BMC Endocrine Disorders

RESEARCH

Open Access

Relationship of different metabolic obesity phenotypes with reflux esophagitis: a propensity score matching analysis

Tao He[1,2†], Peng Wang[1,2†], Li-Xia Wang[1,2†], Meng-Han Tong[1,2] and Zhi-Jun Duan[1,2*]

Abstract

Background Obesity is associated with an increased risk of reflux esophagitis (RE). Metabolic abnormalities have been implicated in the pathogenesis of RE. However, the role of metabolic status in the risk of RE among individuals with varying degrees of obesity remains unclear. Therefore, our study aimed to assess the association between metabolic obesity phenotypes and the risk of RE.

Methods This study included a cohort of 24,368 participants aged 18 years and older who underwent upper gastrointestinal endoscopy at the First Affiliated Hospital of Dalian Medical University during health checkups between January 1, 2008, and December 31, 2021. Among these participants, a total of 9,947 individuals were classified into four groups based on their obesity phenotype: metabolically healthy normal weight (MHNW), metabolically healthy obesity (MHO), metabolically unhealthy normal weight (MUNW), and metabolically unhealthy obesity (MUO). To account for potential confounding factors, multivariate logistic regression analysis was applied to examine the association between metabolic obesity phenotypes and the risk of RE, with stratification by sex and age.

Results Among all participants, the MUNW, MHO, and MUO groups demonstrated a higher risk of RE when compared to the MHNW group. After controlling for all confounding factors, the MUO group exhibited the highest risk, with an odds ratio (OR) of 3.723 (95% CI: 2.751–5.040) in males and 5.482 (95% CI: 4.080–7.367) in females. The prevalence of RE increased in proportion to the number of metabolic risk factors. Subgroup analyses, which accounted for all confounders, revealed that the MHO, MUNW, and MUO phenotypes were associated with an elevated risk of RE in individuals under 60 years old as well as those over 60 years old. Interestingly, a more comprehensive analysis indicated that obesity may have a greater effect on the risk of RE than metabolic disorders.

Conclusions Both metabolic disorders and obesity were associated with an increased risk of RE. The effect of obesity on RE prevalence may be stronger than that of metabolic disorders, emphasizing the significance of obesity regardless of metabolic health status. Clinical interventions should address not only obesity but also metabolic disorders in order to reduce the risk of RE.

†Tao He, Peng Wang and Li-Xia Wang contributed equally to this work.

*Correspondence:
Zhi-Jun Duan
cathydoctor@sina.com

Full list of author information is available at the end of the article

Keywords Metabolic obesity phenotype, Reflux esophagitis, Sex difference, Metabolic disorders, Age difference, Obesity phenotype

Introduction

The prevalence of reflux esophagitis (RE) has been steadily increasing due to improved living standards and changes in lifestyle and dietary habits. RE has become a significant public health issue in Asia [1]. RE can indeed lead to the development of Barrett's esophagus (BE) or esophageal adenocarcinoma (EAC), both of which can significantly impact a patient's quality of life [2]. Reducing the occurrence of RE can lower the chances of developing BE and EAC [3]. Hence, it becomes imperative to meticulously ascertain the risk factors associated with RE and accurately pinpoint individuals who are predisposed to an elevated risk of developing this condition. Such discernment is crucial to establishing effective preventive and intervention measures tailored to each individual's needs and circumstances.

Obesity, the paramount menace to global public health, is a prominent risk factor for RE. A meta-analysis of 22 studies revealed that the obese population is at an elevated risk for the prevalence of RE [4]. Obesity is inherently linked to a cluster of metabolic abnormalities, including dyslipidemia, hypertension, and hyperglycemia [5]. Retrospective case-control research conducted in China found that metabolic syndrome (Mets) was correlated with RE [6]. However, the metabolic characteristics of obese individuals are different, and the effect on RE is not yet fully understood. Certain individuals with obesity do not exhibit metabolic disorders and are classified as having metabolically healthy obesity (MHO) [7]. The MHO phenotype can present distinct disease outcomes compared with a metabolically unhealthy phenotype and a metabolically healthy normal weight (MHNW) phenotype [8]. Recent studies conducted in the past decade have indicated that individuals with MHO may face a higher risk of developing cardiovascular disease, Hashimoto's thyroiditis (HT), non-alcoholic fatty liver disease (NAFLD), and certain types of cancers compared to those with MHNW [9–11].

However, the existing evidence on the combined effects of obesity and different metabolic phenotypes on the risk of RE is limited. Moreover, since RE and metabolic health status often manifests differently across various sex and age groups, it is important to investigate whether this association is influenced by sex and age. Therefore, in this study, we aimed to distinguish between obesity and metabolic health status by considering the components of metabolic abnormalities and obesity status. Subsequently, we examined the relationship between different obesity phenotypes and RE while exploring sex-specific associations and the potential modifying role of age in this relationship. The ultimate goal was to provide valuable insights for clinical prevention and intervention strategies.

Materials and methods

We reviewed the clinical records of 24,368 subjects aged 18 years and older who underwent routine health checkups, including physical examinations, blood tests, and upper gastrointestinal endoscopy, at the First Affiliated Hospital of Dalian Medical University between January 1, 2008, and December 31, 2021. The study excluded participants who had missing values on height, weight, and information on metabolic syndrome (n=6,962), were underweight (body mass index (BMI) < 18.5 kg/m^2; n=4,614), were currently taking drugs such as H2-receptor antagonists or proton pump inhibitors (PPIs) (n=1,102), had a history of gastric surgery (n=277), and had been previously diagnosed with gastric or esophageal cancer (n=1,466). Finally, 9,947 participants were recruited for the analysis. They were categorized into two groups: 2,316 individuals with RE and 7,631 individuals without RE. Subsequently, individuals were further divided into four specific groups: MHNW with 1,739 individuals, MHO with 1,329 individuals, metabolically unhealthy normal weight (MUNW) 3,885 individuals, and metabolically unhealthy obese (MUO) with 2,994 individuals (Fig. 1). The First Affiliated Hospital of Dalian Medical University Ethics Committee granted ethical approval for this study (PJ-KS-KY-2020-04)), and informed consent for the use of all participant data was obtained, adhering to the principles of the Helsinki Declaration. Clinical trial number: not applicable.

Data collection

Anthropometrics

Data on demographic characteristics, personal medical history, body weight, height, and medication use were recorded by trained nurses according to standardized methods. Demographic characteristics included age, sex, smoking status, and alcohol consumption. In addition, personal medical history included any instances of diabetes mellitus, hypertension, surgery, or malignancy. Medication history included current use of antihypertensive drugs, hypoglycemic agents, lipid-lowering drugs, PPIs, and H2-receptor drugs. All subjects underwent anthropometric assessments while donning lightweight undergarments and in a state of fasting following voiding. Weight and height were gauged with an accuracy of 0.1 kg and 0.1 cm, respectively. Blood pressure using an electronic sphygmomanometer (HEM-770 A Fuzzy)

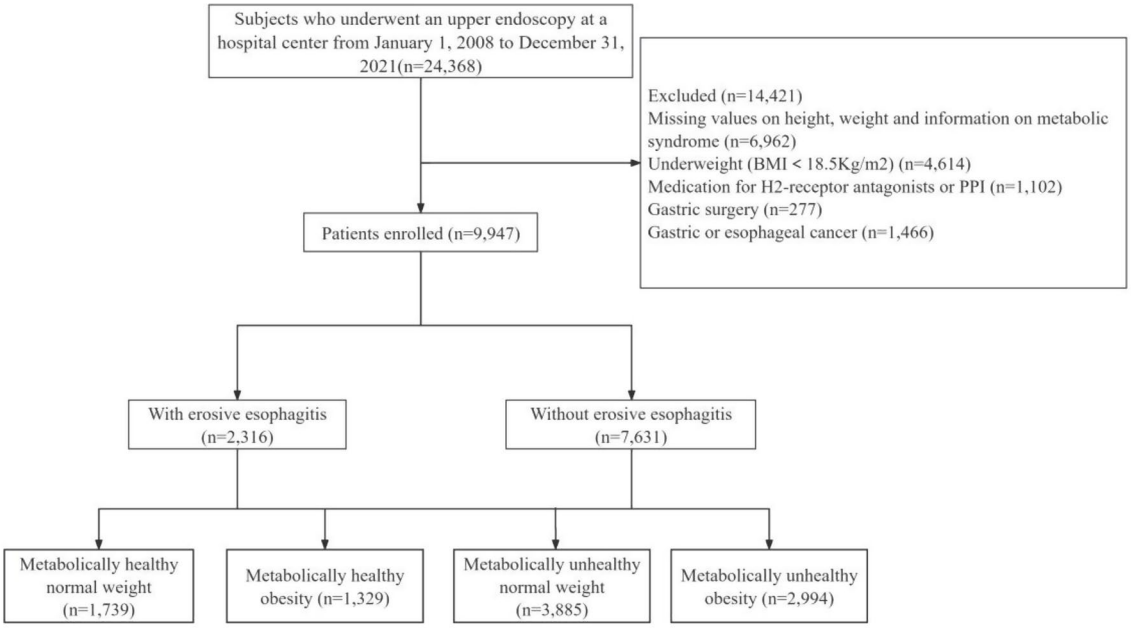

Fig. 1 Flowchart of the study participants

was assessed at the conclusion of the physical examination while the participant was seated, and a minimum of 10 min of rest was provided prior to the measurements.

Laboratory indicators

Blood samples were obtained after an overnight fast of at least 8 h. The following biochemical parameters, including albumin (ALB), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), and uric acids (UA) were measured by the Roche Cobas c701 automatic analyzer (Roche Diagnostics, Germany). All blood specimens were tested within 24 h at the Medical Laboratory Center of the First Affiliated Hospital of Dalian Medical University.

Evaluation of *H. Pylori* infection

Helicobacter pylori infection was defined as a positive result in either the ^{13}C-urea breath test (UBT) or the rapid urease test. Specimens were obtained through endoscopic biopsy, fixed with formalin, and then confirmed with Giemsa staining. The rapid urease test was considered positive if the color of the gel changed to pink or red after 24 h at room temperature.

To conduct the test, an initial breath sample was collected after a 4 h fasting period. The patient orally received 100 mg of ^{13}C-urea powder (UBiTkit; Otsuka Pharmaceutical, Tokyo, Japan) dissolved in 100 mL of water. After 20 min, the second breath sample was taken, and the cutoff value for a positive result was set at 2.5%. Subsequently, the collected samples underwent analysis using an isotope ratio mass spectrometer (UBiT-IR300; Otsuka Pharmaceutical).

Gastrointestinal endoscopy

The definition of RE was based on the results of the upper gastrointestinal endoscopy (GIF-H260, -HQ260; Olympus; Tokyo, Japan). All the recruited people were divided into two groups: those with RE and those without RE. Two authors who were unaware of the initial endoscopy records visually reviewed and reevaluated all the endoscopy results. The severity of RE was classified using the Los Angeles categorization (LA) as follow: [12]

(1) Grade A: One (or more) mucosal break no longer than 5 mm, that does not extend between the tops of two mucosal folds.

(2) Grade B: One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds.

(3) Grade C: One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference.

(4) Grade D: One (or more) mucosal break which involves at least 75% of the esophageal circumference.

Gastroesophageal reflux disease questionnaire (GerdQ)

All participants independently completed the GerdQ questionnaire, which was developed as part of the Diamond study [13, 14]. This simple questionnaire asks participants to report the frequency of specific symptoms—heartburn, regurgitation, epigastric pain, nausea, sleep disturbances, or the use of over-the-counter

medications due to these symptoms—experienced over the previous seven days. The GerdQ uses a four-point Likert scale (0–3) to assess the frequency of four positive predictors of GERD: heartburn, regurgitation, sleep disturbances caused by reflux, and the use of over-the-counter medications for reflux symptoms. Additionally, it employs a reversed Likert scale (3–0) to score two negative predictors: epigastric pain and nausea. The total score from the questionnaire ranges from 0 to 18. GerdQ has been widely used in numerous studies, with most validation studies establishing a cut-off score of 8. A score of 8 or higher indicates a high likelihood of GERD [15–17].

Definitions

The BMI was calculated as weight divided by height squared (kg/m^2). Obesity was defined according to the World Health Organization Criteria for East Asians (BMI ≥ 25 kg/m^2) [18, 19]. Metabolic status was assessed using the Adult Treatment Panel III criteria [20], and having less than two of the following criteria was defined as metabolically healthy: (1) systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg; (2) fasting blood glucose ≥ 5.6 mmol/L; (3) high-density lipoprotein-cholesterol < 1.03 mmol/L for males and < 1.29 mmol/L for females; and (4) triglycerides ≥ 1.7 mmol/L. Finally, for BMI criteria, participants were categorized into four phenotypes: (1) MHNW: BMI < 25 kg/m^2 and fewer than two metabolic syndrome components; (2) MHO: BMI ≥ 25 kg/m^2 and fewer than two metabolic syndrome components; (3) MUNW: BMI < 25 kg/m^2 and at least two metabolic syndrome components; (4) MUO: BMI ≥ 25 kg/m^2 and at least two metabolic syndrome components.

Statistical analysis

All statistical analyses were performed using the SPSS 26.0 software package (SPSS Institute, Chicago, IL). Continuous variables were assessed for normal distribution using the Shapiro–Wilk test and reported as mean ± standard deviation. Categorical variables were presented as frequencies and percentages. We performed propensity score matching (PSM) on RE and No-RE groups to adjust for differences in patient background and to reduce selection bias in anon-randomized study. We matched age, BMI, smoking, alcohol, and H. pylori to adjust potential confounding effects according to the differences in baseline characteristics between the patients with and without RE group. After matching, the absolute standardized mean differences to diagnose the balance after matching were less than 0.1. Gender-specific comparisons of basic characteristics were conducted using a *t*-test for continuous variables and the chi-square test for categorical variables. If more than two groups were compared, continuous variables were compared using one-way analysis of variance (ANOVA). Tukey's multiple comparisons test was used for post-hoc comparisons after the ANOVA tests. Kruskal-Wallis test was used for nonparametric statistical analysis. Mann-Whitney test with Bonferroni correction was used as post-hoc analysis for nonparametric statistical analysis. Logistic regression analysis was employed to investigate the associations between different metabolic obesity phenotypes and the prevalence of RE. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the MHO, MUNW, and MUO groups, with the MHNW group as the reference category. Furthermore, separate analyses were performed to examine the prevalence of RE for different metabolic obesity phenotypes based on sex and age. A significance level of <0.05 (two-tailed p-value) was considered statistically significant.

Results

Patient characteristics before and after PSM

The study included 9,947 subjects, with 4,219 males and 5,728 females. The prevalence of RE was 24.2% in males and 22.6% in females. Baseline characteristics of the subjects are shown separately for males and females according to the prevalence of RE (Tables 1 and 2). Regardless of gender, individuals diagnosed with RE exhibited several notable differences compared to those without the diagnosis. They were more likely to be older and have higher GERDQ score, SBP, DBP, FBG, TC, TG, LDL, UA, AST, ALT, and GGT levels, as well as a higher incidence of smoking, alcohol consumption, and *H. pylori* infection. Additionally, they showed lower levels of ALB and HDL (all $p<0.05$). After matching, significant differences remained in unadjusted factors, except for ALT and GGT in females, and SBP, HDL and AST in males.

Patient characteristics based on metabolic obesity phenotype

The baseline characteristics of the female participants ($n=5,728$) are summarized in Table 3 according to their metabolic obesity phenotypes. There were 866 (15.0%) in the MHNW group, 685 (12.0%) in the MHO group, 2,444 (42.7%) in the MUNW group, and 1,733 (30.3%) in the MUO group. The prevalence of RE was 11.7% in the MHNW group, 23.8% in the MHO group, 20.6% in the MUNW group, and 30.5% in the MUO group ($p<0.05$) (Fig. 2A). Among female participants, there was a significant increase in the prevalence of RE with an increasing number of metabolic risk factors ($p<0.05$) (Fig. 2B). The average age of females was 65.23 ± 11.86 years. Individuals with the MUNW and MUO phenotypes exhibited significantly higher SBP, DBP, FBG, TG, UA, AST, ALT, GGT, GERDQ score, smoking, and lower levels of HDL and ALB compared to those with the MHNW and MHO phenotypes (all $p<0.001$). Individuals with the MHO

Table 1 Patient characteristics in females before and after propensity score matching

Variables	Before matching			After matching		
	No RE	RE	*p*-value	No RE	RE	*p*-value
No. of participants	4432	1296		1224	1224	
Age, years	64.93 ± 11.77	66.26 ± 12.11	< 0.001	66.27 ± 11.18	66.19 ± 12.14	0.863
Smoking, n (%)	562 (12.7)	235 (18.1)	< 0.001	197 (16.1)	200 (16.3)	0.869
Alcohol, n (%)	439 (9.9)	354 (27.3)	< 0.001	311 (25.4)	317 (25.9)	0.781
H. pylori, n (%)	2253 (50.8)	852 (65.7)	< 0.001	780 (63.7)	780 (63.7)	1
GERDQ, score	5.98 ± 1.62	10.47 ± 2.97	< 0.001	4.31 ± 1.29	10.56 ± 2.97	< 0.001
BMI, kg/m^2	24.82 ± 4.13	25.23 ± 3.58	0.001	24.96 ± 4.10	25.25 ± 3.57	0.058
SBP, mm Hg	128.54 ± 20.62	130.64 ± 13.75	0.001	127.76 ± 19.85	130.86 ± 13.31	< 0.001
DBP, mm Hg	79.29 ± 9.57	80.82 ± 9.32	< 0.001	78.79 ± 9.55	80.87 ± 9.33	< 0.001
FBG, mm Hg	5.62 ± 1.54	6.18 ± 2.15	< 0.001	5.54 ± 1.36	6.14 ± 2.20	< 0.001
TC, mmol/L	4.23 ± 1.21	6.22 ± 2.42	< 0.001	4.09 ± 1.18	6.07 ± 1.74	< 0.001
TG, mmol/L	1.55 ± 0.33	2.06 ± 0.34	< 0.001	1.51 ± 0.32	2.06 ± 0.33	< 0.001
HDL, mmol/L	1.18 ± 0.34	1.13 ± 0.31	< 0.001	1.19 ± 0.35	1.14 ± 0.31	< 0.001
LDL, mmol/L	2.47 ± 0.78	4.79 ± 2.47	< 0.001	2.47 ± 0.86	4.57 ± 2.34	< 0.001
UA, μmol/L	285.67 ± 74.05	357.12 ± 128.51	< 0.001	282.62 ± 74.18	350.48 ± 127.07	< 0.001
AST, U/L	21.69 ± 11.11	23.34 ± 17.95	< 0.001	21.37 ± 8.96	23.20 ± 18.39	0.002
ALT, U/L	25.25 ± 20.62	27.86 ± 27.76	< 0.001	26.38 ± 23.77	26.88 ± 28.18	0.637
GGT, U/L	33.41 ± 40.81	39.71 ± 49.59	< 0.001	35.06 ± 46.54	37.17 ± 43.25	0.245
ALB, g/dL	41.38 ± 5.35	39.56 ± 5.42	< 0.001	41.69 ± 5.31	39.57 ± 5.40	< 0.001

Abbreviations BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALB, albumin; RE, reflux esophagitis

Table 2 Patient characteristics in males before and after propensity score matching

Variables	Before matching			After matching		
	No RE	RE	*p*-value	No RE	RE	*p*-value
No. of participants	3199	1020		952	952	
Age, years	64.66 ± 13.30	67.61 ± 12.71	< 0.001	66.95 ± 12.47	67.01 ± 12.67	0.922
Smoking, n (%)	880 (27.5)	377 (37.0)	< 0.001	348 (36.6)	332 (34.9)	0.444
Alcohol, n (%)	633 (19.8)	416 (40.9)	< 0.001	374 (39.3)	350 (36.8)	0.257
H. pylori, n (%)	1635 (51.1)	696 (68.2)	< 0.001	656 (68.9)	628 (66.0)	0.187
GERDQ, score	7.21 ± 2.74	11.54 ± 2.82	< 0.001	9.86 ± 2.20	11.61 ± 2.82	< 0.001
BMI, kg/m^2	24.91 ± 4.14	25.77 ± 3.46	< 0.001	25.73 ± 4.43	25.65 ± 3.43	0.658
SBP, mm Hg	131.24 ± 18.43	134.26 ± 15.58	< 0.001	135.19 ± 21.64	134.14 ± 15.74	0.227
DBP, mm Hg	80.44 ± 16.87	84.52 ± 27.68	< 0.001	80.45 ± 18.15	84.72 ± 28.30	< 0.001
FBG, mm Hg	5.67 ± 1.65	5.99 ± 1.90	< 0.001	5.69 ± 1.40	5.96 ± 1.94	< 0.001
TC, mmol/L	4.36 ± 1.41	6.28 ± 1.45	< 0.001	4.50 ± 1.39	6.20 ± 1.45	< 0.001
TG, mmol/L	1.68 ± 0.36	1.96 ± 0.49	< 0.001	1.70 ± 0.36	1.93 ± 0.48	< 0.001
HDL, mmol/L	1.15 ± 0.49	1.11 ± 0.33	0.016	1.13 ± 0.49	1.12 ± 0.32	0.677
LDL, mmol/L	2.99 ± 1.65	3.68 ± 2.52	< 0.001	2.99 ± 1.62	3.56 ± 2.42	< 0.001
UA, μmol/L	288.91 ± 71.46	358.96 ± 128.10	< 0.001	294.58 ± 68.46	353.08 ± 128.81	< 0.001
AST, U/L	20.65 ± 5.27	21.32 ± 12.71	0.017	21.09 ± 5.41	21.29 ± 13.03	0.670
ALT, U/L	24.73 ± 22.17	28.50 ± 24.99	< 0.001	24.53 ± 20.02	27.96 ± 25.41	0.001
GGT, U/L	15.91 ± 4.16	28.06 ± 14.54	< 0.001	29.06 ± 14.77	16.03 ± 4.05	< 0.001
ALB, g/dL	41.51 ± 5.26	39.49 ± 5.35	< 0.001	41.11 ± 5.31	39.43 ± 5.39	< 0.001

Abbreviations BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, Triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALB, albumin; RE, reflux esophagitis

and MUO phenotypes also had higher BMI levels compared to those with the MHNW and MUNW phenotypes (all $p<0.001$). Furthermore, the MHO, MUNW, and MUO phenotypes exhibited a higher prevalence of *H. pylori* infection compared to the MHNW phenotype (all $p<0.05$). In addition, alcohol consumption, LDL, and age significantly differed among the four groups (all $p<0.001$).

Table 3 Baseline characteristics of study participants based on different metabolic obesity phenotypes in females

Variables	MHNW	MHO	MUNW	MUO	*p*-value
No. of participants	866	685	2444	1733	
Age, years	63.63 ± 11.97	64.82 ± 12.28	65.07 ± 11.73*	66.41 ± 11.70*,†,‡	0.003
Smoking, n (%)	117 (13.5)	104 (15.2)	290 (11.9) *,†	285 (16.4) *,†,‡	< 0.001
Alcohol, n (%)	97 (11.2)	75 (10.9)	421 (17.2) †	235 (13.6) ‡	< 0.001
H. pylori, n (%)	438 (50.6)	359 (52.4) *	1318 (53.9) *	990 (57.1) *,†,‡	0.009
GERDQ, score	6.43 ± 2.18	7.07 ± 2.86*	6.87 ± 2.63*	7.43 ± 3.05*,†,‡	< 0.001
BMI, kg/m^2	22.06 ± 1.78	29.00 ± 3.53*	22.26 ± 1.73†	28.47 ± 3.06*,†,‡	< 0.001
SBP, mm Hg	117.37 ± 11.53	120.18 ± 11.17*	131.13 ± 14.78*,†	135.34 ± 25.75*,†,‡	< 0.001
DBP, mm Hg	74.75 ± 6.76	74.71 ± 6.79	81.06 ± 9.92*,†	82.02 ± 9.53*,†,‡	< 0.001
FBG, mm Hg	5.02 ± 0.45	4.98 ± 0.45	6.02 ± 1.90*,†	6.03 ± 1.94*,†	< 0.001
TC, mmol/L	4.49 ± 0.90	4.61 ± 0.89	4.70 ± 2.05*	4.77 ± 1.94*	0.001
TG, mmol/L	1.15 ± 0.29	1.44 ± 0.27*	1.77 ± 0.27*,†	1.87 ± 0.37*,†,‡	< 0.001
HDL, mmol/L	1.53 ± 0.38	1.28 ± 0.38*	1.08 ± 0.26*,†	1.07 ± 0.23*,†	< 0.001
LDL, mmol/L	2.78 ± 1.13	2.88 ± 0.92	3.02 ± 1.93*	3.11 ± 1.71*,†	< 0.001
UA, μmol/L	260.15 ± 70.34	261.65 ± 74.21	314.45 ± 99.65*,†	320.74 ± 92.69*,†	< 0.001
AST, U/L	19.02 ± 7.57	18.65 ± 6.20	23.02 ± 12.95*,†	23.59 ± 16.28*,†	< 0.001
ALT, U/L	21.96 ± 22.51	22.14 ± 25.21	27.03 ± 18.56*,†	27.55 ± 25.69*,†	< 0.001
GGT, U/L	28.35 ± 38.21	30.12 ± 28.95	35.21 ± 47.65*,†	37.96 ± 42.67*,†	< 0.001
ALB, g/dL	41.66 ± 5.29	41.58 ± 5.40	40.77 ± 5.33*,†	40.77 ± 5.58*,†	< 0.001

Abbreviations BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, Triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALB, albumin; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity

Values with normal distribution are presented as mean (SD); categorical variables are presented as n (%)

*Significant difference compared with MHNW phenotype, $P<0.05$

†Significant difference compared with MHO phenotype, $P<0.05$

‡Significant difference compared with MUNW phenotype, $P<0.05$

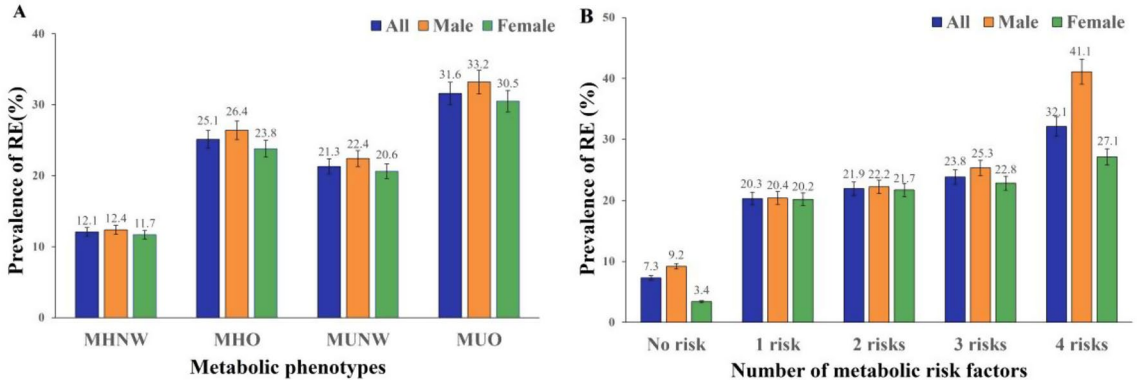

Fig. 2 The prevalence of RE among the different metabolic obesity phenotypes by sex. (**A**) The prevalence of RE among different obesity phenotypes. (**B**) The prevalence of RE among the phenotypes with different numbers of metabolic risk factors

The baseline characteristics of the male participants (n=4,219) are summarized in Table 4 according to their metabolic obesity phenotypes. There were 873 (20.7%) in the MHNW group, 644 (15.3%) in the MHO group, 1,444 (34.2%) in the MUNW group, and 1,261 (29.8%) in the MUO group. The prevalence of RE was 12.4% in the MHNW group, 26.4% in the MHO group, 22.4% in the MUNW group, and 33.2% in the MUO group ($p<0.05$) (Fig. 2A). Among male participants, there was a significant increase in the prevalence of RE with an increasing number of metabolic risk factors ($p<0.05$) (Fig. 2B). The average age of males was 65.38 ± 13.22 years. SBP, DBP, FBG, TG, UA, AST, ALT, GGT, GERDQ score, smoking, and alcohol consumption in the MUNW and MUO groups were significantly higher compared to the MHNW and MHO groups, while BMI was higher in the MHO and MUO groups (all $p<0.05$). Moreover, the MHNW, MHO, and MUNW groups were younger compared to the MUO group ($p<0.05$). In addition,

Table 4 Baseline characteristics of study participants based on different metabolic obesity phenotypes in males

Variables	MHNW	MHO	MUNW	MUO	*p*-value
No. of participants	873	644	1441	1261	
Age, years	64.25 ± 13.20	64.91 ± 13.61	65.09 ± 13.59	66.72 ± 12.48*,†,‡	< 0.001
Smoking, n (%)	204 (23.4)	173 (26.9) *	496 (34.4) *,†	384 (30.5) *,†,‡	< 0.001
Alcohol, n (%)	140 (16.0)	110 (17.1)	445 (30.9) *,†	354 (28.1) *,†	< 0.001
H. pylori, n (%)	425 (51.8)	344 (53.4) *	793 (55.0) *	742 (58.8) *,†	0.008
BMI, kg/m^2	22.11 ± 1.75	30.52 ± 17.56*	22.40 ± 1.66*,†	29.69 ± 13.92*,‡	< 0.001
GERDQ, score	7.67 ± 3.01	8.38 ± 3.39*	8.13 ± 3.25*	8.76 ± 3.49*,‡	< 0.001
SBP, mm Hg	121.67 ± 11.03	128.11 ± 11.31*	134.37 ± 14.60*,†	138.34 ± 23.29*,†,‡	< 0.001
DBP, mm Hg	75.01 ± 7.00	75.13 ± 6.82	84.61 ± 23.26*,†	85.46 ± 24.47 *,†	< 0.001
FBG, mm Hg	5.08 ± 0.88	5.09 ± 0.87	6.04 ± 1.95*,†	6.19 ± 1.96*,†	< 0.001
TC, mmol/L	4.66 ± 1.07	4.74 ± 1.03	4.89 ± 1.76*	4.91 ± 2.02*	0.001
TG, mmol/L	1.32 ± 0.32	1.55 ± 0.33*	1.82 ± 0.23*,†	2.04 ± 0.37*,†,‡	< 0.001
HDL, mmol/L	1.43 ± 0.29	1.37 ± 0.38	1.01 ± 0.48*,†	0.95 ± 0.40*,†,‡	< 0.001
LDL, mmol/L	2.99 ± 1.16	3.01 ± 1.21	3.23 ± 2.37*	3.26 ± 2.04*,†	0.001
UA, μmol/L	271.78 ± 98.28	278.94 ± 87.94	319.33 ± 92.41*,†	327.77 ± 83.59*,†	< 0.001
AST, U/L	19.55 ± 11.69	19.21 ± 6.72	22.87 ± 13.61*,†	24.64 ± 24.54*,†	< 0.001
ALT, U/L	21.56 ± 19.59	21.64 ± 22.30	29.58 ± 54.41*,†	33.00 ± 167.96*,†	0.018
GGT, U/L	26.60 ± 31.06	24.71 ± 25.19	34.86 ± 53.65*,†	38.98 ± 63.20*,†	< 0.001
ALB, g/dL	41.66 ± 5.19	41.33 ± 5.09	40.82 ± 5.35*	40.66 ± 5.55*,†	< 0.001

Abbreviations BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, Triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; ALB, albumin; MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity

Values with normal distribution are presented as mean (SD); categorical variables are presented as n (%)

*Significant difference compared with MHNW phenotype, *P*<0.05

†Significant difference compared with MHO phenotype, *P*<0.05

‡Significant difference compared with MUNW phenotype, *P*<0.05

significant differences were observed in *H. pylori* infection, TC, LDL, and ALB among the four groups (all $p<0.001$).

Figure 3 presents the percentage of RE severity and GERDQ scores (≥8) among different metabolic phenotypes in RE groups for females (A and C) and males (B and D). For females, the majority of patients in the MHNW group fall within LA-A (83/82.2%) and have a GERDQ score<8 (718/82.9%). In contrast, the MUO group shows a higher severity, with 59.1% (312) of patients in LA-A, 22.5% (119) in LA-B, and 18.4% (97) in LA-C/D. Additionally, 32.0% (555) of the MUO group have a GERDQ score≥8 ($p<0.05$). For males, most patients in the MHNW group are classified as LA-A (76/70.4%) and have a GERDQ score<8 (488/55.9%). However, the MUO group demonstrates greater severity, with 48.9% (205) in LA-A, 17.7% (74) in LA-B, and 33.4% (140) in LA-C/D. Furthermore, 43.4% (547) of MUO group exhibit a GERDQ score≥8 ($p<0.05$).

Association between different metabolic obesity phenotypes and prevalence of RE by sex

The logistic regression analysis results for the prevalence of RE based on different obesity phenotypes according to sex are displayed in Table 5. The findings demonstrate that, regardless of sex, the MHO, MUNW, and MUO phenotypes were associated with an increased risk of RE compared to the MHNW phenotype ($p<0.001$). In all groups, after adjusting for age, BMI, smoking, alcohol consumption, and *H. pylori* infection, the adjusted ORs (95% CI) for the prevalence of RE comparing MHO, MUNW, and MUO phenotypes participants with MHNW phenotypes were 3.742 (2.960–4.731), 1.763 (1.490–2.085), and 4.590 (3.720–5.665), respectively. In males, after adjusting for age, BMI, smoking, alcohol consumption, and *H. pylori* infection, participants with the MHO phenotype (OR: 3.110; 95% CI:2.235–4.328) had a significantly higher risk of RE than those MHNW and MUNW (OR: 1.721; 95% CI:1.349–2.195) phenotypes, respectively. Individuals with MUO (OR:3.723; 95% CI:2.751–5.040) had the highest OR (95% CI) among all phenotypes. Similarly, in females, after adjusting for age, BMI, smoking, alcohol consumption, and *H. pylori* infection, participants with the MHO phenotype (OR:4.330; 95% CI:3.096–6.055) had a significantly higher risk of RE than those MHNW and MUNW (OR:1.803; 95% CI:1.424–2.283) phenotypes, respectively. Individuals with MUO (OR:5.482; 95% CI:4.080–7.367) had the highest OR (95% CI) among all phenotypes.

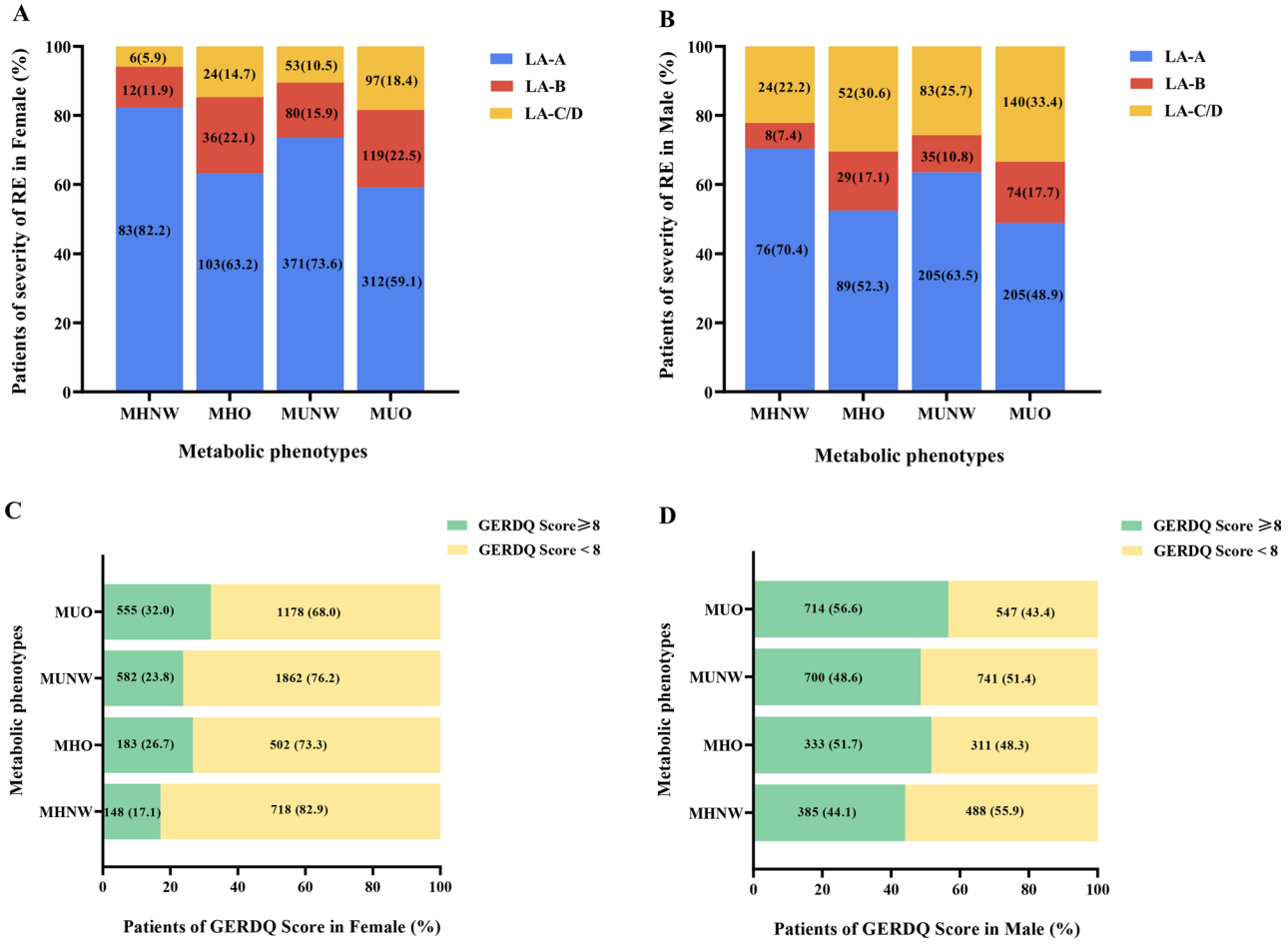

Fig. 3 The percentage of severity of RE and GERDQ score (≥ 8) among the different metabolic obesity phenotypes by sex. (**A**) The severity of RE among different obesity phenotypes in female. (**B**) The severity of RE among different obesity phenotypes in male (**C**) The GERDQ score among different obesity phenotypes in female. (**D**) The GERDQ score among different obesity phenotypes in male

Association between different metabolic obesity phenotypes and prevalence of RE by age

Analyses stratified by the age of the association between different metabolic obesity phenotypes and RE are shown in Table 6. Regardless of age, the MHO, MUNW, and MUO phenotypes were all risk factors for RE compared with the MHNW phenotype ($p<0.001$). In all groups, after adjusting for age, BMI, smoking, alcohol consumption, and *H. pylori* infection, the adjusted ORs (95% CI) for the prevalence of RE comparing MHO, MUNW, and MUO phenotypes participants with MHNW phenotypes were 3.788 (2.966–4.778), 1.776 (1.501–2.102), 4.713 (3.820–5.815), respectively. In participants younger than 60 years of age, after adjusting for sex, BMI, smoking, alcohol consumption, and *H. pylori* infection, participants with the MHO phenotype (OR: 3.966; 95% CI:2.502–6.288) had a significantly higher risk of RE than those with MHNW and MUNW (OR: 1.971; 95% CI:1.410–2.760) phenotypes, respectively. Individuals with MUO (OR:6.080; 95% CI:3.944–9.255) had the highest OR (95% CI) among all phenotypes. Similarly, in participants older than 60 years of age, after adjusting for age, BMI, smoking, alcohol consumption, and *H. pylori* infection, participants with the MHO phenotype (OR:3.707; 95% CI:2.814–4.874) had a significantly higher risk of RE than those MHNW and MUNW (OR:1.691; 95% CI:1.391–2.055) phenotypes, respectively. Individuals with MUO (OR:4.28; 95% CI:0.3.331–5.491) had the highest OR (95% CI) among all phenotypes.

Discussion

This study presents a cross-sectional analysis of physical examination data from the general population. We investigated the association between different metabolic obesity phenotypes and the prevalence of RE. Our findings demonstrate that the MHO, MUNW, and MUO phenotypes are significantly associated with an increased risk of RE compared to the MHNW phenotype. Together, our study found that the prevalence of RE is higher in individuals with obesity compared to those without obesity, regardless of metabolic health status, which confirms the significance of maintaining a healthy weight in preventing

Table 5 Association of metabolic obesity phenotypes at baseline with risk of RE by sex

Variables	Cases	Model 1		Model 2		Model 3	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
All							
MHNW	1,739	1(Reference)		1(Reference)		1(Reference)	
MHO	1,329	2.448(2.023–2.961)	< 0.001	3.575(2.846–4.490)	< 0.001	3.742(2.960–4.731)	< 0.001
MUNW	3,885	1.980(1.681–2.332)	< 0.001	1.986(1.685–2.340)	< 0.001	1.763(1.490–2.085)	< 0.001
MUO	2,994	3.387(2.875–3.989)	< 0.001	4.798(3.912–5.885)	< 0.001	4.590(3.720–5.665)	< 0.001
Male							
MHNW	873	1(Reference)		1(Reference)		1(Reference)	
MHO	644	2.540(1.945–3.318)	< 0.001	3.071 (2.227–4.234)	< 0.001	3.110(2.235–4.328)	< 0.001
MUNW	1,441	2.046(1.615–2.592)	< 0.001	2.046(1.614–2.594)	< 0.001	1.721(1.349–2.195)	< 0.001
MUO	1,261	3.525(2.792–4.450)	< 0.001	4.159(3.100–5.581)	< 0.001	3.723(2.751–5.040)	< 0.001
Female							
MHNW	866	1(Reference)		1(Reference)		1(Reference)	
MHO	685	2.365(1.802–3.104)	< 0.001	4.149(2.997–5.745)	< 0.001	4.330(3.096–6.055)	< 0.001
MUNW	2,444	1.968(1.564–2.475)	< 0.001	1.985(1.577–2.499)	< 0.001	1.803(1.424–2.283)	< 0.001
MUO	1,733	3.319(2.633–4.183)	< 0.001	5.559(4.172–7.406)	< 0.001	5.482(4.080–7.367)	< 0.001

MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity

Model 1: not adjusted

Model 2: adjusted for age, and BMI

Model 3: adjusted for age, BMI, smoking, alcohol, and *H. pylori*

Table 6 Association of metabolic obesity phenotypes at baseline with risk of RE by age

Variables	Cases	Model 1		Model 2		Model 3	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
All							
MHNW	1,739	1(Reference)		1(Reference)		1(Reference)	
MHO	1,329	2.448(2.023–2.961)	< 0.001	3.628(2.889–4.555)	< 0.001	3.788(2.996–4.788)	< 0.001
MUNW	3,885	1.980(1.681–2.332)	< 0.001	2.041(1.731–2.406)	< 0.001	1.776(1.501–2.102)	< 0.001
MUO	2,994	3.387(2.875–3.989)	< 0.001	4.994(4.072–6.126)	< 0.001	4.713(3.820–5.815)	< 0.001
<60 years							
MHNW	559	1(Reference)		1(Reference)		1(Reference)	
MHO	411	2.734(1.879–3.976)	< 0.001	3.734(2.389–5.836)	< 0.001	3.966(2.502–6.288)	< 0.001
MUNW	1,160	2.185(1.575–3.031)	< 0.001	2.216(1.596–3.078)	< 0.001	1.971(1.410–2.760)	< 0.001
MUO	768	4.379(3.152–6.084)	< 0.001	5.595(3.955–8.938)	< 0.001	6.080(3.944–9.255)	< 0.001
≥ 60 years							
MHNW	1,180	1(Reference)		1(Reference)		1(Reference)	
MHO	918	2.351(1.883–2.935)	< 0.001	3.585(2.749–4.676)	< 0.001	3.707(2.814–4.874)	< 0.001
MUNW	2,725	1.899(1.571–2.296)	< 0.001	1.972(1.630–2.386)	< 0.001	1.691(1.391–2.055)	< 0.001
MUO	2,226	3.045(2.520–3.679)	< 0.001	4.606(3.636–5.835)	< 0.001	4.248(3.331–5.419)	< 0.001

MHNW, metabolically healthy normal weight; MHO, metabolically healthy obesity; MUNW, metabolically unhealthy normal weight; MUO, metabolically unhealthy obesity

Model 1: not adjusted

Model 2: adjusted for sex, and BMI

Model 3: adjusted for sex, BMI, smoking, alcohol, and *H. pylori*

RE. Further exploration revealed that the MHO, MUNW, and MUO phenotypes were independently related to a higher risk of RE, regardless of sex and age.

Many studies have shown that metabolic components increase the risk of RE [4, 21], and the association between obesity and RE has been confirmed in many epidemiological studies [22, 23]. However, obesity promotes insulin resistance, which causes a range of metabolic abnormalities that are determinants of Mets [24]. Thus, it presents a challenge to ascertain the causal involvement of obesity in RE or whether obesity, along with its related metabolic disorders, collectively promotes the development of RE. In recent years, numerous observational studies have evidenced metabolic obesity phenotypes as indicators of a wide range of metabolic diseases and potential risk factors for future health complications

[25–27]. Assessing the risk of RE in all metabolism–obesity phenotypes could help to elucidate the role of obesity in the occurrence and development of RE.

Previous research has shown a significant association between obesity and RE. While the exact mechanisms connecting obesity and RE remain unclear, several mechanisms have been implicated to explain this association. Obese individuals experience an elevation in lower esophageal sphincter (LES) pressure, which impairs the anti-reflux barrier and subsequently leads to the development of gastroesophageal reflux (GER). This phenomenon may be associated with compensatory mechanisms triggered by heightened intra-abdominal pressure [28, 29]. Saliva secretion, gravity, and esophageal motility collectively determine the esophageal clearance rate. Obesity often results in reduced saliva secretion and impaired esophageal motility, compromising the function of esophageal clearance [30–32]. Vicente Ortiz et al. [33] found that obese individuals demonstrate reduced esophageal sensitivity to acid perfusion, potentially affecting esophageal clearance function. Recently, esophageal inflammation mediated by cytokines has been proposed as a mechanism underlying the pathogenesis of RE [34]. Visceral adipose tissue functions as a significant depot of adipocyte-derived factors, releasing cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), leptin, adiponectin, and other molecules. These mediators can induce systemic effects, influencing and amplifying systemic inflammatory responses [35–37]. Our study observed that obesity was a risk factor for RE, even in metabolically healthy individuals. These findings indicate that obesity alone may serve as a significant risk factor for RE. Our results support the traditional perspective that obesity elevates the risk of developing RE. This association is likely attributable to factors such as heightened intra-abdominal pressure, increased episodes of transient LES relaxation, and heightened esophageal acid exposure, which are commonly associated with obesity.

Consistent with our findings, multiple studies have found metabolic disorders to be significantly associated with RE, though the mechanism underlying this association is uncertain [23, 38–40]. This may be related to the use of antihypertensive medications. Calcium channel blockers have been shown to have the power to suppress the contractions of the esophageal muscle and ease the pressure on the esophageal sphincter [39]. Our study found that high SBP and DBP were associated with RE, regardless of sex. In addition, the association of RE with hyperglycemia has been investigated in previous studies [41, 42]. High glucose levels can lead to increased stomach acid production, which contributes to the development of gastroesophageal reflux symptoms [43]. This is consistent with our study. The RE group had higher glucose levels than the non-RE group. A study suggested that hyperlipidemia was significantly associated with RE and that a high-fat diet could decrease the risk of depression in hyperlipidemic patients [44]. Moreover, another study demonstrated that elevated lipid levels can impair esophageal clearance and weaken the LES, ultimately contributing to the development of RE [45]. Our research found that high TG, TC, LDL, and low HDL were risk factors for RE. Especially in patients with RE, metabolic disorders are more severe in males than females. As was found in previous studies, dyslipidemia, hypertension, and hyperglycemia can increase the risk of RE. Hence, our study highlights the importance of metabolic abnormality modification regardless of the obesity status.

However, the aforementioned study did not compare the effects of obesity and metabolic abnormalities on the risk of RE. In our study, we expanded upon the existing definition of obesity by concurrently assessing metabolic status. This allowed us to propose a risk of RE assessment strategy based on metabolic obesity phenotypes. The present study showed a difference in RE prevalence between MUNW and MHO groups. The MHO group has a higher prevalence of RE than the MUNW group. However, the prevalence of RE in these two groups was still significantly higher than in the MHNW group, suggesting that obesity was the most important risk factor for RE independent of metabolically unhealthy phenotypes. Obesity and metabolic abnormality posed a joint effect on the risk of RE, and the MUO group had the highest prevalence of RE. Hence, our study highlights the importance of obesity modification regardless of metabolic status. A retrospective study demonstrated that MHO was associated with an increased risk of erosive esophagitis, but metabolic unhealthiness alone was not [46]. Moreover, another large cohort of studies speculated that MHO is not protective against GER disease and that MHO was associated with an increased prevalence of erosive esophagitis [47]. These results suggested that obesity rather than metabolic health was a greater risk factor for RE. This phenomenon was likely due to the accumulation of visceral fat in MHO phenotype [26]. A prospective study revealed that patients with the MHO phenotype frequently underwent a deterioration in their metabolic health status over an extended period of follow-up, ultimately transitioning into the MUO phenotype. This investigation indicates that the MHO phenotype cannot be considered a consistently stable metabolic obesity phenotype [48]. Therefore, we should keep a normal weight regardless of metabolic health status. Although MHO had a higher risk of RE than those with the MUNW and MHNW phenotypes, MUO had the highest risk of developing RE in both sexes. The levels of age, SBP, DBP, FBG, TG, TC, LDL, UA, AST, ALT, GGT, and ALB significantly differed among the four

groups, being more abnormal in MUO than MHNW, MHO, and MUNW in our study. Therefore, combining obesity and metabolic status into metabolic obesity phenotypes can identify more individuals with RE risk. Physicians could make early interventions for abnormal obesity phenotypes by using the metabolic obesity phenotypes, reducing the economic cost of treating RE and its complication, typically EAC and BE.

While studies on sex differences in the association of obesity phenotypes with RE are still lacking, our study found that females have a higher risk of RE in MHO, MUNW, and MUO phenotypes than males after adjusting for confounding factors. Furthermore, our study showed that the prevalence of RE in males was significantly higher than in females in all phenotypes. The reason for this sex difference is unclear, although several possible explanations exist. First, men have a higher tendency to accumulate visceral adipose tissue compared to women, which highlights the increased risk of obesity-related health hazards in men [49]. Second, visceral adipose tissue was more biologically active than fat located in other regions [50]. Excessive accumulation of visceral adipose tissue can contribute to chronic low-grade inflammation, leading to the development of RE [45, 51]. Finally, estrogen enhances nitric oxide production, a vasodilator that promotes smooth muscle relaxation. This can result in the relaxation of the LES and subsequently increase the occurrence of reflux. Previous studies have reported age as a major risk factor for RE [52]. Thus, we further analyzed the association of metabolic obesity phenotypes with RE in different age groups. Interestingly, we found that individuals under 60 years with MHO, MUNW, and MUO phenotypes had a higher risk of RE than individuals older than 60 years. The reason for this age difference is uncertain. Still, it may be related to the fact that the deleterious effects of leptin on RE may somehow be alleviated in elderly individuals since aging is related to leptin resistance and decreased receptors for this hormone [53]. The changes in body composition and muscle loss are associated with aging. Further studies using body composition data can enhance our understanding of the underlying mechanisms.

This study had several notable strengths. First, the study included a large sample size and a trained Gastroenterologist diagnosed RE by endoscopy. Second, we investigated the association between metabolic obesity phenotypes and the development of RE with respect to sex and age. Finally, we performed a more detailed analysis to better understand the association between metabolic obesity phenotypes and RE. Despite its contributions, our study has its drawbacks. First, this study was conducted with a cross-sectional study design. We were unable to infer causality in the findings. Second, obesity in our study was diagnosed based solely on BMI because waist circumference was not routine data. Conducting additional research that includes waist circumference and other body composition measurements could provide a more comprehensive understanding of the relationship between obesity phenotypes and RE. Third, although the study has adjusted for potential confounders in the multivariable analysis, there remained unmeasured residual confounding factors, such as dietary patterns, psychosocial stress, and socioeconomic status, which may influence our risk estimates. Last, we could not investigate the association between BE or EAC and metabolic obesity phenotypes.

Conclusions

The present results indicated that MHO, MUNW, and MUO were associated with a higher risk of RE than MHNW. Furthermore, MHO is not a health status and is at higher risk of RE compared to MUNW, which suggests obesity plays a key role in the development of RE. In our study, we found a significant association between metabolic obesity phenotypes and the occurrence of RE regardless of sex and age. The prevalence of RE increased as the number of metabolic risk factors increased. Our findings emphasize the importance of considering metabolic health status in obese individuals when assessing the risk of RE. However, while focusing on patients with metabolic abnormalities, we must also recognize the importance of addressing MHO individuals. Individuals with MHO should maintain a healthy weight and lifestyle to mitigate the risk of developing RE.

Abbreviations

RE	Reflux esophagitis
MHNW	Metabolically healthy normal weight
MHO	Metabolically healthy obesity
MUNW	Metabolically unhealthy normal weight
MUO	Metabolically unhealthy obesity
BE	Barrett's esophagus
EAC	Esophageal adenocarcinoma
Mets	Metabolic syndrome
HT	Hashimoto's Thyroiditis
NAFLD	Non-alcoholic fatty liver disease
LA	Los Angeles
GerdQ	Gastroesophageal reflux disease questionnaire
PSM	Propensity score matching
Alb	Albumin
FPG	Fasting plasma glucose
TC	Total cholesterol
TG	Triglycerides
LDL-C	Low-density lipoprotein-cholesterol
HDL-C	High-density lipoprotein-cholesterol
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GGT	Gamma-glutamyl transpeptidase
UA	Uric acids
UBT	Urea breath test
BMI	Body mass index
LES	Lower esophageal sphincter
GER	Gastroesophageal reflux
IL-1	Interleukin-1
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-alpha

OR Odds ratio
CI Confidence interval

Acknowledgements
Authors are grateful to all members of Gastroenterology Department of The First Affiliated Hospital of Dalian Medical University and Yufei Li for their contributions to the manuscript preparation.

Author contributions
TH was primarily responsible for the data analysis and writing of the manuscript. TH and ZJD significantly revised the draft, interpreted the data, and involved in data analyses. PW, LXW, and MHT collected the information and participated in data interpretation. All authors read and approved the final manuscript.

Funding
Not applicable.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was executed in conformity with the ethical principles stipulated in the Declaration of Helsinki and received approval from the Institutional Review Board of the First Affiliated Hospital of Dalian Medical University for all protocols involving human subjects (PJ-KS-KY-2020-04). Informed consent was obtained in writing from all participants before they participated in the study. Clinical trial number: not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Gastroenterology, The First Affiliated Hospital of Dalian Medical University, Dalian 116011, China
[2]Dalian Central Laboratory of Integrative Neuro-gastrointestinal Dynamics and Metabolism Related Diseases Prevention and Treatment, Dalian 116011, China

Received: 24 October 2023 / Accepted: 30 October 2024
Published online: 07 November 2024

References

1. Diab N, Patel M, O'Byrne P, Satia I. Narrative review of the mechanisms and Treatment of Cough in Asthma, Cough variant asthma, and non-asthmatic eosinophilic bronchitis. Lung. 2022;200(6):707–16.
2. Mehta RS, Staller K, Chan AT. Review of gastroesophageal reflux disease. JAMA. 2021;325(14):1472.
3. Muthusamy VR, Wani S, Gyawali CP, Komanduri S. AGA clinical practice update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review. Clin Gastroenterol Hepatology: Official Clin Pract J Am Gastroenterological Association. 2022;20(12):2696–e27062691.
4. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut. 2018;67(3):430–40.
5. Lee YB, Kim DH, Kim SM, Kim NH, Choi KM, Baik SH, Park YG, Han K, Yoo HJ. Hospitalization for heart failure incidence according to the transition in metabolic health and obesity status: a nationwide population-based study. Cardiovasc Diabetol. 2020;19(1):77.
6. Wu P, Ma L, Dai GX, Chen Y, Tong YL, Wang C, Yao LW, Jiang YX, Xu SC, Ai ZS. The association of metabolic syndrome with reflux esophagitis: a case-control study. Neurogastroenterology Motility: Official J Eur Gastrointest Motil Soc. 2011;23(11):989–94.
7. Stefan N, Häring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1(2):152–62.
8. Kramer CK, Zinman B, Retnakaran R. Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. Ann Intern Med. 2013;159(11):758–69.
9. Man S, Lv J, Yu C, Deng Y, Yin J, Wang B, Li L, Liu H. Association between metabolically healthy obesity and non-alcoholic fatty liver disease. Hep Intl. 2022;16(6):1412–23.
10. Yang H, Xia Q, Shen Y, Chen TL, Wang J, Lu YY. Gender-specific impact of metabolic obesity phenotypes on the risk of Hashimoto's Thyroiditis: a Retrospective Data Analysis using a Health Check-Up database. J Inflamm Res. 2022;15:827–37.
11. Cao Z, Zheng X, Yang H, Li S, Xu F, Yang X, Wang Y. Association of obesity status and metabolic syndrome with site-specific cancers: a population-based cohort study. Br J Cancer. 2020;123(8):1336–44.
12. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45(2):172–80.
13. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, Lind T. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Aliment Pharmacol Ther. 2009;30(10):1030–8.
14. Dent J, Vakil N, Jones R, Bytzer P, Schöning U, Halling K, Junghard O, Lind T. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. Gut. 2010;59(6):714–21.
15. Jonasson C, Wernersson B, Hoff DA, Hatlebakk JG. Validation of the GerdQ questionnaire for the diagnosis of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2013;37(5):564–72.
16. Suzuki H, Matsuzaki J, Okada S, Hirata K, Fukuhara S, Hibi T. Validation of the GerdQ questionnaire for the management of gastro-oesophageal reflux disease in Japan. United Eur Gastroenterol J. 2013;1(3):175–83.
17. Zavala-Gonzales MA, Azamar-Jacome AA, Meixueiro-Daza A, Ramos A, Roesch-Dietlen JJR, Remes-Troche F. Validation and diagnostic usefulness of gastroesophageal reflux disease questionnaire in a primary care level in Mexico. J Neurogastroenterol Motil. 2014;20(4):475–82.
18. Appropriate body-mass. Index for Asian populations and its implications for policy and intervention strategies. Lancet (London England). 2004;363(9403):157–63.
19. Hsu WC, Araneta MR, Kanaya AM, Chiang JL, Fujimoto W. BMI cut points to identify at-risk Asian americans for type 2 diabetes screening. Diabetes Care. 2015;38(1):150–8.
20. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486–97.
21. Herbella FA, Sweet MP, Tedesco P, Nipomnick I, Patti MG. Gastroesophageal reflux disease and obesity. Pathophysiology and implications for treatment. J Gastrointest Surgery: Official J Soc Surg Aliment Tract. 2007;11(3):286–90.
22. Azami M, Salamati M, Ranjbar R, Sahebkar A. The association between metabolic syndrome and erosive esophagitis: a systematic review and meta-analysis. EXCLI J. 2021;20:1532–43.
23. Fu S, Xu M, Zhou H, Wang Y, Tan Y, Liu D. Metabolic syndrome is associated with higher rate of gastroesophageal reflux disease: a meta-analysis. Neurogastroenterology Motility: Official J Eur Gastrointest Motil Soc. 2022;34(5):e14234.
24. Myers J, Kokkinos P, Nyelin E. Physical activity, Cardiorespiratory Fitness, and the metabolic syndrome. Nutrients 2019, 11(7).
25. Wu Q, Xia MF, Gao X. Metabolically healthy obesity: is it really healthy for type 2 diabetes mellitus? World J Diabetes. 2022;13(2):70–84.
26. Elías-López D, Vargas-Vázquez A, Mehta R, Cruz Bautista I, Del Razo Olvera F, Gómez-Velasco D, Almeda Valdes P, Aguilar-Salinas CA. Natural course of metabolically healthy phenotype and risk of developing cardiometabolic diseases: a three years follow-up study. BMC Endocr Disorders. 2021;21(1):85.
27. Arnlöv J, Ingelsson E, Sundström J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation. 2010;121(2):230–6.

28. Zurita Macías Valadez LC, Pescarus R, Hsieh T, Wasserman L, Apriasz I, Hong D, Gmora S, Cadeddu M, Anvari M. Laparoscopic limited Heller myotomy without anti-reflux procedure does not induce significant long-term gastro-esophageal reflux. Surg Endosc. 2015;29(6):1462–8.
29. Suter M, Dorta G, Giusti V, Calmes JM. Gastro-esophageal reflux and esophageal motility disorders in morbidly obese patients. Obes Surg. 2004;14(7):959–66.
30. Valezi AC, Herbella FAM, Schlottmann F, Patti MG. Gastroesophageal reflux disease in obese patients. J Laparoendoscopic Adv Surg Techniques Part A. 2018;28(8):949–52.
31. Côté-Daigneault J, Leclerc P, Joubert J, Bouin M. High prevalence of esophageal dysmotility in asymptomatic obese patients. Can J Gastroenterol Hepatol. 2014;28(6):311–4.
32. Koppman JS, Poggi L, Szomstein S, Ukleja A, Botoman A, Rosenthal R. Esophageal motility disorders in the morbidly obese population. Surg Endosc. 2007;21(5):761–4.
33. Ortiz V, Alvarez-Sotomayor D, Sáez-González E, Díaz-Jaime FC, Iborra M, Ponce J, Garrigues V. Decreased esophageal sensitivity to Acid in Morbidly obese patients: a cause for concern? Gut Liver. 2017;11(3):358–62.
34. Dunbar KB, Agoston AT, Odze RD, Huo X, Pham TH, Cipher DJ, Castell DO, Genta RM, Souza RF, Spechler SJ. Association of Acute Gastroesophageal Reflux Disease with Esophageal histologic changes. JAMA. 2016;315(19):2104–12.
35. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011;29:415–45.
36. Nam SY, Choi IJ, Ryu KH, Park BJ, Kim HB, Nam BH. Abdominal visceral adipose tissue volume is associated with increased risk of erosive esophagitis in men and women. Gastroenterology. 2010;139(6):1902–11. e1902.
37. Varkaneh Kord H, G MT, Zand HOS, Nazary H, Fatahi A, Mokhtari S, Salehi-Sahlabadi Z, Tan A, Rahmani SC. The influence of fasting and energy-restricted diets on leptin and adiponectin levels in humans: a systematic review and meta-analysis. Clin Nutr. 2021;40(4):1811–21.
38. Song HJ, Shim KN, Yoon SJ, Kim SE, Oh HJ, Ryu KH, Ha CY, Yeom HJ, Song JH, Jung SA, et al. The prevalence and clinical characteristics of reflux esophagitis in koreans and its possible relation to metabolic syndrome. J Korean Med Sci. 2009;24(2):197–202.
39. Mohammadi M, Ramezani Jolfaie N, Alipour R, Zarrati M. Is metabolic syndrome considered to be a risk factor for gastroesophageal reflux disease (non-erosive or erosive esophagitis)? A systematic review of the evidence. Iran Red Crescent Med J. 2016;18(11):e30363.
40. Fukunaga S, Nakano D, Tsutsumi T, Kawaguchi T, Eslam M, Yoshinaga S, Abe H, Nouno R, Joh S, Mitsuyama K, et al. Lean/normal-weight metabolic dysfunction-associated fatty liver disease is a risk factor for reflux esophagitis. Hepatol Research: Official J Japan Soc Hepatol. 2022;52(8):699–711.
41. Bou Daher H, Sharara AI. Gastroesophageal reflux disease, obesity and laparoscopic sleeve gastrectomy: the burning questions. World J Gastroenterol. 2019;25(33):4805–13.
42. Loke SS, Yang KD, Chen KD, Chen JF. Erosive esophagitis associated with metabolic syndrome, impaired liver function, and dyslipidemia. World J Gastroenterol. 2013;19(35):5883–8.
43. Hirata A, Kishida K, Nakatsuji H, Inoue K, Hiuge-Shimizu A, Funahashi T, Shimomura I. High prevalence of gastroesophageal reflux symptoms in type 2 diabetics with hypoadiponectinemia and metabolic syndrome. Nutr Metabolism. 2012;9(1):4.
44. Nam SY, Park BJ, Cho YA, Ryu KH, Choi IJ, Park S, Kim YW. Different effects of dietary factors on reflux esophagitis and non-erosive reflux disease in 11,690 Korean subjects. J Gastroenterol. 2017;52(7):818–29.
45. Rieder F, Biancani P, Harnett K, Yerian L, Falk GW. Inflammatory mediators in gastroesophageal reflux disease: impact on esophageal motility, fibrosis, and carcinogenesis. Am J Physiol Gastrointest Liver Physiol. 2010;298(5):G571–581.
46. Baeg MK, Ko SH, Ko SY, Jung HS, Choi MG. Obesity increases the risk of erosive esophagitis but metabolic unhealthiness alone does not: a large-scale cross-sectional study. BMC Gastroenterol. 2018;18(1):82.
47. Kim TJ, Lee H, Baek SY, Kim K, Min YW, Min BH, Lee JH, Son HJ, Rhee PL, Kim JJ. Metabolically Healthy Obesity and the risk of Erosive Esophagitis: a Cohort Study. Clin Translational Gastroenterol. 2019;10(9):e00077.
48. Eshtiaghi R, Keihani S, Hosseinpanah F, Barzin M, Azizi F. Natural course of metabolically healthy abdominal obese adults after 10 years of follow-up: the Tehran lipid and glucose study. Int J Obes. 2015;39(3):514–9.
49. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93(1):359–404.
50. Francisco V, Ruiz-Fernández C, Pino J, Mera A, González-Gay MA, Gómez R, Lago F, Mobasheri A, Gualillo O. Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. Biochem Pharmacol. 2019;165:196–206.
51. Macdougall CE, Wood EG, Loschko J, Scagliotti V, Cassidy FC, Robinson ME, Feldhahn N, Castellano L, Voisin MB, Marelli-Berg F, et al. Visceral adipose tissue Immune Homeostasis is regulated by the crosstalk between adipocytes and dendritic cell subsets. Cell Metabol. 2018;27(3):588–e601584.
52. Richter JE, Rubenstein JH. Presentation and epidemiology of gastroesophageal reflux disease. Gastroenterology. 2018;154(2):267–76.
53. Gulcelik NE, Halil M, Ariogul S, Usman A. Adipocytokines and aging: adiponectin and leptin. Minerva Endocrinol. 2013;38(2):203–10.

Publisher's note