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ORIGINAL ARTICLE

Association between metabolic syndrome and gastric cancer risk: results from the Health Examinees Study

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Abstract

Background Previous studies suggested that metabolic syndrome (MetS) might create a pro-cancer environment and increase cancer incidence. However, evidence on the risk of gastric cancer (GC) was limited. This study aimed to evaluate the association between MetS and its components and GC in the Korean population.

Methods Included were 108,397 individuals who participated in the large-scale prospective cohort study, the Health Examinees-Gem study during 2004–2017. The multivariable Cox proportional was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) on the association between MetS and its components with GC risk. Age was used as the time scale in the analyses. The stratified analysis was performed to determine the joint effect of lifestyle factors and MetS on GC risk in different groups.

Results During the mean follow-up of 9.1 years, 759 cases of newly diagnosed cancer (408 men and 351 women) were identified. Overall, participants with MetS had a 26% increased risk of GC than those without MetS (HR 1.26; 95% CI 1.07–1.47); the risk increased with the number of MetS components (p for trend 0.01). Hypertriglyceridemia, low HDL-cholesterol, and hyperglycemia were independently associated with the risk of GC. The potential joint effect of MetS and current smokers (p for interaction 0.02) and obesity (BMI ≥ 25.0) (p for interaction 0.03) in GC.

Conclusions In this prospective cohort study, we found that MetS were associated with an increased risk of GC in the Korean population. Our findings suggest that MetS may be a potentially modifiable risk factor for GC risk.

Keywords Stomach neoplasms · Metabolic syndrome · Cohort studies · Life style

Introduction

Although gastric cancer (GC) incidence appears to have declined in the past years, GC still ranks fifth for incidence and fourth for cancer mortality, contributing significantly to the worldwide cancer burden [1]. However, the global incidence rate of gastric cancer is not uniformly distributed and varies among geographical regions and ethnicities. The highest GC incidence rates are observed in Eastern Asia and Eastern Europe. Over 70% of new cases and deaths occur in developing countries and are more common in men [2]. GC is a multifactorial disease; infections, lifestyle, and genetic factors have a role in GC risk. Helicobacter pylori (*H. pylori*) infection may be the most widely recognized cause of GC, but less than 5% of those infected develop GC [3]. Additionally, dietary factors such as salt-preserved foods and lifestyle factors like alcohol consumption and smoking were considered GC risk factors [4], which are also responsible for metabolic disorders. Although many risk factors of GC are deemed preventable in advance, it seems complicated to identify populations that need intervention or to control indicators that need early management.

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Metabolic syndrome (MetS) is a cluster of metabolic disorders, including central obesity, elevated blood pressure, fasting plasma glucose, and dyslipidemia [5]. MetS as a chronic inflammatory disease might create a pro-cancer environment and increase cancer incidence. Several epidemiological studies suggest that MetS and its components may independently or in combination increase the risk of several types of cancer, such as pancreatic cancer [6, 7], colorectal cancer [8–10], post-menopausal breast cancer [11–13], and liver cancer [14] playing a carcinogenic role in cancers. However, the studies on the association between MetS and GC risk are limited and contradictory. Several studies reported the differently affected by gender and region [15–17] and proposed irrelevant results [18–20]. To our knowledge, few studies are performed based on prospective cohort studies and had limitations of short observation periods and lack enough GC cases to evaluate the results. They also did not consider MetS components combination and lacked information in GC anatomic subsites and histological type.

Therefore, we evaluated the association between MetS and its components and gastric cancer in the Korean population in the present study. Additionally, investigate the joint effect of lifestyle factors on the association of MetS and GC.

Methods

Data source and study population

The Health Examinees (HEXA) study is a large-scale community-based prospective cohort study. HEXA study recruited participants aged 40–69 years from 38 general hospitals and health examination centers in eight regions around Korea [21]. The baseline survey and data collection were conducted between 2004 and 2013. HEXA-G is a sample subset of the HEXA study, after excluding 21 health centers due to differences in quality control and biospecimen collection processes and the short duration of follow-up. HEXA study design and HEXA-G selection criteria have been published elsewhere [21, 22].

Information at recruitment was collected through a self-administered questionnaire that included demographic and lifestyle information, medical history, and dietary factors. Clinical information was tested by blood. In addition, the study linked incident cancer data from the Korea Central Cancer Registry of Korea National Cancer Center until 2018 and death data from Statistics Korea until 2018.

Among 139,267 HEXA-G participants, we excluded those who did not consent for data linkage with the Korea Central Cancer Registry ($n=23,211$) and were diagnosed with cancer either before baseline or within the same year of baseline survey ($n=4037$); participants with missing information on MetS related variables ($n=3505$) were excluded; participants who diagnosed with GC within two lag year after index date were further excluded. Finally, 108,397 participants, including 37,350 men and 71,047 women, were included in the analysis (Fig. 1). The follow-up of the study participants was defined as the period between the time the baseline study was completed until the date of GC diagnosis, death, or the last follow-up date (December 31, 2018).

All participants were provided with written informed consent before entering the study and were followed up according to a standardized study protocol, and all research was performed in accordance with relevant guidelines. The datasets generated and analysed during the current study are not publicly available due to protect the information of cohort participants but are available from the corresponding

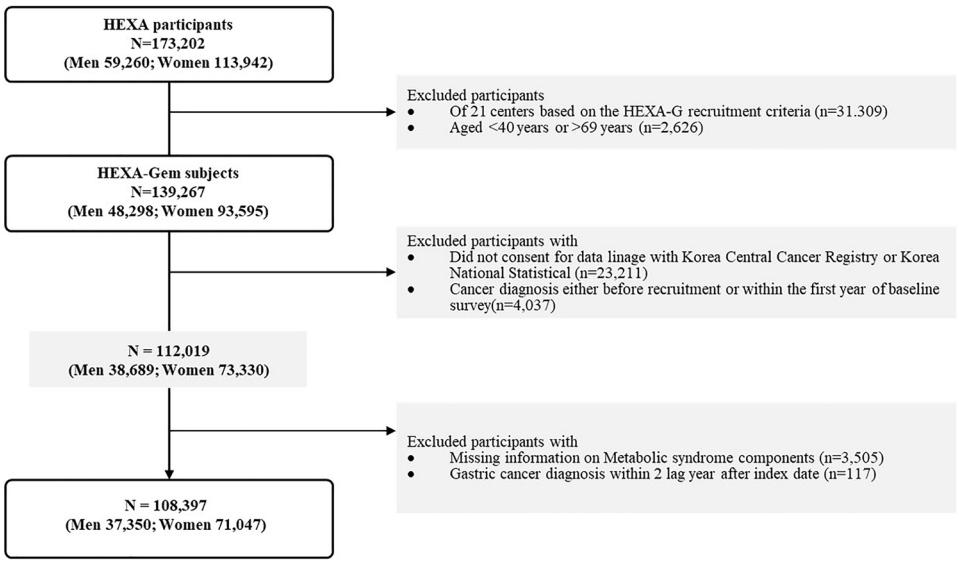

Fig. 1 Flow chart of the study population. HEXA Health Examinees Study

author upon reasonable request. This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. E-2009–117-1159, E-2110–004-1257) and the Ethics Committee of the Korean Genome and Epidemiology Study (KoGES) of the Korea National Institute of Health (IRB No. 2014–08-02-3C-A).

Identification of gastric cancer

The primary outcome was the first occurrence of GC based on the International Classification of Diseases, 10th Revision (ICD-10) coded C16.0 to 16.9. We further classified GC by anatomic subsites according to cardia (C16.0) and non-cardia (C16.1–16.6). Histology subtypes were assessed as intestinal and diffuse type according to the International Classification of Diseases for Oncology 3 codes for Lauren classification: Intestinal type GC, 8012, 8021, 8022, 8031, 8032, 8046,8050, 8082, 8143, 8144, 8201, 8210, 8211, 8220, 8221, 8255, 8260, 8261, 8262, 8263, 8310, 8323, 8480, 8481, 8510, 8512, 8570, and 8576; Diffuse type GC, 8020, 8041, 8044, 8141, 8142, 8145, 8490, and 8806 [23].

Definition of metabolic syndrome

We defined MetS and components according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and modified the waist circumference based on Korean population criteria [24, 25]. MetS were defined as participants who satisfied at least 3 of the 5 criteria: (1) Abdominal obesity (men ≥ 90 cm; women ≥ 85 cm); (2) Hypertriglyceridemia (≥ 150 mg/dL); (3) Low HDL-cholesterol (men ≤ 40 mg/dL; women ≤ 50 mg/dL); (4) Elevated blood pressure (≥ 130/85 mm Hg); (5) Hyperglycemia (≥ 100 mg/dL). This MetS definition criterion was commonly used in health examination centers in Korea.

Statistical analyses

Baseline characteristics were compared using the Student's *t*-test and Chi-square test for continuous and categorical variables. The multivariable Cox proportional, using age as the time-scale, were estimated hazard ratios (HRs) and 95% confidence intervals (CIs) on the association of the MetS, number of MetS components, and individual MetS components with GC risk. We performed analyzes on the total and stratified by gender. Furthermore, we assessed the MetS components and GC risk separately by 1 unit increased risk estimation for each component. In addition to quarter cut-points (Waist circumference: ≤ 81.0 cm, 81.0–86.0 cm, 86.0–90.5 cm, and > 90.5 cm in men, ≤ 72.2 cm, 72.2–78.0 cm, 78.0–83.4 cm, and > 83.4 cm in women; Triglycerides: ≤ 72 mg/dL, 72–104 mg/dL, 104–152 mg/dL, and > 152 mg/dL; High-density lipoprotein cholesterol: > 56 mg/dL, 47–56 mg/dL, 41–47 mg/dL, and ≤ 41 mg/dL in men, > 64 mg/dL, 55–64 mg/dL, 47–55 mg/dL, and ≤ 47 mg/dL in women; Systolic blood pressure: ≤ 110 mm Hg, 110–120 mm Hg, 120–131 mm Hg, and > 131 mm Hg; Diastolic blood pressure: ≤ 70 mm Hg, 70–76 mm Hg, 76–81 mm Hg, and > 81 mm Hg; Fasting glucose: ≤ 85 mg/dL, 85–91 mg/dL, 91–99 mg/dL, and > 99 mg/dL), were calculated separately within each component and investigated the linear trend.

We performed two models in our analysis. Model 1 was adjusted for sex, and Model 2 was additionally adjusted for smoking status (current, former or never), alcohol consumption (current, former or never), family history of cancer, education level (middle school or less, high school or college, undergraduate or more), regular exercise (yes or no), and energy intake (kcal/day).

We further analyzed the associations between MetS and GC anatomic subsite and histologic type. Additionally, in this study, we considered a healthy lifestyle, including physical activity (based on a questionnaire of whether performed sweating physical activities at least once per week), normal body weight (less than 25.0 kg/m^2), non-smoking, and non-alcohol intake, to investigate the joint effect of lifestyle factors on the association of MetS and GC. Finally, we divided the population into four risk groups based on MetS status and each lifestyle factor. In these analyses, we did not adjust the corresponding factors. Additive interaction was tested using a likelihood ratio test.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and were considered statistically significant with *p*-values less than 0.05.

Results

A total of 759 new GC diagnoses (408 men and 351 women) were identified during a mean 9.1-year follow-up.

Characteristics of study subjects

Table 1 shows the characteristics of participants with and without MetS. According to the definitions of the MetS, about 23% of study participants have three or more MetS components. Individuals with MetS were older, less educated, more likely to drink, had a history of diabetes or hypertension and had higher BMI than those without MetS (Table 1). Moreover, men who had MetS were more likely to be smokers, and women who had MetS were more likely to be single (Supplementary Table 1).

Table 1 Baseline characteristics of the HEXA-G study population included in the analysis for Metabolic syndrome

Characteristics	Total ($N = 108,397$)				p-value[a]
	Non-MetS		MetS		
	N	%	*N*	%	
Number of participants	83,517	76.96	24,880	22.93	
Follow-up year (mean ± SD)	9.13	1.92	9.13	1.87	0.10
Age (mean ± SD)	52.00	7.91	56.00	7.79	< 0.01
Gender					< 0.01
Men	27,620	73.95	9730	26.05	
Women	55,897	78.68	15,150	21.32	
Family history of gastric cancer	7277	8.71	2045	8.22	0.04
Education					< 0.01
≤ Middle school	22,872	27.39	9920	39.87	
High school diploma	36,343	43.52	9612	38.63	
≥ College degree	23,452	28.08	5028	20.21	
Marital status					< 0.01
Single	8,427	10.09	2763	11.11	
Married/cohabitation	75,090	89.91	22,117	88.89	
Alcohol consumption					< 0.01
Never	41,667	49.89	12,813	51.50	
Former	2763	3.31	959	3.85	
Current	38,647	46.27	11,001	44.22	
Smoking status					< 0.01
Never	61,455	73.58	16,750	67.32	
Former	11,896	14.24	4278	17.19	
Current	9746	11.67	3729	14.99	
Regular physical activity	38,229	45.77	12,301	49.44	< 0.01
History of diabetes	3211	3.84	3762	15.12	< 0.01
History of hypertension	11,773	14.10	8618	34.64	< 0.01
History of dyslipidemia	6620	7.92	3597	14.46	< 0.01
BMI (kg/m^2, mean ± SD)	23.13	2.63	25.76	2.80	< 0.01
Total energy intake (kcal, mean ± SD)	1696.64	567.76	1696.64	553.16	0.49
Waist circumference (cm)	78.20	8.04	87.00	7.39	< 0.01
Triglycerides (mg/dL)	91.0	62.22	176.0	120.68	< 0.01
HDL cholesterol (mg/dL)	55.0	12.54	44.0	9.58	< 0.01
Systolic blood pressure (mm Hg)	120.0	13.81	131.5	14.20	< 0.01
Diastolic blood pressure (mm Hg)	74.0	9.29	80.0	9.38	< 0.01
Fasting glucose (mg/dL)	89.0	16.17	101.0	28.36	< 0.01

HEXA-G Health Examinees-Gem study, *SD* standard deviation, *BMI* body mass index, *HDL* high-density lipoprotein

[a]Student's t-test for continuous variables; Chi-square test for categorical variables

MetS and its components and risk of GC

Table 2 shows the association between MetS and GC risk. Overall, participants with MetS had a 26% increased risk of GC than those without MetS (HR 1.26; 95% CI 1.07–1.47), and an increasing number of Mets components showed a significant linear (p for trend 0.01).). Hypertriglyceridemia (HR 1.16; 95% CI 1.00–1.36), low HDL-cholesterol (HR 1.17; 95% CI 1.01–1.37), and hyperglycemia (HR 1.17; 95% CI 1.00–1.37) were independently associated with GC. When the analysis was stratified by gender, the association with GC risk was significantly increased in men (HR 1.30; 95%CI 1.06–1.60) but marginally increased in women (HR 1.24; 95% CI 0.98–1.57) (Table 3). Men (p for trend 0.03) and

Table 2 Hazard ratios and 95% confidence intervals of gastric cancer according to Metabolic syndrome

Variables	Total 108,397 (GC = 759)								
	Person-Year	Participants	GC	HR[a]	95% CI		HR[b]	95% CI	
Metabolic syndrome									
Non-MetS	767,179	83,517	524	1.00	Ref		1.00	Ref	
MetS	227,991	24,880	235	1.25	1.07	1.46	1.26	1.07	1.47
Number of MetS's components									
0	247,368	27,032	146	1.00	ref		1.00	ref	
1	285,257	31,018	192	0.98	0.79	1.21	0.96	0.77	1.19
2	234,554	25,467	186	1.03	0.83	1.29	1.01	0.81	1.26
3	147,804	16,094	157	1.31	1.04	1.64	1.29	1.03	1.63
4	65,393	7,140	60	1.09	0.81	1.48	1.08	0.80	1.47
5	14,793	1,646	18	1.42	0.87	2.32	1.46	0.89	2.39
p for trend				0.01			0.01		
Waist circumference (cm) [c]									
WC < 85/90	623,849	68,348	451	1.00	ref		1.00	ref	
WC ≥ 85/90	371,320	40,049	308	0.96	0.83	1.11	1.06	0.91	1.23
Triglycerides (mg/dL)									
TG < 150	738,583	80,298	514	1.00	ref		1.00	ref	
TG ≥ 150	256,586	28,099	245	1.27	1.09	1.48	1.16	1.00	1.36
HDL-C (mg/dL) [d]									
HDL-C > 40/50	675,300	73,749	494	1.00	ref		1.00	ref	
HDL-C ≤ 40/50	319,869	34,648	265	1.05	0.90	1.22	1.17	1.01	1.37
Blood pressure (mm Hg)									
BP < SBP130 or DBP85	641,973	69,849	451	1.00	ref		1.00	ref	
BP ≥ SBP130 or DBP85	353,196	38,548	308	1.02	0.88	1.18	0.98	0.84	1.13
Fasting glucose (mg/dL)									
FG < 100	762,825	82,717	520	1.00	ref		1.00	ref	
FG ≥ 100	232,344	25,680	239	1.28	1.09	1.49	1.17	1.00	1.37

GC gastric cancer, *HR* hazard ratio, *CI* confidence interval, *MetS* metabolic syndrome, *WC* waist circumference, *TG* triglycerides, *HDL* high-density lipoprotein cholesterol, *BP* blood pressure, *FG* fasting glucose

[a]Adjusted for sex

[b]Additionally adjusted for smoking (current, former or never), alcohol consumption (current, former or never), family history of cancer (yes or no), education (middle school or less, high school or college, undergraduate or more), regular exercise (yes or no), energy intake(kcal/day)

[c]Waist circumferences was classified by men 90 cm; women 85 cm

[d]HDL-D were classified by men 40 mg/dL; women 50 mg/dL

women (*p* for trend 0.05) showed a significant linear trend in the number of MetS components. Among men, increased HR for GC was observed in participants with hyperglycemia (HR 1.27; 95% CI 1.04–1.55), marginally increased for abdominal obesity (HR 1.21; 95% CI 0.99–1.48), and low HDL-C (HR 1.21; 95% CI 0.97–1.51). Whereas among women, marginally increased HR of GC was observed in participants with low HDL-C (HR 1.22; 95% CI 0.99–1.52). The risk of GC was examined at the quartile level of individual MetS components, using the first quartile as the reference category (Supplementary Table 2). In total participants, triglycerides (*p* for trend 0.05) and HDL-cholesterol (*p* for trend 0.01) showed a positive trend. A positive trend was found for fasting glucose (*p* for trend 0.03) in men, and HDL-cholesterol (*p* for trend 0.04) in women.

Furthermore, we evaluated the relationship between combinations of MetS components and GC risk (Supplementary Table 3). The following four combinations were associated with an increased risk of GC: abdominal obesity, hypertriglyceridemia, and low HDL-C (HR 1.49; 95% CI 1.03–2.15); abdominal obesity, hypertriglyceridemia, and elevated blood pressure (HR 1.52; 95% CI 1.01–2.29); abdominal obesity, low HDL-C, and triglycerides (HR 1.94; 95% CI 1.23–3.07); low HDL-C, triglycerides, and elevated blood pressure (HR 1.91; 95% CI 1.05–3.47).

Table 3 Hazard ratios and 95% confidence intervals of gastric cancer according to Metabolic syndrome by gender

Variables	Men 37,350 (GC = 408)						Women 71,047 (GC = 351)						*p* for interaction
	Person-Year	Participants	GC	HR[a]	95% CI		Person-Year	Participants	GC	HR[a]	95% CI		
Metabolic syndrome													< 0.01
Non-MetS	253,074	27,620	275	1.00	Ref		514,104	55,897	249	1.00	Ref		
MetS	89,027	9,730	133	1.30	1.06	1.60	138,964	15,150	102	1.24	0.98	1.57	
Number of MetS's components													0.05
0	67,894	7406	70	1.00	Ref		179,473	19,626	76	1.00	Ref		
1	96,687	10,555	97	0.89	0.66	1.21	188,571	20,463	95	1.04	0.77	1.41	
2	88,493	9659	108	1.06	0.78	1.43	146,060	15,808	78	0.98	0.70	1.35	
3	58,134	6352	90	1.33	0.97	1.81	89,671	9,742	67	1.29	0.91	1.82	
4	25,533	2783	33	1.09	0.72	1.65	39,860	4,357	27	1.12	0.71	1.76	
5	5,360	595	10	1.57	0.81	3.06	9,433	1,051	8	1.41	0.67	2.94	
p for trend				0.03						0.05			
Waist circumference (cm)[b]													< 0.01
WC < 85/90	68,348	26,468	265	1.00	Ref		382,540	41,880	186	1.00	Ref		
WC ≥ 85/90	40,049	10,882	143	1.21	0.99	1.48	270,528	29,167	165	1.03	0.83	1.28	
Triglycerides (mg/dL)													0.05
TG < 150	214,231	23,366	251	1.00	Ref		524,352	56,932	263	1.00	Ref		
TG ≥ 150	127,870	13,984	157	1.11	0.91	1.36	128,716	14,115	88	1.20	0.94	1.54	
HDL-C (mg/dL)[c]													0.01
HDL-C > 40/50	260,733	28,467	295	1.00	Ref		414,567	45,282	199	1.00	Ref		
HDL-C ≤ 40/50	81,368	8,883	113	1.21	0.97	1.51	238,501	25,765	152	1.22	0.99	1.52	
Blood pressure (mm Hg)													0.28
BP < SBP130/DBP85	188,253	20,556	225	1.00	ref		453,720	49,293	226	1.00	Ref		
BP ≥ SBP130/DBP85	153,848	16,794	183	0.92	0.76	1.12	199,348	21,754	125	1.02	0.81	1.27	
Fasting glucose (mg/dL)													< 0.01
FG < 100	228,973	24,857	239	1.00	ref		533,853	57,860	281	1.00	ref		
FG ≥ 100	113,129	12,493	169	1.27	1.04	1.55	119,215	13,187	70	0.95	0.73	1.24	

GC gastric cancer, *HR* hazard ratio, *CI* confidence interval, *Mets* metabolic syndrome, *WC* waist circumference, *TG* Triglycerides, *HDL* high-density lipoprotein cholesterol, *BP* blood pressure, *FG* fasting glucose

[a]Adjusted for sex, smoking (current, former or never), alcohol consumption (current, former or never), family history of cancer (yes or no), education (middle school or less, high school or college, undergraduate or more), regular exercise (yes or no), energy intake(kcal/day)

[b]Waist circumference was classified by men 90 cm; women 85 cm

[c]HDL-D were classified by men 40 mg/dL; women 50 mg/dL

In anatomic subsite analysis, 35 (4%) cases were cardia GC and 821 (96%) cases were non-cardia GC. We found a significant positive association between MetS and non-cardia GC (HR 1.29; 95% CI 1.10–1.50); however, cardia GC seems to be too few cases to assess the association. In histologic type analysis, 192 (21.9%) cases were diffuse-type GC, while 544 (62.0%) cases were intestinal-type GC. We found a significant positive association between MetS and intestinal-type GC (HR 1.29; 95% CI 1.08–1.55) (Supplementary Table 4).

Joint effects between MetS and lifestyle factors on the risk of GC

The assessment of joint effects between MetS and lifestyle factors is presented in Table 4. We found that joint effects of MetS and current smokers, alcohol drinkers, and irregular exercisers independently remained significantly associated with the risk of GC. For the effect of MetS and physical activity, the results showed that the risk of GC increased in participants who had MetS and performed regular exercise (HR 1.37, 95% CI 1.09–1.72) and those with MetS and irregular exercise (HR 1.32, 95% CI 1.05–1.65). For the effect of MetS and BMI, the results showed that the risk of GC was only substantially increased in participants with MetS and obesity (BMI ≥ 25.0) (HR 1.33; 95% CI 1.10–1.60), whereas no significance in MetS and normal BMI. The potential joint effect of MetS and current smokers (p for interaction 0.02) and obesity (BMI ≥ 25.0) (p for interaction 0.03) in GC.

Discussion

In this population-based large-scale prospective cohort study of over a hundred thousand people, we found that MetS were associated with an increased risk of GC in the Korean population. Moreover, GC is independently associated with hypertriglyceridemia, low HDL cholesterol, and hyperglycemia. In addition, smoking status and MetS, BMI and MetS joint effects were strongly related to the risk of GC compared to their individual effects.

Many previous studies reported that obesity, hypertension, hypertriglyceridemia, and hyperglycemia were associated with increased GC risk [26–28]. With the prevalence of MetS increasing globally, this public health issue has been paid much attention to in recent decades. However, so far, not many previous studies have investigated the association between MetS and GC risk, and few studies performed by prospective cohort design [26, 27, 29], especially in Asian countries. There is little evidence of the association between metabolic syndrome and the risk of gastric cancer performed in the western population [27, 28, 30]. Moreover, these few

Table 4 Hazard ratios and 95% confidence intervals for gastric cancer associated with metabolic syndrome joint effect by lifestyle factors

Joint effect	Person-year	Participants	GC	Non-MetS			MetS			*P* for interaction
				HR	95% CI		HR	95% CI		
Current smoking[a]										0.02
No	720,142	78,205	436	1.00	Ref		1.29	1.05	1.59	
Yes	269,378	29,649	317	1.20	0.95	1.51	1.46	1.12	1.92	
Alcohol consumption [b]										0.08
No	501,437	54,480	318	1.00	Ref		1.28	1.01	1.63	
Yes	453,986	49,648	400	1.18	0.97	1.44	1.41	1.10	1.81	
Regular Exercise [c]										0.23
Yes	463,337	50,530	328	1.00	Ref		1.37	1.09	1.72	
No	528,392	57,508	426	1.11	0.93	1.32	1.32	1.05	1.65	
Body mass index (kg/m2) [d]										0.03
< 25.0	673,142	73,311	467	1.00	Ref		1.17	0.92	1.49	
≥ 25.0	321,708	35,060	292	1.03	0.85	1.26	1.33	1.10	1.60	

GC gastric cancer, *HR* hazard ratio, *CI* confidence interval, *Mets* metabolic syndrome

[a]Adjusted for alcohol consumption (current, former or never), family history of cancer (yes or no), education level (middle school or less, high school or college, undergraduate or more), regular exercise (yes or no), energy intake (kcal/day)

[b]Adjusted for smoking status (current, former or never), family history of cancer (yes or no), education level (middle school or less, high school or college, undergraduate or more), regular exercise (yes or no), energy intake (kcal/day)

[c]Adjusted for smoking status (current, former or never), alcohol consumption (current, former or never), family history of cancer (yes or no), education level (middle school or less, high school or college, undergraduate or more), energy intake (kcal/day)

[d]Adjusted for smoking status (current, former or never), alcohol consumption (current, former or never), family history of cancer (yes or no), education level (middle school or less, high school or college, undergraduate or more), regular exercise (yes or no), energy intake (kcal/day)

cohort studies on the association between MetS and GC have reported inconsistent results with a null [17, 28, 31] or only a positive association in men [30].

In this study, we found that those who have MetS at baseline survey had an increased risk of GC than those without MetS, and having a higher number of MetS components increased the risk of GC. Similar to our findings, in a Norway cohort study, where 192,903 participants were followed for 10.6 years, reported an increased GC risk of 1.44 (1.14–1.82) in individuals with MetS compared to non-MetS [27]. In this study, the sex-specific analyses were also significant for men and women [27]. Furthermore, a 12-year follow-up of 564,596 adults in the European multicohorts pooled analysis reported that a higher number of MetS components increased the risk of developing GC (p for trend 0.05) [30]. This study also showed that hyperglycemia, hypertriglyceridemia, and low HDL cholesterol increased GG risk. Other studies supported similar study results for the elevated fasting glucose effect; a Japanese study reported that fasting plasma glucose significantly increased the HR for gastric cancer (HR 3.0. 95%CI 1.5–6.4) [32]. Similarly, in a Norway cohort study, the researchers also found that participants with higher glucose levels had a higher risk of GC [27]. In our meta-analysis of published data, the result also shows a significantly increased risk of GC with high glucose. For other components of MetS, we found that the lower HDL-C was associated with GC, especially showing a trend in women. The potential molecular mechanisms linking HDL-cholesterol to GC remain unclear, and the correlation between them needs further explanation. However, there is consistent evidence that lower HDL-C levels are associated with an increased risk of gastric cancer in women but not in men [16, 33]. A population-based cohort study in Korea found that cholesterol levels, including HDL-C, are inversely related to the risk of gastric cancer among postmenopausal women [34]. Although the exact mechanism of a protective effect of estrogen on gastric cancer is still unclear, it is known that estrogen has anti-inflammatory and anti-oxidant effects [35, 36]. In addition, research reported that estrogen increases the apoptosis of gastric cancer cells [37]. Cholesterol is considered as a major precursor of estrogen, and a possible explanation is that those with high cholesterol level may have relatively high estrogen levels [34]. Other studies have shown that lower HDL-C levels are associated with a higher incidence of gastric dysplasia [38].

An unhealthy lifestyle might play an essential role in mediating the tumorigenesis of MetS. A westernized diet, lack of exercise, frequent drinking, and stress create a complex pro-cancer environment by increasing the prevalence of metabolic diseases [39, 40]. If metabolic syndrome develops first and is left untreated, it creates a pro-cancer environment and significantly increases gastric cancer. In the present study, the HRs increased when MetS and ever smoker, ever drinker and high BMI were jointly assessed for risk of GC compared to MetS who were evaluated alone. Smoking is a well-known risk factor for several cancers; previous studies have reported that MetS and laryngeal cancer were stronger in current smokers than in never smokers suggesting more pronounced effects of MetS on laryngeal cancer [41]. Other studies examined the combined effects of smoking and MetS on the prognosis of patients with colorectal cancer risk and reported that colorectal cancer risk for current smokers with MetS was 1.62 times as high as the sum of risks exposed to each risk factor alone [42]. The extent to which smoking modifies the association between MetS and the risk of GC remains to be elucidated. In previous studies, we have reported the individual effect of alcohol consumption and obesity on the GC risk using the HEXA cohort. The results showed that frequent intake of alcohol increases GC risk [22], and obesity is associated with an increased risk of GC [43]. Alcohol is thought to exert its carcinogenic effect via reactive oxygen production; it acts in the same pathway as the MetS. Few previous studies have shown that physical activity is inversely related to GC [44, 45]. The reasons for these inconsistent findings are hard to verify. Measurement of physical activity is complex, and at least some of the mixed results are likely explained by differences in exposure measurement and intensity cut-offs [44].

The mechanisms linked to MetS and the risk of GC remain uncertain. Several previous studies reported that MetS were considered an additive or synergistic factor in promoting cancer, including GC [30, 46]. Specifically, these components may promote cancer development by generating reactive oxygen species, increasing hormone production/bioavailability, including estrogen, insulin-like growth factor-1, insulin, and adipokines; and providing an energy-rich environment [47–49]. The association between the MetS and the risk of cancer mechanism proposed by most previous studies focused on obesity and insulin resistance. It is accepted that insulin resistance is generally considered the primary mechanism responsible for many manifestations of MetS [50, 51]. Since obesity, inflammation, and insulin resistance are interrelated, when a variety of metabolic abnormalities combination work together, the risks of energy imbalance, inflammation, insulin sensitivity, angiogenesis, lipid metabolism, cell proliferation, and atherosclerosis will have a multiplier effect, which may lead to an increased risk of gastric cancer.

Furthermore, impaired insulin secretion and insulin resistance increased the production of reactive oxygen species. More significant oxidative stress causes DNA damage, leading to mutational changes in oncogenes and tumor suppressor genes, which may be related to gastric carcinogenesis [52]. Hyperglycemia and consequent elevated insulin-like growth factors (IGF) are involved in the development of stomach tissues [53]. Long fluctuation in glucose levels

increases oxidative stress, endothelial dysfunction, and subclinical inflammation [54], possibly promoting gastric organ damage. Moreover, previous research has demonstrated that insulin enhances the stimulatory effects of epidermal growth factors on the proliferation of cultured gastric epithelial cells, which may predispose the gastric mucosa to genetic or epigenetic changes and, thereby, to the development of carcinogenesis [55]. Scarce glucose might result from the overexpression of glucose transporters and type II hexokinase, which are both confirmed in gastric cancer tissues [56].

One of the strengths of this study is that it was a large-scale prospective cohort study, which included representative participants from the Korean population. Furthermore, this cohort study was linked with death data from Statistics Korea, which could more accurately assess the follow-up period and provide more accurate results. At present, few cohort studies could consider the vital state of follow-up.

A limitation of the present study is that the well-established risk factor for gastric cancer is chronic infection with H.pylori. However, this study did not consider the effect of H.pylori on the association between MetS and gastric cancer development due to the loss of data about H.pylori infection. Although we were unable to determine whether the increased risk of GC in MetS was due to H.pylori, the correlation between MetS and H.pylori infection may be etiologically linked to GC since MetS components have been reported to increase GC risk independently of H.pylori infection in the Japanese population [57]. However, in the Korean population, no endoscopic differences were found in the proportions of H.pylori infection between glucose levels [58]. Moreover, regarding obesity, although BMI may play a modest role in developing GC among individuals with H.pylori infection, a significant association between BMI and GC risk has been reported only in H.pylori uninfected individuals in Korean Multi-Center Cohort study [59]. The authors described that BMI could play a modest role in the development of GC compared to H.pylori infection. In addition, although the relationship between hypertension and gastric cancer is not well known, the considered changes in the stomach's mucosa in patients with portal hypertension [60]. Gastric vascular congestion in portal hypertension gastropathy may suppress H.pylori colonization [61]. However, evidence indicated that gastric disease caused by blood pressure abnormalities such as gastric vascular congestion are not associated with the possibility of H.pylori infection [62]. Therefore independently of *H.pylori* infection, explaining the MetS and its components and GC risk are clinically meaningful. In addition, in this study, regular exercise combined with MetS, whether done or not, increases the risk of GC. That may be due to possible misclassficaition of the definition of physical activity. In this study, physical activity was investigated using interviewer-administered questionnaires. Information concerning regular exercise was based on who answered about performing regular sweating physical activities [21]. When considering the problem of "frequent" frequency, the minimum range is once or twice a week. With the questionnaire and definition, more people are likely to be defined as 'regular exercise' than they performed. Furthermore, we could not consider some related confounders, dietary factors such as salty food, due to lack of data. Subsequent research needs further research. Finally, the association between medication use and development of the metabolic syndrome is increasingly being recognized for several common medications [63]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), for example, have been shown to slightly improve insulin resistance while having no effect on circulating lipids or body weight. In the present study, we lacked information on specific Mets components medication intake, which may affect the association of gastric cancer risk. Thus, future research is warranted to clarify the effect of MetS components medication use and gastric cancer risk.

In conclusion, MetS were associated with an increased risk of GC in the Korean population. Our findings suggest that MetS may be a potentially modifiable GC risk factor. We also recommend that smoking cessation and body mass index control are necessary while managing and intervening in MetS to prevent GC risk.

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Author contributions DH and DK conceived and designed the study. DH performed the data analysis and drafted the first manuscript. AS, J-KL, and DK collected the data and obtained study funding. W-KS, Kde la T, H-WL, S M, AS, J-KL, and DK provided a critical review of the manuscript for important intellectual content.

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Data availability Data from the Health Examinees (HEXA) study is part of the Korean Genome and Epidemiology Study (KoGES), conducted by Korea Disease Control and Prevention Agency (KDCA; formerly Korea Centers for Disease Control and Prevention), Republic of Korea. The Korea Central Cancer Registry (KCCR) data is provisioned by the KDCA in cooperation with the National Cancer Center of Korea as a part of the KoGES. The dataset used for the analysis in this study is maintained and managed by the Division of Population Health

Research at the National Institute of Health, which is a part of the Korea Disease Control and Prevention Agency. The Health Examinees Study dataset has been merged with the cancer registry data provided by the National Cancer Center of Korea in a collaborative agreement. It contains some personal data that may potentially be sensitive to the patients, even though researchers are provided with an anonymized dataset that excludes resident registration numbers. Other researchers may request access to the data by contacting the following individuals at the Division of Population Health Research, National Institute of Health, Korea Disease Control and Prevention Agency: Director Dr. Kyoungho Lee (khlee3789@korea.kr).

Declarations

Conflict of interest No potential conflicts of interest were disclosed.

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