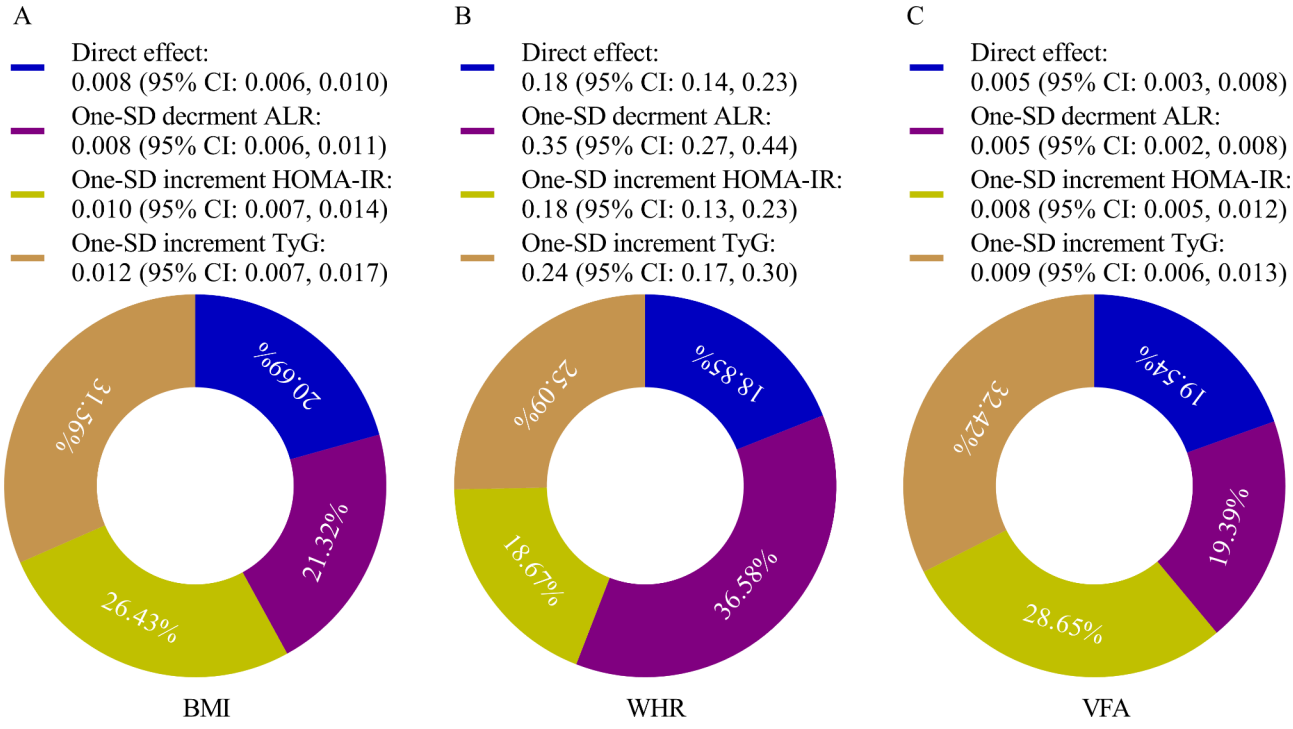


**Fig. 5** Mediating effects of of adipose-related metabolic activities on association between adiposity and incident HF. (**A**) Percentages of ALR, HOMA-IR, and TyG indirect effects in the association between BMI and AF. (**B**) Percentages of ALR, HOMA-IR, and TyG indirect effects in the association between WHR and AF. (**C**) Percentages of ALR, HOMA-IR, and TyG indirect effects in the association between VFA and AF. BMI, body mass index; WHR, waist-to-hip circumference ratio; VFA, visceral fat area; ALR, adiponectin-to-leptin ratio; HOMA-IR, homeostatic model assessment of insulin resistance; TyG, triglyceride-glucose index

### Mediating effects of adipose-related metabolic activities on association between adiposity and incident HF

The mediating effect analysis results showed that ALR, HOMA-IR, and TyG play significant mediating roles in the associations of BMI, WHR, and VFA with incident HF even after adjustment for potential confounders (all $P_{adj.}$<0.05, Fig. 5). ALR exhibited the lowest, while TyG had the highest mediating effect in the association between BMI and HF. ALR was the highest and HOMA_IR was the lowest in the association between WHR and HF. ALR was the lowest and TyG was the highest in the association between VFA and HF.

### Changes in adiposity and metabolic measurements during follow-up period

The differences in the changes in FPG, HbA1c, BMI, WHR, VFA, ALR, HOMA-IR, and TyG were not significant between euglycemia, prediabetes, uncontrolled diabetes, and well-controlled diabetes during follow-up period (all $P$>0.05, **Supplementary Fig. 5**).

## Discussion

In the present prospective cohort study, adipose distribution and accumulation significantly attenuated the association between glucose metabolic disorder and incident HF in community-dwelling older individuals. The attenuating effect of WHR on the association between glucose metabolic disorder and incident HF was stronger compared to that of BMI and VFA. Higher metabolic activities were an important mediator for adiposity to attenuate the association between glucose metabolic disorder and incident HF.

The association between glucose metabolic disorder and HF risk has been well-established [3, 14–16]. In a

pooled analysis of community-based the National Heart, Lung and Blood Institute cohorts comprising 10,387 participants, Patel et al. [35] identified interactions of diabetes with BMI, WC, and fat mass in the risk of HF. On the other hand, weight loss has been demonstrated to significantly reduce incident HF risk [16, 28].

In the present study, the high rate of incident HF was significantly associated with prediabetes, uncontrolled diabetes, and even well-controlled diabetes. However, these associations were significantly attenuated by BMI, WHR, and VFA. The PARp and interaction analyses results also confirmed these findings. The data revealed that adiposity modified the association between glucose metabolic disorder and incident HF in community-dwelling older individuals.

Based on a community-dwelling black population cohort, Pandey et al. [36] suggested that greater risk of HF is associated with higher levels of visceral adipose tissue and BMI, but not with subcutaneous adipose tissue. In the present study, WHR exhibited a greater attenuating effect on the association between glucose metabolic disorder and incident HF than BMI and VFA. WHR was responsible for eliminating the significant associations between incident HF and well-controlled diabetes. Moreover, there was a linear association between incident HF and WHR and U-shaped associations between BMI and VFA. WHR has been suggested to have the strongest and most consistent association with mortality compared to BMI and fat mass index in UK adults [35]. A cross-sectional study including 3572 adults demonstrated that WHR is better than VFA to assess hyperglycemia risk among healthy Chinese population [55]. The strength of the association between VFA and glucose metabolic level was less than WHR, whereas, slightly stronger than body mass index. Our results is consistent with these findings. This indicates that WHR is the most appropriate adiposity measure for predicting the risk of HF compared to BMI and VFA.

Among the three adiposity measures in the present study, BMI was demonstrated to be stronger correlated with subcutaneous rather than visceral adipose tissue volumes [56, 57]. VFA only reflects the visceral adipose tissue volumes, whereas WHR represents both subcutaneous and visceral adipose accumulation simultaneously [58, 59].

Differences in metabolic activities, including insulin resistance, adipocytokine secretion, and lipid and glucose metabolism between subcutaneous and visceral adipose tissues, have been previously elucidated [60, 61]. Subcutaneous adipose tissue exerts a protective "metabolic sink" effect to reduce the metabolic toxicity caused by abnormal adipose accumulation [60, 61]. The function of visceral adipose tissue is the opposite to that of subcutaneous adipose tissue [29, 33, 62, 63]. Excess visceral adiposity accumulation has been demonstrated as the main drivers of the resistance to the inhibitory effect of insulin on lipolysis, low free fatty acid uptake, inflammatory cytokine secretion, immune cell infiltration, oxidative stress, as well as neurohormonal dysregulation, which directly to the cardiovascular system, causing endothelial dysfunction and cardiometabolic diseases [64–67]. The fundamental studies showed that preadipocytes from the visceral fat depots having lower adipogenic capacity, which relates to adipocyte hypertrophy, compared with those from the subcutaneous fat compartments [64, 68, 69].

Adipose tissue has been demonstrated to be a sophisticated and highly active endocrine organ, involving low ALR, insulin resistance, and hypertriglyceridemia [47]. Adiponectin and leptin are two major pleiotrophic adipokines that are produced and predominately secreted by adipose tissue [43, 70]. As is known, HOMA-IR and TyG are markers of IR used to assess diabetes and obesity is an important driving factor for the development of diabetes [64]. Adipose tissue is a determinants of systemic insulin sensitivity, which is associated with impaired glucose metabolism [67]. Excessive adiposity accumulation not only strengthens IR in diabetes, but itself also is a major driver for IR. A longitudinal study conducted by Burrows et al. [71] demonstrated that HOMA-IR was significant higher in subjects with persistent and recent-onset obesity than those never obese. Kailuan study [72] revealed that TyG acts as a mediator in the process of cardiovascular diseases caused by obesity. In the present study, in contrast to the negative association with ALR, BMI, WHR, VFA, and incident HF were positively associated with HOMA-IR and TyG. The mediation analyses results further suggested that the low ALR and high HOMA-IR and TyG were the mediators in the process of adiposity causing new-onset HF.

Studies have demonstrated that high HOMA-IR [73, 74] and TyG [75–77] are associated with the high occurrence rate of incident HF. Both adiposity-associated hypoadiponectinemia and hyperleptinemia exert detrimental effects on cardiovascular function and promote myocardial remodeling and left ventricular dysfunction [47, 70, 78]. Low ALR is regarded as a predictive and reliable biomarker for insulin resistance and cardiovascular disorders [47, 79]. Therefore, the present study data demonstrated that adiposity-associated metabolic activities act as a bridge between adiposity and the weakened association between glucose metabolic disorder and incident HF.

In this study, VFA was measured using BIA. The accuracy, reliability, and clinical utility of VFA measured using BIA have been validated by X-ray computed tomography (CT) and MRI [80, 81]. Patel KV and colleagues found that fat mass measured using BIA was closely related

to estimated measures of fat mass that was validated by dual-energy X-ray absorptiometry data [35]. VFA measured using BIA has been suggested as an useful, noninvasive, and inexpensive substitute for CT measurements in population investigations. We also compared the VFA measured using BIA and MRI in randomly selected 30 male and 30 female in this study. The data showed there was a good consistency between the VFAs determined using MRI and using BIA.

### Strengths and limitations

One of the present study strengths was that adiposity was identified as an important modifier in the process of HF caused by abnormal glucose metabolism. Second, Fine-Gray models accounting for competing risk of death and restricted cubic splines were utilized to limit the possible bias in the associations of glucose metabolic disorder and adiposity with incident HF. Third, the potential bridging effect of adiposity-associated metabolic activities on the association between adiposity and incident HF was investigated. It provided an insight into the adiposity modifying effect on the association between glucose metabolic disorder and cardiovascular disorders.

However, there were some limitations in the study that need to be addressed. First, the data did not fully elucidate the 'obesity paradox' in the incident HF during the follow-up period [82, 83]. Second, the study results may not fully elucidate the mechanism of the modifying effect of adiposity, although the intrinsic adipose tissue characteristics, including insulin resistance and secretions of adiponectin and leptin, were explored in the study. Third, the study participants were aged ≥ 60 years and were primarily recruited from the Shandong area. Whether these findings are applicable to other populations should be validated by further studies. Fourth, other comorbidity factors in older adults, such as angina, chronic lung disease, and depression, were not considered in the study. These comorbidities are closely associated with an increased risk of HF [3, 5]. We did not assess participants' cardiorespiratory fitness and muscle strength in the study. Evidence showed that cardiorespiratory fitness [84–87] and muscle strength [88] are closely related to and predict HF. Fifth, the clinical type of HF was not distinguished in the study. The modifying effect of adiposity on the association between glucose metabolic disorder and different clinical HF types may vary. In addition, VFA measured by BIA may still be underestimated compared with MRI and CT, although the accuracy and reliability of BIA in measuring VFA have been validated [89, 90], as well as the VFA measures using BIA were corrected by MRI in 60 participants in this study.

## Conclusion

Adiposity eliminates the association between incident HF and glucose metabolic disorder in older individuals, and WHR may be the best indicator for evaluating adiposity. Adiposity-associated metabolic activities may serve as an important mediator for adiposity to eliminate the association between glucose metabolic disorder and HF risk. However, further studies involving multiethnic groups, younger individuals, psychological distress groups, and clinical HF subtypes are needed in the future.

### Abbreviations

| | |
|---|---|
| HF | Heart failure |
| BMI | Body mass index |
| WC | Waist circumference |
| WHR | Waist-to-hip ratio |
| FPG | Fasting plasma glucose |
| HbA1c | Hemoglobin A1c |
| VFA | Visceral fat area |
| TG | Triglyceride |
| HOMA-IR | Homeostatic model assessment of insulin resistance |
| ALR | Adiponectin-to-leptin ratio |
| TyG | Triglyceride-glucose index |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| eGFR | Estimated glomerular filtration rate |
| SD | Standard deviation |
| IQR | Interquartile range |
| PARp | Population attributable risk percentage |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-024-02418-5.

Supplementary Material 1

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### Author contributions

Z.L., J.W., and W.L. were responsible for the study design and statistical support, and were primarily responsible for the final content. L.H., X.W., and P.L. were involved in drafting the manuscript, preparing and analyzing the data, and the visualization of the results. H.Z., Y.Y., and Z.L. thoroughly repeated and validated the statistical analysis. All authors made substantial contributions to manuscript revisions, and carefully reviewed and approved the final version.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Competing interests

The authors declare no competing interests.

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