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Research Article

Relationship between Obesity Phenotypes and Cardiovascular Risk in a Chinese Cohort

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ABSTRACT

Objective: The changing living patterns in China are accompanied by an increase in prevalence of cardiovascular disease for which obesity is a significant factor. This study investigated the association between obesity phenotypes and risk of cardiovascular disease in a Chinese cohort.

Methods: A sample of 10,826 community-dwelling individuals aged 40–79 years (mean age 62.2 ± 12.0 years) were stratified by categories of body mass index (BMI) (normal weight: BMI < 24 kg/m^2; overweight: BMI of 25–28 kg/m^2; obese: BMI > 28 kg/m^2) and metabolic status and divided into six phenotypes: (1) normal metabolic status and normal weight; (2) normal metabolic status and overweight; (3) normal metabolic status and obese; (4) normal weight and dysmetabolic status; (5) dysmetabolic status and overweight; (6) dysmetabolic status and obese. The Atherosclerotic Cardiovascular Disease (ASCVD) risk score was determined based on cardiovascular risk factors.

Results: Prevalence of overweight and obesity was 15.2% and 25.2% respectively. After adjusting for confounding factors, ASCVD score was significantly higher in men [Odds Ratio (OR): 9.796, 95% confidence interval (CI): 5.833–16.450; $p < 0.001$] and women [OR: 5.821, 95% CI: 4.253–7.968; $p < 0.001$] with obese and dysmetabolic status compared to normal. The odds of reporting ASCVD risk was significantly higher in men (OR: 3.432, 95% CI: 1.965–5.996; $p < 0.001$) and women (OR: 4.647, 95% CI: 3.327–6.491; $p < 0.001$) with obese and dysmetabolic status compared to those with obese and normal metabolic status. In addition, the odds of reporting ASCVD risk was significantly lower in men (OR: 0.317, 95% CI: 0.142–0.707; $p = 0.005$) and women (OR: 0.487, 95% CI: 0.320–0.739; $p = 0.001$) with the overweight–dysmetabolic status phenotype compared to those with an overweight–normal metabolic phenotype.

Conclusion: Obese dysmetabolic individuals had the highest ASCVD risk score in all phenotypes. When BMI category was overweight, BMI played a more important role than metabolic status, whereas when BMI category was obesity, risk was more affected by metabolic status.

HIGHLIGHTS

What is already known about this subject?

- Obesity presents a major risk for cardiovascular disease.
- Some studies provide evidence that obesity has better outcome compared to lean counterparts.

What does this study add?

- This study provides information that obese dysmetabolic individuals show the highest Atherosclerotic Cardiovascular Disease (ASCVD) risk score in all phenotypes in the whole cohort.
- This study also indicates that body mass index (BMI) plays a more important role for estimation of CV risk than metabolic status in overweight, whereas risk is more affected by metabolic status in obesity.

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1. INTRODUCTION

The prevalence of cardiovascular disease in China is rising, with the current population with coronary heart disease being estimated to be 11 million [1]. Cardiovascular disease is the major cause of death in the Chinese, and the burden of disease is severe. Overweight/obesity is a significant factor of cardiovascular risk [1]. Obesity affects almost one-third of the Chinese population and presents an increasingly serious health problem, with incidence of obesity in China ranking second in the world [2].

The association of obesity and cardiovascular disease has two aspects. Obesity is generally accepted as an independent risk factor of many cardiovascular diseases; however, in some groups the long-term prognoses for obese patients with cardiovascular disease are often better than for lean patients [3,4]. This paradox has been shown to exist in those undergoing coronary intervention, hypertension, heart failure and even the general population [5–9].

Metabolic syndrome is strongly associated with obesity [6], and is also a clear risk of coronary heart disease [1,10]. One-third of the Chinese population suffers from metabolic syndrome [11]. This situation is as serious as obesity.

Our study used the first severe 10-year Atherosclerotic Cardiovascular Diseases (ASCVD) score [12] to evaluate the risk in elderly Chinese, and analyzed the relationship of obesity and its related metabolic syndrome to ASCVD. We have attempted to avoid the influence of comorbidities, weakness and other influencing factors on the obesity paradox [5].

2. MATERIALS AND METHODS

2.1. Participants

A sample of 10,826 individuals aged 40–79 years (mean age 62.23 ± 12.0 years) was randomly selected from a community-dwelling eligible population and attended Jiading District Jiangqiao Community Health Service Center for laboratory and clinical and investigation to determine their cardiovascular risk according to the American College of Cardiology/American Heart Association-ASCVD (ACC/AHA-ASCVD) risk score [13]. Exclusion criteria were those with cancer, CVD and any who had no data on obesity phenotypes. The study received approval by the Ethics Committee of Ruijin Hospital North, Shanghai Jiaotong University School of Medicine and all participants gave written informed consent.

2.2. Measurements

A standardized questionnaire was given to all participants and data collected for age, gender, smoking habits, medical history, consumption of alcohol and use of medications. Height was measured with a wall-mounted stadiometer to the nearest 0.5 cm without shoes and body weight was measured on a balance calibrated to the nearest 0.1 kg with minimum clothing and without shoes. Waist Circumference (WC) was measured at the maximum point of normal expiration at the midpoint between the iliac crest and lowest rib margin and the iliac crest with the subject standing. Measurements were made with an upstretched tape meter and recorded to the nearest 0.1 cm.

Blood samples were obtained after 12–14 h of overnight fasting. Serum Total Cholesterol (TC), Low-density Lipoprotein Cholesterol (LDL-C), High-density Lipoprotein Cholesterol (LDL-C), Triglycerides (TG), Fasting Blood Glucose (FBG), serum Uric Acid (UA), serum Creatinine (Cr), and glycosylated hemoglobin (HbA1c) were obtained from patient medical records. The Modification of Diet in Renal Disease (MDRD) formula [14] was used to calculate the estimated Glomerular Filtration Rate (eGFR). Glycosylated hemoglobin was determined by the BIO-RAD D-10TM kit. Seated blood pressure measurements were obtained in 12-h fasting individuals in the morning (7–9 am) with a standard manual sphygmomanometer after a 10-min rest and using the average of two readings in both arms. Pulse Pressure (PP) was calculated as the difference between Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) was calculated as (DBP) + (PP)/3.

The ACC/AHA-ASCVD risk score was determined using values of TC, HDL-C, LDL-C, age, blood pressure, gender, presence of diabetes, and smoking status [13]. Status of current smoking was defined as having smoked the last cigarette within 1 week of when blood pressure measurements were taken.

2.3. Definitions

Weight and metabolic status were used to determine obesity phenotypes. Categories of overweight and obesity were based on thresholds of body mass index (BMI) with overweight and obesity defined as BMI between 24 and 28 kg/m^2 and >28 kg/m^2 respectively, according to published values for the Chinese population [15]. The presence of metabolic syndrome defined dysmetabolic status according to the definition of the Joint Interim Statement (JIS). JIS defines metabolic syndrome as the presence of any three of the following five risk factors: (1) abdominal obesity, defined as WC ≥80 cm in women and ≥80 cm in men [15]; (2) reduced HDL-C 40 mg/dl in men, <50 mg/dl in women or undergoing pharmacological treatment for reduced HDL-C; (3) elevated Triglycerides (TG) levels ≥150 mg/dl or on pharmacological treatment for elevated TG; (4) elevated blood pressure (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg) or on antihypertensive treatment; and (5) elevated FBG ≥ 100 mg/dl or on pharmacological treatment for elevated glucose [16]. There were six obesity phenotypes defined: (1) normal metabolic status and normal weight; (2) normal metabolic status and overweight; (3) normal metabolic status and obese; (4) dysmetabolic status and normal weight; (5) dysmetabolic status and overweight; (6) dysmetabolic status and obese.

The ACC/AHA-ASCVD risk score was defined as high risk when the score ≥7.5% and low risk when score <7.5% [14].

2.4. Statistical Analysis

Continuous variables are expressed as mean ± SD, and frequencies (percentage) are reported for categorical variables. Continuous and categorical variables were compared using *t*-test and Chi-square test respectively for males and females. To compare continuous and categorical variables among the groups of obesity phenotypes, Analysis of Variance (ANOVA) and Chi-square test respectively were used. Logistic regression analysis was used to compute the Odds Ratios (ORs). Sex specific ORs with 95% confidence intervals were computed for the total cohort and for males and females separately; model 1 was unadjusted, whereas model 2 was adjusted for age, sex and smoking status. Analyses were performed with SPSS 24.0 for Windows (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

3. RESULTS

Mean age and BMI of participants were 62.2 ± 12.0 years and 24.6 ± 3.4 kg/m^2 respectively. Table 1 shows baseline characteristics. Of the 10,826 participants, 4683 were male (43.3%). Mean age for males and females was 63.0 ± 11.8 and 61.7 ± 12.1 years respectively. The male population had a significantly greater height, larger waist circumference, higher Diastolic Blood Pressure (DBP) and Systolic Blood Pressure (SBP), greater BMI, higher FBG, higher glycosylated hemoglobin, higher triglycerides, a lower total cholesterol driven by lower HDL-C and lower LDL-C, lower eGFR, lower uric acid, higher ASCVD risk score, and higher rate of left ventricular hypertrophy. None of the women were smokers compared to 37.2% of men.

Prevalence of overweight and obesity was 15.2% and 25.2% respectively. The least and most common obesity phenotypes were and overweight–dysmetabolic status (2.1% in men and 1.3% in women) and normal weight–normal metabolic status (19.2% in men and 27.2% in women) respectively. The characteristics of the participants included in the analysis according to the metabolic status and BMI category are shown in Table 2.

Table 3 shows the odds of reporting ASCVD risk for weight, metabolic status, and different obesity phenotypes in men and women separately. After adjusting for confounding variables, the OR of reporting ASCVD risk were significantly higher in both men (OR: 6.133, 95% CI: 4.524–8.315; $p < 0.001$) and women (OR: 3.708, 95% CI: 3.123–4.402; $p < 0.001$) with dysmetabolic status, compared those with normal metabolic status. For weight status, both obese men (OR: 4.221, 95% CI: 2.817–6.326; $p < 0.001$) and women (OR: 2.628, 95% CI: 2.069–3.339; $p < 0.001$) were more likely to report a higher ASCVD risk score compared to their normal weight counterparts; both overweight men (OR: 3.124, 95% CI: 2.322–4.203; $p < 0.001$) and women (OR: 1.567, 95% CI: 1.311–1.872; $p < 0.001$) were more likely to report higher ASCVD risk score compared to their normal weight counterparts.

For obesity phenotypes and after adjusting for confounding variables, the odds of reporting ASCVD risk was significantly higher in men (OR: 9.796, 95% CI: 5.833–16.450; $p < 0.001$, Table 4) and women (OR: 5.821, 95% CI: 4.253–7.968; $p < 0.001$, Table 5) with obese dysmetabolic status, in men (OR: 9.542, 95% CI: 5.991–15.197; $p < 0.001$) and women (OR: 4.875, 95% CI: 3.697–6.429; $p < 0.001$) with normal weight–dysmetabolic status, in men (OR: 7.361, 95% CI: 4.415–12.272; $p < 0.001$) and women (OR: 2.770, 95% CI: 2.136–3.592; $p < 0.001$) with overweight–normal metabolic status, compared to those with normal weight–normal metabolic status. In addition, in men the odds of reporting ASCVD risk was significantly higher with the overweight–dysmetabolic status phenotype (OR: 2.766, 95% CI: 1.418–5.394; $p = 0.003$) and the obese–normal metabolic status phenotype (OR: 2.830, 95% CI: 1.946–4.116; $p < 0.001$) compared to those with a normal weight–normal metabolic phenotype. However, there was no statistical significance among women.

The odds of reporting ASCVD risk was significantly higher in men (OR: 3.432, 95% CI: 1.965–5.996; $p < 0.001$) and women (OR: 4.647, 95% CI: 3.327–6.491; $p < 0.001$) with obese–dysmetabolic

Table 1 | Characteristics of the study subjects

Characteristics	Total (*n* = 10,826)	Men (*n* = 4683)	Women (*n* = 6143)	*p*-value
Age (years)	62.23 ± 12.0	62.97 ± 11.81	61.67 ± 12.14	<0.001
Height (cm)	159.80 ± 8.58	166.28 ± 6.68	154.87 ± 6.27	<0.001
Weight (kg)	62.95 ± 10.63	68.73 ± 10.14	58.54 ± 8.71	<0.001
Waist (cm)	83.19 ± 9.30	86.22 ± 8.68	80.89 ± 9.09	<0.001
BMI (kg/m^2)	24.60 ± 3.35	24.84 ± 3.27	24.41 ± 3.41	<0.001
Smoking, *n* (%)	1742 (16.1)	1742 (37.2)	0 (0)	<0.001
Glucose (mmol/L)	5.36 ± 1.59	5.43 ± 1.67	5.31 ± 1.52	<0.001
HbA1c (%)	5.79 ± 0.97	5.83 ± 1.03	5.76 ± 10.91	0.001
Triglycerides (mmol/L)	1.63 ± 1.23	1.67 ± 1.28	1.61 ± 1.19	0.019
Total cholesterol (mmol/L)	5.01 ± 0.99	4.79 ± 0.94	5.18 ± 0.99	<0.001
LDL-C (mmol/L)	3.18 ± 0.86	3.06 ± 0.82	3.28 ± 0.87	<0.001
HDL-C (mmol/L)	1.40 ± 0.36	1.29 ± 0.33	1.48 ± 0.36	<0.001
Creatinine (μmol/L)	71.76 ± 20.96	82.29 ± 18.73	63.73 ± 18.92	<0.001
eGFR [mL/(min·1.73 m^2)]	87.92 ± 15.99	86.44 ± 15.22	89.05 ± 16.47	<0.001
Uric acid (μmol/L)	317.86 ± 83.94	358.65 ± 81.97	286.77 ± 71.15	<0.001
ASCVD10-y (%)	14.03 ± 12.12	19.53 ± 12.46	10.00 ± 10.11	<0.001
SBP (mmHg)	136.43 ± 19.63	137.16 ± 18.74	135.87 ± 20.27	0.001
DBP (mmHg)	85.55 ± 10.38	87.57 ± 10.54	84.01 ± 9.99	0.001
PP (mmHg)	50.88 ± 16.03	49.59 ± 14.87	51.86 ± 16.79	<0.001
MAP (mmHg)	102.51 ± 11.97	104.10 ± 11.91	101.29 ± 11.87	<0.001
HR (bpm)	73.98 ± 11.34	71.74 ± 11.31	75.68 ± 11.06	<0.001
LVH, *n* (%)	686 (6.3)	481 (10.3)	205 (3.3)	<0.001

Data are mean ± SD or percentage as marked. *p*-value: independent *t*-test analysis of variance for numeric variables and Chi-square test for categoric variables. eGFR is an estimate of GFR for the modified MDRD formula, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular diseases; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; HR, heart rate; LVH, left ventricular hypertrophy.

Table 2 Characteristics of the study subjects in different metabolic status

Characteristics	Normal metabolic status			Dysmetabolic status			*p*-value
	Normal (*n* = 5028)	Overweight (*n* = 1150)	Obese (*n* = 1667)	Normal (*n* = 1421)	Overweight (*n* = 500)	Obese (*n* = 1060)	
Age (years)	60.37 ± 12.94	64.31 ± 10.21	62.04 ± 11.67	64.92 ± 10.27	64.20 ± 11.18	64.57 ± 10.76	<0.001
Male gender, *n* (%)	2081 (41.39)	435 (37.83)	815 (48.89)	658 (46.31)	228 (45.60)	444 (43.96)	<0.001
Height (cm)	160.08 ± 8.31	159.85 ± 8.68	159.65 ± 8.26	160.18 ± 8.79	157.70 ± 9.71	159.17 ± 9.15	<0.001
Weight (kg)	56.91 ± 7.74	59.23 ± 7.65	67.03 ± 7.24	68.11 ± 7.63	74.8 ± 9.97	76.69 ± 9.72	<0.001
Waist (cm)	77.19 ± 7.08	82.31 ± 6.63	85.71 ± 5.69	85.55 ± 5.34	92.82 ± 7.46	95.71 ± 6.74	<0.001
BMI (kg/m^2)	22.14 ± 1.90	23.11 ± 1.48	26.23 ± 0.84	26.47 ± 0.85	30.01 ± 2.51	30.21 ± 2.23	<0.001
Smoking, *n* (%)	664 (13.21)	167 (14.52)	290 (17.40)	283 (19.92)	108 (54.0)	230 (21.70)	<0.001
Glucose (mmol/L)	4.98 ± 1.15	6.02 ± 1.95	5.04 ± 1.16	6.07 ± 2.00	5.02 ± 1.01	6.20 ± 2.15	<0.001
HbA1c (%)	5.56 ± 0.75	6.14 ± 1.19	5.63 ± 0.68	6.20 ± 1.20	5.64 ± 0.66	6.28 ± 1.24	<0.001
Triglycerides (mmol/L)	1.22 ± 0.72	2.50 ± 1.67	1.35 ± 0.64	2.34 ± 1.52	1.24 ± 0.39	2.33 ± 1.79	<0.001
Total cholesterol (mmol/L)	4.94 ± 0.95	5.12 ± 1.00	4.99 ± 0.93	5.11 ± 1.08	4.90 ± 0.93	5.15 ± 1.09	<0.001
LDL-C (mmol/L)	3.11 ± 0.83	3.25 ± 0.92	3.23 ± 0.82	3.26 ± 0.90	3.17 ± 0.82	3.29 ± 0.89	<0.001
HDL-C (mmol/L)	1.54 ± 0.36	1.17 ± 0.29	1.42 ± 0.29	1.18 ± 0.29	1.43 ± 0.28	1.20 ± 0.29	<0.001
Creatinine (μmol/L)	70.59 ± 20.12	71.09 ± 18.35	72.73 ± 17.51	73.37 ± 20.77	71.88 ± 15.86	74.26 ± 31.70	<0.001
eGFR [mL/(min·1.73 m^2)]	89.95 ± 15.93	86.11 ± 15.89	87.92 ± 15.51	85.18 ± 15.69	86.38 ± 14.52	84.62 ± 16.82	<0.001
Uric acid (μmol/L)	296.13 ± 78.57	324.32 ± 80.92	325.41 ± 79.65	347.08 ± 88.66	332.73 ± 77.01	355.87 ± 85.03	<0.001
ASCVD10-y (%)	10.93 ± 10.68	16.58 ± 12.21	13.04 ± 10.99	19.03 ± 13.29	15.28 ± 11.31	19.45 ± 13.62	<0.001
Optimal (%)	4.5 ± 6.8	5.3 ± 6.8	6.4 ± 4.9	6.5 ± 4.9	6.6 ± 4.9	6.7 ± 4.8	<0.001
SBP (mmHg)	120.0 ± 11.3	123.3 ± 10.3	125.0 ± 10.1	141.4 ± 17.1	143.8 ± 17.1	147.1 ± 18.5	<0.001
DBP (mmHg)	78.8 ± 7.4	79.6 ± 6.2	80.2 ± 6.0	88.0 ± 9.9	89.2 ± 9.6	90.4 ± 9.8	<0.001
PP (mmHg)	41.2 ± 9.7	43.6 ± 9.7	44.8 ± 10.5	53.3 ± 15.3	54.6 ± 15.5	56.7 ± 16.7	<0.001
MAP (mmHg)	92.5 ± 7.6	94.2 ± 6.4	95.2 ± 5.7	105.8 ± 10.5	107.4 ± 10.3	109.3 ± 10.8	<0.001
HR (bpm)	72.1 ± 10.5	70.8 ± 9.9	71.6 ± 10.1	74.8 ± 11.5	73.7 ± 11.3	75.3 ± 11.2	<0.001
ALT	16.2 ± 18.9	18.4 ± 9.3	21.8 ± 12.5	18.2 ± 12.9	22.1 ± 16.5	25.3 ± 15.3	<0.001
AST	20.2 ± 13.9	20.3 ± 6.3	21.7 ± 7.6	21.0 ± 9.5	22.2 ± 12.4	23.8 ± 9.7	<0.001
LVH, *n* (%)	12 (0.6)	15 (3.1)	4 (2.5)	54 (1.9)	116 (6.0)	44 (4.2)	<0.001

Data are mean ± SD or percentage as marked. *p*-value: independent *t*-test analysis of variance for numeric variables and Chi-square test for categoric variables. eGFR is an estimate of GFR for the modified MDRD formula, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular diseases; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; HR, heart rate; ALT, alanine transaminase; AST, Aspartate transaminase; LVH, left ventricular hypertrophy.

Table 3 Odds ratios and 95% confidence intervals for ASCVD among men and women

	Phenotype	ASCVD (G)	*p*-value	ASCVD (N)	*p*-value
		OR (95% CI)		OR (95% CI)	
Model 1	Normal metabolic status	(Ref.)		(Ref.)	
	Dysmetabolic status	2.996 (2.714–3.307)	<0.001	1.046 (1.042–1.050)	<0.001
Model 2	Normal metabolic status	(Ref.)		(Ref.)	
	Dysmetabolic status	4.653 (4.013–5.395)	<0.001	1.077 (1.070–1.084)	<0.001
Model 1	Normal weight	(Ref.)		(Ref.)	
	Overweight	1.874 (1.697–2.070)	<0.001	1.027 (1.023–1.031)	<0.001
	Obese	2.800 (2.433–3.222)	<0.001	1.039 (1.034–1.044)	<0.001
Model 2	Normal weight	(Ref.)		(Ref.)	
	Overweight	1.954 (1.679–2.273)	<0.001	1.030 (1.023–1.036)	
	Obese	3.289 (2.681–4.035)	<0.001	1.044 (1.036–1.052)	
Model 1	Normal weight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and normal metabolic status	2.466 (2.121–2.866)	<0.001	1.040 (1.035–1.046)	<0.001
	Obese and normal metabolic status	1.430 (1.265–1.615)	<0.001	1.017 (1.012–1.023)	<0.001
	Normal weight and dysmetabolic status	4.134 (3.539–4.831)	<0.001	1.054 (1.049–1.060)	<0.001
	Overweight and dysmetabolic status	2.231 (1.797–2.770)	<0.001	1.031 (1.023–1.039)	<0.001
	Obese and dysmetabolic status	4.106 (3.436–4.906)	<0.001	1.055 (1.049–1.061)	<0.001
Model 2	Normal weight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and normal metabolic status	3.761 (2.980–4.747)	<0.001	1.063 (1.053–1.073)	0.001
	Obese and normal metabolic status	1.351 (1.112–1.643)	0.002	1.015 (1.006–1.024)	0.001
	Normal weight and dysmetabolic status	6.649 (5.246–8.427)	<0.001	1.076 (1.066–1.086)	<0.001
	Overweight and dysmetabolic status	1.776 (1.276–2.473)	<0.001	1.011 (0.998–1.024)	0.110
	Obese and dysmetabolic status	7.717 (5.905–10.084)	<0.001	1.082 (1.072–1.093)	<0.001

(*Continued*)

Table 3 | Odds ratios and 95% confidence intervals for ASCVD among men and women—*Continued*

Phenotype	ASCVD (G) OR (95% CI)	*p*-value	ASCVD (N) OR (95% CI)	*p*-value
Obese and normal metabolic status	(Ref.)		(Ref.)	
Normal weight and dysmetabolic status	4.308 (3.326–5.581)	<0.001	1.075 (1.062–1.089)	<0.001
Overweight and dysmetabolic status	1.308 (0.926–1.848)	0.128	0.996 (0.980–1.013)	0.661
Obese and dysmetabolic status	4.785 (3.619–6.328)	<0.001	1.043 (1.036–1.051)	<0.001
Overweight and normal metabolic status	(Ref.)		(Ref.)	
Overweight and dysmetabolic status	0.461 (0.322–0.660)	<0.001	0.933 (0.915–0.951)	<0.001

Model 1: Unadjusted. Model 2: Adjusting for age, sex, smoking. Ref, Reference; G, categorical variables; N, continuous variables.

Table 4 | Odds ratios and 95% confidence intervals for ASCVD among men

	Phenotype	ASCVD (G) OR (95% CI)	*p*-value	ASCVD (N) OR (95% CI)	*p*-value
Men					
Model 1	Normal metabolic status	(Ref.)		(Ref.)	
	Dysmetabolic status	2.640 (2.109–3.304)	<0.001	1.046 (1.040–1.052)	<0.001
Model 2	Normal metabolic status	(Ref.)		(Ref.)	
	Dysmetabolic status	6.133 (4.524–8.315)	<0.001	1.111 (1.099–1.122)	<0.001
Model 1	Normal weight	(Ref.)		(Ref.)	
	Overweight	1.900 (1.539–2.347)	<0.001	1.024 (1.018–1.030)	<0.001
	Obese	2.234 (1.649–3.025)	<0.001	1.038 (1.030–1.045)	<0.001
Model 2	Normal weight	(Ref.)		(Ref.)	
	Overweight	3.124 (2.322–4.203)	<0.001	1.047 (1.037–1.057)	<0.001
	Obese	4.221 (2.817–6.326)	<0.001	1.066 (1.054–1.078)	<0.001
Model 1	Normal weight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and normal metabolic status	2.582 (1.781–3.744)	<0.001	1.043 (1.033–1.052)	<0.001
	Obese and normal metabolic status	1.608 (1.256–2.059)	<0.001	1.016 (1.008–1.024)	<0.001
	Normal weight and dysmetabolic status	3.503 (2.479–4.949)	<0.001	1.051 (1.042–1.059)	<0.001
	Overweight and dysmetabolic status	1.863 (1.186–2.927)	<0.001	1.026 (1.014–1.038)	<0.001
	Obese and dysmetabolic status	3.065 (2.074–4.529)	<0.001	1.055 (1.046–1.065)	<0.001
Model 2	Normal weight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and normal metabolic status	7.361 (4.415–12.272)	<0.001	1.096 (1.080–1.113)	<0.001
	Obese and normal metabolic status	2.830 (1.946–4.116)	<0.001	1.033 (1.020–1.046)	<0.001
	Normal weight and dysmetabolic status	9.542 (5.991–15.197)	<0.001	1.110 (1.095–1.126)	<0.001
	Overweight and dysmetabolic status	2.766 (1.418–5.394)	0.003	1.026 (1.006–1.045)	0.010
	Obese and dysmetabolic status	9.796 (5.833–16.450)	<0.001	1.121 (1.104–1.139)	<0.001
	Obese and normal metabolic status	(Ref.)		(Ref.)	
	Normal weight and dysmetabolic status	3.364 (2.010–5.630)	<0.001	1.095 (1.076–1.114)	<0.001
	Overweight and dysmetabolic status	0.931 (0.456–1.900)	0.844	0.996 (0.972–1.021)	0.750
	Obese and dysmetabolic status	3.432 (1.965–5.996)	<0.001	1.112 (1.090–1.135)	<0.001
	Overweight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and dysmetabolic status	0.317 (0.142–0.707)	0.005	0.920 (0.895–0.947)	<0.001

Model 1: Unadjusted. Model 2: Adjusting for age, sex, smoking. Ref, Reference; G, categorical variables; N, continuous variables.

status, compared to those with obese–normal metabolic status, all adjusted for confounding variables. The odds of reporting ASCVD risk was significantly lower in men (OR: 0.317, 95% CI: 0.142–0.707; p = 0.005) and women (OR: 0.487, 95% CI: 0.320–0.739; p = 0.001) with the overweight–dysmetabolic status phenotype compared to those with an overweight-normal metabolic phenotype.

4. DISCUSSION

Our study suggested that obesity with metabolic syndrome in all groups have the highest risk of ASCVD, and this result is not unexpected. Obesity and metabolic syndrome are risk factors for ASCVD, and their additive effects may further increase the risk of ASCVD. Different factors such as the elevated risk of complications associated with obesity (type 2 diabetes, hyperlipidemia, hypertension). Cytokines secret by adipose tissue (e.g., tumor necrosis factor, interleukin-6, and fibrinogen activation inhibitors), increased heart and blood flow load by adipose tissue, insulin resistance and lipid toxicity would increase the risk of ASCVD in obesity [17,18].

Metabolic syndrome has been found to be associated with ASCVD, and its effects are independent of insulin resistance [19]. Metabolic risk factors (elevated blood pressure, elevated blood glucose, atherogenic dyslipidemia, a prothrombotic state and a proinflammatory state) affect the atherogenic process. But because of the

Table 5 Odds ratios and 95% confidence intervals for ASCVD among women

	Phenotype	ASCVD (G)	*p*-value	ASCVD (N)	*p*-value
		OR (95% CI)		OR (95% CI)	
Women					
Model 1	Normal metabolic status	(Ref.)		(Ref.)	
	Dysmetabolic status	4.085 (3.621–4.609)	<0.001	1.071 (1.064–1.078)	<0.001
Model 2	Normal metabolic status	(Ref.)		(Ref.)	
	Dysmetabolic status	3.708 (3.123-4.402)	<0.001	1.067 (1.057–1.078)	<0.001
Model 1	Normal weight	(Ref.)		(Ref.)	
	Overweight	1.873 (1.691–2.124)	<0.001	1.030 (1.024–1.037)	<0.001
	Obese	3.456 (2.920–4.090)	<0.001	1.051 (1.043–1.059)	<0.001
Model 2	Normal weight	(Ref.)		(Ref.)	
	Overweight	1.567 (1.311–1.872)	<0.001	1.020 (1.011–1.030)	<0.001
	Obese	2.628 (2.069–3.339)	<0.001	1.032 (1.021–1.043)	<0.001
Model 1	Normal weight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and normal metabolic status	3.412 (2.851–4.083)	<0.001	1.062 (1.052–1.071)	<0.001
	Obese and normal metabolic status	1.270 (1.073–1.504)	0.006	1.015 (1.006–1.024)	<0.001
	Normal weight and dysmetabolic status	5.396 (4.475–6.508)	<0.001	1.075 (1.066–1.085)	<0.001
	Overweight and dysmetabolic status	2.778 (2.124–3.634)	<0.001	1.044 (1.032–1.056)	<0.001
	Obese and dysmetabolic status	5.848 (4.733–7.226)	<0.001	1.076 (1.065–1.086)	<0.001
Model 2	Normal weight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and normal metabolic status	2.770 (2.136–3.592)	<0.001	1.053 (1.039–1.067)	<0.001
	Obese and normal metabolic status	0.995 (0.790–1.253)	0.966	1.002 (0.988–1.016)	0.785
	Normal weight and dysmetabolic status	4.875 (3.697–6.429)	<0.001	1.063 (1.049–1.077)	<0.001
	Overweight and dysmetabolic status	1.372 (0.939–2.003)	0.102	1.005 (0.987–1.024)	0.589
	Obese and dysmetabolic status	5.821 (4.253–7.968)	<0.001	1.067 (1.052–1.082)	<0.001
	Obese and normal metabolic status	(Ref.)		(Ref.)	
	Normal weight and dysmetabolic status	4.117 (3.020–5.611)	<0.001	1.075 (1.054–1.096)	<0.001
	Overweight and dysmetabolic status	1.288 (0.863–1.923)	0.215	1.002 (0.979–1.026)	0.851
	Obese and dysmetabolic status	4.647 (3.327–6.491)	<0.001	1.080 (1.058–1.101)	<0.001
	Overweight and normal metabolic status	(Ref.)		(Ref.)	
	Overweight and dysmetabolic status	0.487 (0.320–0.739)	0.001	0.943 (0.919–0.968)	<0.001

Model 1: Unadjusted. Model 2: Adjusting for age, sex, smoking. Ref, Reference; G, categorical variables; N, continuous variables.

mutual influence and common basis, different metabolic factors are not weighted equally [17], and so it is difficult to determine the impact on each factor of atherosclerosis [10].

Dyslipidemia may be the most understandable atherogenic factor and easier to control. Elevated blood pressure may also influence vascular endothelial function, making cholesterol more likely to be deposited on the endothelium. Elevated blood glucose enhances effects of oxidative stress in the arterial wall, glycosylation of arterial wall proteins, deposition of advanced glycation end products in the arterial wall, and activation of protein kinase C [20]. All these lead to atherosclerosis. Inflammatory conditions may also accelerate arterial endothelial dysfunction [10], leading to the formation of atherosclerosis.

Our study suggested that ASCVD risk is also higher in patients with obesity and normal metabolic status compared to patients with normal weight metabolic syndrome, indicating that abnormal metabolic state has a greater impact on ASCVD than obesity, which may be associated with the mechanism of the obesity paradox. The effects of metabolic syndrome have been discussed above. Current investigations on the obesity paradox suggested that obesity may have some benefits. These may involve earlier treatment for abnormal metabolic state [21], better cognitive function with adipose tissue [22], nutritional reserves for acute stress events and increased metabolic needs [23], adipose tissue productions including beneficial hormones and cytokines [5]. The above benefits may offset the adverse effects of obesity. Therefore, obese individuals without metabolic syndrome may be obese and relatively healthy. Studies have confirmed that endothelial function with obesity may still be normal [24]. Obese insulin-sensitive individuals had a favorable metabolic profile compared to the obese insulin-resistant group [25]. The state of healthy obesity may be unstable and affected by lifestyle, and may progress to metabolic syndrome [26,27] so that it increases the risk of ASCVD.

It should be noted that the assessment of metabolic syndrome does not include all major risks of ASCVD, such as age, smoking status and lipid levels, so this assessment cannot be used to replace ASCVD risk assessment [10].

According to gender analysis, there was no statistical difference in the risk of ASCVD in women with different weight and metabolic status. However, in the case of metabolic abnormalities, the risk of ASCVD in women increased significantly, suggesting that the effects of metabolic abnormalities on women were more pronounced than obesity. Compared to men, women's physiological structure, hormone levels, and vascular endothelial function have unique characteristics [28]. A study showed that serum Follicle-stimulating Hormone (FSH) levels were negatively associated with 10-year ASCVD risk in postmenopausal women regardless of central obesity. FSH and numerous metabolic risks perturbations were independent of the measure of adiposity [29]. This suggests that women's ASCVD risk factors may be more affected by hormone levels than obesity. However, further investigations are needed due to the large number of confounding factors.

In addition, our study suggested that overweight with abnormal metabolism and obesity with normal metabolism cannot determine the risk of ASCVD. When BMI is due to overweight, BMI is more important than metabolic factors. When BMI is due to obesity, metabolic factors are more important than BMI.

The above results suggest that in addition to metabolic factors, the predictive value of obesity for ASCVD varies. This may be because BMI alone cannot effectively determine the type of obesity and estimate its risk. A study [30] suggested that abdominal obesity indices (waist-to-height ratio), but not BMI, predicted prevalent ASCVD and its risk factors in this elderly Chinese population. Another study in Filipino women also yielded similar results [30].

Both men and women may experience decreased muscle mass and loss of bone structure with age [31], which affect the accuracy of BMI. The presence of abdominal obesity is more highly correlated with metabolic risk factors than is an elevated BMI [10]. Therefore, it is easier to determine the type of metabolism and ASCVD risk with abdominal obesity indices, visceral adiposity index [26] and percent body fat [27]. The China-PAR Project [32] developed effective tools including waist circumference with good performance for 10-year ASCVD risk among the Chinese population. Furthermore, as described above, adipose tissue may have both beneficial and adverse effects, and thus the confounding effects of obesity/overweight and metabolic abnormalities make it difficult to determine the clinical endpoint.

In conclusion, our study extended our previous observations [33] and suggested that abnormal metabolic status may have a greater impact on ASCVD than obesity. "Obesity and health" may be one of the mechanisms of the obesity paradox. However, further studies are needed due to the numerous factors of metabolic syndrome and mutual influence.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

AA and J. Zuo contributed in study conceptualization and writing (review and editing) the manuscript. J. Zuo, YH, SZ and J. Zhao contributed in data curation, formal analysis and writing (original draft). J. Zuo and SZ contributed in funding acquisition and project administration. AA, J. Zuo, IT and MB contributed in supervised the project. J. Zuo, YH and SZ contributed in formal analysis and writing (original draft) the manuscript.

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