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ORIGINAL RESEARCH ARTICLE

Combined associations of obesity and metabolic health with subclinical left ventricular dysfunctions: Danyang study

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Abstract

Aims The association of strictly defined metabolic healthy obese (MHO) with subclinical cardiac function was unclear. Our study aims to examine the role of MHO in subclinical cardiac dysfunction in a Chinese population.

Methods and results The study subjects were recruited from Danyang from 2017 to 2019. Obesity was defined by body mass index (BMI) categories (normal weight, overweight and obesity). Metabolic health was strictly defined as having neither any of the guidelines recommended metabolic syndrome components nor insulin resistance. Thus, subjects were grouped by BMI categories and metabolic health status as six groups. Preclinical systolic (global longitudinal strain [GLS]) and diastolic function were assessed by 2D speckle tracking, and transmitral and tissue Doppler imaging, respectively. The 2757 participants (mean age ± standard deviation, 52.7 ± 11.7 years) included 1613 (58.5%) women, 999 (36.2%) obese, 2080 (75.4%) metabolically unhealthy and 93 (3.4%) MHO participants. After adjustment for covariates, the trend was similar for left ventricular (LV) ejection fraction ($P_{trend} \geq 0.07$) but significantly worse for GLS, e′ and E/e′ ($P_{trend} \leq 0.02$) across the six groups or passing from normal weight to obese individuals irrespective of metabolic status. MHO participants had lower GLS (20.4 vs. 21.4%) and e′ (9.6 vs. 10.6 cm/s) compared with controls ($P < 0.0001$) but had similar GLS ($P = 0.47$) compared with metabolically unhealthy obese (MUO). Regardless of obesity status, metabolically unhealthy participants had worse diastolic function compared with their metabolically healthy counterparts ($P \leq 0.0004$). Compared with controls, MHO individuals were at higher risk of subclinical LV systolic dysfunction (OR = 3.44, 95% CI = 1.25–9.49, $P = 0.02$). These results were robust to sensitivity analysis.

Conclusions MHO was substantially associated with worse subclinical systolic function although early diastolic dysfunction seemed to be more accentuated in MUO.

Keywords Subclinical myocardial abnormalities; Obesity; Insulin resistance; Metabolic status

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Introduction

Obesity has become a major public health problem globally because of its growing epidemic trend.[1] Although amounting evidence demonstrates that obesity and the associated metabolic abnormalities such as insulin resistance (IR), hypertension, dyslipidaemia and dysglycaemia contributed to the development of cardiovascular disease, including increased risk of heart failure (HF),[2–4] some people with obesity are protected from many of the adverse cardiometabolic effects and are considered 'metabolically healthy obese' (MHO).[5] The reported prevalence of MHO, ranging from 6%[6] to 60%[7] of adults with obesity, depends on the definition of metabolic health.

Recent studies have shown that, compared with metabolically healthy normal weight (MHNW) individuals, MHO

individuals were associated with adverse alterations in subclinical systolic and diastolic function,[8,9] evaluated by the global longitudinal strain (GLS) and early diastolic velocities (e′) with advanced echocardiographic imaging techniques, which may precede the future development of HF. Notably, left ventricular (LV) GLS by speckle-tracking echocardiography can detect subtle systolic abnormality before reduction in left ventricular ejection fraction (LVEF) and predict development of HF as well as cardiovascular morbidity and mortality in asymptomatic individuals.[10–12] However, previous studies defining metabolic health solely relied on metabolic syndrome components,[8,9] not IR, and the latter is better suited for the definition of metabolic health because its pathophysiology seems to be largely attributable to IR.[13] Therefore, numerous MHO individuals reported in previous studies are not truly metabolically healthy, but simply have fewer metabolic abnormalities than those with metabolically unhealthy obesity (MUO). Additionally, potential important confounders such as physical activity and smoking have not been controlled in previous studies. Whether MHO is associated with excess risk of subclinical cardiac dysfunction still needs to be demonstrated.

To address this, the present study, therefore, is aimed to examine the combined associations of obesity and metabolic health with subclinical systolic and diastolic function in a larger sample of Chinese population.

Methods

Study population

This cross-sectional analysis was based on the data of an ongoing, longitudinal and multistage cohort study on comprehensive cardiovascular risk factors in Danyang, China.[14] The study subjects were recruited from Danyang County, a plain area approximately 70 km east of Nanjing. We invited all residents of 18 years or older to take part in the study. The Danyang Study was undertaken in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Jiangsu Province Hospital of Chinese Medicine. All patients gave informed written consent.

A total of 3032 subjects (participation rate 70.7%) were enrolled in the period from 2017 to 2019. We excluded 275 subjects from this analysis because of missing information (n = 105) or extreme values of echocardiographic measurements (n = 3) or poor quality of images (n = 47) or LVEF $<$ 50% (n = 7) or body mass index (BMI) $<$ 18.5 kg/m^2 (n = 93) or if there was not adequate blood sample for insulin measurement (n = 20). Thus, the total number of subjects analysed was 2757.

Field work

One experienced physician measured each patient's blood pressure (BP) using a validated Omron 7130 oscillometric BP monitor (Omron, Kyoto, Japan), anthropometrics, and collected a standardized questionnaire. Venous blood samples were drawn after overnight fasting for biochemical measurements. For further details on BP, anthropometric and biochemical measurements and the definitions of hypertension, physical activity, coronary heart disease (CHD), diabetes mellitus and dyslipidaemia, please see the Supporting Information.

Echocardiographic measurements

Conventional and advanced echocardiographic measures were performed with the Philips CX50 device (Phillips, Bothell, WA, USA), as recommended by the American Society of Echocardiography (ASE).[15] Speckle-tracking analysis was performed offline using dedicated software (QLAB Software version 9 Cardiac Motion/Mechanics Quantification, Philips). Echocardiographic measurements included M-mode, pulse wave Doppler and tissue Doppler measurements. For the details on the methods of echocardiographic measurements and the definitions of left ventricular hypertrophy (LVH), subclinical LV systolic dysfunction and LV diastolic dysfunction, please see the Supporting Information.

Definition of body size metabolic health phenotypes

Obesity was defined according to the World Health Organization (WHO) Asia-Pacific definitions of obesity[16] as BMI $\geq$ 25 kg/m^2, overweight as 23 $\leq$ BMI $<$ 25 kg/m^2 and normal weight as BMI $<$ 23 kg/m^2. Metabolic status was defined according to both the International Diabetes Federation/National Heart, Lung, and Blood Institute/American Heart Association/World Heart Federation/International Atherosclerosis Society/International Association for the Study of Obesity guidelines as outlined in the harmonized Joint Scientific Statement criteria for Metabolic Syndrome (MetS)[17] and homoeostasis model assessment of insulin resistance (HOMA-IR) criteria.[18] MHO was defined as obese individuals having none of the MetS components and without IR.[19] For the details on the definitions of MetS and IR, please see the Supporting Information.

Thus, subjects were grouped by BMI categories and metabolic health status as metabolically healthy normal weight (MHNW, n = 416), metabolically healthy overweight (MHOW, n = 168), metabolically healthy obese (MHO, n = 93), metabolically unhealthy normal weight (MUNW, n = 603),

metabolically unhealthy overweight (MUOW, n = 571) or metabolically unhealthy obese (MUO, n = 906).

Statistical methods

For database management and statistical analysis, we used SAS software (Version 9.4, SAS institute, Cary, NC, USA). Data are listed as mean ± standard deviation for continuous variables and as a number with percentage for discrete variables, respectively.

Differences between groups for baseline characteristics and echocardiographic parameters were compared using the one-way ANOVA. Pairwise comparisons were evaluated using a two-sample t-test for continuous variables and a χ^2 test for discrete variables, with Bonferroni correction for multiple testing. For LV function parameters, LVEF, GLS, e′ and the ratio of early diastolic peak flow (E) to e′ (E/e′), we further compared these parameters among the groups using analysis of covariance (ANCOVA) and Bonferroni post hoc analysis, while controlling for the potential confounders. We additionally examined the association between each parameter and metabolically defined body size phenotypes using crude and multivariable-adjusted linear mixed effects models to test for trends in echocardiographic parameters across six groups (in the order of MHNW, MHOW, MHO, MUNW, MUOW and MUO) and across obesity groups (in the order of normal weight, overweight and obese) stratified by metabolic healthy status, respectively. Finally, we performed multiple logistic regression to examine the associations of subclinical LV systolic dysfunction across the groups of metabolically defined body size phenotypes.

Sensitivity analysis was performed in participants (1) excluding overt heart disease (n = 53), such as CHD (n = 41), or valvular dysfunction more than moderate degree (n = 5), or hypertrophic cardiomyopathy (n = 3), or significant arrhythmia (n = 4) and (2) separately for men and women to investigate potential differences by sex. (3) For comparability with other studies, we also performed sensitivity analysis with different definitions of metabolic health. Metabolic health was defined as (a) having ≤2 of the above-mentioned five metabolic syndrome components[17]; or (b) having ≤1 abnormalities excluding waist circumference[20]; or (c) presence of IR.[21] For all tests, a two-sided value of $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study participants

Of the 2757 participants with anthropometric, biochemical and echocardiographic measurements, 1613 (58.5%) were women, and the mean age, BMI and waist circumference were 52.7 ± 11.7 years, 24.2 ± 3.1 kg/m^2 and 84.2 ± 8.5 cm, respectively. 999 (36.2%) participants were obese, 929 (33.7%) had MetS, 690 (25.0%) had IR, and 93 (3.4%) were defined as MHO with 9.3% of obese participants presenting metabolically healthy status. *Table 1* shows the comparisons in the characteristics between the six groups. For details on the post hoc analysis between groups, please see *Table S1*. MHO participants were younger, had lower BMI and heart rate and higher eGFR and had higher proportion of highest educational level compared with their MUO counterparts (all $P \leq 0.02$, *Table S2*). The MHO had worse metabolic parameters (higher BP, HOMA-IR, triglycerides, and lower HDL cholesterol), and were more likely to be male gender, and current smokers than MHNW participants (all $P \leq 0.02$, *Table S2*).

Association between metabolically defined body size phenotypes and LV function

Table 2 shows the comparisons in the echocardiographic measurements between the six groups. MHO participants had higher GLS and e′, and lower E/e′ ratio (all $P \leq 0.001$) but similar LVEF and proportions of subclinical LV systolic dysfunction ($P \geq 0.053$, *Table 2*) compared with their MUO counterparts. The MHO had worse echocardiographic parameters (lower GLS and e′), and had higher proportions of subclinical LV systolic dysfunction (all $P \leq 0.0002$) but similar E/e′ ratio (P = 0.23, *Table 2*) than MHNW participants.

In unadjusted analysis, preclinical systolic (decreased GLS), systolic (decreased LVEF) and diastolic (lower e′ and higher E/e′ ratio) function were also worse across the six groups (all $P_{trend} \leq 0.002$, *Figure 1*). Additionally, the worse trends of GLS and e′ were observed passing from normal weight to obese individuals irrespective of their metabolic status (all $P_{trend} < 0.0001$, *Figure 1B,C*), whereas regarding LVEF and E/e′ ratio the worse trend was only significant passing from normal weight to obese individuals in metabolically unhealthy subgroup (all $P_{trend} < 0.0001$, *Figure 1A,D*). For details on comparisons between metabolic unhealthy and their healthy counterparts irrespective of their obesity status, or between obese and normal weight individuals irrespective of their metabolic status, please see *Figure 1*.

After adjustment for age, sex, heart rate, current smoking and alcohol drinking, education, physical activity, γ-glutamyltransferase, estimated glomerular filtration rate, LVMI, LVEF (except for measure of LVEF) and e′ velocity as a marker of diastolic dysfunction (except for measures of diastolic function) as confounding factors, the worse trends of GLS, e′ and E/e′ ratio were observed across the six groups or passing from normal weight to obese individuals irrespective of their metabolic status (all $P_{trend} \leq 0.02$, *Figure 2B–D*). However, the trend was similar for LVEF ($P_{trend} \geq 0.07$, *Figure 2A*). Obese participants presented lowest values of GLS and e′

Table 1 Characteristics of the study subjects across metabolically defined body size phenotypes

Characteristics	Total (n = 2757)	MHNW (n = 416)	MHOW (n = 168)	MHO (n = 93)
Age, years	52.7 ± 11.7	47.6 ± 11.5	49.3 ± 10.3	47.6 ± 10.6
Male, *n* (%)	1,144 (41.5)	114 (27.4)	54 (32.1)	48 (51.6)
Body mass index, kg/m^2	24.2 ± 3.1	20.9 ± 1.2	24.0 ± 0.6	26.6 ± 1.4
Waist circumference, cm	84.2 ± 8.5	75.3 ± 5.4	82.3 ± 4.5	88.8 ± 5.5
Systolic blood pressure, mmHg	126.8 ± 18.6	109.1 ± 9.3	111.3 ± 9.1	114.5 ± 8.7
Diastolic blood pressure, mmHg	81.6 ± 10.5	71.9 ± 6.9	74.1 ± 6.0	75.5 ± 6.2
Heart rate, beats per minute	73.1 ± 10.2	72.5 ± 10.2	71.2 ± 9.2	70.9 ± 10.4
Current smokers, *n* (%)	627 (22.7)	70 (16.8)	21 (12.5)	25 (26.9)
Alcohol drinkers, *n* (%)	529 (19.2)	39 (9.4)	29 (17.3)	15 (16.1)
Hypertension, *n* (%)	1,098 (398)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus, *n* (%)	244 (8.9)	0 (0.0)	0 (0.0)	0 (0.0)
Dyslipidaemia, *n* (%)	851 (30.9)	34 (8.2)	13 (7.7)	8 (8.6)
Coronary heart disease, *n* (%)	41 (1.5)	1 (0.2)	1 (0.6)	1 (1.1)
Antihypertensive treatment, *n* (%)	604 (21.9)	0 (0.0)	0 (0.0)	0 (0.0)
Antihyperglycemic treatment, *n* (%)	169 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)
Lipid-lowering therapy, *n* (%)	38 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Physical activity, *n* (%)				
Inactive	584 (21.2)	75 (18.0)	27 (16.1)	13 (14.0)
Moderately inactive	1,616 (58.6)	251 (60.4)	108 (64.3)	59 (63.4)
Moderately active	508 (18.4)	77 (18.5)	31 (18.4)	19 (20.4)
Active	49 (1.8)	13 (3.1)	2 (1.2)	2 (2.2)
Education, *n* (%)				
No schooling/primary	1,442 (52.3)	191 (45.9)	78 (46.4)	41 (44.1)
Secondary	1,075 (39.0)	179 (43.0)	71 (42.3)	37 (39.8)
Vocational/university	240 (8.7)	46 (11.1)	19 (11.3)	15 (16.1)
Fasting plasma glucose, mmol/L	5.34 ± 1.23	4.80 ± 0.40	4.88 ± 0.39	4.85 ± 0.35
HOMA-IR	1.63 (1.10–2.44)	1.07 (0.75–1.39)	1.35 (0.96–1.70)	1.32 (1.01–1.82)
Total cholesterol, mmol/L	4.90 ± 0.97	4.68 ± 0.88	4.77 ± 0.80	4.83 ± 0.84
HDL cholesterol, mmol/L	1.47 ± 0.32	1.69 ± 0.30	1.60 ± 0.27	1.52 ± 0.29
Triglycerides, mmol/L	1.43 (0.99–2.14)	0.97 (0.75–1.24)	1.10 (0.83–1.40)	1.17 (0.82–1.35)
γ-Glutamyltransferase, units/L	19.0 (13.0–30.0)	13.0 (10.0–18.0)	15.0 (11.0–21.5)	18.0 (13.0–27.0)
Serum creatinine, μmol/L	66.2 ± 14.0	62.8 ± 12.1	65.0 ± 12.6	68.9 ± 13.4
eGFR, ml/(min 1.73m^2)	98.7 ± 13.9	103.6 ± 13.0	101.2 ± 12.4	101.5 ± 10.8

Data are mean ± standard deviation, median with interquartile range in parenthesis, or number with percentage in parenthesis. MHNW indicates metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment of insulin resistance; and eGFR, estimated glomerular filtration rate. For definitions of hypertension, diabetes, dyslipidaemia and coronary heart disease, see Methods.

Table 1 (continued)

Characteristics	MUNW (n = 603)	MUOW (n = 571)	MUO (n = 906)	P_{anova}
Age, years	54.3 ± 11.1	54.8 ± 10.9	53.8 ± 12.0	<0.0001
Male, *n* (%)	207 (34.3)	259 (45.4)	462 (51.0)	<0.0001
Body mass index, kg/m^2	21.4 ± 1.2	24.1 ± 0.6	27.4 ± 2.3	<0.0001
Waist circumference, cm	77.9 ± 5.2	84.8 ± 4.6	92.0 ± 6.5	<0.0001
Systolic blood pressure, mmHg	129.5 ± 17.9	131.6 ± 17.0	134.3 ± 17.8	<0.0001
Diastolic blood pressure, mmHg	82.6 ± 10.1	84.3 ± 9.5	85.9 ± 9.9	<0.0001
Heart rate, beats per minute	74.4 ± 10.6	72.4 ± 9.8	73.6 ± 10.3	<0.0001
Current smokers, *n* (%)	114 (18.9)	147 (25.7)	250 (27.6)	<0.0001
Alcohol drinkers, *n* (%)	101 (16.8)	127 (22.2)	218 (24.1)	<0.0001
Hypertension, *n* (%)	267 (44.3)	293 (51.3)	538 (59.4)	<0.0001
Diabetes mellitus, *n* (%)	44 (7.3)	66 (11.6)	134 (14.8)	<0.0001
Dyslipidaemia, *n* (%)	181 (30.0)	221 (38.7)	394 (43.5)	<0.0001
Coronary heart disease, *n* (%)	7 (1.2)	12 (2.1)	19 (2.1)	0.09
Antihypertensive treatment, *n* (%)	137 (22.7)	149 (26.1)	318 (35.1)	<0.0001
Antihyperglycemic treatment, *n* (%)	34 (5.6)	46 (8.1)	89 (9.8)	<0.0001
Lipid-lowering therapy, *n* (%)	9 (1.5)	9 (1.6)	20 (2.2)	0.014
Physical activity, *n* (%)				0.20
Inactive	146 (24.2)	134 (23.5)	189 (20.9)	
Moderately inactive	336 (55.7)	320 (56.0)	542 (59.8)	
Moderately active	112 (18.6)	109 (19.1)	160 (17.7)	
Active	9 (1.5)	8 (1.4)	15 (1.6)	
Education, *n* (%)				0.004
No schooling/primary	318 (52.7)	304 (53.2)	510 (56.3)	
Secondary	241 (40.0)	218 (38.2)	329 (36.3)	
Vocational/university	44 (7.3)	49 (8.6)	67 (7.4)	
Fasting plasma glucose, mmol/L	5.30 ± 1.13	5.54 ± 1.59	5.64 ± 1.33	<0.0001
HOMA-IR	1.36 (0.96–1.95)	1.78 (1.20–2.55)	2.40 (1.68–3.45)	<0.0001
Total cholesterol, mmol/L	4.94 ± 0.96	5.02 ± 1.00	4.94 ± 1.02	<0.0001
HDL cholesterol, mmol/L	1.50 ± 0.32	1.42 ± 0.31	1.35 ± 0.29	<0.0001
Triglycerides, mmol/L	1.55 (1.05–2.13)	1.69 (1.15–2.42)	1.84 (1.24–2.74)	<0.0001
γ-Glutamyltransferase, units/L	16.0 (12.0–25.0)	20.0 (14.0–33.0)	24.0 (17.0–38.0)	<0.0001
Serum creatinine, μmol/L	65.0 ± 14.2	66.7 ± 13.0	68.4 ± 15.2	<0.0001
eGFR, ml/(min 1.73m^2)	97.7 ± 13.9	97.3 ± 13.5	97.3 ± 14.5	<0.0001

Data are mean ± standard deviation, median with interquartile range in parenthesis, or number with percentage in parenthesis. MHNW indicates metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment of insulin resistance; and eGFR, estimated glomerular filtration rate. For definitions of hypertension, diabetes, dyslipidaemia and coronary heart disease, see Methods.

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Table 2 Echocardiographic measurements of the study subjects across metabolically defined body size phenotypes

Echocardiographic measurements	Total (n = 2757)	MHNW (n = 416)	MHOW (n = 168)	MHO (n = 93)	MUNW (n = 603)	MUOW (n = 571)	MUO (n = 906)	P^a MHO vs. MUO	P^a MHO vs. MHNW
Left ventricular structure									
LVEDD, mm	45.9 ± 3.7	43.7 ± 3.2	45.5 ± 3.3	46.5 ± 3.4	44.6 ± 3.5	46.1 ± 3.3	47.5 ± 3.6	0.01	<0.0001
Relative wall thickness	0.39 ± 0.04	0.38 ± 0.04	0.38 ± 0.04	0.38 ± 0.04	0.39 ± 0.04	0.39 ± 0.04	0.39 ± 0.04	0.002	0.71
LV mass index, g/m^2	81.1 ± 14.9	72.1 ± 10.8	76.8 ± 11.1	77.7 ± 12.2	79.3 ± 13.8	83.6 ± 14.5	85.9 ± 15.9	<0.0001	0.0006
LV hypertrophy, n (%)	217 (7.9)	3 (0.7)	5 (3.0)	3 (3.2)	43 (7.1)	53 (9.3)	110 (12.1)	0.01	0.04
LV systolic function									
LV ejection fraction, %	66.9 ± 3.3	67.5 ± 3.2	66.8 ± 3.0	66.8 ± 2.9	67.2 ± 3.3	67.1 ± 3.2	66.5 ± 3.4	0.33	0.06
GLS, %	20.9 ± 2.1	22.1 ± 2.0	21.7 ± 1.9	20.6 ± 2.0	21.4 ± 1.9	20.7 ± 1.9	19.9 ± 2.0	0.001	<0.0001
Subclinical LVSD, n (%)	249 (9.0)	8 (1.9)	6 (3.6)	9 (9.7)	19 (3.2)	48 (8.4)	159 (17.6)	0.053	0.0002
LV diastolic function									
E peak, cm/s	74.8 ± 16.7	80.9 ± 15.9	78.8 ± 16.3	75.1 ± 14.8	75.5 ± 16.4	72.0 ± 16.4	72.4 ± 16.8	0.13	0.002
E/A ratio	1.06 ± 0.35	1.30 ± 0.37	1.19 ± 0.32	1.16 ± 0.35	1.05 ± 0.34	0.97 ± 0.31	0.96 ± 0.32	<0.0001	0.0002
e′, cm/s	9.4 ± 2.5	11.5 ± 2.4	10.5 ± 2.2	10.3 ± 2.4	9.6 ± 2.3	8.8 ± 2.2	8.4 ± 2.2	<0.0001	<0.0001
E/e′ ratio	8.3 ± 2.2	7.2 ± 1.5	7.7 ± 1.6	7.5 ± 1.6	8.1 ± 2.1	8.5 ± 2.2	9.0 ± 2.4	<0.0001	0.23

Data are mean ± standard deviation, or number with percentage in parenthesis. For definitions of left ventricular hypertrophy and subclinical left ventricular systolic dysfunction, see Methods.
MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese; LVEDD, left ventricular end diastolic dimension; LV, left ventricular; GLS, global longitudinal strain; LVSD, left ventricular systolic dysfunction.
[a]*P*-values were calculated using *F*-test.

irrespective of their metabolic status (all $P < 0.0001$, *Figure 2B,C*). Additionally, MHO participants had higher adjusted means of e′ (9.6 vs. 8.7 cm/s, $P < 0.0001$, *Figure 2C*) and lower E/e′ ratio (7.9 vs. 9.0, $P < 0.0001$, *Figure 2D*) but similar GLS (20.4 vs. 20.3%, $P = 0.47$, *Figure 2B*) compared with their MUO counterparts. Finally, irrespective of their obesity status, metabolically unhealthy participants had worse diastolic function (lower e′ and higher E/e′ ratio) compared with their metabolically healthy counterparts (all $P \leq 0.0004$, *Figure 2C,D*).

Association between metabolically defined body size phenotypes and subclinical LV systolic dysfunction

The prevalence of subclinical LV systolic dysfunction and LV diastolic dysfunction were 9.0% (n = 249) and 3.2% (n = 88), respectively. Because of limited statistical power, we excluded subclinical LV diastolic dysfunction from further analysis. Compared with the MHNW participants (reference group), all other metabolically defined body size phenotypes were associated with higher risk of subclinical LV systolic dysfunction ($P \leq 0.0007$) except that of MHOW and MUNW individuals (OR = 1.89, 95% CI = 0.65–5.53, $P = 0.25$, and OR = 1.66, 95% CI = 0.72–3.83, $P = 0.24$, respectively) in a crude model (*Table 3*). After adjustment for the aforementioned covariates, compared with the MHNW, only obese individuals (MHO or MUO groups) were still significantly associated with an increased odds ratio of subclinical LV systolic dysfunction ($P \leq 0.02$, *Figure 3*). MHO individuals were at higher risk of subclinical LV systolic dysfunction (OR = 3.44, 95% CI = 1.25–9.49, $P = 0.02$, *Figure 3*), and this was even similar to the risk in MUO group. MUNW, compared with MHNW participants, had similar risk of subclinical LV systolic dysfunction (OR = 0.65, 95% CI = 0.27–1.56, $P = 0.34$, *Figure 3*).

Sensitivity analysis

Sensitivity analysis show similar results after excluding overt heart disease (see *Table S3* and *Figure S1*). There was no essential difference between men and women although regarding GLS somewhat stronger trend observed passing from normal weight to obese individuals in metabolically healthy subgroup of women (*Figures S2* and *S3*).

Results were qualitatively similar to the main analysis although somewhat stronger when a traditional definition of metabolic health was used (i.e. having ≤2 of the five metabolic syndrome components or ≤1 abnormalities excluding waist circumference) (*Tables S4* and *S5* and *Figures S4* and *S5*). Finally, when metabolic health was defined as

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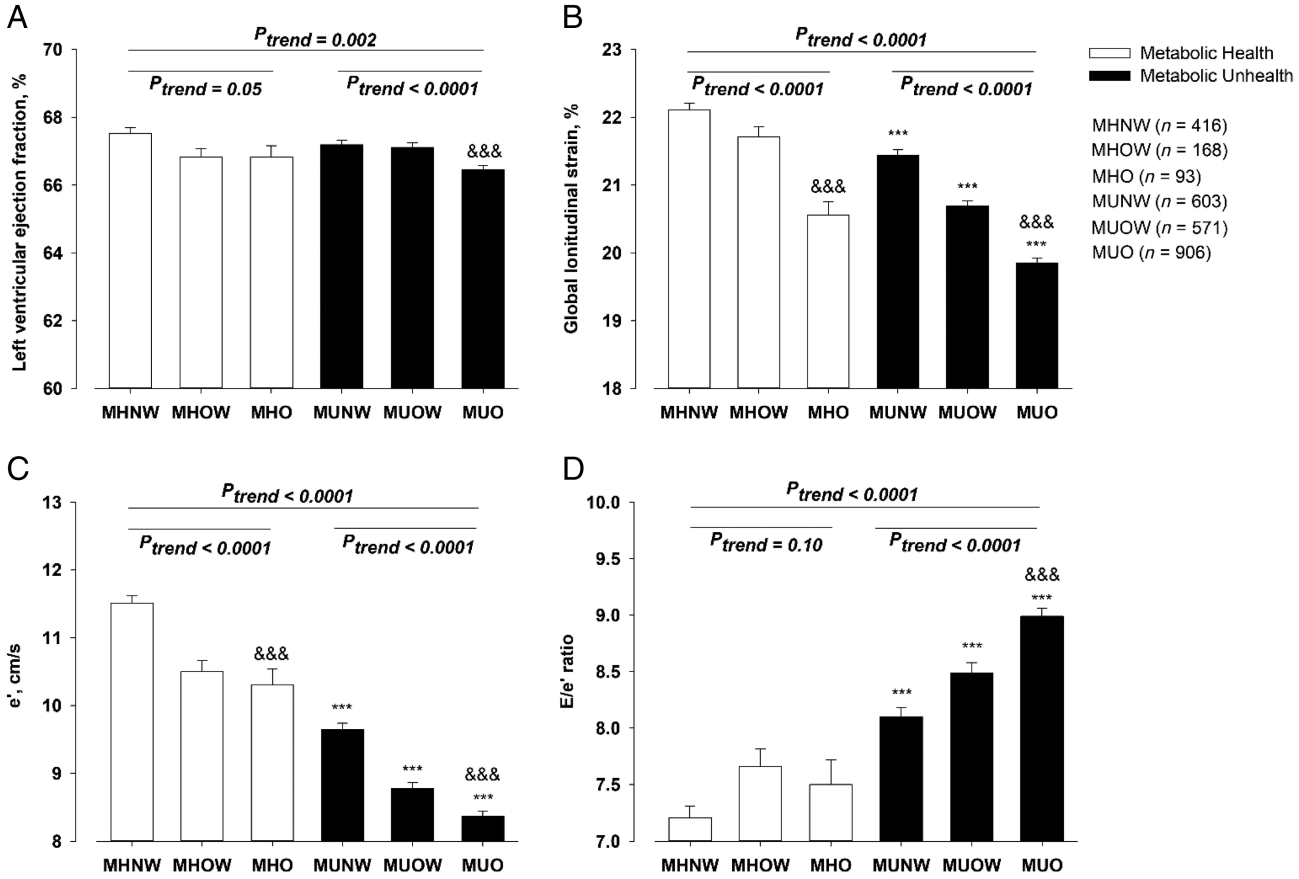
Figure 1 Comparisons of crude mean values of systolic and diastolic function measures among study groups. (A) Left ventricular ejection fraction. (B) Global longitudinal strain. (C) e′. (D) E/e′ ratio. White and black bars indicate mean values of echocardiography parameters in metabolically healthy and unhealthy individuals, respectively. The *P*-value for trend across six groups (in the order of MHNW, MHOW, MHO, MUNW, MUOW and MUO) and across obesity groups (in the order of normal weight, overweight and obese) stratified by metabolically healthy status are given, respectively. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; metabolically unhealthy vs. healthy counterparts. $^{\&}P < 0.05$; $^{\&\&}P < 0.01$; $^{\&\&\&}P < 0.001$; obese vs. normal weight individuals. MHNW, metabolically healthy normal weight; MHOW, metabolically overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically overweight; MUO, metabolically unhealthy obese. Metabolic health was defined as individuals having none of five metabolic syndrome components and without insulin resistance.



absence of IR, similar results were obtained except that of significant difference with GLS between MHO and MUO groups (20.4 vs. 20.1%, *P* = 0.004) (*Table S6* and *Figure S6*).

Discussion

The key findings of our current study can be summarized as follows. First, regardless of the definitions of metabolic health and its status, obesity per se was significantly associated with decreased GLS and accordingly associated with a higher risk of subclinical LV systolic dysfunction in subjects even with preserved LVEF. Second, diastolic dysfunction, expressed as the lower e′ and higher E/e′ ratio, appeared to be more accentuated in poor metabolic health status than obesity. Finally, the prevalence of MHO is about 9.3% of obese individuals. MHO had lower GLS and decreased e′ compared with controls and even similar GLS compared with MUO participants.

To the best of our knowledge, our study, which is the first and largest to address the association of strictly defined MHO (i.e. obese individuals having neither any of MetS components nor IR) with subclinical cardiac dysfunction, indicates that obesity and metabolic dysfunction are important contributors to adverse alterations in preclinical cardiac function even in the absence of overt heart disease. Most notably, MHO is not a benign status, and also associates with subclinical cardiac dysfunction. As these subtle cardiac mechanics impairments are not only sensitive markers of early myocardial abnormalities but also predictors of clinical and prognostic relevance in patients with HF,[22,23] our finding therefore could have important clinical implications for HF prevention by controlling obesity and tackling its related metabolic risk.

Figure 2 Comparisons of adjusted mean values of systolic and diastolic function measures among study groups after multivariable adjustment. (A) Left ventricular ejection fraction. (B) Global longitudinal strain. (C) e′. (D) E/e′ ratio. White and black bars indicate adjusted mean values of echocardiography parameters in metabolically healthy and unhealthy individuals, respectively. The analysis was adjusted for age, sex, heart rate, current smoking and alcohol drinking, education, physical activity, γ-glutamyltransferase, estimated glomerular filtration rate, LVMI, LVEF (except for measure of LVEF) and e′ as a marker of diastolic dysfunction (except for measures of diastolic function). The *P*-value for trend across six groups (in the order of MHNW, MHOW, MHO, MUNW, MUOW and MUO) and across obesity groups (in the order of normal weight, overweight and obese) stratified by metabolically healthy status are given, respectively. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; metabolically unhealthy vs. healthy counterparts. $^{\&}P < 0.05$; $^{\&\&}P < 0.01$; $^{\&\&\&}P < 0.001$; obese vs. normal weight individuals. MHNW, metabolically healthy normal weight; MHOW, metabolically overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically overweight; MUO, metabolically unhealthy obese. Definition of metabolic health is the same as *Figure1*.

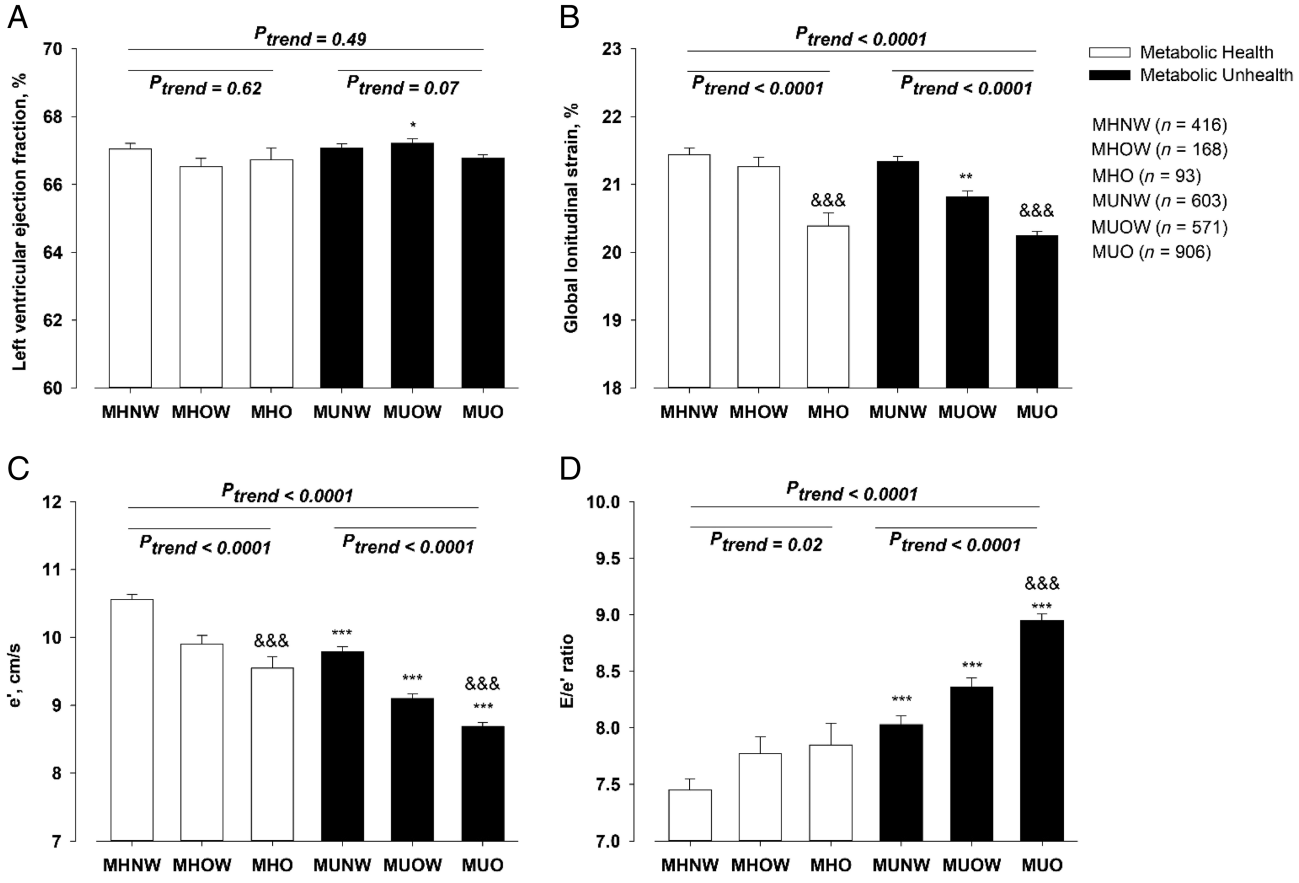


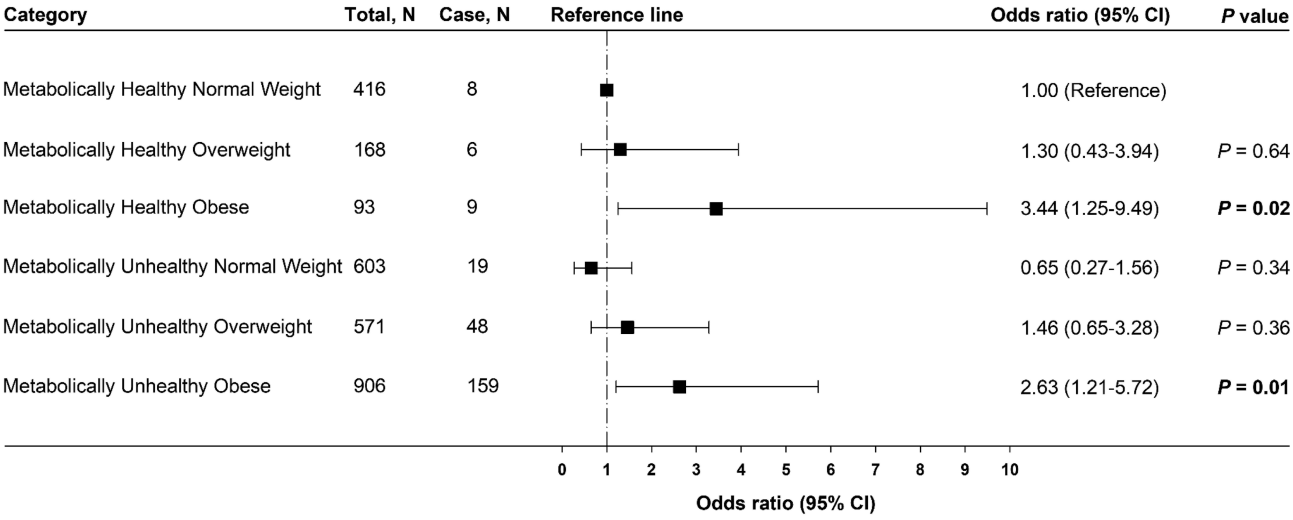
Table 3 Associations between metabolically defined body size phenotypes and subclinical left ventricular systolic dysfunction

	Subclinical left ventricular systolic dysfunction			
Groups	Total, *N*	Case, *N*	Odds ratio (95% CI)	*P*
MHNW	416	8	1 (Reference)	
MHOW	168	6	1.89 (0.65–5.53)	0.25
MHO	93	9	5.46 (2.05–14.57)	0.0007
MUNW	603	19	1.66 (0.72–3.83)	0.24
MUOW	571	48	4.68 (2.19–10.00)	<0.0001
MUO	906	159	10.85 (5.28–22.3)	<0.0001

Values are odds ratio with 95% CI in parenthesis.
MHNW, metabolically healthy normal weight; MHOW, metabolically healthy overweight; MHO, metabolically healthy obese; MUNW, metabolically unhealthy normal weight; MUOW, metabolically unhealthy overweight; MUO, metabolically unhealthy obese; CI, confidence intervals.

Until now, there have been two studies that investigated the associations of obesity and metabolic health with preclinical LV systolic and diastolic function. The first small study (*n* = 190) investigated preclinical differences in systolic and diastolic function in 124 obese individuals with MetS, 37 obese individuals without MetS and 29 non-obese controls.[8] Similar to our study, Wang et al.[8] demonstrated that obesity was associated with lower GLS regardless of the presence or absence of MetS. However, they did not observe significant differences in preclinical diastolic function as reflected by e′ and E/e′ ratio between obese without MetS and control groups. The second relatively large study (*n* = 789) investigated the subclinical alterations in LV function according to obesity and metabolic health status in a Korean population.[9]

Figure 3 Multivariate odds ratios of subclinical left ventricular systolic dysfunction in study groups. The metabolically healthy normal weight participants were considered as a reference group. The analysis was adjusted for age, sex, heart rate, current smoking and alcohol drinking, education, physical activity, γ-glutamyltransferase, estimated glomerular filtration rate, LVMI, LVEF and e′ velocity. Definition of metabolic health is the same as *Figure1*.



Similarly, they reported that obesity and poor metabolic health status were associated with subclinical decrement in GLS and E/e′ ratio.[9] Nevertheless, in their study, MHO participants had similar GLS compared with controls but had higher GLS compared with MUO individuals. The discrepancies between the studies of ours and theirs may be due to several important factors including sample size and potential confounders that needed to be controlled. First, our study was population-based with 2757 subjects, which have a strong power to find context-dependent associations. Second, previous studies relating obesity and metabolic health to cardiac function did not fully adjust for potentially important covariates such as physical activity and smoking, which may account for the differences between metabolically healthy and unhealthy participants. In our present study, we found that the significant associations of preclinical cardiac function with obesity and metabolic health remained significant after full adjustment for physical activity and smoking.

However, up to now, no previous study had used rigorous definition of metabolic health (having a normal HOMA-IR and no MetS abnormalities) to explore the associations of metabolic health obesity with subclinical systolic and diastolic measures. The WHO recommended that the components that used to define metabolic dysfunction should be included IR[24] because IR plays a central role in the pathophysiology of metabolic dysfunction.[13] Therefore, our study further augments previous research[8,9] by showing that obesity is substantially associated with subclinical systolic function even in the optimal metabolic health, which strongly challenges the contention that MHO is a benign condition and adds to the evidence base that MHO convey a high risk for future development of HF.

In our study, the prevalence of MHO could be seen in 9.3% of obese individuals. Previous studies showed that the prevalence of MHO ranging from 6% to 60% of adults with obesity.[25] The difference in prevalence might be owing to the criteria used to define metabolic health. Similar to our study, one study used the same criteria to define metabolic health and reported the prevalence of MHO was 7.0%.[26]

Strengths and limitations

We used a more rigorous definition of metabolic health (having a normal HOMA-IR and no MetS abnormalities) in a relatively large sample of Chinese subjects, which made it possible to ascertain whether strictly defined MHO was associated with subclinical cardiac dysfunction or not. The information on medical history and blood biochemical measurement enables us to perform sensitivity analysis of various commonly used definitions of metabolic health, and the substantial information on covariates (physical activity, education, smoke and alcohol) allowed adjustment for a collection of potential confounders, albeit we cannot exclude the possibility of uncollected variables. Nevertheless, the design of the study could as well allow potential confounders to be part of LV systolic or diastolic dysfunction. Notwithstanding these strengths, our study has limitations. First, the cross-sectional design of our study does not allow any conclusion on the prognostic value of the observed subclinical LV

systolic dysfunction. Future prospective study is warranted to explore the cause inference. Another limitation when comparing our results with previous studies is the lack of consistency in the definition of MHO.[8,9] However, to overcome this limitation, we applied the rigorous definition to represent truly metabolic health and further compared several alternative definitions in sensitivity analysis, all of which produced similar results. Third, left atrial volume index was not included in LV diastolic function evaluation. Finally, IR was based on HOMA-IA model but not hyperinsulinaemic–euglycaemic clamp. The latter is considered as the golden standard for assessing IR. Nonetheless, HOMA-IR has been reported previously to be strongly correlated with hyperinsulinaemic–euglycaemic clamp.[27]

Conclusions

In conclusion, our large-scale population study demonstrates that obesity was associated with worse subclinical systolic function, even in the presence of metabolic health. The presence of metabolic abnormalities was associated with decreased preclinical diastolic function, regardless of obesity status. Of note, MHO individuals also present lower GLS and decreased e′. Our results highlight the importance of obesity and metabolic health in subclinical systolic dysfunction prevention and support the notion that MHO may also have detrimental cardiovascular effects. Controlling obesity by adopting a healthy lifestyle or medical therapy is therefore warranted to prevent subclinical systolic dysfunction and subsequent development of HF, regardless of metabolic health.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of the study subjects across metabolically defined body size phenotypes (post-hoc analysis).
Table S2. Characteristics of the study subjects across metabolically defined body size phenotypes.
Table S3. Sensitivity analysis: associations between metabolically defined body size phenotypes and subclinical left ventricular systolic dysfunction after exclusion of overt heart disease.
Table S4. Sensitivity analysis: associations between metabolically defined body size phenotypes and subclinical left ventricular systolic dysfunction where "metabolically healthy" is defined as having ≤ 2 of the five metabolic syndrome components.
Table S5. Sensitivity analysis: associations between metabolically defined body size phenotypes and subclinical left ventricular systolic dysfunction where "metabolically healthy" is defined as having ≤ 1 abnormalities excluding waist circumference.
Table S6. Sensitivity analysis: associations between metabolically defined body size phenotypes and subclinical left ventricular systolic dysfunction where "metabolically healthy" is defined as without insulin resistance.
Figure S1. Comparisons of adjusted mean values of systolic and diastolic function measures among study groups after multivariable adjustment after exclusion of overt heart disease.
Figure S2. Comparisons of adjusted mean values of systolic and diastolic function measures among study groups after multivariable adjustment in men.
Figure S3. Comparisons of adjusted mean values of systolic and diastolic function measures among study groups after multivariable adjustment in women.
Figure S4. Comparisons of adjusted mean values of systolic and diastolic function measures among study groups after multivariable adjustment where "metabolically healthy" is defined as having ≤ 2 abnormalities excluding waist circumference.

Figure S5. Comparisons of adjusted mean values of systolic and diastolic function measures among study groups after multivariable adjustment where "metabolically healthy" is defined as having ≤ 1 abnormalities excluding waist circumference.

Figure S6. Comparisons of adjusted mean values of systolic and diastolic function measures among study groups after multivariable adjustment where "metabolically healthy" is defined as without insulin resistance.

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