

# The Gastric Connection: Serum Gastric Biomarkers, Metabolic Syndrome and Transition in Metabolic Status

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**Objective:** Inflammation plays a crucial role in the development of metabolic syndrome (MetS). However, the roles of pepsinogens (PGs) and gastrin, known biomarkers linked to gastric inflammation, in MetS and the transition of MetS status are unclear. This research aimed to explore the relationship between MetS, the transition of MetS status, and levels of gastric biomarkers.

**Methods:** This large-scale cross-sectional study included 19162 participants aged 18–80 years between August 2021 and March 2024. Serum levels of the gastric biomarkers PGI, PGII, and gastrin-17 were analyzed using enzyme-linked immunosorbent assay. In addition, the relationship between transitions of MetS status based on 1032 MetS-negative participants from baseline to the second health exam after 2 years was considered. The association between MetS and the transitions of MetS status and gastric biomarkers was analyzed using logistic regression models.

**Results:** The prevalence of MetS in the study population was 31.4%, with higher rates in males (35.2%) than females (24.6%). Gastrin-17 levels were markedly elevated in participants with MetS, a trend observed in both genders. In the logistic regression analysis, after adjusting for confounding factors, gastrin-17 levels were strongly and positively correlated with MetS in the entire cohort and in males but not in females. Male participants with MetS had lower levels of PGI and PGII than those without MetS, whereas the opposite trend was observed in females. Logistic regression analysis indicated that PGI and PGII were not independently associated with MetS. During the follow-up of 2 years, 199 (19.28%) of the 1032 MetS-negative participants transitioned to MetS-positive status. As compared to the stable MetS-negative subjects, transition from MetS-negative to MetS-positive was associated with higher levels of gastrin-17, especially in males, but not in females.

**Conclusion:** Gastrin-17 is a promising biomarker for MetS, exhibiting potential utility in monitoring the transition of MetS status and revealing gender difference.

**Keywords:** gastric biomarkers, gastrin-17, metabolic syndrome, transition, gender difference

## Introduction

Metabolic syndrome (MetS) is characterized by a constellation of risk factors, including central obesity, high blood pressure, elevated fasting glucose, high triglyceride (TG) levels, and low high-density lipoprotein cholesterol (HDL) levels.<sup>1</sup> Notably, more than one billion people suffer from MetS worldwide<sup>2</sup> and the prevalence of MetS has increased in

both developing and developed nations over the past few decades. The prevalence of MetS was 27.93% in North America, 27.65% in South America, 21.27% in Asia, 16.04% in Africa, and 10.47% in Europe.<sup>3</sup> The Chinese Nutrition and Health Surveillance (2015–2017) reported that almost one-third (31.1%) of Chinese adults have MetS.<sup>4</sup> Besides, recent study shown that the prevalence of the middle-aged and elderly Chinese diagnosed with MetS was 41.87%.<sup>5</sup> The prevalence of MetS also exhibit sexual dimorphism due to sex-related effects on key components like insulin-resistance and abdominal fat.<sup>6</sup> Interestingly, several studies demonstrated that the prevalence of MetS was higher in men than women before the age of 60 but the ratio inverted after this age.<sup>7–9</sup> In a prospective cohort study indicated that female sex was associated with decreased probability of developing MetS.<sup>10</sup> Early identification of MetS is vital for identifying individuals at heightened risk for atherosclerotic cardiovascular diseases (ASCVD). However, despite extensive research, the intricate pathophysiology of MetS remains incompletely understood.

Emerging evidence suggests that chronic systemic inflammation and the resultant production of pro-inflammatory cytokines play a pivotal role in MetS development.<sup>11,12</sup> Activation of nuclear factor kappa B in MetS induces a state of chronic low-grade inflammation and phosphorylate insulin receptor causing insulin resistance.<sup>13–15</sup> Pro-inflammatory cytokines (tumor necrosis factor  $\alpha$ , interleukin-1 $\beta$ , interleukin-6, etc) derived from adipose tissue, liver, muscle and other tissues also contribute to insulin resistance.<sup>16–19</sup> The gastrointestinal tract, particularly the stomach, is a critical site for initiating this chronic inflammation. *Helicobacter pylori* (*H. pylori*) infection, a major cause of gastric inflammation, influences lipid and glucose metabolism, potentially exacerbating atherosclerosis and MetS.<sup>20–23</sup> Several studies have shown that *H. pylori* induced insulin resistance by activation of pro-inflammatory factors like C-reactive protein, production of reactive oxygen species, alteration of ghrelin and leptin levels and increased production of lipopolysaccharides.<sup>24–27</sup> Besides, *H. pylori* also promotes the synthesis of polyunsaturated ether phospholipids leading to susceptibility to ferroptosis<sup>28</sup> and contributes to atherosclerosis by inducing endothelial dysfunction,<sup>29</sup> dysregulation of lipid metabolism (increased total cholesterol and triglyceride levels and reduced high-density lipoprotein levels),<sup>30–32</sup> and hyperhomocysteinemia.<sup>33</sup> Moreover, gastric biomarkers, including pepsinogen (PG) I, PGII, and gastrin, are also associated with gastric inflammation.<sup>34</sup> Previous studies have indicated a clinical association between serum gastric biomarkers and blood pressure, fasting blood glucose (FBG), TG, and uric acid levels.<sup>23,35–37</sup> However, the relationships between these gastric biomarkers and MetS have not been examined, and the mechanisms by which gastric biomarkers influence metabolic indices are not clear. The levels of gastric biomarkers are influenced by many factors such as certain drugs (eg, proton pump inhibitors, PPIs) and gastric diseases (eg, *H. pylori* infection, chronic atrophic gastritis). For example, *H. pylori* infection induces heparin-binding EGF-like growth factor which activates the mitogen-activated protein kinase pathway resulting in an increased gastrin expression.<sup>38</sup> Long-term PPI therapy leads to hypergastrinemia via inducing acid suppression which interferes with antral D and G cells.<sup>39</sup> This cross-sectional study aimed to investigate the associations between serum gastric biomarkers (PGI, PGII, and gastrin-17) and MetS. Additionally, we sought to explore whether these biomarkers exhibit sexual dimorphism and were associated with transitions of MetS status based on 1032 MetS-negative participants from baseline to the second health exam after 2 years.

## Material and Methods

### Study Population

This present study was conducted at the Health Management Medicine Center of Third Xiangya Hospital, Central South University, from August 2021 to March 2024. We collected basic information and data on serum levels of PGI, PGII, and gastrin-17 from 19162 participants. Transitions in MetS status of MetS-negative subjects were examined from baseline to the second exam after 2 years in 1032 participants from the total 19162 participants. This study was approved by the Institutional Review Board of the Third Xiangya Hospital (ethical approval number: I21102), with all procedures followed by the Declaration of Helsinki, and all essential permissions were obtained from the government and health commission. Written Informed consent was signed by each participant. All personal information was anonymized during analysis and reporting to ensure confidentiality and privacy.

## Measurement of Serum Levels of Gastrin-17, PGI, and PGII

Serum samples were collected following an overnight fast, processed within 30 min post-collection, and stored at  $-80^{\circ}\text{C}$  until analysis. The serum samples were analyzed using enzyme-linked immunosorbent assay (ELISA) kits specifically designed for gastrin-17 (catalog No. 601 035CN, Biohit, Plc., Helsinki, Finland), PGI, catalog No. 601 010.01CN, Biohit, Plc.), and PGII (catalog No. 601 020.02CN, Biohit, Plc). The tests were conducted according to the manufacturer's instructions. Standard curves for PGI, PGII, and gastrin-17 were used to determine the concentrations in unknown samples.

## Covariates

Baseline characteristics, including demographic, clinical, and laboratory data, were systematically collected. A history of hypertension (HBP), diabetes mellitus (DM), dyslipidemia, ASCVD, smoking, and alcohol consumption was ascertained from the medical records. ASCVD included coronary heart disease, stroke, and peripheral arterial disease. Medication histories spanning the past three months were recorded, focusing on antihypertensive drugs, antidiabetic agents, antiplatelet drugs, statins, PPIs, and histamine 2 (H<sub>2</sub>)-receptor antagonists. Physical measurements such as height, body mass, waist circumference (WC), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were obtained. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters. Laboratory parameters, including creatinine (Cr), FBG, total cholesterol (TC), TG, HDLC, low-density lipoprotein cholesterol (LDLC), and glycosylated hemoglobin (HbA1C) levels, were measured. The presence of *H. pylori* infection was determined for each participant using a  $^{13}\text{C}$  urea breath test, as previously described.<sup>40</sup>

## Definition of MetS

MetS was defined according to the criteria set by the International Diabetes Federation.<sup>41</sup> A MetS diagnosis required meeting at least three of the following five criteria: (1) WC  $\geq 80$  cm (females) or  $\geq 90$  cm (males); (2) TG  $> 1.7$  mmol/L or on specific treatment for this lipid abnormality; (3) HDLC  $< 1.29$  mmol/L (females) or  $< 1.03$  mmol/L (males); (4) BP  $\geq 130/85$  mmHg or treatment for or diagnosis of hypertension; and (5) FBG  $> 5.6$  mmol/L or diagnosis of type 2 DM.

## Statistical Analysis

Continuous variables are presented as the means with standard deviations or medians with interquartile range (IQRs) for normally and non-normally distributed data, respectively. Categorical variables are reported as numbers and percentages. For continuous variables, the Student's *t*-test and Mann–Whitney *U*-test were used for inter-group comparisons, whereas for categorical variables, Pearson's  $\chi^2$  test was used to assess inter-group differences. For better clinical interpretation, patients were separated into three groups based on levels of gastrin-17, PGI, and PGII, and the PGI/PGII ratio was subgrouped into tertiles. Independent risk factors for MetS were evaluated using binary logistic regression analysis with adjustment for age, sex, and other possible confounders. After assessing multicollinearity using the variance inflation factor (VIF), independent variables showing no multicollinearity (VIF  $< 10$ ) and having  $P < 0.05$  were entered into the logistic regression models. Results are displayed as odds ratios (ORs) with 95% confidence intervals (CIs). Data analysis and visualization were conducted using SPSS 22.0 (SPSS, Inc., Chicago, IL, United States) and Origin Pro 2022 software (Origin Lab Corporation, Northampton, MA, United States). The Correlation Heatmap was plotted using <http://www.bioinformatics.com.cn>, an online platform. Statistical significance was established at  $P < 0.05$ .

## Results

### Descriptive Analysis of Enrolled Participants with and without MetS

The characteristics of the MetS-positive and MetS-negative groups are shown in Table 1. A total of 19162 participants (12271 males and 6891 females) are included in this study. Among these, 6012 (31.4%) were diagnosed with MetS, including 4316 males and 1696 females, indicating a higher prevalence of MetS in males (35.2%) compared to females (24.6%). Univariate analysis revealed that participants with MetS were older and had higher rates of HBP, DM, hyperlipidemia, ASCVD, *H. pylori* infection, smoking, alcohol consumption, and medication usage than participants

**Table 1** Baseline Characteristics of Participants with and without Metabolic Syndrome

Variables	Total (n = 19162)	Metabolic Status		P value
		MetS-Negative (n = 13150)	MetS-Positive (n = 6012)	
Age (yr)	48 (40–55)	47 (38–54)	51 (44–56)	< 0.001
Sex (male), n (%)	12,271 (64.04)	7955 (60.49)	4316 (71.79)	< 0.001
HBP, n (%)	4102 (21.41)	1576 (11.98)	2526 (42.02)	< 0.001
DM, n (%)	1629 (8.50)	434 (3.30)	1195 (19.88)	< 0.001
Hyperlipidemia, n (%)	7712 (40.25)	3406 (25.90)	4306 (71.62)	< 0.001
ASCVD, n (%)	301 (1.57)	165 (1.25)	136 (2.26)	< 0.001
Smoking, n (%)	4741 (24.74)	2963 (22.53)	1778 (29.57)	< 0.001
Drinking, n (%)	5982 (31.22)	3810 (28.97)	2172 (36.13)	< 0.001
<i>H. pylori</i> infection, n (%)	3601 (18.79)	2366 (17.99)	1235 (20.54)	< 0.001
<b>Medication history, n (%)</b>				
Antihypertensive	1498 (7.82)	990 (7.53)	508 (8.45)	0.029
Antidiabetic	516 (2.69)	317 (2.42)	199 (3.31)	< 0.001
Statins	805 (4.20)	473 (3.60)	332 (5.52)	< 0.001
Antiplatelet	305 (1.59)	165 (1.25)	140 (2.33)	< 0.001
PPI/H2 blocker	380 (1.98)	226 (1.72)	154 (2.56)	< 0.001
<b>Metabolic index</b>				
BMI (kg/m <sup>2</sup> )	24.36 (22.25–26.57)	23.33 (21.39–25.26)	26.60 (24.84–28.47)	< 0.001
WC (cm)	84 (77–91)	81 (74–87)	92 (86–97)	< 0.001
SBP (mmHg)	123 (112–134)	118 (109–128)	133 (123–142)	< 0.001
DBP (mmHg)	76 (68–84)	73 (66–80)	83 (75–89)	< 0.001
TC (mmol/L)	5.03 (4.43–5.68)	4.94 (4.37–5.57)	5.22 (4.60–5.92)	< 0.001
TG (mmol/L)	1.49 (1.00–2.31)	1.22 (0.87–1.67)	2.40 (1.81–3.56)	< 0.001
HDLC (mmol/L)	1.27 (1.10–1.47)	1.34 (1.17–1.53)	1.13 (0.99–1.28)	< 0.001
LDLC (mmol/L)	2.85 (2.33–3.39)	2.88 (2.39–3.40)	2.75 (2.15–3.37)	< 0.001
FBG (mmol/L)	5.35 (4.99–5.83)	5.21 (4.90–5.51)	5.88 (5.42–6.58)	< 0.001
HbA1c (%)	5.60 (5.30–5.90)	5.50 (5.30–5.70)	5.80 (5.50–6.20)	< 0.001
Cr (μmol/L)	74.00 (62.00–85.00)	73.00 (61.00–84.00)	76.00 (65.00–86.00)	< 0.001
<b>Gastric biomarkers</b>				
Gastrin-17 (pmol/L)	1.65 (0.78–3.52)	1.59 (0.71–3.33)	1.80 (0.93–4.04)	< 0.001
PGI (ng/mL)	81.75 (60.94–110.02)	81.83 (61.16–109.55)	81.53 (60.51–111.26)	0.535
PGII (ng/mL)	7.40 (5.00–11.30)	7.38 (4.99–11.23)	7.42 (5.04–11.41)	0.489
PGI/II	10.95 (7.97–15.07)	10.95 (8.00–15.04)	10.96 (7.94–15.19)	0.988

**Note:** Values were given as median (interquartile range).

**Abbreviations:** MetS, Metabolic syndrome; HBP, Hypertension; DM, Diabetes mellitus; ASCVD, Atherosclerotic cardiovascular diseases; *H. pylori*, *Helicobacter pylori*; PPI, Proton pump inhibitor; H2, Histamine 2; BMI, Body mass index; WC, Waist circumference; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, Total cholesterol; TG, Triglycerides; HDLC, High-density lipoprotein cholesterol; LDLC, Low-density lipoprotein cholesterol; FBG, Fasting blood glucose; HbA1c, Glycosylated hemoglobin; Cr, Creatinine; PGI, Pepsinogen I; PGII, Pepsinogen II.

without MetS. Participants with MetS also had higher BMI, WC, SBP, DBP, and levels of TC, TG, FBG, HbA1c, and Cr than those without MetS.

## Gastrin-17, PGI, and PGII Levels in Participants with and without MetS

The median (IQR) levels of gastrin-17, PGI, and PGII, and the PGI/PGII ratio of all participants are shown in Table 1. Serum levels of gastrin-17 in the MetS-positive group were higher than those in the MetS-negative group [1.80 (IQR, 0.93–4.04) vs 1.59 (0.71–3.33) pmol/L]. The serum levels of PGI and PGII and the PGI/PGII ratio were not significantly different between participants with or without MetS.

## Baseline Characteristics and Gastric Biomarkers of Males and Females

The demographic characteristics of individuals in the sex-based subgroups are shown in [Table S1](#). Male participants were slightly younger and had significantly higher proportion of individuals with HBP, DM, hyperlipidemia, smoking, drinking, and hypertensive medication history than female participants. Males also had higher median BMI, WC, SBP, and DBP levels of TG, HDLC, LDLC, FBG, HbA1c, Cr, gastrin-17, PGI, PGII, and PGI/PGII ratio than females.

## Characteristics and Gastric Biomarkers of Participants with or Without MetS Stratified by Sex

The demographics and clinical markers of male and female participants with and without MetS are shown in [Table S2](#). Both male and female participants with MetS were older and more likely to have HBP, DM, ASCVD, hyperlipidemia, *H. pylori* infection, alcohol consumption, and medication history (except for hypertensive medication history) than those without MetS. They also had higher BMI, WC, SBP, DBP, TC, TG, FBG, and HbA1c levels. HDLC levels were lower in the MetS-positive group. The median levels of gastrin-17 were higher in participants with MetS in both sexes. The concentrations of PGI and PGII and the PGI/PGII ratio showed sexual dimorphism, as displayed in [Table 2](#). Males with MetS had lower levels of PGI and PGII and a higher PGI/PGII ratio than males without MetS, whereas females with MetS had higher levels of PGI and PGII and a lower PGI/PGII ratio than females without MetS.

## Analysis of the Association Between Gastric Biomarkers and MetS Using Logistic Regression Models

To better explore the relationship between gastric biomarkers and MetS, we categorized patients into three groups according to biomarker levels and performed a logistic regression analysis ([Table 3](#)). We used VIF analysis to confirm multicollinearity and conducted independent stepwise regression analyses for all the adjusted models. [Table S3](#) shows the results of the multicollinearity analysis; variables with VIF > 10 were removed from the final models. For the overall group comparison, in Model 1 was adjusted for age and sex, both the second and the third gastrin-17 tertiles were significantly correlated with MetS (tertile 2: OR, 1.225; 95% CI, 1.133–1.324;  $P < 0.001$ ; and tertile 3: OR, 1.465; 95% CI, 1.353–1.587;  $P < 0.001$ ) compared to the first gastrin-17 tertile. The second and third PGI tertiles were negatively correlated with MetS (tertile 2: OR, 0.837; 95% CI, 0.767–0.913;  $P < 0.001$ ; and tertile 3: OR, 0.742; 95% CI, 0.665–0.828;  $P < 0.001$ ) compared to the first PGI tertile. Compared with the first PGII tertile, the second and third PGII-level tertiles were negatively associated with MetS. Similar results were also found in Model 2 when adjusted for age, sex, HBP, DM, hyperlipidemia, ASCVD, smoking, drinking, *H. pylori* infection, and medication history. In Model 3 was adjusted for age, sex, HBP, DM, hyperlipidemia, ASCVD, smoking, drinking, *H. pylori* infection, medication history, BMI, WC, SBP, DBP, TG, HDLC, FBG, HBA1C, and Cr levels, only the second and third gastrin-17 tertiles were

**Table 2** Multivariable Logistic Regression Analysis of the Relationship Between Gastric Biomarkers and Transition of MetS Status

		Model 1				Model 2				Model 3			
		P value	OR	95% CI for OR		P value	OR	95% CI for OR		P value	OR	95% CI for OR	
All participants	Gastrin-17	<b>0.001</b>	<b>1.089</b>	<b>1.037</b>	<b>1.144</b>	<b>0.001</b>	<b>1.131</b>	<b>1.051</b>	<b>1.217</b>	<b>0.008</b>	<b>1.112</b>	<b>1.028</b>	<b>1.203</b>
	PGI	0.983	0.999	0.944	1.058	0.925	0.997	0.937	1.061	0.5	0.974	0.901	1.052
	PGII	0.182	0.996	0.989	1.002	0.25	0.995	0.988	1.003	0.765	0.999	0.989	1.008
	PGI/PGII	0.661	0.991	0.951	1.032	0.205	0.965	0.912	1.02	0.17	0.952	0.888	1.021
Males	Gastrin-17	<b>0.004</b>	<b>1.09</b>	<b>1.028</b>	<b>1.157</b>	<b>0.004</b>	<b>1.09</b>	<b>1.028</b>	<b>1.157</b>	<b>0.009</b>	<b>1.111</b>	<b>1.026</b>	<b>1.202</b>
	PGI	0.983	0.999	0.943	1.059	0.983	0.999	0.943	1.059	0.582	0.979	0.906	1.057
	PGII	0.185	0.996	0.989	1.002	0.185	0.996	0.989	1.002	0.719	0.998	0.988	1.008
	PGI/PGII	0.877	0.997	0.956	1.039	0.877	0.997	0.956	1.039	0.314	0.965	0.901	1.034

**Notes:** Adjusted model 1: for all participants, adjusted for age and sex; for males, adjusted for age; Adjusted model 2: for all participants, adjusted for age, sex, hypertension (HBP), hyperlipidemia, smoking; for males, adjusted for age and HBP. Adjusted model 3: for all participants, adjusted for age, sex, HBP, hyperlipidemia, smoking, BMI, waist, SBP, DBP, TC, TG, HDLC, FBG, HbA1c, and Cr levels; for males, adjusted for age, HBP, BMI, waist, SBP, DBP, TC, TG, HDLC, FBG, and HbA1c. Bold values indicate  $P < 0.05$ .

**Table 3** Multivariable Logistic Regression Analysis of the Relationship Between Gastric Biomarkers and Metabolic Syndrome According to Tertiles

	Model 1				Model 2				Model 3			
	P value	OR	95% CI for OR		P value	OR	95% CI for OR		P value	OR	95% CI for OR	
All participants												
Gastrin-17 tertiles												
Tertile 1 (< 1.10)	Reference				Reference				Reference			
Tertile 2 (1.10–2.63)	< 0.001	1.225	1.133	1.324	< 0.001	1.223	1.114	1.343	0.015	1.158	1.029	1.304
Tertile 3 (> 2.63)	< 0.001	1.465	1.353	1.587	< 0.001	1.334	1.211	1.470	0.026	1.150	1.017	1.300
PGI tertiles												
Tertile 1 (< 69.21)	Reference				Reference				Reference			
Tertile 2 (69.21–98.35)	< 0.001	0.837	0.767	0.913	< 0.001	0.825	0.744	0.916	0.191	0.916	0.803	1.045
Tertile 3 (> 98.35)	< 0.001	0.742	0.665	0.828	< 0.001	0.713	0.626	0.813	0.211	0.899	0.762	1.062
PGII tertiles												
Tertile 1 (< 5.84)	Reference				Reference				Reference			
Tertile 2 (5.84–9.65)	0.012	0.883	0.801	0.973	0.020	0.871	0.776	0.979	0.974	1.002	0.865	1.162
Tertile 3 (> 9.65)	0.043	0.868	0.757	0.995	0.044	0.845	0.718	0.996	0.552	1.065	0.865	1.311
PGI/II tertiles												
Tertile 1 (< 8.95)	Reference				Reference				Reference			
Tertile 2 (8.95–13.35)	0.440	0.965	0.881	1.057	0.185	0.929	0.833	1.036	0.936	1.006	0.876	1.155
Tertile 3 (> 13.35)	0.591	1.032	0.919	1.159	0.505	0.954	0.829	1.096	0.850	1.017	0.851	1.217
Males												
Gastrin-17 tertiles												
Tertile 1 (< 1.13)	Reference				Reference				Reference			
Tertile 2 (1.13–2.68)	< 0.001	1.289	1.174	1.415	< 0.001	1.234	1.102	1.381	0.003	1.235	1.073	1.421
Tertile 3 (> 2.68)	< 0.001	1.471	1.337	1.618	< 0.001	1.292	1.149	1.452	0.013	1.202	1.040	1.391
PGI tertiles												
Tertile 1 (< 73.18)	Reference				Reference				Reference			
Tertile 2 (73.18–104.81)	< 0.001	0.788	0.709	0.876	0.001	0.798	0.703	0.907	0.486	0.945	0.806	1.108
Tertile 3 (> 104.81)	< 0.001	0.687	0.602	0.783	< 0.001	0.674	0.575	0.790	0.068	0.831	0.682	1.014
PGII tertiles												
Tertile 1 (< 6.22)	Reference				Reference				Reference			
Tertile 2 (6.22–9.99)	0.111	0.910	0.809	1.022	0.286	0.927	0.805	1.066	0.366	1.084	0.910	1.292
Tertile 3 (> 9.99)	0.151	0.887	0.753	1.045	0.185	0.875	0.718	1.066	0.151	1.198	0.936	1.532
PGI/II tertiles												
Tertile 1 (< 9.17)	Reference				Reference				Reference			
Tertile 2 (9.17–13.47)	0.720	1.020	0.915	1.137	0.815	0.984	0.863	1.122	0.910	1.010	0.857	1.189
Tertile 3 (> 13.47)	0.119	1.117	0.972	1.283	0.829	1.019	0.861	1.205	0.266	1.127	0.913	1.391

(Continued)

Table 3 (Continued).

	Model 1				Model 2				Model 3			
	P value	OR	95% CI for OR		P value	OR	95% CI for OR		P value	OR	95% CI for OR	
Females												
Gastrin-17 tertiles												
Tertile 1 (< 1.05)	Reference				Reference				Reference			
Tertile 2 (1.05–2.54)	0.598	1.040	0.898	1.205	0.111	1.149	0.969	1.362	0.953	0.993	0.785	1.256
Tertile 3 (> 2.54)	< 0.001	1.438	1.239	1.669	< 0.001	1.416	1.188	1.686	0.863	1.022	0.801	1.304
PGI tertiles												
Tertile 1 (< 60.39)	Reference				Reference				Reference			
Tertile 2 (60.39–87.07)	0.021	0.829	0.707	0.972	0.022	0.807	0.671	0.970	0.214	0.851	0.660	1.098
Tertile 3 (> 87.07)	0.120	0.852	0.697	1.042	0.047	0.789	0.624	0.996	0.556	1.104	0.795	1.533
PGII tertiles												
Tertile 1 (< 5.26)	Reference				Reference				Reference			
Tertile 2 (5.26–8.84)	0.022	0.807	0.671	0.969	0.009	0.755	0.611	0.933	0.128	0.797	0.596	1.068
Tertile 3 (> 8.84)	0.212	0.848	0.655	1.099	0.123	0.790	0.586	1.066	0.105	0.709	0.468	1.075
PGI/II tertiles												
Tertile 1 (< 8.59)	Reference				Reference				Reference			
Tertile 2 (8.59–13.09)	0.170	0.885	0.743	1.054	0.137	0.858	0.701	1.050	0.958	1.008	0.762	1.332
Tertile 3 (> 13.09)	0.290	0.888	0.712	1.107	0.173	0.836	0.647	1.081	0.095	0.739	0.517	1.055

**Notes:** Adjusted model 1: For all participants, adjusted for age and sex; for males and females, adjusted for age; Adjusted model 2: Adjusted for age, sex, hypertension (HBP), diabetes mellitus (DM), hyperlipidemia, atherosclerotic cardiovascular diseases (ASCVD), smoking, drinking, *Helicobacter pylori* (*H. pylori*) infection, and medication history; Adjusted model 3: For all participants and females, adjusted for age, sex, HBP, DM, hyperlipidemia, ASCVD, smoking, drinking, *H. pylori* infection, medication history, and BMI, waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein cholesterol (HDL), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), and creatinine (Cr) levels; for males, adjusted for age, sex, HBP, DM, hyperlipidemia, ASCVD, smoking, drinking, *H. pylori* infection, and medication history, and BMI, WC, SBP, DBP, TG, HDL, LDL, FBG, HbA1c, and Cr levels.

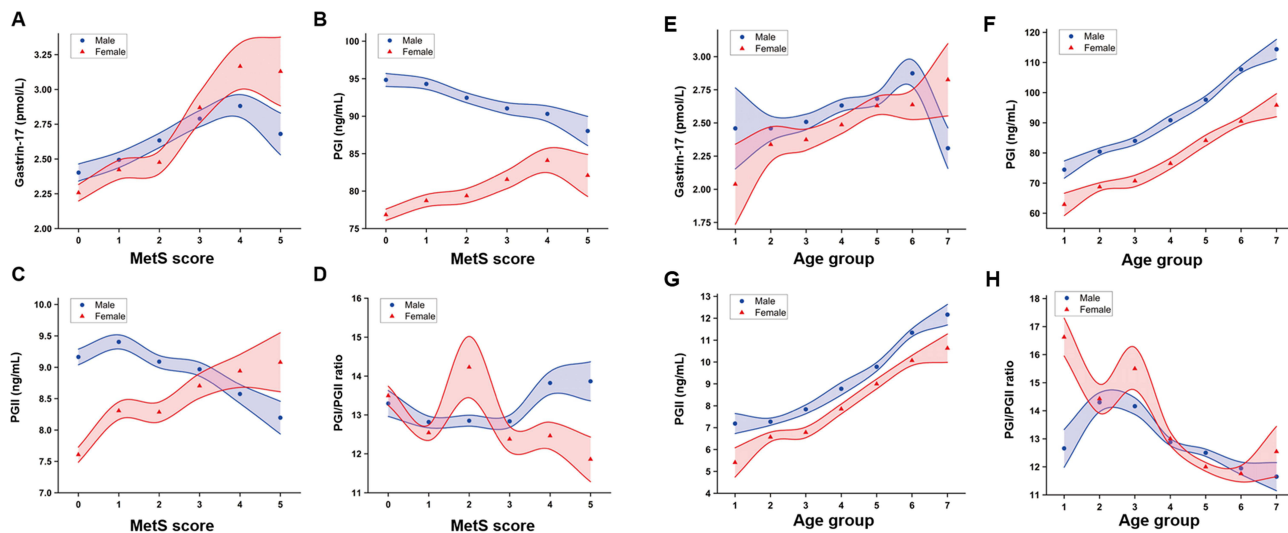
**Abbreviations:** MetS, Metabolic syndrome; HBP, Hypertension; DM, Diabetes mellitus; ASCVD, Atherosclerotic cardiovascular diseases; PPI, Proton pump inhibitor; H2, Histamine 2; BMI, Body mass index; WC, Waist circumference; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; TC, Total cholesterol; TG, Triglycerides; HDL, High-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; FBG, Fasting blood glucose; HbA1c, Glycosylated hemoglobin; Cr, Creatinine; PGI, Pepsinogen I; PGII, Pepsinogen II.

significantly associated with MetS (tertile 2: OR, 1.158; 95% CI, 1.029–1.304;  $P = 0.015$ ; and tertile 3: OR, 1.150; 95% CI, 1.017–1.300;  $P = 0.026$ ) compared to the first gastrin-17 tertile.

In males, the gastrin-17 tertiles and the PGI tertiles showed the same trends as the whole-group analyses for Model 1 and Model 2. In females, for Models 1 and 2, the highest tertile of gastrin-17 was positively associated with MetS and both the middle PGI and PGII tertiles were negatively associated with MetS compared to corresponding lowest tertiles. In Model 3, gastrin-17 showed a positive association with MetS, whereas PGI and PGII showed no significant association with MetS.

## Gastric Biomarkers and MetS Components

The associations between each MetS component and gastric biomarkers are shown in [Table S4](#). The results indicated that gastrin-17 levels were higher in individuals with higher WC and levels of TG, HDL, SBP, DBP, and FBG ( $P < 0.001$ ). PGI levels were higher in individuals with higher levels of WC, SBP, DBP, TG, and HDL. PGII levels were higher in participants with higher levels of TG and HDL. PGI and PGII levels were lower in participants with higher FBG levels. The PGI/II ratio was higher in participants with higher SBP and DBP, and lower levels of HDL and TG. The five components of MetS were combined to calculate a composite MetS score (0–5). As the MetS score increased (0–4), gastrin-17 levels increased both in males and females ([Figure 1A–D](#)).



**Figure 1** The change of gastric biomarkers along with continuous metabolic syndrome severity score and different age groups. **(A)** Gastrin-17; **(B)** Pepsinogen (PG) I; **(C)** PGII; **(D)** PGI/PGII change with metabolic syndrome severity score. Metabolic syndrome (MetS) score: 0–5: Subjects without and with 1, 2, 3, 4, and 5 components of MetS. The error bars are drawn as transparent bands. Transparency has been set for all curves so that data in overlapping regions can be clearly seen. Points indicate mean  $\pm$  SE. MetS: Metabolic syndrome; PGI: Pepsinogen I; PGII: Pepsinogen II. **(E)** Gastrin-17; **(F)** Pepsinogen (PG) I; **(G)** PGII; **(H)** PGI/PGII trends with age. Transparency has been set for all curves so that data in overlapping regions can be clearly seen. The error bars are drawn as transparent bands. The shaded curves represent means  $\pm$  SE. Age groups: 1: < 20 years old; 2: 20–29 years old; 3: 30–39 years old; 4: 40–49 years old; 5: 50–59 years old; 6: 60–69 years old; and 7: > 70 years old. PGI: Pepsinogen I; PGII: Pepsinogen II.

## Relationship Between Gastric Biomarkers and Clinical Parameters

The results of the correlational analysis between serum gastric biomarker levels and clinical parameters are shown in [Figure S1](#). Serum levels of PGI and PGII were positively correlated with age and serum levels of Cr and gastrin-17. [Figure 1E–H](#) shows that PGI and PGII increased with advancing age in patients of both sexes. Gastrin-17 levels were not linearly correlated with age; however, we found that gastrin-17 levels increase gradually with age in participants aged <70 years. Serum PGII levels were strongly correlated with PGI ( $r = 0.604$ ) and the PGI/II ratio. Serum gastrin-17 levels were positively correlated with levels of PGI and PGII and negatively correlated with PGI/II ratio.

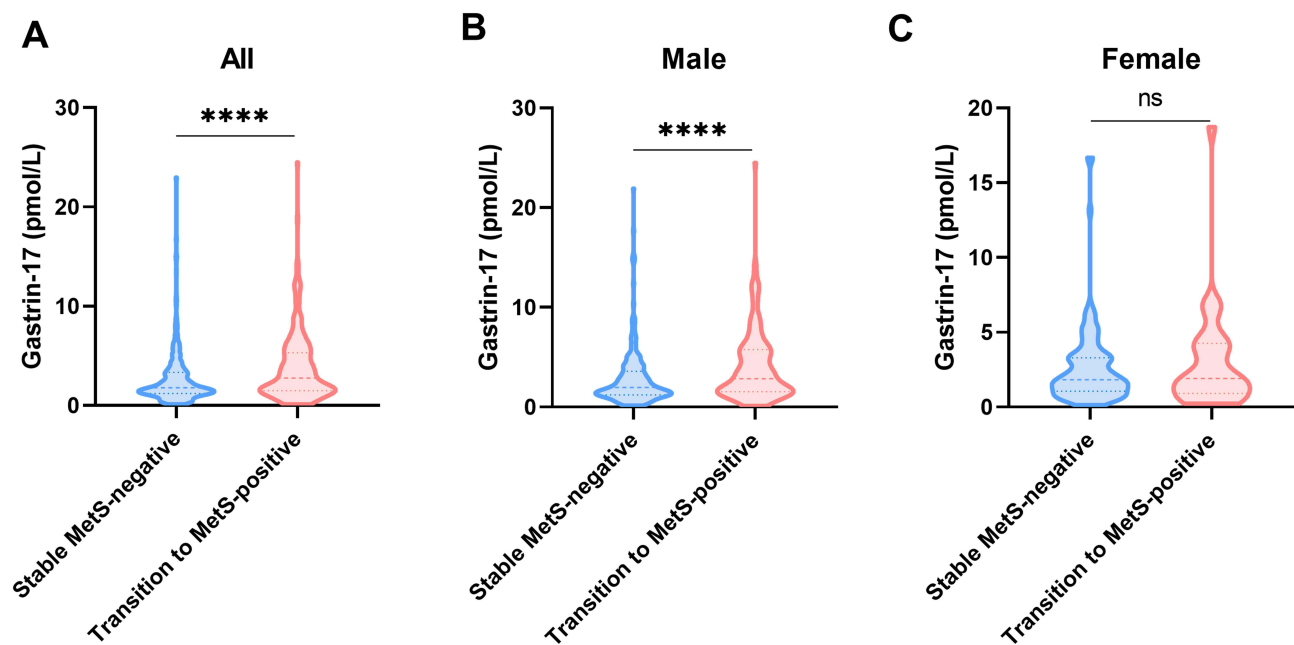
## Relationship Between Gastric Biomarkers and the Transition of MetS Status

Next, we investigated whether gastric biomarkers were associated with the change of MetS status of 1032 MetS-negative individuals during 2 years of follow-up. In total, 19.28% ( $n=199$ ) of MetS-negative individuals transitioned to MetS-positive, 80.72% ( $n=833$ ) maintained MetS-negative status. As compared with participants in stable MetS-negative status, MetS-negative individuals who transitioned to MetS had higher levels of gastrin-17 [2.83 (1.49, 5.64) vs 1.80 (1.22, 3.35) pmol/L] ([Table S5](#) and [Figure 2](#)). In males, the transition to MetS-positive group also had higher levels of gastrin-17 [2.96 (1.54, 5.81) vs 1.82 (1.26, 3.41) pmol/L]. In females, no significant differences were found in gastric biomarkers. The logistic regression analysis showed that gastrin-17 was independently associated with the risk of transition of MetS status in three adjustment models (Model 1: OR, 1.089; 95% CI, 1.037–1.144,  $P = 0.001$ ; Model 2: OR, 1.131; 95% CI, 1.051–1.217,  $P = 0.001$ ; Model 3: OR, 1.112; 95% CI, 1.028–1.203,  $P = 0.008$ ). The similar results were shown in male participants but not in females (Model 1: OR, 1.090; 95% CI, 1.028–1.157,  $P = 0.004$ ; Model 2: OR, 1.131; 95% CI, 1.048–1.220,  $P = 0.002$ ; Model 3: OR, 1.111; 95% CI, 1.026–1.202,  $P = 0.009$ ) ([Table 2](#)).

## Discussion

Few studies have focused on the relationship between gastric biomarkers and MetS. This study represents the first extensive cross-sectional examination of the potential association between MetS and serum gastric biomarkers. Our findings reveal that individuals with MetS exhibit higher serum levels of gastrin-17 compared to those without MetS. This trend persisted in subgroup analyses differentiated by sex. Furthermore, logistic regression analysis indicated that elevated gastrin-17 levels were independently associated with an increased risk of MetS in all participants, as well as in





**Figure 2** Comparisons of gastrin-17 in stable MetS-negative and transition to MetS-positive individuals. (A) Overall, serum levels of gastrin-17 in transition MetS group were higher than stable MetS-negative participants. (B) In males, serum levels of gastrin-17 in transition MetS group were also higher than stable MetS-negative participants. (C) In females, no significant difference was found in serum levels of gastrin-17. \*\*\*\* $p < 0.0001$ .

males specifically. The follow-up study showed that transition from MetS-negative to MetS-positive was associated with higher levels of gastrin-17, especially in males, but not in females.

MetS is a multi-factorial disease that is associated with genetic, epigenetic, and environmental factors. Patients with MetS have an increased risk of ASCVD and all-cause mortality. Considerable research has focused on identifying biomarkers of MetS, including inflammatory markers and oxidative stress indicators, which are central to deciphering its complex pathophysiology and facilitating diagnosis.<sup>42,43</sup> Importantly, chronic low-grade inflammation, a hallmark of MetS, is intricately linked to insulin resistance.<sup>44,45</sup> The gastrointestinal tract and adipose tissue emerge as key sources of circulating inflammatory mediators and play pivotal roles in MetS development.<sup>20,46,47</sup> Serum gastric biomarkers, such as PGs and gastrin-17, are instrumental in assessing gastric mucosal secretory function and are also regarded as markers of gastric inflammation.<sup>34</sup> Non-invasive liquid gastric biopsy, represented by these gastric biomarkers, is minimally invasive, enables repeat sampling, and may be used to simultaneously evaluate the secretory function of gastric mucosa and diagnose pathological conditions, such as atrophic gastritis and MetS. Therefore, understanding the relationship between gastric biomarkers and MetS could also open new avenues for the diagnosis, management, and treatment of MetS.

In this study, among all participants, gastrin-17 was the only biomarker that showed a significant difference between MetS-positive and MetS-negative individuals. This observation was consistent in the multivariate logistic analysis. What is more, higher gastrin-17 levels were associated with the transition of MetS status and revealing gender difference. Gastrin is primarily produced and released by the G cells located in the gastric antrum as a result of various stimuli, including the ingestion of peptides and amino acids, gastric distention, and an increase in stomach pH.<sup>48,49</sup> Once released into the bloodstream, gastrin acts on different tissues and organs, binding to its receptors and executing diverse functions. Although traditionally linked to digestive functions, recent research has identified the potential role of gastrin-17 in the pathogenesis of MetS. Gastrin-17 is associated with glucose metabolism and cardiovascular functions. Parenteral infusion of gastrin-17 increased blood glucose concentration and induced insulin secretion.<sup>50</sup> Intracoronary gastrin-17 increased cardiac perfusion and function via cholecystokinin (CCK) receptors,  $\beta$ -adrenoceptors and nitric oxide release,<sup>51</sup> while high levels of gastrin-17 may contribute to atherosclerotic process by influencing atherosclerotic parameters and blood pressure.<sup>51,52</sup> Hyperglycemia can reduce basal and gastrin-stimulated gastric acid secretion, and changes in gastric pH can stimulate a compensatory increase in gastrin.<sup>53</sup> Individuals with diabetes can display autonomic neuropathy,

which is often accompanied by elevated levels of plasma gastrin.<sup>54,55</sup> This increase may be attributable to a disrupted feedback mechanism caused by neuropathy in the stomach.<sup>56</sup> Gastrin also plays a role in lipid metabolism, as seen in *in vitro* studies where gastrin peptides influenced triacylglycerol secretion in human Hep G2 cells.<sup>57</sup> Additionally, gastrin receptors have been shown to interact with dopamine receptors, affecting blood pressure by modulating sodium excretion.<sup>58</sup> The influence of gastrin on immunity and inflammation, particularly through cholecystokinin B/gastrin receptor-expressing leukocytes, highlights its broader physiological implications.<sup>59</sup> Gastrin has been shown to induce cyclooxygenase-2 in GI cells via activate CCK-2 receptor and dependent on the MAPK signal pathways including ERK5 kinase, transactivation of the epidermal growth factor receptor, and the transcription factors ELK-1.<sup>60,61</sup> Gastrin increases rolling leukocytes but reduces their rolling velocity and enhances their adhesion and emigration into interstitium by activation CCK-2.<sup>62</sup> Besides, gastrin induces the interaction between human mononuclear leukocytes and endothelial cells by increasing endothelial expression of P-selectin and vascular cell adhesion molecule-1.<sup>63</sup> Considering these roles and mechanisms mentioned above, gastrin may play a key role in the development of MetS. Given its role as a marker of gastric inflammation, the involvement of gastrin-17 in MetS could be through a state of chronic inflammation. Future research should focus on discerning whether changes in gastrin-17 levels in MetS are pathogenic, compensatory, or a combination of both, and on elucidating the underlying mechanisms.

Some factors may link serum gastric biomarkers with MetS, such as vascular risk factors, unhealthy life habits, and medication histories. The observed sexual dimorphism in this study could be attributable to the differing prevalence of vascular risk factors and unhealthy lifestyle habits between males and females. Gastrin is the principal hormone regulating gastric acid secretion, and long-term gastric hypoacidity due to treatment with PPIs or H2-receptor antagonists will lead to hypergastrinemia.<sup>64,65</sup> Further, *H. pylori* infection is closely associated with elevated serum levels of PGs and gastrin-17.<sup>66</sup> In our study, individuals with MetS had a higher incidence of *H. pylori* infection and medication history of PPIs or H2-receptor antagonists. Subsequent logistic regression analyses showed that gastrin-17 was associated with MetS independent of *H. pylori* infection and the administration of PPIs or H2 blockers. This observation suggests that gastrin-17 could serve as a reliable and stable biomarker for MetS, irrespective of these confounding factors.

PGI is secreted by the chief cells in the fundic glands, whereas PGII is secreted by both the fundic and pyloric glands.<sup>67</sup> Univariate analysis stratified by sex revealed significant differences in PG levels and the PGI/PGII ratio between individuals with and without MetS. However, these differences were not observed after adjusting for confounding risk factors, suggesting that PG levels may not be independent predictors of MetS. Our study highlights the impact of both age and sex on PGs. Serum PGI and PGII levels are observed to increase progressively with age, a phenomenon potentially attributable to higher rates of *H. pylori* infection in older individuals.<sup>68,69</sup> Owing to physiological atrophy and decreased gastric acid secretion ability in older adults, the stomach is in a prolonged low-acid environment, which to some extent hinders the transformation of PGI into pepsin, resulting in the accumulation of PGI and PGII levels.<sup>69</sup> Of note, gastric biomarkers showed significant differences between males and females. The gastrin-17, PGI, and PGII levels and the PGI/PGII ratios were higher in males than in females, aligning with previous findings.<sup>70</sup> Owing to longer histories of smoking and alcohol consumption, males are much more likely to have gastric inflammation than females. Therefore, the inflammatory indicators PGI and PGII also are generally higher in males. Gastrin-17, an unstable indicator, is affected by various factors, including geographical location, diet, hormonal status, and lifestyle habits. Differences in circulating sex hormone levels and lifestyle differences between females and males could contribute to the sexual dimorphism observed in gastrin-17 levels.<sup>71</sup> Therefore, when utilizing PGs and gastrin as biomarkers for gastric diseases, the influence of age and sex must be considered. For clinical applications, establishing different normal reference values for various age groups and sexes is essential to accurately interpret these biomarkers.

In this study, levels of serum gastrin-17 were positively correlated with serum levels of PGI and PGII and negatively correlated with the PGI/PGII ratio. Clinically, the presence of antral atrophic gastritis may be suspected when gastrin levels are low, and the presence of atrophic gastritis of the corpus may be suspected when gastrin levels are high. When PGI levels and/or the PGI/PGII ratio are low, corpus atrophic gastritis may be present. Therefore, in disease states, gastrin-17 levels should be negatively correlated with serum levels of PGI levels and the PGI/PGII ratio and positively correlated with PGII levels. We assume that the inconsistencies between the anticipated results and our findings might be

because of differences in the study population, because our population was relatively healthier than that of those examined in previous studies.

This study has certain limitations. Our participants were recruited from a single-center, hospital-based population instead of a natural population; therefore, there may be some sampling bias, and multicenter validation is required. Additionally, although we found correlations between gastric biomarkers and MetS, the direct or indirect effects of gastrin-17, at both physiological and pathological levels, on blood pressure, glucose, and lipid metabolism remain unclear. These mechanisms warrant further investigation in future studies.

## Conclusions

Our research demonstrates gastrin-17 is correlated with MetS and also a potential biomarker for MetS, indicating the promising application of gastrin-17 in monitoring the transition of MetS. Besides, sexual dimorphism was observed in prevalence and transition of MetS associated with gastrin-17.

## Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the first author.

## Statement of Ethics

Study protocol and consent forms were approved by the Ethics Committee of the Third Xiangya Hospital (I21102), with all procedures followed by the World Medical Association Declaration of Helsinki, and all essential permissions were obtained from the government and health commission. This study utilized a broad consent form, which was signed by each participant undergoing a physical examination prior to their examination. All personal information was anonymized during analysis and reporting to ensure confidentiality and privacy.

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## Disclosure

The authors report no conflicts of interest in this work.

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