Review article

Kosin Medical Journal 2024;39(1):26-34
pISSN: 2005-9531 • eISSN: 2586-7024
https://doi.org/10.7180/kmj.24.108

KMJ
KOSIN MEDICAL JOURNAL

Gastric cancer and metabolic syndrome

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Gastric cancer (GC), a prevalent disease in Asian countries, presents a substantial global health challenge. The risk factors for GC include *Helicobacter pylori* infection, diet, smoking, alcohol, and metabolic syndrome (MetS). This review meticulously examines the intricate connections between MetS and GC, focusing on visceral adipocytes, hormonal factors, obesity, and their impact on survival outcomes. Visceral adipocytes, which secrete inflammatory cytokines and hormones, play a pivotal role in influencing cancer development. Hormonal factors demonstrate nuanced associations with specific GC subtypes, underscoring the complexity of their impact. Large-scale studies exploring obesity-related factors reveal sex-specific nuances and underscore the importance of considering overall weight and body composition. Furthermore, the review explores the impact of eradication therapy for *H. pylori* infection, which is the most significant factor in the onset of GC, on the components of MetS. Additionally, the influence of MetS on postoperative outcomes and survival in GC patients highlights the interplay between therapeutic interventions and lifestyle factors. This comprehensive exploration sheds light on the multifaceted relationship between MetS and GC, providing valuable insights for future research and preventive strategies.

Keywords: Body mass index; Helicobacter pylori; Metabolic syndrome; Stomach neoplasms

Introduction

Gastric cancer (GC) is the fifth most prevalent malignancy globally and stands as the fourth leading cause of death. Particularly, the prevalence of GC is high in Asian countries, including South Korea [1]. Several previous studies consider *Helicobacter pylori*, male sex, diet, smoking, and alcohol as risk factors for GC [2-5]. Metabolic syndrome (MetS) was initially defined by Reaven in 1988 and has since been recognized as a set of risk factors associated with cardiovascular diseases [6]. These factors include hypertension, dyslipidemia, insulin resistance, glucose intolerance, and abdominal obesity. The World Health Organization established the initial diagnostic criteria for MetS [7]. MetS is a condition defined by the presence of a minimum of three out of five factors., including abdominal obesity, elevated triglyceride (TG), decreased high-density lipoprotein cholesterol (HDL-C), hypertension, and higher fasting glucose (Table 1) [8]. Recognized as a universal and serious health concern worldwide, MetS poses a significant risk to individuals' health [9]. Based on the Korea National Health and Nutrition Examination Survey, criteria for abdominal obesity in Korean adults were established. The Korean Society for the Study of Obesity referenced a study from the 1998 survey and set the waist circumference (WC) cutoff at ≥90 cm for males and ≥85 cm for females [10]. The prevalence of MetS in South Korea has been steadily increasing, rising from 24.9% in 1998 to 29.2% in 2001, 30.4% in 2005, and

Received: February 6, 2024; **Revised:** March 12, 2024; **Accepted:** March 14, 2024
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Table 1. The clinical diagnostic criteria for metabolic syndrome

Component	Cutoff point
Waist circumference[a)]	Male ≥90 cm
	Female ≥85 cm
Elevated triglycerides	≥150 mg/dL
	Or receiving drug treatment for elevated triglycerides
Reduced HDL-C	Male <40 mg/dL
	Female <50 mg/dL
	Or receiving drug treatment for reduced HDL-C
Elevated blood pressure	≥130/85 mmHg
	Or receiving antihypertensive drug treatment with a history of hypertension
Elevated fasting glucose	≥100 mg/dL
	Or receiving drug treatment for elevated glucose

Diagnostic criteria: presence of three or more of the five factors.
HDL-C, high-density lipoprotein cholesterol.
[a)]The cutoff point for Waist circumference follows the standards set by the Korean Society for the Study of Obesity [10].

reaching 31.3% in 2007 [11]. MetS and its components have been shown to increase the incidence of various types of cancer, including pancreatic [12,13], small intestine [14], colorectal [15-19], breast [20,21], and liver cancer [22,23]. The research results regarding the connection between MetS and cancer mortality rates are particularly fascinating. In a study that delved into the relationship between MetS and cancer mortality, involving 33,230 males aged 20 to 88, it was discovered that 28% of the participants exhibited signs of MetS [24]. During an average observation period of 14 years, 685 participants faced mortality due to cancer, and the presence of MetS correlated with a 56% higher risk of cancer-related death [24]. In 2012, a meta-analysis was published reporting the association between various types of cancer, such as liver, colorectal, and bladder cancers, and MetS [25]. Particularly in males, a correlation was observed with colorectal, bladder, and liver cancers. In females, associations were identified with pancreatic, postmenopausal breast, endometrial, and colorectal cancers [25]. The relationship between MetS and GC has garnered increasing interest, driven by numerous studies exploring the complex mechanisms and associations. Such clinical research involves various designs including case series, prospective, retrospective cohort studies, case-control, and cross-sectional, each with its own strengths and limitations [26], thus requiring careful consideration by clinicians for application in real-world clinical practice. This review explores various aspects of this complex relationship, including the role of MetS in GC.

Mechanisms between MetS and cancer

MetS has connections to diverse types of cancers, and each specific risk factor contributing to MetS is also linked to the development of cancer [27]. As previously mentioned, MetS is a conglomerate of various risk factors, with abdominal adipocytes, particularly situated in the abdominal region, emerging as crucial contributors to cancer development [28]. Additionally, it includes insulin-like growth factor (IGF-I), estrogen signaling, hyperinsulinemia, hyperglycemia, and inflammation [28]. Located mainly in the abdominal region, these cells centrally contribute to malignancy by releasing inflammatory cytokines such as tumor necrosis factor-α and interleukin-6, along with hormones like leptin, thereby fostering the development of malignant tumors [29]. Specifically, leptin, a key player in this intricate interplay, is implicated in promoting neoplastic transformations, cancer cell proliferation, and the facilitation of tumor vasculature [29,30]. Abdominal adipose tissue serves as a significant site for estrogen production, particularly influencing cell proliferation, differentiation, and apoptosis in males and postmenopausal females [28,31]. The interplay among MetS, insulin resistance, and hyperinsulinemia establishes an environment favorable to cancer cells, characterized by increased levels of growth factors, adhesion factors, and inflammatory cytokines [28]. Furthermore, increased blood glucose are associated with the risk of various types of cancer [32]. Diverse mechanisms underlie the association between MetS and cancer. In this review, I will systematically unravel how this applies to GC and explore if there are additional factors that can explain the relationship between GC and MetS (Table 2).

Impact of MetS on GC subtypes

GC can be divided based on location into cardia GC and non-cardia GC. Recent advancements have been achieved through epidemiological studies examining environmental risk factors for GC. Cardia GC exhibits potential connections with gastroesophageal reflux, white ethnicity, male sex, and smoking [33], Conversely, the predominant factors

Table 2. The association between metabolic syndrome and gastric cancer

MetS on GC subtypes
· Cardia GC is associated with factors such as gastroesophageal reflux, white race, male sex, and tobacco smoking.
· Non-cardia GC is linked to chronic *Helicobacter pylori* infection, salt-preserved foods, and alcohol abuse.
· Obesity shows a positive correlation with the risk of cardia GC, while the impact of BMI or waist circumference varies.
· Hormonal factors, including IGF-1 and leptin, exhibit diverse associations with different subtypes of GC.
MetS and its components
· MetS is associated with an increased risk of GC, with sex-specific impacts on lipid profiles and hormonal factors.
· Obesity in early adulthood increases GC risk, emphasizing the relationship between BMI, physical activity, and MetS.
MetS and *H. pylori* infection
· *H. pylori* eradication is linked to reduced GC incidence and mortality.
· A correlation exists between *H. pylori* and MetS, influencing lipid profiles in a sex-specific manner.
· Changes in MetS-related factors after eradication therapy suggest a potential link between MetS and GC.
MetS and survivors, prognosis
· GC survivors exhibit a lower risk of MetS , potentially due to the therapeutic approach of gastrectomy.
· Preoperative MetS significantly shortens survival time after GC surgery, impacting postoperative outcomes.
· The association between presurgical MetS complications and GC-specific mortality varies with lifestyle factors such as smoking.

MetS, metabolic syndrome; GC, gastric cancer; BMI, body mass index; IGF-1, insulin-like growth factor.

contributing to non-cardia GC include *H. pylori* infection [34], the intake of salt-preserved foods [35], and alcohol abuse [36]. In a meta-analysis assessing the correlation between GC incidence and body mass index (BMI), elevated BMI demonstrated a positive association with the risk of cardia GC [37]. However, there was no significant association observed with non-cardia GC [37]. In the meta-analysis, obesity (BMI ≥30 kg/m^2) exhibited an elevated risk (odds ratio [OR], 1.13; 95% confidence interval [CI], 1.03–1.24) for GC compared to individuals with normal weight (BMI 18.5–25 kg/m^2), whereas overweight individuals (BMI 25–30 kg/m^2) did not show a statistically significant association [38]. Based on the location of GC, both overweight (OR, 1.22; 95% CI, 1.05–1.42) and obesity (OR, 1.61; 95% CI, 1.15–2.24) were correlated with an elevated risk for cardia GC [38]. Among the proposed hypotheses regarding the correlation between obesity and cardia GC, the reflux theory holds widespread acceptance. Obesity is suggested to contribute to the development of gastroesophageal reflux disease by elevating intra-abdominal pressure [39].

In addition, there have been reports that approached the perspective of sex and WC. In a previous study, higher WC (relative risk [RR], 1.48; 95% CI, 1.24–1.78) was significantly associated with increased risk of total gastroesophageal cancer [40]. Notably, the association is pronounced in cardia GC, displaying a positive correlation with WC. However, the link with non-cardia GC does not reach statistical significance. This nuanced observation suggests that the impact of WC on GC risk may vary depending on the anatomical location of the cancer. In line with this, a case-control study nested in the General Practitioner Research Database in the United Kingdom indicates that being overweight (BMI >25 kg/m^2) is positively linked with esophageal adenocarcinoma (OR, 1.67; 95% CI, 1.22–2.30) and cardia GC (OR, 1.46; 95% CI, 0.98–2.18) [41]. However, no significant association was observed in non-cardia GC [41]. These studies suggest that the impact of BMI or WC might vary depending on the location of GC.

An intriguing study has explored the impact of hormones on the location of GC. A thorough examination utilizing data from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study reveals compelling associations between hormonal factors and specific subtypes of GC [42]. IGF-1 emerges as a significant factor, exhibiting a positive association with both cardia and non-cardia GC [42]. Specifically, in EPIC males, IGF-1 demonstrated a positive association with cardia GC (OR, 1.94) and non-cardia GC (OR, 1.63) [42]. Similar findings were observed in UK-Biobank females, where IGF-1 (hazard ratio, 1.76) was positively associated with cardia GC [42]. Leptin (OR, 2.72) in EPIC males and C-peptide (OR, 2.17) in EPIC females exhibited positive associations with non-cardia GC [42]. Moreover, sex hormone-binding globulin (HR, 1.29) demonstrated a positive association with cardia GC in UK-Biobank males. In contrast, ghrelin showed an inverse association with non-cardia GC in both EPIC and ATBC males, and dehydroepiandrosterone exhibited an inverse association with cardia GC in EPIC and ATBC males combined [42]. These findings underscore the complexity of the relationship between hormonal factors and different subtypes of GC, providing valuable insights into the nuanced

interplay that may contribute to the diverse etiology of this malignancy.

Pathologically, it can be categorized into intestinal, diffuse, mixed, and indeterminate types based on the Lauren classification system [43]. Diffuse-type GC is known to occur more commonly in younger individuals and females compared to intestinal-type GC [44,45]. Additionally, it is typically detected at more advanced stages, leading to a poorer prognosis [46]. In a large retrospective cohort study investigating the correlation between BMI and the Lauren classification of GC, findings indicated that among females classified as underweight (BMI <18.5 kg/m^2), there was a higher incidence of diffuse-type GC. Conversely, in females classified as overweight (BMI >30 kg/m^2), intestinal-type GC was more commonly observed [47]. In contrast, intestinal-type GC was more common regardless of weight among males [47]. In premenopausal females, there is a higher prevalence of diffuse-type GC, and research indicates that female reproductive function might contribute to preventing intestinal-type GC. The incidence of intestinal-type GC tends to rise after menopause [48,49]. Estrogen is not only produced in the ovaries but also in adipose tissue, playing a significant role in the etiology and outcomes of female obesity [50]. The influence of BMI is apparent in the development of both diffuse-type and intestinal-type GC, suggesting a complex interplay with intricately involved mechanisms.

MetS and its component

Recent large-scale studies aim to unravel the intricate connections between high-risk behaviors, including obesity, MetS and physical activity. Diving into this wealth of information, the relationship between GC and MetS sparks ongoing debates.

In a retrospective analysis of data from the National Health Insurance Corporation of Korea, the association between MetS and the incidence of GC was explored among approximately 7.8 million patients [51]. Relative to the control group, both the pre-MetS group (HR, 1.08; 95% CI, 1.04–1.12) and the MetS group (HR, 1.26; 95% CI, 1.20–1.32) exhibited a significantly increased risk of GC [51]. In another analysis, males with obesity (BMI ≥30 kg/m^2) showed an increased risk of GC (HR, 1.31; 95% CI, 1.05–1.64), not in females [52]. The Health Examinees-Gem study specifically explores the impact of early adulthood obesity (BMI ≥30 kg/m^2 at age 35) on the risk of GC [53]. Compared to individuals with normal weight (BMI 18.5–23.0 kg/m^2), those with obesity (HR, 1.94; 95% CI, 1.26–2.97) in early adulthood faced a high risk of GC [53]. When stratified by sex, obesity at the age of 35 was significantly linked to an elevated risk of GC in both males (HR, 1.79; 95% CI, 1.02–3.13) and females (HR, 2.35; 95% CI, 1.21–4.60) [53]. However, in late adolescence, there were no significant associations between obesity and the risk of GC, regardless of sex [53]. In the MetS and Cancer Project conducted in Austria, Norway, and Sweden, elevated glucose levels (HR, 1.58; 95% CI, 1.14–2.20) and TG (HR, 1.20; 95% CI, 1.06–1.36 per mmol) were significantly correlated with an increased risk of GC in females, not males [54]. In another meta-analysis, diabetes (RR, 1.11; 95% CI, 1.00–1.24) showed a significant association with the occurrence of GC [55]. Subgroup analyses within Asian studies demonstrated a more pronounced correlation between diabetes and the incidence of GC (RR, 1.19, 95% CI, 1.07–1.32). Moreover, individuals with diabetes experienced an elevated mortality rate from GC (RR, 1.29; 95% CI, 1.04–1.59) compared to those without diabetes [55]. In the Cohort of Norway and the third Nord-Trøndelag Health Study, MetS significantly increased the risk of GC incidence (HR, 1.44; 95% CI, 1.14–1.82) [56]. In females, elevated WC (HR, 1.71; 95% CI, 1.05–2.80), hypertension (HR, 2.41; 95% CI, 1.44–4.03), and non-fasting blood glucose (HR, 1.74; 95% CI, 1.18–2.56) were associated with an increased risk of GC, while no such association was observed in males [56].

Intricacies in the relationship between factors of MetS and GC emerge from a comprehensive study conducted in China [57]. GC patients exhibit distinctive metabolic profiles, including altered lipid levels, hypertension, and increased WC, with notable gender-specific impacts. In a study, involving 808 GC patients and 1,146 healthy controls, brings forth significant findings. Compared to the control group, GC patients exhibit elevated TG, decreased HDL-C, and a higher prevalence of hypertension [57]. Subgroup analyses reveal distinct patterns for males and females. In the male subgroup, elevated BMI (OR, 1.97; 95% CI, 1.47–2.66), hypertension (OR, 1.86; 95% CI, 1.35–2.58), and diabetes (OR, 2.06; 95% CI, 1.41–3.40) increase the risk of GC. Conversely, in the female subgroup, lower HDL-C (OR, 2.53; 95% CI, 1.58–4.13), hypertension (OR, 2.75; 95%

CI, 1.50–5.04), and diabetes (OR, 1.81; 95% CI, 1.47–2.38) are linked to an increased risk of GC [57]. Furthermore, MetS is correlated with poorly differentiated tumors and an advanced pathological TNM stage [57], adding a layer of complexity to our understanding of how metabolic factors influence GC progression.

In a South Korean cohort study, postmenopausal females showed an inverse correlation between total cholesterol (TC) (HR, 0.88; 95% CI, 0.84–0.92), HDL-C (HR, 0.89; 95% CI, 0.85–0.92), low-density lipoprotein cholesterol (LDL-C) (HR, 0.92; 95% CI, 0.89–0.97), and the risk of GC [58]. In recent research, components of MetS, including elevated TG (HR, 1.16; 95% CI, 1.00– 1.36), low HDL-C (HR, 1.17; 95% CI, 1.01–1.37), and high blood glucose (HR, 1.17; 95% CI, 1.00–1.37), were independently linked to GC [59].

MetS and physical activity

A epidemiological meta-analysis suggested that overweight could exhibit a protective effect against GC risk in Asian adult [60]. However, analyzing weight without considering various body compositions can introduce biases. A recent population-based prospective cohort study reported that male (HR, 1.70; 95% CI, 1.01–2.89) and female (HR, 2.47; 95% CI, 1.15–5.32) with higher levels of body mass that excludes fat had a higher risk of GC [61]. Interestingly, fat mass was recognized as a factor providing protection against GC in female [61]. This may be associated with the secretion of estrogen, known to have a protective effect against GC, especially in females [62]. Taken together the research on the impact of BMI and physical activity should be regarded sex/gender factor differently. Contrarily, a recent meta-analysis considering 14 studies found no association between MetS and GC risk [63]. Nevertheless, the analysis observed an increased risk of GC in Western females with MetS (HR, 1.24; 95% CI, 1.05–1.47) [63]. This complex interplay underscores the importance of considering both overall weight and body composition when exploring the link between obesity-related factors and GC risk.

A South Korean study delves into the intricate relationship between MetS, physical activity, and GC risk, shedding light on the nuances of these interconnected factors. Korean individuals diagnosed with MetS have a higher risk of GC (HR, 1.26; 95% CI, 1.07–1.47) [59]. Notably, the risk escalates (HR, 1.33; 95% CI, 1.10–1.60) among individuals with MetS who are obese (BMI ≥25.0 kg/m^2). Interestingly, the risk of GC does not show a notable increase among those with MetS who maintain a normal weight [59]. Adding another layer of complexity, the study explores the impact of exercise on GC risk within the context of MetS. Both regular exercisers (HR, 1.37; 95% CI, 1.09–1.72) and irregular exercisers (HR, 1.32; 95% CI, 1.05–1.65) exhibit elevated risks of GC in the presence of MetS [59]. A case-control study evaluating the association between physical activity and GC incidence reported a 20% to 40% reduction in the risk of developing GC when comparing engaging in strenuous activity at least three times a week to less than once a month [64].

This highlights the intricate interplay between physical activity patterns, MetS, and the development of GC, emphasizing the necessity for a nuanced comprehension of these elements for effective risk assessment and prevention strategies. The intertwined relationship between weight, body composition, physical activity and metabolic factors in GC risk demands a nuanced perspective. The protective and risk-associated roles of different components emphasize the importance of considering sex as major factors for unraveling the complex web of obesity-related factors and their influence on GC risk.

MetS and *H. pylori* infection

H. pylori eradication has been well-established to reduce the incidence of GC (RR, 0.54; 95% CI, 0.40–0.72) and GC-related mortality (RR, 0.61; 95% CI, 0.40–0.92) [65]. Several studies published on the correlation between *H. pylori* and MetS. In Japan, the group with *H. pylori* infection (HR, 4.20; 95% CI, 1.60–11.10) had a higher risk of GC compared to the non-infected group [66]. Additionally, an elevated fasting blood glucose (HR, 3.00; 95% CI, 1.50–6.40) increased the risk for GC [66]. In a multicenter study in South Korea involving 15,195 individuals, 43.2% tested positive for *H. pylori* [67]. Compared to individuals negative for *H. pylori*, those positive for *H. pylori* showed higher levels of BMI, WC, TC, and LDL-C, while HDL-C levels were lower [67]. The prevalence of MetS was 27.2% in *H. pylori*-positive individuals and 21.0% in those negative for *H. pylori* (p<0.05), and *H. pylori* antibody positivity was associated with the occurrence of MetS (OR, 1.19; 95% CI, 1.09–1.31) [67]. The impact of *H. pylori* on MetS and lipid has been investigated

with a focus on sex differences [68]. Analysis found associations between *H. pylori* infection and TC (OR, 1.01; 95% CI, 1.00–1.01) in males and HDL-C (OR, 0.98; 95% CI, 0.97–1.00) in females [68]. In both *H. pylori*-positive male and female groups, the prevalence of MetS was higher, though not statistically significant. This suggests *H. pylori* may influence lipid profiles related to MetS, with its effect varying by sex.

However, these studies have limitations in definitively proving causality between *H. pylori* infection and lipid profiles. Taking this into consideration, several studies analyzing changes in MetS-related factors after eradication therapy have also been published. A study conducted in Iran reported reductions in TC, LDL-C, fasting plasma glucose, hemoglobin A1c, and WC after eradication therapy [69]. In Japan, a study reported that LDL-C levels did not significantly change after *H. pylori* eradication, but HDL-C levels increased significantly post-eradication [70]. Consequently, the LDL-C/HDL-C ratio, considered a predictive parameter for assessing the severity of myocardial infarction or atherosclerosis, significantly decreased after eradication [70]. A meta-analysis reported that HDL-C and TG levels increased after eradication therapy [71]. Specifically, in an analysis focusing on four randomized controlled trials, the increase in HDL-C was significant, but not for TG [71]. Previous studies had the drawback of relatively short follow-up periods after eradication therapy. However, a recent domestic study analyzed metabolic parameters for more than 1 year after eradication therapy [72]. The study revealed that in females, HDL-C levels increased, while LDL-C levels decreased after eradication therapy [72]. In other words, the association between MetS and *H. Pylori* infection may further support the link between MetS and GC.

MetS and survivors, prognosis

Recent strides in endoscopic resection notwithstanding, surgical resection remains the cornerstone of GC treatment. Postoperative outcomes, particularly concerning MetS, have been a focal point in numerous studies within the realm of GC patients. Among cancer survivors, especially those with GC, the risk of developing MetS (OR, 0.42; 95% CI, 0.20–0.86) was lower [73]. This intriguing association may be attributed to the common therapeutic approach of gastrectomy, a procedure often undertaken for curative purposes, potentially contributing to the observed reduced risk of MetS in GC survivors.

An in-depth analysis using data from the Fujian Prospective Investigation of Cancer explored the influence of preoperative MetS on the long-term prognosis after GC surgery [74]. During a 15-year follow-up involving 3,012 individuals, 1,331 experienced GC-related mortality. Those with preoperative MetS had a significantly shorter median survival time of 31.3 months compared to those without MetS. The concurrent presence of MetS before surgery was linked to a 2.3-fold increase in the risk of GC mortality (p<0.001) [74].

In a retrospective analysis forecasting postoperative survival outcomes in GC, considering presurgical MetS, a cohort of 2,779 patients was scrutinized, encompassing both smokers and never-smokers. Intriguingly, presurgical MetS complications were significantly associated with heightened GC-specific mortality in smokers, manifesting as a 2.73-fold higher risk, while no such association was observed in never-smokers [75]. These findings underscore the intricate interplay between MetS and postoperative outcomes in GC patients, shedding light on potential nuances influenced by therapeutic interventions and individual lifestyle factors such as smoking.

Conclusion

The intricate relationship between MetS and GC involves various interconnected factors. Overall, considering these intricate connections is crucial for comprehensive risk assessment and effective prevention strategies in the context of GC. However, most studies have been retrospective, making it somewhat challenging in establishing a causal relationship. Investigating the mechanisms that underlie the association between MetS and GC requires crucial future prospective research.

Article information

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions

All the work was done by HHJ.

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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
2. Lee YY, Derakhshan MH. Environmental and lifestyle risk factors of gastric cancer. Arch Iran Med 2013;16:358–65.
3. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol 2006;12:354–62.
4. Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, et al. A meta-analysis on alcohol drinking and gastric cancer risk. Ann Oncol 2012;23:28–36.
5. den Hoed CM, Kuipers EJ. Gastric cancer: how can we reduce the incidence of this disease? Curr Gastroenterol Rep 2016;18:34.
6. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
7. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–53.
8. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–5.
9. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014;2014:943162.
10. Kim BY, Kang SM, Kang JH, Kang SY, Kim KK, Kim KB, et al. 2020 Korean Society for the Study of Obesity guideline for the management of obesity in Korea. J Obes Metab Syndr 2021;30:81–92.
11. Lim S, Shin H, Song JH, Kwak SH, Kang SM, Won Yoon J, et al. Increasing prevalence of metabolic syndrome in Korea: the Korean National Health and Nutrition Examination Survey for 1998-2007. Diabetes Care 2011;34:1323–8.
12. Xia B, He Q, Pan Y, Gao F, Liu A, Tang Y, et al. Metabolic syndrome and risk of pancreatic cancer: a population-based prospective cohort study. Int J Cancer 2020;147:3384–93.
13. Johansen D, Stocks T, Jonsson H, Lindkvist B, Bjorge T, Concin H, et al. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the Metabolic Syndrome and Cancer Project. Cancer Epidemiol Biomarkers Prev 2010;19:2307–17.
14. Nagel G, Bjorge T, Jaensch A, Peter RS, Haggstrom C, Lang A, et al. Metabolic factors and the risk of small intestine cancers: pooled study of 800 000 individuals in the metabolic syndrome and cancer project. Int J Cancer 2021;149:66–74.
15. Kim J, Park EY, Park E, Lim MK, Oh JK, Kim B. Metabolic syndrome and colorectal cancer risk: results of propensity score-based analyses in a community-based cohort study. Int J Environ Res Public Health 2020;17:8687.
16. Pais R, Silaghi H, Silaghi AC, Rusu ML, Dumitrascu DL. Metabolic syndrome and risk of subsequent colorectal cancer. World J Gastroenterol 2009;15:5141–8.
17. Shin CM, Han K, Lee DH, Choi YJ, Kim N, Park YS, et al. Association among obesity, metabolic health, and the risk for colorectal cancer in the general population in Korea using the National Health Insurance Service-National Sample Cohort. Dis Colon Rectum 2017;60:1192–200.
18. Jin EH, Han K, Lee DH, Shin CM, Lim JH, Choi YJ, et al. Association between metabolic syndrome and the risk of colorectal cancer diagnosed before age 50 years according to tumor location. Gastroenterology 2022;163:637–48.
19. Choi YJ, Lee DH, Han KD, Shin CM, Kim N. Abdominal obesity, glucose intolerance and decreased high-density lipoprotein cholesterol as components of the metabolic syndrome are associated with the development of colorectal cancer. Eur J Epidemiol 2018;33:1077–85.
20. Wani B, Aziz SA, Ganaie MA, Mir MH. Metabolic syndrome and breast cancer risk. Indian J Med Paediatr Oncol 2017;38:434–9.
21. Lee JA, Yoo JE, Park HS. Metabolic syndrome and incidence of breast cancer in middle-aged Korean women: a nationwide cohort study. Breast Cancer Res Treat 2017;162:389–93.
22. Jinjuvadia R, Patel S, Liangpunsakul S. The association between metabolic syndrome and hepatocellular carcinoma: systemic review and meta-analysis. J Clin Gastroenterol 2014;48:172–7.
23. Osaki Y, Taniguchi S, Tahara A, Okamoto M, Kishimoto T. Metabolic syndrome and incidence of liver and breast cancers in Japan. Cancer Epidemiol 2012;36:141–7.
24. Jaggers JR, Sui X, Hooker SP, LaMonte MJ, Matthews CE, Hand GA, et al. Metabolic syndrome and risk of cancer mortality in

men. Eur J Cancer 2009;45:1831–8.
25. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 2012;35:2402–11.
26. Kim DJ, Kil SY, Son J, Lee HS. How to conduct well-designed clinical research. Kosin Med J 2022;37:187–91.
27. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obes Rev 2015;16:1–12.
28. Micucci C, Valli D, Matacchione G, Catalano A. Current perspectives between metabolic syndrome and cancer. Oncotarget 2016;7:38959–72.
29. Garofalo C, Surmacz E. Leptin and cancer. J Cell Physiol 2006;207:12–22.
30. Dutta D, Ghosh S, Pandit K, Mukhopadhyay P, Chowdhury S. Leptin and cancer: pathogenesis and modulation. Indian J Endocrinol Metab 2012;16(Suppl 3):S596–600.
31. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
32. Stattin P, Bjor O, Ferrari P, Lukanova A, Lenner P, Lindahl B, et al. Prospective study of hyperglycemia and cancer risk. Diabetes Care 2007;30:561–7.
33. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut 2010;59:39–48.
34. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 2001;345:784–9.
35. Kim HJ, Lim SY, Lee JS, Park S, Shin A, Choi BY, et al. Fresh and pickled vegetable consumption and gastric cancer in Japanese and Korean populations: a meta-analysis of observational studies. Cancer Sci 2010;101:508–16.
36. Sung NY, Choi KS, Park EC, Park K, Lee SY, Lee AK, et al. Smoking, alcohol and gastric cancer risk in Korean men: the National Health Insurance Corporation Study. Br J Cancer 2007;97:700–4.
37. Chen Y, Liu L, Wang X, Wang J, Yan Z, Cheng J, et al. Body mass index and risk of gastric cancer: a meta-analysis of a population with more than ten million from 24 prospective studies. Cancer Epidemiol Biomarkers Prev 2013;22:1395–408.
38. Lin XJ, Wang CP, Liu XD, Yan KK, Li S, Bao HH, et al. Body mass index and risk of gastric cancer: a meta-analysis. Jpn J Clin Oncol 2014;44:783–91.
39. Wu AH, Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. Cancer 2003;98:940–8.
40. Du X, Hidayat K, Shi BM. Abdominal obesity and gastroesophageal cancer risk: systematic review and meta-analysis of prospective studies. Biosci Rep 2017;37:BSR20160474.
41. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 2005;16:285–94.
42. Sanikini H, Biessy C, Rinaldi S, Navionis AS, Gicquiau A, Keski-Rahkonen P, et al. Circulating hormones and risk of gastric cancer by subsite in three cohort studies. Gastric Cancer 2023;26:969–87.
43. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma: an attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965;64:31–49.
44. Lee JY, Gong EJ, Chung EJ, Park HW, Bae SE, Kim EH, et al. The characteristics and prognosis of diffuse-type early gastric cancer diagnosed during health check-ups. Gut Liver 2017;11:807–12.
45. Santoro R, Carboni F, Lepiane P, Ettorre GM, Santoro E. Clinicopathological features and prognosis of gastric cancer in young European adults. Br J Surg 2007;94:737–42.
46. Park JC, Lee YC, Kim JH, Kim YJ, Lee SK, Hyung WJ, et al. Clinicopathological aspects and prognostic value with respect to age: an analysis of 3,362 consecutive gastric cancer patients. J Surg Oncol 2009;99:395–401.
47. Jo HH, Kim N, Jang J, Choi Y, Park J, Park YM, et al. Impact of body mass index on survival depending on sex in 14,688 patients with gastric cancer in a tertiary hospital in South Korea. Gut Liver 2023;17:243–58.
48. Jung YJ, Kim HJ, Park CH, Park SJ, Kim N. Effects of reproductive factors on Lauren intestinal-type gastric cancers in females: a multicenter retrospective study in South Korea. Gut Liver 2022;16:706–15.
49. Kim SM, Min BH, Lee J, An JY, Lee JH, Sohn TS, et al. Protective effects of female reproductive factors on Lauren intestinal-type gastric adenocarcinoma. Yonsei Med J 2018;59:28–34.
50. Leeners B, Geary N, Tobler PN, Asarian L. Ovarian hormones and obesity. Hum Reprod Update 2017;23:300–21.
51. Yoo H, Kim H, Lee JH, Lee KS, Choi MJ, Song HR, et al. Study on the relevance of metabolic syndrome and incidence of gastric cancer in Korea. Int J Environ Res Public Health 2019;16:1101.
52. Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, et al. Body mass index and cancer risk in Korean men and women. Int J Cancer

2008;123:1892–6.
53. Lee HW, Huang D, Shin WK, de la Torre K, Yang JJ, Song M, et al. Obesity at early adulthood increases risk of gastric cancer from the Health Examinees-Gem (HEXA-G) study. PLoS One 2022;17:e0260826.
54. Lindkvist B, Almquist M, Bjorge T, Stocks T, Borena W, Johansen D, et al. Prospective cohort study of metabolic risk factors and gastric adenocarcinoma risk in the Metabolic Syndrome and Cancer Project (Me-Can). Cancer Causes Control 2013;24:107–16.
55. Tian T, Zhang LQ, Ma XH, Zhou JN, Shen J. Diabetes mellitus and incidence and mortality of gastric cancer: a meta-analysis. Exp Clin Endocrinol Diabetes 2012;120:217–23.
56. Lin Y, Ness-Jensen E, Hveem K, Lagergren J, Lu Y. Metabolic syndrome and esophageal and gastric cancer. Cancer Causes Control 2015;26:1825–34.
57. Li F, Du H, Li S, Liu J. The association between metabolic syndrome and gastric cancer in Chinese. Front Oncol 2018;8:326.
58. Lim JH, Shin CM, Han K, Yoo J, Jin EH, Choi YJ, et al. Nationwide cohort study: cholesterol level is inversely related with the risk of gastric cancer among postmenopausal women. Gastric Cancer 2022;25:11–21.
59. Huang D, Shin WK, De la Torre K, Lee HW, Min S, Shin A, et al. Association between metabolic syndrome and gastric cancer risk: results from the Health Examinees Study. Gastric Cancer 2023;26:481–92.
60. Bae JM. Body mass index and risk of gastric cancer in Asian adults: a meta-epidemiological meta-analysis of population-based cohort studies. Cancer Res Treat 2020;52:369–73.
61. Liu AR, He QS, Wu WH, Du JL, Kuo ZC, Xia B, et al. Body composition and risk of gastric cancer: a population-based prospective cohort study. Cancer Med 2021;10:2164–74.
62. Mohammadi M. Role of obesity in the tumorigenesis of gastric cancer. Int J Prev Med 2020;11:148.
63. Mariani M, Sassano M, Boccia S. Metabolic syndrome and gastric cancer risk: a systematic review and meta-analysis. Eur J Cancer Prev 2021;30:239–50.
64. Campbell PT, Sloan M, Kreiger N. Physical activity and stomach cancer risk: the influence of intensity and timing during the lifetime. Eur J Cancer 2007;43:593–600.
65. Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut 2020;69:2113–21.
66. Yamagata H, Kiyohara Y, Nakamura S, Kubo M, Tanizaki Y, Matsumoto T, et al. Impact of fasting plasma glucose levels on gastric cancer incidence in a general Japanese population: the Hisayama study. Diabetes Care 2005;28:789–94.
67. Lim SH, Kim N, Kwon JW, Kim SE, Baik GH, Lee JY, et al. Positive association between Helicobacter pylori infection and metabolic syndrome in a Korean population: a multicenter nationwide study. Dig Dis Sci 2019;64:2219–30.
68. Seo KI, Heo JJ, Kim SE, Park SJ, Park MI, Moon W, et al. Sex differences between Helicobacter pylori infection and cholesterol levels in an adult health checkup program. Helicobacter 2020;25:e12704.
69. Mokhtare M, Mirfakhraee H, Arshad M, Samadani Fard SH, Bahardoust M, Movahed A, et al. The effects of Helicobacter pylori eradication on modification of metabolic syndrome parameters in patients with functional dyspepsia. Diabetes Metab Syndr 2017;11 Suppl 2:S1031–5.
70. Iwai N, Okuda T, Oka K, Hara T, Inada Y, Tsuji T, et al. Helicobacter pylori eradication increases the serum high density lipoprotein cholesterol level in the infected patients with chronic gastritis: a single-center observational study. PLoS One 2019;14:e0221349.
71. Watanabe J, Hamasaki M, Kotani K. The effect of Helicobacter pylori eradication on lipid levels: a meta-analysis. J Clin Med 2021;10:904.
72. Park J, Kim N, Kim WS, Lim SH, Choi Y, Jo HH, et al. Long-term effects of the eradication of Helicobacter pylori on metabolic parameters, depending on sex, in South Korea. Gut Liver 2023;17:58–68.
73. Lee JY, Park NH, Song YS, Park SM, Lee HW, Kim KH, et al. Prevalence of the metabolic syndrome and associated factors in Korean cancer survivors. Asian Pac J Cancer Prev 2013;14:1773–80.
74. Hu D, Peng F, Lin X, Chen G, Zhang H, Liang B, et al. Preoperative metabolic syndrome is predictive of significant gastric cancer mortality after gastrectomy: the Fujian Prospective Investigation of Cancer (FIESTA) Study. EBioMedicine 2017;15:73–80.
75. Zhang X, Hu D, Deng X, Lin J, Zheng X, Peng F, et al. Prediction of presurgical metabolic syndrome for gastric cancer-specific mortality is more evident in smokers: the FIESTA study. Cancer Med 2023;12:3419–32.