ORIGINAL RESEARCH

Metabolic Risk Factors and Left Ventricular Diastolic Function in Middle-Aged Chinese Living in the Tibetan Plateau

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Background—Data regarding the metabolic risk factors clustering on the risk of left ventricular diastolic dysfunction (LVDD) are lacking among people living at high altitude and under hypoxic conditions. In this study, we explored the association between metabolic risk factor clustering and LVDD among the Tibetan population of China.

Methods and Results—We conducted a cross-sectional survey in a representative sample of 1963 Tibetans in 2014 to 2016. Grading LVDD was based on recommendations for the evaluation of LV diastolic function by echocardiography (2009). The prevalence of LVDD among 1963 participants (mean age: 51.51 years, 41.11% male) was 34.39%. Odds ratios (95% CI) of LVDD for the 1, 2, and 3 to 5 risk factors clustering were 1.45 (0.96–2.17), 2.68 (1.8–3.98), and 2.9 (1.9–4.43), respectively (*P* for trend <0.001). The association between metabolic risk factors clustering and LVDD was much more pronounced in the middle-aged group than in the elderly (*P* for interaction=0.0170). High altitude was one of the major independent risk factors for LVDD; however, habitation altitude had no significant effect on the association between metabolic risk factors and LVDD (*P* for interaction=0.1022). The multivariable dominance analysis indicated that abdominal obesity, hypertension, and elevated blood glucose were the significant contributors to LVDD.

Conclusions—There was a significant positive association between the metabolic risk factor clustering number and LVDD among a population living at high altitude, especially in middle-aged adults. However, habitation altitude itself has no significant effect on the association between metabolic risk factors and LVDD. **(*J Am Heart Assoc*. 2019;8:e010454. DOI: 10.1161/JAHA.118.010454.)**

Key Words: cluster • left ventricular diastolic dysfunction • metabolic • risk factor • Tibet

The metabolic syndrome is associated with the development of cardiovascular or other chronic disease, and also can increase the risk of mortality from cardiovascular disease and all-cause mortality,[1] which is characterized by a clustering of metabolic risk factors, including abdominal obesity, raised blood pressure and glucose concentration, and dyslipidemia.[2] Left ventricular (LV) diastolic dysfunction, an early sign of cardiac dysfunction, is a predictor of congestive heart failure, myocardial ischemia, and fatal cardiovascular events.[3–6] Even in asymptomatic patients, grade I (impaired relaxation pattern) diastolic dysfunction was associated with a 5-fold higher 3- to 5-year mortality in comparison with subjects with normal diastolic function.[7] Some evidences suggest that abdominal obesity,[8,9] hypertension,[10,11] and elevated blood glucose[12,13] are the independent risk factors for LV diastolic dysfunction. Furthermore, a few studies suggested that metabolic syndrome (3 metabolic risk factors or more) could lead to the development of diastolic dysfunction via mechanisms independent of LV mass.[14,15]

In the Chinese adult population, metabolic syndrome has become an important public health problem in the mainland,[16,17] especially in the Tibetan Plateau.[18–20] There are

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Clinical Perspective

What Is New?

- This study is the first to report the association between metabolic risk factor clustering and left ventricular diastolic dysfunction among people living at high altitude.

What Are the Clinical Implications?

- There was a significant positive association between the metabolic risk factor clustering number and the risk of left ventricular diastolic dysfunction, especially in middle-aged adults.
- High altitude is one of the major probable independent risk factors for left ventricular diastolic dysfunction besides metabolic risk factors.

more than 140 million people living at high altitude (>2400 m) and under hypoxic conditions in the world[21]; however, the previous studies[14,15] were only focused on a nonhighland population. The metabolic risk factors clustering on the risk of LV diastolic dysfunction (LVDD) have not been well documented among them. In this study, we explored the effects of the metabolic risk factors on LV diastolic function among adults who live in a high-altitude area of China, and investigated whether the association between metabolic risk factors and LVDD declined or increased with habitation altitude.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The cross-sectional study on prevalence of chronic cardiopulmonary disease in the Tibet area was conducted from 2014 to 2016 (Figure S1 shows the Tibet position on the map of China). A 4-stage stratified sampling method was used to select representative samples.[22] Six districts or counties were selected in both urban (2 districts) and rural (4 counties) areas of Tibet using the probability proportional to size method. Using the simple random sampling method, 2 streets or 2 townships were selected within each district or county; then, using the simple random sampling method, 3 communities or villages were chosen within each street and township, respectively. Finally, also using the simple random sampling method, a given number of participants from each of the sex/age strata from communities or villages were chosen using the lists compiled from the local government registers of households. To meet the sample size, 3504 participants aged 35 years or older were selected, and 2707 participants were recruited (response rate 77.25%). The exclusion criteria of this study included the following: history or findings of cardiovascular disease including significant valvular heart disease (ie, greater than mild valvular insufficiency or stenosis), and/or hypertrophic cardiomyopathy, and/or congenital heart disease. After exclusion of 744 participants with a prior history of significant heart disease (myocardial infarction, atrial fibrillation, chronic heart failure, valvular heart disease, etc) and/or major chronic disease (kidney disease, chronic obstructive pulmonary disease, rheumatic immune disease and tumor) and/or absence of echocardiography/blood routine measurement, 1963 participants were eligible for the final analysis. Written informed consent was obtained from each participant. The Ethics Committee of Fuwai Hospital (Beijing, China) approved the study.

Data Collection

The survey was carried out in the participant's residential sites using internationally standardized methods following a common protocol. A standardized questionnaire was developed by the coordinating center, Fuwai Hospital (Beijing, China). Data on demographics including education, occupation, and lifestyle were recorded by interview. Smoking status was classified into 3 categories: nonsmokers, former smokers, and current smokers (over the past 30 days). Alcohol consumption was classified into 2 categories: current drinkers and nondrinkers. Family history of cardiovascular disease was defined as at least 1 of the subjects' parents or siblings had a history of coronary heart disease or stroke. Blood pressure was measured with the Omron HBP-1300 Professional Portable Blood Pressure Monitor (Omron, Kyoto, Japan) 3 times on the right arm supported at heart level after the participant had been sitting at rest for 5 minutes, with 30 s between each measurement. The average of the 3 readings was used for analysis. Body weight was obtained using Omron body fat and weight measurement device (V-body HBF-371; Omron). Body mass index was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was measured (accurate to 0.1 cm) midway between the bottom edge of the last rib and iliac crest in the midaxillary plane using a cloth tape directly touching the participant's skin. The clinical evaluation of LV function was based on echocardiography in coronary artery disease, and the collection data of cardiac ultrasound examination included M-mode and 2-dimensional measurements, heart value structure, and Doppler flow parameters. All the experienced sonographers had to attend a series of standard training to

ensure accuracy of the diagnosis results. Laboratory analyses were performed by a central core laboratory (Beijing Adicon Clinical Laboratories, Inc, Beijing, China) using standardized techniques. All blood samples were obtained in the morning after an at least 8-hour overnight fast. The serum glucose was determined using an enzymatic method. The serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides were determined using enzymatic methods with an autoanalyzer.

The metabolic risk factors were defined according to the revised National Cholesterol Education Program ATP III criteria (2004) with modification on waist circumference cutoff to be more appropriate for an Asian population.[23] The metabolic risk factors were diagnosed with the following criteria: (1) Elevated blood pressure: ≥130/85 mm Hg or taking antihypertensive drugs; (2) Abdominal obesity: waist circumference ≥90 cm in men and ≥80 cm in women; (3) High triglycerides level ≥1.69 mmol/L (150 mg/dL); (4) Reduced high-density lipoprotein cholesterol level <1.03 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women; and (5) High blood glucose: fasting plasma glucose level ≥5.6 mmol/L (100 mg/dL) or taking hypoglycemic medications. For analysis, the study subjects were categorized into 4 groups according to the metabolic risk factors clustering number: Absent group (0 criteria), single abnormal component group (1 criterion), premetabolic syndrome group (2 criteria), and metabolic syndrome group (≥3 criteria).

Grading diastolic dysfunction was based on Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography (2009).[7] The grading scheme is mild or grade I (impaired relaxation pattern), moderate or grade II (pseudonormal LV filling, PNF), and severe (restrictive filling) or grade III. Assessment should take into consideration patients' ages and heart rates (mitral E, E/A ratio, and annular e′ decrease with increasing heart rate). (1) In patients with mild diastolic dysfunction, the mitral E/A ratio <0.8, DT >200 ms, isovolumic relaxation time ≥100 ms, predominant systolic flow is seen in pulmonary venous flow (S>D), annular e′ is <8 cm/s, and the E/e′ ratio is <8 (septal and lateral). (2) In patients with moderate diastolic dysfunction (grade II), the mitral E/A ratio is 0.8 to 1.5 (pseudonormal) and decreases by ≥50% during the Valsalva maneuver, the E/e′ (average) ratio is 9 to 12, and e′ is <8 cm/s. Other supporting data include an Ar velocity >30 cm/s and an S/D ratio <1. In some patients with moderate diastolic dysfunction, LV end-diastolic pressure is the only pressure that is increased (ie, mean left atrial [LA] pressure is normal) and is recognized by Ar-A duration ≥30 ms. Grade II diastolic dysfunction represents impaired myocardial relaxation with mild-to-moderate elevation of LV filling pressures. (3) With severe diastolic dysfunction (grade III), restrictive LV filling occurs with an E/A ratio ≥2, DT <160 ms, isovolumic relaxation time ≤60 ms, systolic filling fraction ≤40%, mitral A flow duration shorter than Ar duration, and average E/e′ ratio >13 (or septal E/e′ ≥15 and lateral E/e′ >12). In our study, individuals were free-living participants and the LV diastolic dysfunction of grade II or III prevalence was relatively low. Furthermore, even grade I dysfunction was associated with higher mortality in comparison with normal ones, so we split the participants into normal/abnormal LV diastolic function groups for analysis of which abnormal group was including LV diastolic dysfunction grade I–III.

Statistical Analysis

Characteristics of the study participants were described by metabolic risk factors clustering number, using percentages with the corresponding 95% CI for categorical variables and means (95% CI) for continuous variables, and group differences were assessed by χ^2 test or 1-way ANOVA, respectively. The linear trend between continuous variables and the number of metabolic syndrome components was evaluated by linear regression analysis. The trend between dichotomous variables' positive rate and the metabolic risk factors clustering number was based on the Cochran-Armitage trend test in χ^2 test. Ten years old was a common age group interval for scientific research, so the participants were divided into 4 groups by their age (35–44, 45–54, 55–64, ≥65 years old); by referring to the related literatures,[24,25] the altitude levels were divided into 3000 to 3500 m (most of Linzhi area), 3500 to 4000 m (most of Lhasa area), and ≥4000 m (most of Naqu area).

Odds ratios (95% CI) for the associations of metabolic risk factors with LV diastolic function (abnormal versus normal) in total or different subgroup of sex, age, and habitation altitude were calculated using multivariate logistic regression analysis. The interaction term of habitation altitude with metabolic risk factor clustering number grades was added to estimate the effect on LVDD. In all statistical models, we adjusted for the following: (1) demographics: age, sex, areas, ethnicity, education, and altitude of habitation; (2) cardiac risk factors: smoking, alcohol drinking, and family history of cardiovascular disease; (3) medical therapy: antihypertensive medication, lipid-lowering medicine, and hypoglycemic drug; (4) the major parameters of LV structure: relative wall thickness and LV mass index. All the covariates were chosen for their established or presumed influence on the LV diastolic function.

Dominance analysis was used for the relative importance of 5 components in logistic regression model to evaluate the relative importance of the independent variable by calculating and comparing the average incremental contribution ΔR^2 of a variable relative to all possible subset models (all different combinations containing the given variable), and the ΔR^2 was calculated as the difference between the 2 pseudo R^2s of logistic regression when the predictor is added to the

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Table 1. Characteristics of Participants

	Total (n=1963)	Number of Metabolic Risk Factors				*P* Value	*P* for Trend
		0 (n=259)	1 (n=553)	2 (n=614)	3 to 5 (n=537)		
Age, y	51.5 (51.0–52.0)	47.4 (46.2–48.6)	50.3 (49.4–51.2)	53.2 (52.3–54.0)	52.8 (51.9–53.6)	<0.001	<0.001*
Male (%)	807 (41.1)	130 (50.2)	220 (39.8)	220 (35.8)	237 (44.1)	<0.001	0.536
Rural (%)	1175 (59.9)	172 (66.4)	356 (64.4)	399 (65.0)	248 (46.2)	<0.001	0.190
Ethnicity (%)							
Han	124 (6.3)	26 (10.0)	31 (5.6)	36 (5.9)	31 (5.8)	0.071	0.245
Minorities	1839 (93.7)	233 (90.0)	522 (94.4)	578 (94.1)	506 (94.2)		
Education (≥middle school)	377 (19.2)	56 (21.6)	97 (17.5)	104 (16.9)	120 (22.4)	0.060	0.926
Altitude of habitation (%)							
3000–3500, m	539 (27.5)	102 (39.4)	183 (33.1)	158 (25.7)	96 (17.9)	<0.001	…
3500–4000, m	1018 (51.9)	92 (35.5)	260 (47.0)	356 (58.0)	310 (57.7)		
≥4000, m	406 (20.7)	65 (25.1)	110 (19.9)	100 (16.3)	131 (24.4)		
SpO_2 (%)	87.7 (87.5–88.0)	89.2 (88.5–90.0)	88.3 (87.8–88.8)	87.4 (86.9–87.8)	86.9 (86.3–87.4)	<0.001	<0.001*
Smoking (%)							
Current	293 (14.9)	50 (19.3)	79 (14.3)	80 (13.0)	84 (15.6)	<0.001	…
Former	189 (9.6)	19 (7.3)	42 (7.6)	42 (6.8)	86 (16.0)		
Never	1481 (75.4)	190 (73.4)	432 (78.1)	492 (80.1)	367 (68.3)		
Alcohol drinking (%)	582 (29.6)	73 (28.2)	153 (27.7)	166 (27.0)	190 (35.4)	0.008	0.307
Family history of CVD (%)	120 (6.1)	14 (5.4)	30 (5.4)	29 (4.7)	47 (8.8)	0.026	0.336
SBP, mm Hg	132.3 (131.3–133.3)	113.7 (112.7–114.8)	126.6 (124.9–128.4)	138.7 (137.0–140.4)	139.8 (138.0–141.6)	<0.001	<0.001*
DBP, mm Hg	82.0 (81.4–82.6)	71.8 (70.9–72.7)	78.4 (77.4–79.5)	85.0 (83.9–86.0)	87.1 (86.05–88.2)	<0.001	<0.001*
BMI, kg/m^2	25.7 (25.6–25.9)	22.3 (22.0–22.6)	24.3 (24.0–24.6)	26.5 (26.2–26.8)	28.0 (27.7–28.3)	<0.001	<0.001*
WC, cm							
Male	89.8 (89.1–90.5)	79.9 (78.1–81.1)	85.9 (84.7–87.0)	93.6 (92.5–94.8)	95.4 (94.3–96.6)	<0.001	<0.001*
Female	87.7 (87.0–88.4)	73.8 (72.9–74.6)	83.3 (82.2–84.4)	90.5 (89.6–91.5)	94.8 (93.6–95.9)	<0.001	<0.001*
Total cholesterol, mmol/L	4.81 (4.76–4.85)	4.54 (4.44–4.65)	4.67 (4.6–4.74)	4.94 (4.87–5.02)	4.92 (4.83–5.01)	<0.001	<0.001*
HDL-cholesterol, mmol/L							
Male	1.35 (1.33–1.37)	1.42 (1.39–1.46)	1.42 (1.38–1.47)	1.34 (1.3–1.38)	1.26 (1.22–1.3)	<0.001	<0.001*
Female	1.53 (1.51–1.55)	1.62 (1.59–1.66)	1.58 (1.55–1.6)	1.56 (1.53–1.59)	1.40 (1.36–1.44)	<0.001	<0.001*
LDL-cholesterol, mmol/L	2.87 (2.83–2.9)	2.67 (2.57–2.77)	2.74 (2.68–2.8)	2.98 (2.91–3.04)	2.96 (2.89–3.03)	<0.001	<0.001*
Triglycerides, mmol/L	1.09 (1.06–1.11)	0.81 (0.78–0.84)	0.91 (0.89–0.94)	1.09 (1.05–1.13)	1.40 (1.33–1.46)	<0.001	<0.001*

Continued

Table 1. Continued

	Total (n=1963)	Number of Metabolic Risk Factors				*P* Value	*P* for Trend
		0 (n=259)	1 (n=553)	2 (n=614)	3 to 5 (n=537)		
FPG, mmol/L	4.91 (4.84–4.99)	4.57 (4.51–4.63)	4.66 (4.58–4.73)	4.93 (4.8–5.06)	5.33 (5.13–5.53)	<0.001	<0.001*
Medical therapy (%)							
Antihypertensive	334 (17.0)	0 (0.0)	54 (9.8)	126 (20.5)	154 (28.7)	<0.001	0.001†
Hypoglycemic	26 (1.3)	0 (0.0)	0 (0.0)	5 (0.8)	21 (3.9)	<0.001	0.129
Statin	174 (8.9)	0 (0.0)	0 (0.0)	15 (2.4)	159 (29.6)	<0.001	0.184

Data are means and their 95% CIs, and the categorical variables are presented as absolute numbers with percentages, n (%). Abnormal left ventricular diastolic function included impaired relaxation pattern, pseudonormal, and restrictive filling. *P*<0.05: The group difference assessed by χ^2 test or 1-way ANOVA was significant. BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-cholesterol, high-density lipoprotein cholesterol; LDL-cholesterol, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SpO_2, oxygen saturation; WC, waist circumference.

**P* for trend <0.05: There was a significant positive or negative linear association between continuous variables, and the number of metabolic syndrome components was evaluated by linear regression analysis.

†*P* for trend <0.05: the trend between dichotomous variables' positive rate and the metabolic risk factors clustering number based on Cochran-Armitage trend test in χ^2 test was statistically significant.

model.[26,27] All the analyses were carried out using SAS version 9.3 (SAS institute, Cary, NC). The 2-sided *P*<0.05 were considered significant.

Results

Characteristics of the Study Population

Characteristics of the 1963 (mean age: 51.5 years, 41.1% male) study participants are shown in Table 1. Age, diastolic blood pressure, waist circumference, total cholesterol, fasting plasma glucose, and the antihypertensive medicine use rate gradually increase with the number of metabolic risk factors clustering (*P* values for trend <0.001).

Table 2 shows LV structure and function echocardiographic parameters among the 4 groups. The LVESD, LV posterior wall thickness, relative wall thickness, LV mass index, and LV ejection fraction are similar across the 4 groups. Also, there are remarkable positive linear associations between the number of metabolic risk factors and the LA diameter, interventricular septum thickness and LV posterior wall thickness, while the E/A ratio decreased from 1.25 to 1.00 as the number of risk factors increased (*P* values for trend <0.05).

LVDD and Metabolic Risk Factor Clustering Number

Overall, 34.39% (95% CI: 32.28–36.49%) of the 1963 participants have LVDD. The prevalence of LVDD in male participants (37.05%, 95% CI: 33.71–40.39%) is higher than in female participants (32.53%, 95% CI: 29.82–35.23%, *P*=0.038), and is increased with age (35–44 years, 13.38%; 45–54 years, 29.54%; 55–64 years, 53.02%; and ≥65 years, 63.43%; *P*<0.0001) or the elevating altitude of habitation (3000–3500 m, 25.97%; 3500–4000 m, 36.15% and ≥4000 m, 41.13%; *P*<0.0001) (Figure).

Figure shows the prevalence of LVDD range from 17.76% (95% CI: 13.59–22.88%) in absent group to 42.46% (95% CI: 38.26–46.65%) among those with 3 to 5 risk factors (*P* for linear trend <0.05). In subanalyses, there is a significantly linear relationship between the prevalence of LVDD and the metabolic risk factor clustering number among the male 35 to 45 years group or ≥4000 m altitude habitation subgroups (*P* value for linear trend <0.05).

Multivariable Analysis of the Association Between Metabolic Risk Factor Clustering Number and LVDD

Table 3 shows the multivariate odds ratios for the association of metabolic risk factor clustering number and LVDD. In the

Table 2. Echocardiographic Parameters of LV Structure and Function

	Total (n=1963)	Number of Metabolic Risk Factors				*P* Value	*P* for Trend
		0 (n=259)	1 (n=553)	2 (n=614)	3 to 5 (n=537)		
LV structure							
LVEDD, mm	41.96 (41.56–42.36)	41.25 (40.65–41.85)	41.39 (41.02–41.77)	41.71 (41.33–42.08)	43.18 (41.86–44.51)	0.003	0.110
LVESD, mm	29.51 (26.11–32.92)	27.27 (26.78–27.77)	27.3 (26.99–27.61)	27.96 (27.62–28.31)	34.64 (22.19–47.09)	0.346	0.179
LA diameter, mm	28.21 (28.02–28.41)	27.51 (26.91–28.11)	27.76 (27.41–28.12)	28.55 (28.2–28.9)	28.63 (28.27–28.98)	<0.001	0.046
IVSD, mm	9.18 (9.07–9.29)	8.75 (8.63–8.87)	9.12 (8.79–9.46)	9.18 (9.04–9.32)	9.44 (9.32–9.56)	0.003	0.036
LVPWD, mm	9.45 (9.32–9.58)	9.20 (8.9–9.51)	9.38 (9.09–9.67)	9.48 (9.34–9.61)	9.62 (9.33–9.9)	0.252	0.006
RWT	0.45 (0.44–0.46)	0.45 (0.42–0.48)	0.45 (0.44–0.46)	0.45 (0.45–0.46)	0.45 (0.44–0.46)	0.996	0.095
LV mass index, g/m^2	72.92 (68.52–77.31)	69.22 (66.38–72.06)	73.02 (66.82–79.22)	69.40 (67.59–71.2)	78.63 (64.07–93.19)	0.406	0.279
LV systolic function							
LVEF (%)	62.92 (62.32–63.53)	63.34 (62.6–64.08)	63.89 (61.94–65.84)	62.03 (61.49–62.56)	62.75 (62.19–63.31)	0.121	0.413
LV diastolic function							
E-wave, m/s	0.66 (0.66–0.67)	0.7 (0.68–0.72)	0.68 (0.66–0.69)	0.65 (0.63–0.66)	0.66 (0.64–0.67)	<0.001	0.109
A-wave, m/s	0.72 (0.64–0.81)	0.58 (0.57–0.6)	0.63 (0.62–0.65)	0.68 (0.67–0.7)	0.93 (0.61–1.24)	0.037	0.082
E/A ratio	1.07 (1.05–1.09)	1.25 (1.2–1.29)	1.12 (1.09–1.16)	1.01 (0.97–1.04)	1.00 (0.95–1.05)	<0.001	0.048

Data are means and their 95% CIs. *P*<0.05: The group difference assessed by 1-way ANOVA was significant. *P* for trend <0.05: There was a significant positive or negative linear association between parameters value and metabolic risk factors number assessed by linear regression analysis. IVSD indicates interventricular septum thickness; LA, left atrial; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; LVESD, LV end-systolic diameter; LVPWD, LV posterior wall thickness; RWT, relative wall thickness.

overall multivariate-adjusted analysis, the odds ratios (95% CI) for the 1, 2, and 3 to 5 risk factors clustering relative to the absent group are 1.45 (0.96–2.17), 2.68 (1.8–3.98), and 2.9 (1.9–4.43), respectively, independent of LV ventricular mass index, relative wall thickness, and other confounding factors (*P* value for trend <0.001). In addition, LV diastolic function is much more remarkably influenced by metabolic risk factors clustering in the middle-age group, and even 2 risk factors clustering was associated with a higher risk; the odds ratios (95% CI) are 5.53 (2.02–15.15) for the 35 to 45 years old group and 3.65 (1.84–7.25) for the 45 to 55 years old group. However, metabolic risk factor clustering is not significantly associated with risk of LVDD among the ≥65 years old elderly group (*P*=0.0170 for interaction between metabolic risk factor clustering number grades and age group in the overall model).

Multivariate analysis demonstrates that high altitude is one of the major independent risk factors for LVDD (Figure S2). Compared with altitude 3000 to 3500 m (reference), the odds ratio (95% CI) is 1.83 (1.37–2.45) for altitude 3500 to 4000 m, and 3.82 (2.66–5.50) for altitude ≥4000 m, respectively. Habitation altitude itself, however, has no significant effect on the association between metabolic risk factors and LVDD (*P* for interaction by habitation altitude=0.1022 in Table 3). A further investigation, analyzing a similar database from Xinjiang province where most of the population is not living at high altitude (Tables S1 and S2) and obtaining similar results, suggests that more metabolic risk factors are associated with higher risk of LVDD at various altitude gradients without evidence of an interaction between metabolic risk factor clustering number grades and altitude level (*P* for interaction=0.0945 in Table S2). As shown in Table 4, abdominal obesity, elevated blood pressure, and high blood glucose are significantly associated with LVDD. Additionally, to determine the contribution of each metabolic risk factor to the LVDD, a multivariable dominance analysis model was developed; the results from the model indicate that abdominal obesity (percent of contribution 34.53%), hypertension (percent of contribution 33.16%), and elevated blood glucose (percent of contribution 32.31%) are the 3 significant contributors.

Discussion

Metabolic Risk Factors Clustering and LVDD

This study demonstrated a significant positive association between the number of metabolic risk factors and the prevalence of LVDD independent of LV structure and other potential factors. Our results were consistent with prior studies suggesting that metabolic syndrome (≥3 metabolic risk factors) could lead to the development of diastolic

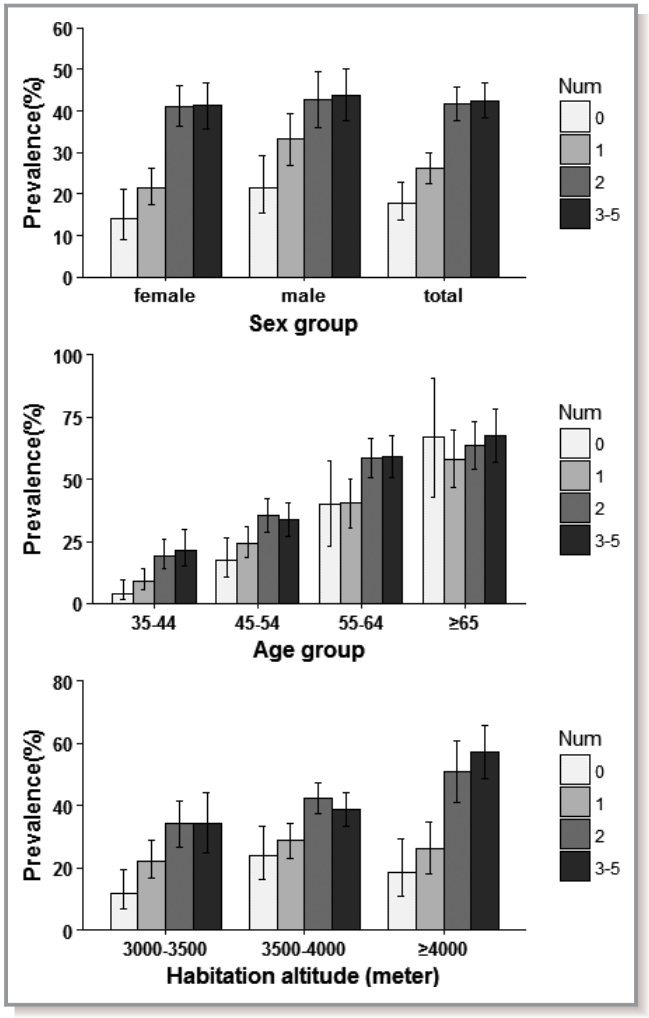

Figure. Prevalence of left ventricular diastolic dysfunction by sex, age, and habitation altitude. NUM indicates metabolic risk factors clustering number.

dysfunction via mechanisms independent of LV mass.[14,15] In accordance, Hwang et al showed that metabolic syndrome itself acted as a risk factor for developing LVDD, even after the adjustment for blood pressure.[10] Given the indication that LVDD represents an early sign of cardiac dysfunction and fatal cardiovascular events,[3–6] on some level, the following studies therefore provided evidence supporting our findings. The previously published post hoc analysis of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial of 2287 subjects showed that for each end point (fatal or nonfatal myocardial infarction, heart failure, percutaneous coronary intervention), there was a significant trend for increasing risk as the metabolic risk factor number increased.[28] However, in the stratified multivariable analysis by age, we found that even 2 risk factors clustering was associated with a higher risk in the middle-age group; however, more metabolic risk factors clustering was not significantly associated with greater risk of LVDD for the elderly participants. The probable explanation is that even with the normal aging process, changes in myocardium occur and may modify lusitropic function of the heart including LV diastolic function.[29] Carvalho and colleagues reported that the E/A ratio decreased with advancing age and showed a significant effect of age on diastolic dysfunction[30]; therefore, advancing age may be a more important contributor to LV diastolic function compared with metabolic risk factors among the elderly group.

Separate Metabolic Risk Factors and LVDD

Furthermore, we found that abdominal obesity, hypertension, and elevated blood glucose were the significant and major contribution to the greater LVDD risk. A few studies have evaluated the association of central obesity with LVDD. The KoGES-ARIRANG (Atherosclerosis Risk of Rural Areas in the Korean General Population) study[9] found that waist circumference, a measure of central obesity, was an independent predictor of LVDD. In an analysis of 2181 participants from the HyperGEN study, Selvaraj et al[8] found that central obesity was independently associated with worse cardiac mechanics (reduced LV strain and systolic and early diastolic tissue velocities). In our study, the sex-stratified analysis demonstrated that the association between central obesity and diastolic dysfunction is significant only in men. However, some previous studies[31,32] found that central obesity was associated with diastolic dysfunction that was more pronounced among women. Some reasons are as follows: (1) the 2 prior studies' populations included older people (mean age was 64 years old)[28] or hypertensive patients,[29] which was different from our study; (2) different definition of abdominal obesity might contribute to the "paradox"; both of the prior studies used Treatment Panel III criteria (circumference >102 cm in men and >88 cm in women), but in our study abdominal obesity was defined according to the revised National Cholesterol Education Program ATP III criteria (2004) (waist circumference ≥90 cm in men and ≥80 cm in women). The mechanism behind the association between the abdominal obesity and abnormalities in LV diastolic function had not been well understood. With excess adipose tissue, particularly visceral deposition, macrophages infiltrate the adipocytes and secrete large amounts of proinflammatory molecules, which causes endothelial dysfunction and cardiac dysfunction.[33] Hypertension is usually the key risk factor among metabolic risk factors for the development of cardiovascular morbidity and mortality in Asian populations.[34,35] In recent years, a lack of knowledge about healthy behavior has contributed to the higher hypertension prevalence in the less developed area of Tibet in China.[36] Several studies[10,11] have reported that high blood

Table 3. Adjusted Odds Ratios for the Associations of Metabolic Risk Factor Clustering Number With LV Diastolic Dysfunction

	n (%)	Number of Metabolic Risk Factors				*P* for Trend
		0 (Ref)	1	2	3 to 5	
Total	1963 (100)	1.00	1.45 (0.96–2.17)	2.68 (1.8–3.98)	2.9 (1.9–4.43)	<0.001
Sex						
Male	807 (41.1)	1.00	1.52 (0.87–2.68)	2.71 (1.55–4.74)	3.83 (2.13–6.88)	<0.001
Female	1156 (58.9)	1.00	1.42 (0.78–2.61)	2.67 (1.49–4.79)	2.23 (1.19–4.18)	0.001
P for interaction by sex=0.8177						
Age (y)						
35–44	598 (30.5)	1.00	2.32 (0.82–6.58)	5.53 (2.02–15.15)	5.85 (2.04–16.75)	<0.001
45–54	667 (34.0)	1.00	2.1 (1.04–4.24)	3.65 (1.84–7.25)	3.17 (1.54–6.51)	<0.001
55–64	430 (21.9)	1.00	0.94 (0.4–2.21)	1.89 (0.84–4.24)	2.12 (0.88–5.1)	0.006
≥65	268 (13.6)	1.00	0.63 (0.2–1.97)	0.68 (0.22–2.16)	1.22 (0.36–4.2)	0.337
P for interaction by age=0.0170						
Habitation altitude						
3000–3500 m	539 (27.5)	1.00	1.3 (0.59–2.84)	2.74 (1.25–5.99)	3.83 (1.6–9.19)	<0.001
3500–4000 m	1018 (51.8)	1.00	1.28 (0.71–2.33)	2.06 (1.16–3.66)	1.87 (1.02–3.45)	0.010
≥4000 m	406 (20.7)	1.00	1.05 (0.44–2.48)	2.6 (1.11–6.08)	3.78 (1.58–9.06)	<0.001
P for interaction by habitation altitude=0.1022						

Values are odds ratios (95% CI). All estimates are adjusted for age (excluded in age-stratified model), sex (excluded in sex-stratified model), areas, ethnicity, education, altitude of habitation (excluded in altitude-stratified model), smoking, alcohol drinking, family history of stroke and coronary heart disease, medical therapy, relative wall thickness, and left ventricular mass index. Ref indicates reference; LV, left ventricular.

pressure was responsible for the development of LVDD, which was in accordance with our results. Tadic et al claimed that higher blood pressure was independently associated with LVDD.[11] However, Masugata et al[37] found that systolic blood pressure variability showed better correlation with LVDD than mean values of systolic blood pressure. Hyperglycemia (including impaired fasting glucose) could not be ignored, which possibly increased the risk of diastolic heart failure even in the absence of diabetes mellitus as well as even in the absence of other comorbidities such as hypertension.[38–40] A prior related study[13] demonstrated that impaired glucose tolerance is a possible contributor to LV hypertrophy and diastolic dysfunction in a relatively large population. The results of Hurk et al[12] showed that glucose status was independently associated with more severe LVDD 8 years later, and LVDD deteriorates more in individuals with than in those without type 2 diabetes mellitus. The possible molecular mechanisms was elevated blood glucose lead to nonenzymatic glycation of vascular and membrane proteins, producing either advanced glycation end-products or reactive oxygen species, which form stable and irreversible cross-links with collagen polymers, thereby decreasing the compliance of the myocardium and vessels; thus, cardiac stiffness increases and this leads to diastolic dysfunction.[41]

Table 4. Multivariate OR (95% CI) of LVDD Associated With the 5 Metabolic Risk Factors

Metabolic Risk Factors	Total	Male	Female
Abdominal obesity	1.36 (1.07–1.73)	1.60 (1.13–2.27)	1.18 (0.83–1.66)
High blood glucose	1.49 (1.05–2.12)	1.22 (0.75–2.00)	1.76 (1.04–2.98)
Elevated TG	1.31 (0.95–1.82)	1.43 (0.88–2.33)	1.15 (0.72–1.85)
Reduced HDL-C	0.84 (0.62–1.15)	1.00 (0.59–1.70)	0.76 (0.51–1.12)
Elevated blood pressure	2.22 (1.73–2.84)	2.41 (1.62–3.60)	2.08 (1.50–2.87)

The model was adjusted for age, sex (excluded in sex-stratified model), areas, ethnicity, education, altitude of habitation, smoking, alcohol drinking, family history of stroke and major heart disease, medical therapy, relative wall thickness and left ventricular mass index. HDL-C indicates high-density lipoprotein cholesterol; LVDD, left ventricular diastolic dysfunction; OR, odds ratio; TG, triglycerides.

High Altitude and the Function of LV

The participants were living in the Tibet Plateau of China with an altitude >3000 m, for which high altitude habitation was the most remarkable characteristic. Results of the present study are consistent with a prior study[42] that identified high altitude as the independent risk factor for LVDD among people living at high altitude. Furthermore, for the healthy children in Tibet, compared with those born and living at sea level, lower systolic and diastolic function of both ventricles has been revealed after they were 14 years old.[43] Maufrais and colleagues[44] found that even short-term high-altitude (4350 m) exposure could impair LV diastolic function, with the greatest effect observed on the second day for 11 male subjects (age 28±8 years) at sea level concomitantly with the occurrence of acute mountain sickness, and the underlying mechanisms of LVDD caused by high-altitude hypoxia include an increased right ventricular afterload, a decrease in LV filling pressure, and a delayed LV untwist.

Limitation

This study has many strengths including a standardized protocol, a stratified multistage random sampling population-based investigation that adjusted known and potential confounding factors; to the best of our knowledge, this is the first study focusing on the effects of the clustering number of the metabolic risk factors on LV diastolic function in Tibet. However, there are some limitations of our study. First, cross-sectional study may preclude a causal relationship between metabolic risk factors and LVDD. Furthermore, a significant positive association between the number of metabolic risk factors and LVDD has been explored; however, this may apply only to the special population of individuals who are 35 years or older in the Tibet area of China with a lack of generalizability to other populations. Finally, we defined and evaluated the LV diastolic function according to the 2009 American Society of Echocardiography (ASE) guidelines, not the latest 2016 version, because the protocol was developed in 2012 to 2014. This may decrease the specificity to assess the association with metabolic risk factors, especially for the older population.

Conclusion

There was a significant positive association between the metabolic risk factor clustering number and the risk of LVDD, especially in middle-aged adults. Abdominal obesity, hypertension, and elevated blood glucose were the major contributors to the greater dysfunction risk. It was also demonstrated that high altitude was one of the major probable independent risk factors for LVDD; however, habitation altitude itself had no significant effect on the association between metabolic risk factors and LVDD. These findings might explain potential mechanisms of the increasing cardiac dysfunction morbidity and cardiovascular disease mortality.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Distribution of participants' habitation altitude in Xinjiang and Tibet.

	n (%), Xinjiang	n (%), Tibet	n (%), Total
＜500 m	1 902(42.0)	0(0.0)	1 902(29.3)
500~1000m	654(14.5)	0(0.0)	654(10.1)
1000~1500m	716(15.8)	0(0.0)	716(11.0)
1500~2000m	0(0.0)	0(0.0)	0(0.0)
2000~2500m	670(14.8)	0(0.0)	670(10.3)
2500~3000m	0(0.0)	0(0.0)	0(0.0)
3000-3500m	547(12.7)	539(27.5)	1 113(17.2)
3500-4000m	7(0.2)	1 018(51.8)	1 025(15.8)
⩾4000m	0(0.0)	406(20.7)	406(6.3)
n (%),Total	4 523(100.0)	1 963(100.0)	6 486(100.0)

Table S2. Adjusted odds ratios (ORs) for the associations of metabolic risk factor clustering number with LV diastolic dysfunction in different altitude in Xinjiang and Tibet.

	n (%)	Number of metabolic risk factors				*P* for trend
		0 (ref)	1	2	3~5	
Province						
Xinjiang	4 523(69.7)	1.00	1.30(1.03~1.63)	1.62(1.29~2.04)	1.74(1.37~2.22)	<0.001
Tibet	1 963(30.3)	1.00	1.45(0.96~2.17)	2.68(1.8~3.98)	2.9(1.9~4.43)	<0.001
Habitation altitude						
＜500 m	1 902(29.3)	1.00	1.19(0.82~1.73)	1.7(1.17~2.46)	1.58(1.08~2.3)	0.0044
500~1000m	654(10.1)	1.00	1.47(0.58~3.71)	2.19(0.89~5.4)	3.4(1.4~8.21)	0.0005
1000~1500m	716(11.0)	1.00	2.29(1.14~4.6)	3.5(1.76~7)	2.87(1.36~6.05)	0.0036
2000~2500m	670(10.3)	1.00	1.51(0.86~2.63)	1.54(0.86~2.75)	1.97(1.02~3.83)	＞0.05
3000-3500m	1 113(17.2)	1.00	1.15(0.74~1.8)	1.44(0.88~2.35)	2.02(1.34~3.6)	0.0120
3500-4000m	1 025(15.8)	1.00	1.31(0.73~2.38)	2.09(1.18~3.71)	1.92(1.04~3.52)	0.0081
≥4000m	406(6.3)	1.00	1.05(0.44~2.48)	2.6(1.11~6.08)	3.78(1.58~9.06)	<0.001
P for interaction by habitation altitude = 0.0945						

Values are ORs (95% confidence interval). All estimates are adjusted for age, sex, province, areas (rural or urban), ethnicity, education, altitude of habitation (excluded in altitude-stratified model), smoking, alcohol drinking, family history of stroke and coronary heart disease, medical therapy, relative wall thickness and left ventricular mass index.

Figure S1. Map of China.

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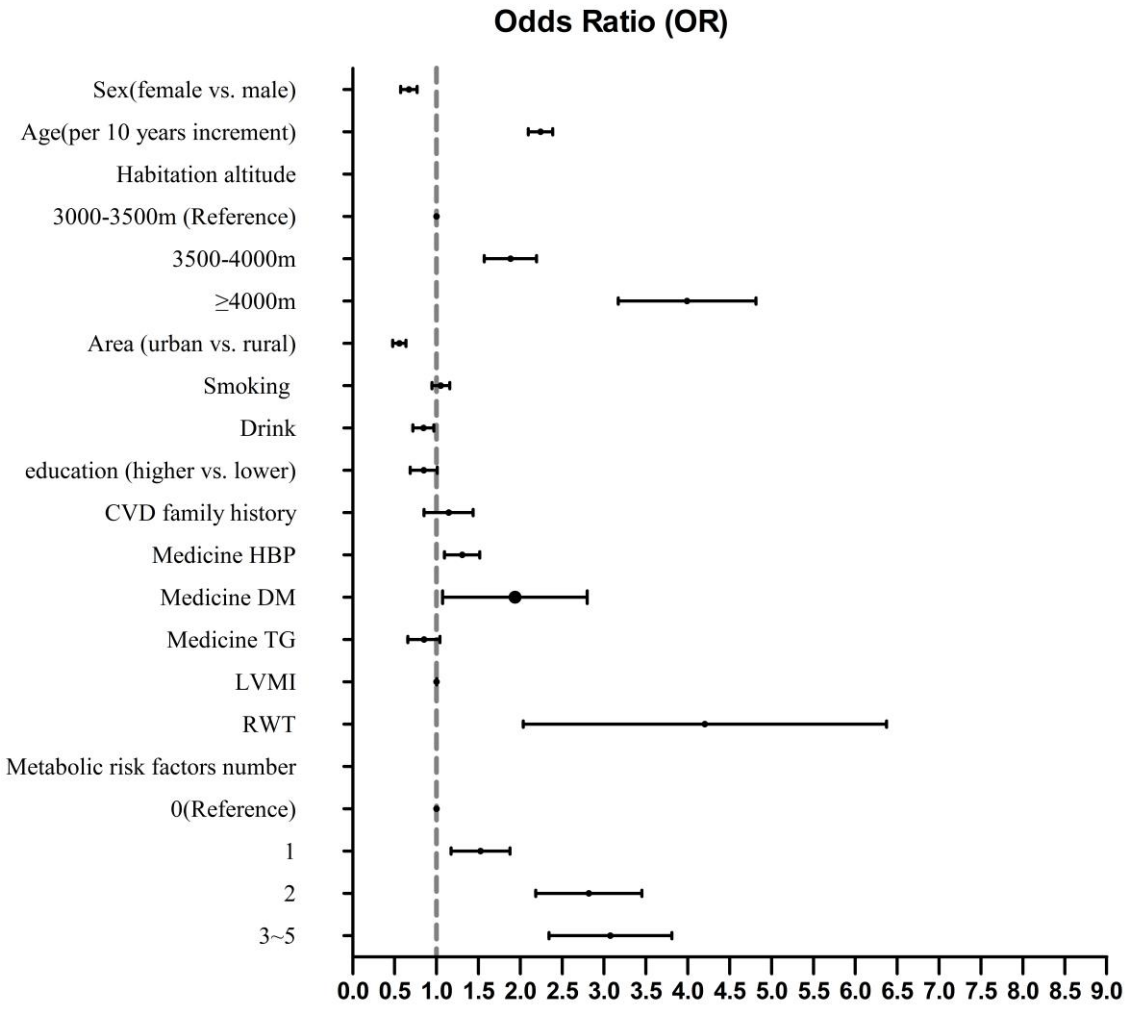
https://wenku.baidu.com/view/a13a14fcdbef5ef7ba0d4a7302768e9950e76e69.html?from=search)

Figure S2 Multivariable-adjusted association between odds ratio for LVDD and the characteristics of participants.



CVD, cardiovascular disease; HBP, high blood pressure; TG, triglycerides; LVMI, left ventricular mass index; RWT, relative wall thickness.