

Association of Metabolic Syndrome with Gastroesophageal Reflux Symptoms in Adults: A Cross-Sectional Study

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ABSTRACT

Background: Both gastroesophageal reflux disease (GERD) and metabolic syndrome (MetS) are prevalent and on the rise and they might be connected by central obesity. There is limited local data.

Objective: The aim of the study was to find out the correlation between MetS and GERD symptoms in adults.

Material and Methods: This cross-sectional study was conducted in the Department of Gastroenterology and Medicine, Mardan Medical Complex, Mardan from July 2022 to December 2022. Adults (age 18 years or older) were enrolled consecutively (n = 315). We measured BMI, waist circumference, blood pressure, blood glucose and blood lipid levels. MetS was diagnosed according to the harmonized criteria and GERD symptoms as a GerdQ score of 8 or more. We used chi-square tests and logistic regression, with $p < 0.05$ as significant.

Results: Of 330 participants (mean age 43.6 ± 11.7 years; 44.2% male), 33.9% had MetS and 35.2% had GERD symptoms. GERD symptoms were more frequent with MetS than without (47.3% vs 28.9%; crude OR 2.21, 95% CI 1.38–3.55; $p < 0.001$); the OR adjusted for age, sex and smoking was 2.22 (95% CI 1.35–3.63). Of the components, only elevated blood pressure was significantly associated with GERD symptoms (OR 1.86, 95% CI 1.16–2.98). Three or more symptoms of GERD were most common (trend $p = 0.018$).

Conclusions: GERD symptoms were twice as likely in those with MetS. If a patient has symptoms for GERD, they may need to be checked for metabolic abnormalities, especially hypertension.

Keywords: Metabolic syndrome, gastroesophageal reflux, abdominal obesity, waist circumference, cross sectional studies, Pakistan.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as reflux of stomach contents which leads to both troublesome symptoms and/or complications¹. It was estimated by a world-wide meta-analysis at approximately 14%, and showed very large regional differences². In the Middle East, prevalence has been reported from 8.7% to 33.1%, and is suggested to have been increasing since the mid-1990s³. The prevalence of GERD in Pakistan has also been studied along with associated risk factors in an area of southern Punjab⁴. The two major symptoms are heartburn and regurgitation, and abdominal fat is a known risk factor for the complications of heartburn⁵.

Metabolic syndrome (MetS) is a cluster of central obesity, raised blood pressure, raised fasting glucose, high triglycerides and low high-density lipoprotein cholesterol (HDL-C). The harmonized joint interim definition requires three of the following five abnormalities and the threshold for waist circumference varies by ethnicity⁶. A meta-analysis of prevalence of MetS in apparently healthy Pakistani adults showed a prevalence of 28.8%⁷.

There is a likely connection between obesity and GERD. Results from a meta-analysis indicated that obesity was correlated with GERD symptoms and their complications⁸ and central obesity was linked to esophageal inflammation, metaplasia and adenocarcinoma⁹. Visceral fat increases intraabdominal pressure and may cause reflux, and adipose tissue produces inflammatory cytokines which may be responsible for weakening the lower esophageal sphincter¹⁰. The relationship between GERD and MetS has been discussed, and is likely to be a connection with prevalence and severity of GERD, the key driver of MetS^{11,12}.

The majority of findings regarding MetS and reflux has been provided by endoscopy-based cohorts from East Asian countries. In Korea, MetS was associated with reflux oesophagitis (odds ratio [OR] 1.42; 95% confidence interval [CI] 1.26–1.60)¹³ and with erosive esophagitis (OR 1.25; 95% CI 1.04–1.49)¹⁴. Japanese data correlated the characteristics of MetS with reflux oesophagitis¹⁵. A meta-analysis of 15 studies and 103,048 participants gave a pooled OR of 1.66 (95% CI 1.38–1.99) for GERD¹⁶. In Taiwan Biobank (121,583 adults, questionnaire-defined GERD), the adjusted OR was only 1.079, and there was no independent association between hyperglycaemia and hypertension¹⁰. Different

case definitions and different populations lead to different effect sizes and the different contributing components.

Although MetS is prevalent in Pakistan, there are few local data available⁷. In the outpatient setting, the diagnosis of reflux is typically made based on symptoms, and questionnaires like the GerdQ can be used to help with that¹⁷. Thus, the correlation of MetS with GERD symptoms was investigated in adults visiting the Gastroenterology and Medicine Departments at Mardan Medical Complex, Mardan.

MATERIALS AND METHODS

This was a cross-sectional study carried out in Departments of Gastroenterology and Medicine of Mardan Medical Complex, Mardan, Khyber Pakhtunkhwa, Pakistan from July 2022 to December 2022, which was conducted according to the STROBE statement¹⁸. This study has been approved by ethical review committee of Bacha Khan Medical college Mardan. All participants gave written informed consent.

Sample size: The sample size was calculated using the single proportion formula for cross-sectional studies $n = Z^2 \cdot P(1 - P)/d^2$ ¹⁹. Taking the pooled MetS prevalence in apparently healthy Pakistani adults ($P = 28.8\%$)⁷, a 95% confidence level ($Z = 1.96$) and 5% absolute precision ($d = 0.05$), the minimum sample was 315 participants ($n = 3.8416 \times 0.288 \times 0.712 / 0.0025 = 315.1$). We enrolled 330.

Participants. Adults (aged 18 years or older) of both sexes were recruited by consecutive non-probability sampling from the outpatient clinics of the two departments. Patients were excluded if they had previously undergone surgery on the upper gastrointestinal tract or gastrointestinal malignancy, previous diagnosis of achalasia or eosinophilic esophagitis, pregnancy, or proton pump inhibitors or H2-receptor antagonists within the last 2 weeks [confirm: edit exclusion criteria to match your protocol].

Data collection: Age, sex, smoking habits, and the use of antihypertensive, antidiabetic and lipid-lowering drugs were taken on a structured proforma. Body height and weight were measured in air and BMI was calculated as weight (kg) / height squared (m²) in light clothing. Waist circumference was measured using a non-stretchable tape at mid-point between the lower costal margin and the iliac crest. Blood pressure was taken sitting, after five minutes of rest. Fasting plasma glucose, triglycerides, HDL-C, total

cholesterol and LDL-C levels were obtained from venous blood after an overnight fast of at least eight hours. These were determined by conventional enzymatic colorimetric assay on an automatic clinical chemistry analyser and where necessary LDL-C was calculated on the basis of Friedewald equation.

Operational definitions: MetS was diagnosed according to the harmonized criteria [6] which required the presence of at least three of the following: (i) waist circumference ≥ 90 cm (men) or ≥ 80 cm (women) (South Asian cut-offs); (ii) triglycerides ≥ 150 mg/dl or lipid-lowering therapy; (iii) HDL-C < 40 mg/dl in men and < 50 mg/dl in women; (iv) blood pressure $\geq 130/85$ mmHg or antihypertensive therapy; and (v) fasting glucose ≥ 100 mg/dl or antidiabetic therapy. The study database coded classification was used for metS status. The six-item GerdQ was used to measure symptoms of GERD in the past week (0–18) over heartburn, regurgitation, epigastric pain, nausea, sleep disturbance, and the use of over the counter medication [17]. GERD symptoms were classified as a score ≥ 8 .

Statistical analysis: We analysed the data in Python 3.13.5 (pandas, SciPy and statsmodels). Continuous variables are given as mean $\pm$ standard deviation and were compared with Welch's t-test. The distribution of triglycerides was right skewed and we therefore reported the median (interquartile range) and used the Mann–Whitney U test. Categorical variables were presented as count and percentage, and compared using the chi-square test. We expressed the association between MetS and GERD symptoms as an odds ratio (OR) with 95% confidence interval (CI), adjusted for age, sex and smoking by binary logistic regression. In the case of the components, all 5 were entered together with the same covariates. The linear-by-linear chi-square test was used to test the trend for symptoms of GERD by number of components. A two-tailed p value < 0.05 was deemed to be significant. In a sensitivity analysis we recalculated MetS directly from the recorded measurements using the cut-offs above.

RESULTS

Participant characteristics. The study included 330 adults: 146 men (44.2%) and 184 women (55.8%), with a mean age of 43.6 ± 11.7 years (range 18–73). 15.8% (52) smoked currently. MetS was present in 112 (33.9%) and GERD symptoms (GerdQ ≥ 8) in 116 (35.2%) (Figure 1A, B), and 53 (16.1%) had both (Figure 1C).

Participants with MetS were older (47.3 ± 12.1 vs 41.7 ± 11.0 years; $p < 0.001$) and less often male (33.9% vs 49.5%; $p = 0.007$)

(Table 1). BMI, waist circumference, systolic blood pressure, fasting glucose and triglycerides were higher and HDL-C was lower, as the definition implies (all $p < 0.001$): BMI 30.0 ± 3.5 vs 24.1 ± 3.8 kg/m², waist 93.6 ± 8.9 vs 80.6 ± 8.5 cm, systolic pressure 126.3 ± 12.5 vs 116.5 ± 11.2 mmHg, glucose 103.8 ± 9.1 vs 89.4 ± 8.2 mg/dL, median triglycerides 172 vs 110 mg/dL, and HDL-C 44.1 ± 6.4 vs 48.2 ± 7.1 mg/dL. In the case of MetS the total cholesterol was found to be higher ($p = 0.001$) while smoking did not differ. The GerdQ score was higher too (7.6 ± 2.7 vs 6.6 ± 2.4 ; $p = 0.001$).

Values are mean $\pm$ SD unless stated. †Median (interquartile range), Mann–Whitney U test; other continuous variables compared with Welch's t-test, categorical variables with the chi-square test. BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; GerdQ, Gastroesophageal Reflux Disease Questionnaire.

Association between MetS and GERD symptoms: GERD symptoms occurred in 47.3% (53/112) of participants with MetS and 28.9% (63/218) of those without ($\chi^2 = 11.02$; $p < 0.001$; Table 2, Figure 2A). The crude OR was 2.21 (95% CI 1.38–3.55) and the OR adjusted for age, sex and smoking was 2.22 (95% CI 1.35–3.63; $p = 0.002$). GerdQ scores were also higher with MetS (Figure 2D). Recalculating MetS from the recorded measurements moved 13 participants (119 classified as MetS), and the association held (OR 1.89, 95% CI 1.18–3.01; $p = 0.007$).

Only elevated blood pressure was significantly associated with GERD symptoms (crude OR 1.86, 95% CI 1.16–2.98; $p = 0.010$) of the 5 components. It remained significant when all five components were entered into with age, sex and smoking (adjusted OR 1.71, 95% CI 1.02–2.86; $p = 0.042$; Table 3). However, abdominal obesity (crude OR 1.52; $p = 0.070$) and elevated fasting glucose (OR 1.51; $p = 0.098$) were in the same direction, but did not reach significance; triglycerides and HDL-C did not. (Figure 2C)

The presence of zero (30.9%), one or two (29.4%) and three (26.8%) components of GERD were approximately the same, and four (53.6%) had the most components. With all five components the figure was 39.1% (9/23) (linear-by-linear $\chi^2 = 5.59$; $p = 0.018$; Figure 2B). Participants with GERD symptoms had more components on average than those without (2.21 ± 1.53 vs 1.80 ± 1.43 ; $p = 0.020$).

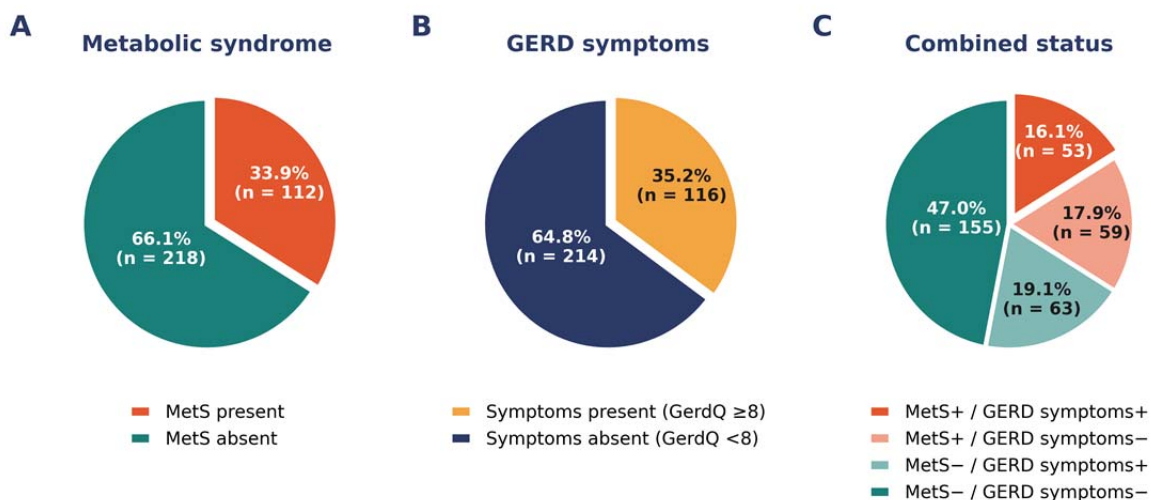


Figure 1: Profile of the study population (N = 330). (A) Metabolic syndrome (MetS) status. (B) Gastroesophageal reflux disease (GERD) symptom status by GerdQ score. (C) Combined MetS and GERD symptom status.

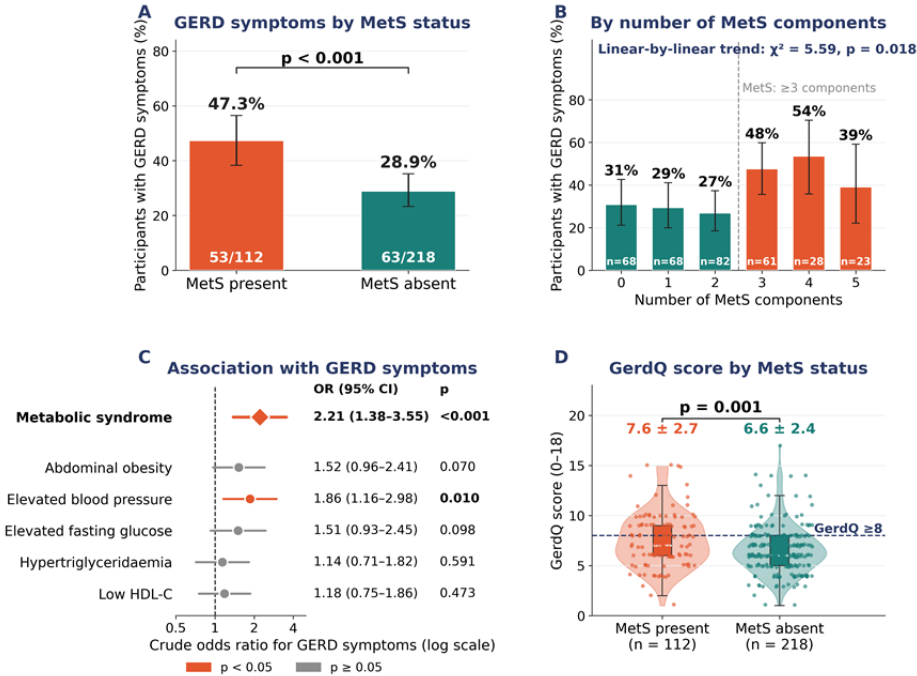


Figure 2: Association of MetS with GERD symptoms. (A) Prevalence of GERD symptoms by MetS status (error bars, 95% Wilson confidence intervals). (B) Prevalence by number of MetS components. (C) Forest plot of crude odds ratios (95% CI) for GERD symptoms. (D) Distribution of GerdQ scores by MetS status (violin, box plot and individual participants; dashed line, GerdQ threshold of 8).

Table 1: Demographic, anthropometric and metabolic characteristics of participants by MetS status (N = 330)

Variable	MetS present (n = 112)	MetS absent (n = 218)	p-value
Age (years)	47.3 ± 12.1	41.7 ± 11.0	<0.001
Male sex, n (%)	38 (33.9%)	108 (49.5%)	0.007
Current smoker, n (%)	13 (11.6%)	39 (17.9%)	0.138
BMI (kg/m ²)	30.0 ± 3.5	24.1 ± 3.8	<0.001
Waist circumference (cm)	93.6 ± 8.9	80.6 ± 8.5	<0.001
Systolic BP (mmHg)	126.3 ± 12.5	116.5 ± 11.2	<0.001
Diastolic BP (mmHg)	81.8 ± 7.7	74.9 ± 7.0	<0.001
Fasting glucose (mg/dL)	103.8 ± 9.1	89.4 ± 8.2	<0.001
Triglycerides (mg/dL), median (IQR)†	172 (132–232)	110 (80–142)	<0.001
HDL-C (mg/dL)	44.1 ± 6.4	48.2 ± 7.1	<0.001
Total cholesterol (mg/dL)	177.2 ± 30.0	166.3 ± 26.7	0.001
LDL-C (mg/dL)	95.0 ± 34.6	94.6 ± 27.9	0.914

Table 2: Association between MetS and GERD symptoms (N = 330)

MetS status	GERD symptoms present, n (%)	GERD symptoms absent, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)*	p-value†
MetS present (n = 112)	53 (47.3%)	59 (52.7%)	2.21 (1.38–3.55)	2.22 (1.35–3.63)	<0.001
MetS absent (n = 218)	63 (28.9%)	155 (71.1%)	1 (reference)	1 (reference)	-

Adjusted for age, sex and smoking (adjusted p = 0.002). †Chi-square test (crude). OR, odds ratio; CI, confidence interval.

Table 3: Association between individual MetS components and GERD symptoms (N = 330)

MetS component (n with component)	GERD symptoms if present, n (%)	GERD symptoms if absent, n (%)	Crude OR (95% CI)	p	Adjusted OR (95% CI)*	p
Abdominal obesity (174)	69 (39.7%)	47 (30.1%)	1.52 (0.96–2.41)	0.070	1.32 (0.75–2.31)	0.338
Elevated blood pressure (112)	50 (44.6%)	66 (30.3%)	1.86 (1.16–2.98)	0.010	1.71 (1.02–2.86)	0.042
Elevated fasting glucose (98)	41 (41.8%)	75 (32.3%)	1.51 (0.93–2.45)	0.098	1.17 (0.65–2.10)	0.597
Hypertriglyceridaemia (116)	43 (37.1%)	73 (34.1%)	1.14 (0.71–1.82)	0.591	0.95 (0.56–1.59)	0.833
Low HDL-C (142)	53 (37.3%)	63 (33.5%)	1.18 (0.75–1.86)	0.473	1.05 (0.63–1.74)	0.865

All five components entered together, adjusted for age, sex and smoking. Each row compares participants with and without the component. OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

DISCUSSION

Out of 330 adults, 33.9% had MetS and 35.2% had GERD symptoms. The association remained significant after adjustment for age, sex and smoking (adjusted OR 2.22; 95% CI 1.35–3.63), and was almost double (47.3% vs 28.9%) with MetS. This direction is similar to the pooled OR of the 15 studies in the meta-analysis (1.66)¹⁶ and the Korean endoscopy studies of reflux and erosive esophagitis (1.48, 1.67, respectively)^{13, 14}. The estimate is larger than our pooled estimate, and than the Taiwan Biobank adjusted

OR of 1.079¹⁰ but the confidence interval contains 1.66. Sample sizes in clinics are small, which means that estimates are not as precise, and case definitions vary from one study to another. Taiwanese research has also explored the relationship between MetS and reflux and erosive esophagitis^{20, 21}.

The prevalence of MetS in the present study is slightly higher than that of apparently healthy adults in Pakistan (28.8%)⁷ which is a clinic-based study. The 35.2% who present with GERD symptoms is significantly higher than the global pooled estimate of

approximately 14%² and higher than the range of 8.7%-33.1% reported in population studies in the Middle East³. Also, a GerdQ cut-off of 8 captures overlapping upper abdominal symptoms and patients at gastroenterology or medicine clinics are not representative of the general population, making it not a community prevalence.

Elevated blood pressure was the only factor that was significantly associated with GERD symptoms (adjusted OR 1.71; 95% CI 1.02–2.86). The direction of these changes was similar (OR approximately 1.5) and was well established with confidence intervals that included 1, for abdominal obesity and elevated glucose, and for triglycerides and HDL-C, little. There is conflicting information. Abdominal obesity, hyper-triglyceridemia, hyperglycaemia and hypertension were associated with GERD in the meta-analysis¹⁶. A Korea study revealed that WC and triglyceride were separately correlated¹³. However, abdominal obesity, triglyceride and low HDL-C were found to be associated with MetS by the Taiwan Biobank, while no association with hypertension or hyperglycaemia was observed¹⁰; the same was observed for erosive esophagitis, which was associated with MetS, impaired liver function and dyslipidaemia²². The component analyses were relatively underpowered because we sized our study to estimate the prevalence of MetS, and a non-significant result for abdominal obesity, which has been associated with esophageal inflammation and neoplasia^{9,10} was not evidence of no effect. We were not able to note what kinds of anti-hypertensive medications individuals were using so we cannot determine if medication is the cause of the blood pressure discovery. For instance, calcium channel blockers reduce the pressure in the sphincter¹⁰.

Similar to the Taiwan Biobank¹⁰ in which symptoms of GERD increased with each additional component, the frequency of symptoms with zero, one or two components were about equal (27–31%) and increased to 48–54% when the third and fourth components were added. The 23 respondents in the fall to 39% with five components have a wide confidence interval so the trend is not strictly graded.

Intra-abdominal pressure is believed to increase in the abdomen and increase the pressure of the lower esophageal sphincter transient relaxation, and cytokines produced by adipose may contribute to this too¹⁰. Because insulin resistance is a key component of MetS, it was correlated with both the prevalence and severity of GERD [11]; however, it was not measured in this study. Obesity itself could be the cause of some of the association [8] and diet and lifestyle associated with weight gain can also play a role²³.

Clinicians should screen adults with GERD symptoms for blood pressure as well as other components of MetS, and screen patients with MetS for GERD symptoms. Weight management and lifestyle changes are already incorporated in guideline based GERD management, and addressing central obesity may be beneficial to both issues²⁴. More prospective testing is needed to determine if treating metabolic abnormalities can decrease symptoms of reflux.

Limitations: Like other cross-sectional reflux studies²⁵ its cross sectional design does not allow it to identify which condition preceded the other. Selection bias is a possibility because it was hospital-based, single-centre and consecutively sampled and the results cannot be generalized. We used a questionnaire to define GERD, which is not based on endoscopy or pH monitoring, and the sensitivity and specificity of the GerdQ were 65% and 71% respectively against the reference standard used to develop the questionnaire¹⁷. Insulin resistance was not measured, alcohol consumption was not assessed, hiatal hernia or *Helicobacter pylori* was not assessed, and some antihypertensive, antidiabetic or lipid-lowering drugs may impact both components of MetS and reflux. There were not enough participants for component and subgroup analyses. There is a need for prospective studies with objective assessment of GERD done in multiple centres.

CONCLUSION

After adjusting for age, sex and smoking, approximately twice as many odds of adults having GERD symptomology when they had MetS in this cross-sectional study conducted at Mardan Medical Complex. The only independent component associated was elevated blood pressure. Clinicians may wish to check patients with GERD symptoms for metabolic abnormalities and to offer weight and lifestyle advice. Longitudinal studies are needed to establish causality.

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AUTHOR CONTRIBUTIONS

Muhammad Sohrab Khan: Conceptualization, study design, data collection, data analysis and interpretation, manuscript drafting, critical revision, and final approval of the manuscript.

Farman Ullah Shah: Literature review, data collection, data interpretation, manuscript review and editing, critical revision, and final approval of the manuscript.

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