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Original Article

Sex Differences in the Effect of Changes in Body Mass Index on the Risk of Developing Gastric Cancer: Findings from a Nationwide Retrospective Cohort Study

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Background/Aims: This study examined sex differences in the effect of changes in body mass index (BMI) on the development of gastric cancer (GC) in South Korea.

Methods: Using data from the National Health Insurance Service–Health Screening Cohort, a retrospective cohort study involving 333,169 Koreans with a median follow-up of 12 years was conducted. BMI was categorized into five groups (<18.5, 18.5–22.9, 23.0–24.9 [reference], 25.0–29.9, and ≥30.0 kg/m^2) and the risk of developing GC was evaluated according to changes in BMI by calculating the hazard ratio (HR) using Cox proportional hazard regression.

Results: Among males, BMI ≥30.0 kg/m^2 was associated with a 1.27-fold higher overall risk of developing GC (95% confidence interval [CI], 1.02 to 1.57), but not in females. For non-cardia GC, a U-shaped association between BMI and risk of developing GC was observed in males, although statistical significance was observed only for BMI 18.5–22.9 kg/m^2. Additionally, an increase in BMI to 23.0–24.9 kg/m^2 was associated with a decreased non-cardia GC risk among males. In females, the largest waist circumference category was significantly associated with an increased risk of developing overall GC (HR, 1.37; 95% CI, 1.07 to 1.74).

Conclusions: This study demonstrated that maintaining a BMI in the range of 23.0–24.9 kg/m^2 is optimal for minimizing the risk of non-cardia GC, particularly in males. In females, visceral obesity, represented by a large waist circumference as a proxy, was associated with an increased risk of developing GC. **(Gut Liver, 2025;19:225-235)**

Key Words: Body mass index; Gastric neoplasm; Sex characteristics; Risk factors; Obesity

INTRODUCTION

While obesity based on global criteria (body mass index [BMI] ≥30.0 kg/m^2) is less common (<10%) in East Asia compared to the West, its prevalence is rapidly rising. Furthermore, the obesity prevalence in 2019, defined by the Asia-Pacific region's threshold (BMI ≥25.0 kg/m^2), has exceeded 25% in East Asia countries such as Japan and Korea.[1,2] This increasing prevalence of obesity has heightened interest in the medical community, prompting extensive research investigating the onset of secondary diseases caused by obesity. Accumulated research has already established that obesity increases the risk for developing several chronic diseases, including type 2 diabetes, coronary heart disease, stroke, asthma, and several cancers.[3-5] Obesity is associated with an increased risk for developing 13 types of cancer, including endometrial, esophageal, breast, colon and rectum, liver, and thyroid cancers.[5]

Obesity increases the risk for developing cardia gastric cancer (GC).[5] However, the link between obesity and the development of non-cardia GC has not yet been clearly identified,[6] although several cohort studies based on East Asian populations have recently reported that both underweight and obesity are significantly associated with an increased risk for non-cardia GC.[7-10] Moreover, only a limited number of studies to date have reported how weight gain

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or loss affects the increase or decrease in risk for GC.[11,12] Therefore, this is an area of research that requires additional follow-up studies. The process of gastrointestinal carcinogenesis is closely related to the increase in inflammatory adipokines and cytokines, and the decrease in anti-inflammatory adipokines caused by visceral obesity.[13] Generally, obesity in men is characterized by fat accumulation in the abdomen, whereas in females, obesity often involves fat accumulation in the hips or thighs. After menopause, visceral fat increases, indicating a sex difference.[14] Therefore, when evaluating the association between obesity and GC, it is necessary to consider anthropometric indices such as waist circumference (WC) and abdominal circumference, which better reflect abdominal obesity compared to BMI.

East Asia, including Korea, have the highest incidence of GC worldwide, with non-cardia GC accounting for >80% of all GC cases in this region.[15] Additionally, the proportion of underweight individuals in this region is considerably higher than in Western countries, including those in North America and Europe.[16,17] Therefore, it may be easier and more efficient to evaluate the relationship between being underweight or obese and the risk for non-cardia GC among East Asian populations. Furthermore, GC exhibits a male predominance, with a male-to-female ratio of approximately 2:1,[18] and several studies have suggested that this difference may be due to female sex hormones.[19,20] Additionally, sex hormone levels are correlated with the severity of obesity[21,22] and menopausal status in females.[22]

Based on this background, this study aimed to evaluate the impact of BMI changes on the development of GC—especially non-cardia GC—considering sex differences.

MATERIALS AND METHODS

1. Study design and data source

This retrospective cohort study used data from the National Health Insurance Service–Health Screening Cohort[23] a cohort consisting of 514,866 subjects randomly sampled from individuals undergoing National Health Service programs provided by the National Health Insurance Service in 2002–2003 in South Korea. Participants included in this cohort were followed up in 2019. During follow-up, information regarding socioeconomic and demographic factors, health behaviors, medical history, family history, laboratory test results, healthcare usage, and death was collected. The study protocol was approved by the Institutional Review Board of the Seoul National University Bundang Hospital (Seongnam, Korea; IRB number: X-2209-780-901). This study was conducted in accordance with the principles of the Declaration of Helsinki for biomedical research involving human subjects and the Guidelines for Good Clinical Practice. Requirements for informed consent were waived by the Institutional Review Board due to the retrospective nature of the study and the use of anonymized patient data.

2. Eligibility criteria and subject selection

The periods 2002–2003 and 2007–2008 were defined as the BMI measurement periods before (T1) and after (T2) the change in BMI, respectively, and subjects with BMI information at these 2 time points were selected. If BMI was measured >1 time within a measurement period, the earliest value was used. Subsequently, individuals with a BMI ≤13 kg/m^2 or ≥50 kg/m^2 were considered to be in the outlier category and were excluded from the study. Additionally, those who had claims records with a main diagnosis code starting with "C" before the examination date when the second BMI was measured were operationally defined as prevalent cancer cases and excluded from the study. After excluding prevalent cases, 334,301 participants remained. Finally, GC cases diagnosed within 2 years of the second BMI measurement were excluded, as we assumed that causality with the second measured BMI could not be guaranteed. Ultimately, therefore, data from 333,169 subjects were included in this study (Fig. 1).

Additionally, an analysis was conducted to assess the association between WC and the risk of GC, considering the potential role of visceral fat in GC development. For this analysis, participants with WC data from 2008 were selected, as WC measurements have been collected as part of the National Health Insurance Service health screening program since that year.

3. Outcome assessment

In this study, the index date was defined as the date of the health examination on which the second BMI was measured. GC incidence cases were defined as subjects with claims records with the International Classification of Diseases, 10th Revision (ICD)-10 code "C16" as the main diagnosis code and an admission code simultaneously at least 2 years after the index date. The study subjects were followed up from the index date to the date of GC confirmation, death, or the date of last follow-up (December 31, 2019), whichever occurred first. In addition, non-cardia GC and cardia GC were defined as patients having claims records with ICD-10 code "C16.1–16.6" and "C16.0" as the main diagnosis code(s), respectively.

4. Changes in BMI, WC, and potential confounder assessment

BMI measurements from 2002–2003 (T1) and 2007–2008 (T2) were used in this study. BMI was categorized into five

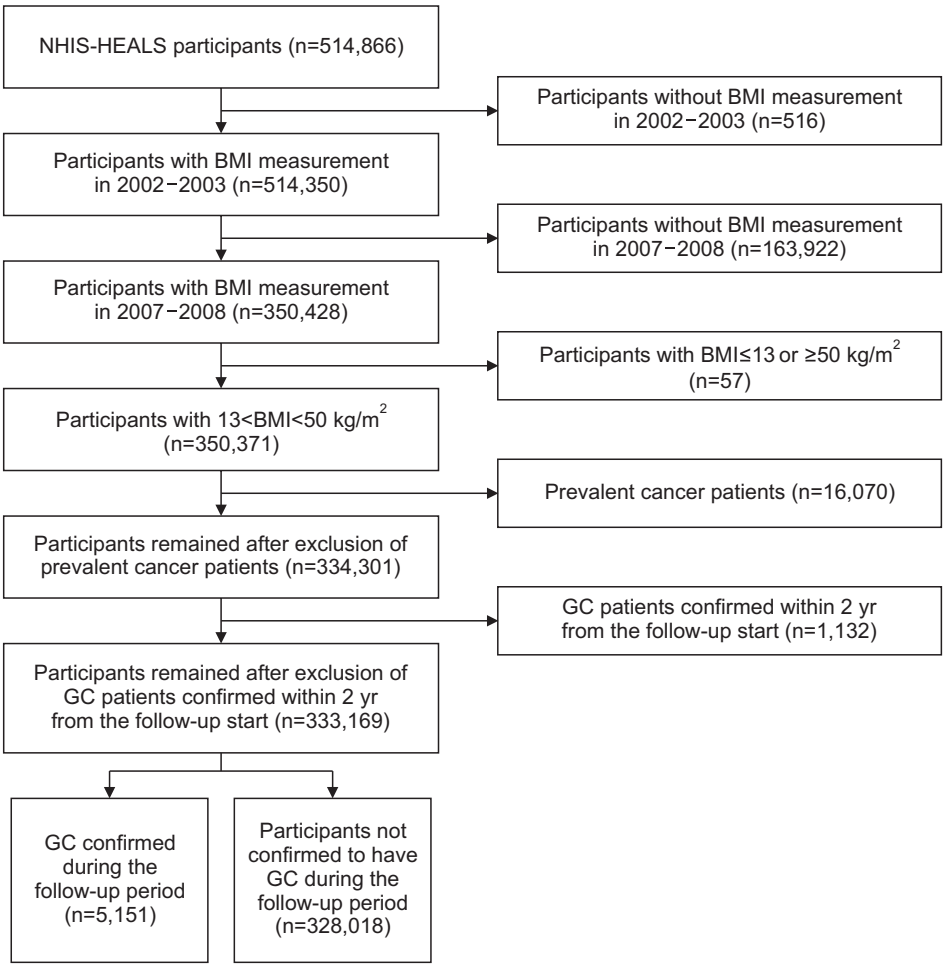


Fig. 1. Flow-diagram of study subject selection. NHIS-HEALS, National Health Insurance Service–Health Screening Cohort; BMI, body mass index; GC, gastric cancer.

groups (<18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, and ≥30.0 kg/m^2) to assess the association between BMI at a single time point and GC risk. When analyzing the change in BMI categories from T1 to T2, using five categories could lead to an overly fragmented sample. Additionally, when evaluating the relationship between BMI levels and non-cardia GC risk, we identified the U-shaped association with the lowest non-cardia GC risk in the BMI range of 23.0–24.9 kg/m^2. Therefore, we used three categorized BMI groups (<23.0, 23.0–24.9, and ≥25.0 kg/m^2) when the association between BMI change and GC risk was assessed. WC measurements in 2008 was divided into five groups based on quintiles within each male (<79.0, 79.0–82.9, 83.0–86.9, 87.0–90.9, and ≥91.0 cm) and female (<72.0, 72.0–75.9, 76.0–80.9, 81.0–85.9, and ≥86.0 cm) population, excluding cases of GC.

The baseline characteristics of the subjects were evaluated according to BMI. Characteristic variables collected on the date of the second BMI measurement or on the most recent date before that were used. Baseline characteristic variables included health behavior information (alcohol consumption and smoking) and health examination results (fasting glucose and cholesterol levels, and systolic and diastolic blood pressures), which were collected during health checkups, as well as age and income information confirmed from qualification data. In addition, the presence of diabetes mellitus, hypertension, and dyslipidemia was confirmed using claims data with ICD-10 codes corresponding to these conditions in the main diagnosis or subdiagnosis code before the index date.

5. Statistical analysis

Baseline characteristics according to BMI were compared using the chi-square test for categorical variables and analysis of variance for continuous variables. Baseline characteristics exhibiting significant differences depending on BMI levels and associations with GC development in univariable analysis at a significance level of 0.05 were considered to be potential confounders.

Risk for GC according to BMI, change in BMI, and WC was evaluated by calculating the hazard ratio (HR) and corresponding 95% confidence interval (CI) based on Cox proportional hazard regression. Potential confounders were included in the regression model as exploratory variables for adjustment. It was hypothesized that the effect

of BMI on GC risk may be due to sex hormone levels depending on BMI. Since sex hormone levels are influenced by menopausal status and information on menopause was unavailable, participants were stratified by age at the time of BMI measurement (<50 and ≥50 years).

An alpha error of 0.05 was applied to test for significance in the statistical analysis. All data management and statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

1. Differences in characteristics according to BMI

This study was based on data from a retrospective cohort consisting of 333,169 subjects, including 5,151 patients with GC, with a median follow-up period of 12 years (interquartile range, 11.4 to 12.5 years) after considering a 2-year latency period. For GC cases, the median of the duration between the second BMI measurement and cancer diagnosis was 6.7 years (interquartile range, 4.3 to 9.3 years). The mean age (60.5 years), proportion of current smokers (23.9%), and proportion of individuals with annual income below the median (40.1%) were highest in the underweight BMI group (<18.5 kg/m^2). In the severely obese group (≥30.0 kg/m^2), the proportion of females (56.9%) and non-smokers (74.9%) were highest (Table 1). Additionally, the proportion of patients with diabetes, hypertension, and dyslipidemia increased sequentially as BMI increased.

2. Risk for GC according to BMI

Overall, severe obesity (≥30.0 kg/m^2) was associated with a significantly increased risk for GC compared with the reference group (23.0–24.9 kg/m^2) among males (HR, 1.27; 95% CI, 1.02 to 1.57). However, no significant differences in risk for GC based on BMI were observed among females (Table 2). Furthermore, a U-shaped association between BMI and risk for non-cardia GC was found among males

Table 1. Baseline Characteristics of Study Subjects According to BMI

Characteristic	BMI in 2007–2008, kg/m^2					p-value
	<18.5	18.5–22.9	23.0–24.9	25.0–29.9	≥30.0	
No.	6,787	116,999	94,309	106,035	9,039	
Age, yr	60.5±11.1	56.7±9.4	56.5±8.7	56.8±8.7	57.2±8.5	<0.01
Sex						<0.01
Male	3,674 (54.1)	60,204 (51.5)	54,155 (57.4)	61,722 (58.2)	3,899 (43.1)	
Female	3,113 (45.9)	56,795 (48.5)	40,154 (42.6)	44,313 (41.8)	5,140 (56.9)	
Smoking status						<0.01
Non-smoker	4,424 (65.2)	80,722 (65.2)	64,113 (68.0)	71,832 (67.7)	6,772 (74.9)	
Past smoker	343 (5.0)	8,295 (14.5)	8,865 (9.4)	10,555 (10.0)	645 (7.1)	
Current smoker	1,623 (23.9)	21,371 (18.5)	15,643 (16.6)	16,962 (16.0)	1,103 (12.2)	
Missing	397 (5.9)	6,611 (1.8)	5,688 (6.0)	6,686 (6.3)	519 (5.8)	
Alcohol drinking						<0.01
Non-drinker	4,348 (64.1)	69,754 (59.6)	52,435 (55.6)	58,450 (55.1)	5,670 (62.7)	
2–3/mo or 1–2/wk	1,551 (22.8)	33,821 (28.9)	30,897 (32.8)	34,628 (32.7)	2,394 (26.5)	
≥3–4/wk	739 (10.9)	11,189 (9.6)	9,252 (9.8)	10,828 (10.2)	773 (8.6)	
Missing	149 (2.2)	2,235 (1.9)	1,725 (1.8)	2,129 (2.0)	202 (2.2)	
Income						<0.01
<50 percentile or beneficiary	2,723 (40.1)	42,396 (36.2)	31,708 (33.6)	35,642 (33.6)	3,401 (37.6)	
≥50 percentile	4,064 (59.9)	74,603 (63.8)	62,601 (66.4)	70,393 (66.4)	5,638 (62.4)	
Fasting glucose, mg/dL	95.8±28.2	96.7±25.0	99.2±25.3	102.1±27.0	106.7±30.3	<0.01
Total cholesterol, mg/dL	185.7±35.2	194.6±35.9	199.5±36.6	202.4±37.3	206.0±39.7	<0.01
SBP, mm Hg	120.8±17.0	122.5±15.9	125.8±15.5	128.9±15.5	132.9±15.9	<0.01
DBP, mm Hg	75.1±10.6	76.1±10.2	78.2±10.0	80.1±10.1	82.3±10.4	<0.01
Past history of diabetes						<0.01
No	5,811 (85.6)	99,235 (84.8)	77,148 (81.8)	83,185 (78.4)	6,392 (70.7)	
Yes	976 (14.4)	17,764 (16.2)	17,161 (18.2)	22,850 (21.6)	2,647 (29.3)	
Past history of hypertension						<0.01
No	5,226 (77.0)	87,219 (74.6)	62,950 (66.7)	60,703 (57.2)	3,850 (42.6)	
Yes	1,561 (23.0)	29,780 (25.4)	31,359 (33.3)	45,332 (42.8)	5,189 (57.4)	
Past history of dyslipidemia						<0.01
No	6,033 (88.9)	97,661 (83.5)	74,183 (78.7)	78,363 (73.9)	5,961 (66.0)	
Yes	754 (11.1)	19,338 (16.5)	20,126 (21.3)	27,672 (26.1)	3,078 (34.0)	

Data are presented as mean±SD or number (%).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Association between BMI and Gastric Cancer Risk According to Sex

BMI, kg/m^2	Total			Male			Female		
	Person-years	No. of cases	HR (95% CI)*	Person-years	No. of cases	HR (95% CI)†	Person-years	No. of cases	HR (95% CI)†
Overall									
<18.5	72,360	109	0.95 (0.78–1.15)	37,571	87	1.02 (0.82–1.27)	34,789	22	0.75 (0.48–1.15)
18.5–22.9	1,341,184	1,759	1.00 (0.93–1.07)	678,711	1,284	1.00 (0.92–1.08)	662,474	475	1.00 (0.87–1.15)
23.0–24.9	1,093,696	1,445	1.00 (reference)	622,815	1,089	1.00 (reference)	470,881	356	1.00 (reference)
25.0–29.9	1,231,519	1,695	1.04 (0.97–1.12)	712,361	1,265	1.05 (0.96–1.14)	519,158	430	1.02 (0.89–1.18)
≥30.0	104,621	143	1.18 (0.99–1.40)	44,677	92	1.27 (1.02–1.57)	59,944	51	1.05 (0.78–1.41)
Non-cardia									
<18.5	72,000	56	1.21 (0.92–1.59)	37,266	42	1.20 (0.87–1.65)	34,734	14	1.22 (0.70–2.12)
18.5–22.9	1,334,395	797	1.13 (1.02–1.26)	673,966	597	1.14 (1.01–1.29)	660,429	200	1.10 (0.88–1.37)
23.0–24.9	1,087,530	579	1.00 (reference)	618,207	444	1.00 (reference)	469,324	135	1.00 (reference)
25.0–29.9	1,224,526	714	1.09 (0.98–1.22)	707,157	543	1.10 (0.97–1.25)	517,368	171	1.08 (0.86–1.35)
≥30.0	103,944	54	1.12 (0.84–1.48)	44,239	35	1.16 (0.82–1.64)	59,705	19	1.05 (0.65–1.70)
Cardia									
<18.5	71,631	2	0.44 (0.11–1.80)	36,994	2	0.55 (0.13–2.27)	34,637	0	NA
18.5–22.9	1,329,759	64	0.96 (0.67–1.39)	670,492	48	0.91 (0.60–1.37)	659,267	16	1.24 (0.56–2.73)
23.0–24.9	1,084,000	54	1.00 (reference)	615,555	44	1.00 (reference)	468,445	10	1.00 (reference)
25.0–29.9	1,220,169	70	1.14 (0.80–1.63)	703,811	48	0.98 (0.65–1.48)	516,358	22	1.78 (0.84–3.77)
≥30.0	103,609	6	1.29 (0.55-3.02)	44,021	3	1.00 (0.31–3.23)	59,588	3	2.08 (0.57–7.60)

BMI, body mass index; HR, hazard ratio; CI, confidence interval; NA, not available.
*Adjusted for age, sex, smoking status, alcohol consumption frequency (drinks per week), past history of diabetes mellitus, and hypertension status with consideration of 2-year latency period; †Adjusted for age, smoking status, alcohol consumption frequency (drinks per week), past history of diabetes mellitus, and hypertension status with consideration of 2-year latency period.

Table 3. Impact of Change in BMI on Overall Gastric Cancer Risk According to Sex

BMI in 2002–2003, kg/m^2	BMI in 2007–2008, kg/m^2	Total			Male			Female		
		Person-years	No. of cases	HR (95% CI)*	Person-years	No. of cases	HR (95% CI)†	Person-years	No. of cases	HR (95% CI)†
<18.5	<18.5	38,186	64	1.00 (reference)	20,448	51	1.00 (reference)	17,737	13	1.00 (reference)
	18.5–29.9	33,459	39	0.75 (0.50–1.11)	16,854	27	0.67 (0.42–1.07)	16,604	12	0.99 (0.45–2.17)
	≥30.0	62	0	NA	37	0	NA	26	0	NA
18.5–29.9	<18.5	34,105	45	0.82 (0.61–1.10)	17,087	36	0.90 (0.65–1.25)	17,018	9	0.60 (0.31–1.15)
	18.5–29.9	3,594,270	4,812	1.00 (reference)	1,979,747	3,581	1.00 (reference)	1,614,524	1,231	1.00 (reference)
	≥30.0	41,353	55	1.09 (0.83–1.42)	19,319	35	1.08 (0.78–1.51)	22,034	20	1.10 (0.70–1.71)
≥30.0	<18.5	69	0	NA	35	0	NA	34	0	NA
	18.5–29.9	38,671	48	0.82 (0.57–1.16)	17,286	30	0.74 (0.48–1.16)	21,385	18	0.94 (0.53–1.69)
	≥30.0	63,206	88	1.00 (reference)	25,322	57	1.00 (reference)	37,884	31	1.00 (reference)
<23.0	<23.0	1,145,760	1,518	1.00 (reference)	578,142	1,121	1.00 (reference)	567,618	397	1.00 (reference)
	23.0–24.9	254,611	322	0.98 (0.87–1.10)	139,015	239	0.97 (0.84–1.12)	115,596	83	1.01 (0.80–1.28)
	≥25.0	29,748	42	1.06 (0.78–1.45)	15,218	29	1.04 (0.72–1.51)	14,530	13	1.15 (0.66–2.01)
23.0–24.9	<23.0	235,211	301	0.93 (0.81–1.06)	123,001	217	0.89 (0.77–1.04)	112,210	84	1.04 (0.80–1.35)
	23.0–24.9	600,450	790	1.00 (reference)	349,960	616	1.00 (reference)	250,491	174	1.00 (reference)
	≥25.0	234,722	318	1.04 (0.92–1.19)	135,312	240	1.03 (1.05–1.07)	99,410	78	1.08 (0.83–1.41)
≥25.0	<23.0	32,574	49	1.05 (0.79–1.39)	15,138	33	1.06 (0.75–1.50)	17,435	16	1.02 (0.62–1.68)
	23.0–24.9	238,635	333	0.97 (0.86–1.10)	133,841	234	0.92 (0.79–1.05)	104,794	99	1.13 (0.91–1.42)
	≥25.0	1,071,670	1,478	1.00 (reference)	606,509	1,088	1.00 (reference)	465,161	390	1.00 (reference)

BMI, body mass index; HR, hazard ratio; CI, confidence interval; NA, not available.
*Adjusted for age, sex, smoking status, alcohol consumption frequency (drinks per week), past history of diabetes mellitus, and hypertension status with consideration of 2-year latency period; †Adjusted for age, smoking status, alcohol consumption frequency (drinks per week), past history of diabetes mellitus, and hypertension status with consideration of 2-year latency period.

(HR, 1.14; 95% CI, 1.01 to 1.29 [for 18.5–22.9 kg/m^2]; HR, 1.10; 95% CI, 0.97 to 1.25 [for 25.0–29.9 kg/m^2]), although statistical significance was reached only for BMI of 18.5–22.9 kg/m^2. In contrast, data supporting this U-shaped association between BMI and risk for non-cardia GC were not found among females. Unlike non-cardia GC, no difference in cardiac GC risk according to BMI was found in either males or females.

When subjects were stratified according to age at the time of BMI measurement, an increased overall risk for GC in the severely obese population and a U-shaped association between risk for non-cardia GC and BMI in males were observed only in individuals ≥50 years of age (Supplementary Tables 1 and 2).

3. Risk for GC according to changes(s) in BMI

The overall risk for GC according to change(s) in BMI is reported in Table 3. Increasing BMI from overweight status (23.0–24.9 kg/m^2) to obese status (≥25.0 kg/m^2) was associated with a significantly increased overall risk for GC among males (HR, 1.03; 95% CI, 1.05 to 1.07). This result implies that, even if individuals were previously at the BMI level with the lowest risk for GC, the risk for developing GC can increase with weight gain. However, this result was observed only in males and not in females. Notably, it was observed that, among males with a BMI <18.5 kg/m^2, the risk for developing GC decreased by a factor of 0.86 for every 1 kg/m^2 increase in BMI, although the difference was not statistically significant (Fig. 2A). This suggests that the risk for GC is quite high in those with BMI <18.5 kg/m^2 and that increasing weight to an optimal level may reduce

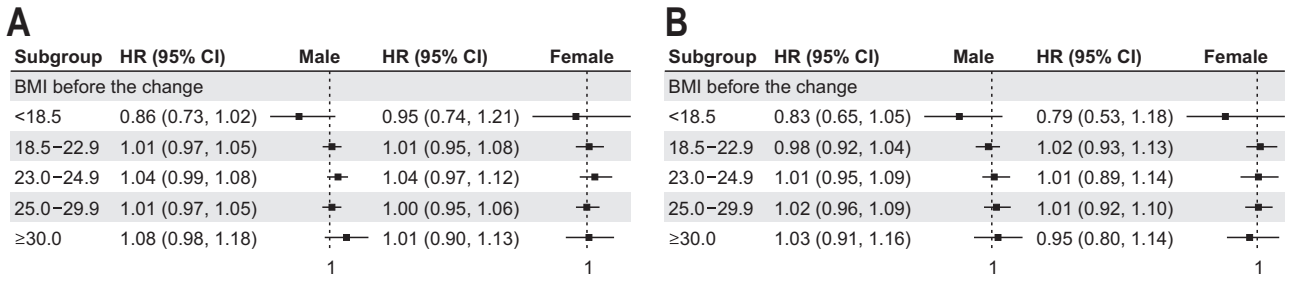


Fig. 2. Risk of developing (A) overall and (B) non-cardia gastric cancer risk by 1 kg/m^2 increase in BMI. HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Table 4. Impact of Change in BMI on Non-Cardia Gastric Cancer Risk According to Sex

BMI in 2002–2003, kg/m^2	BMI in 2007–2008, kg/m^2	Total			Male			Female		
		Person-years	No. of cases	HR (95% CI)*	Person-years	No. of cases	HR (95% CI)†	Person-years	No. of cases	HR (95% CI)†
<18.5	<18.5	37,992	34	1.00 (reference)	20,288	25	1.00 (reference)	17,704	9	1.00 (reference)
	18.5–29.9	33,316	20	0.70 (0.40–1.22)	16,761	15	0.73 (0.38–1.39)	16,555	5	0.60 (0.20–1.78)
	≥30.0	62	0	NA	37	0	NA	26	0	NA
18.5–29.9	<18.5	33,938	22	0.93 (0.61–1.41)	16,942	17	0.97 (0.60–1.57)	16,995	5	0.80 (0.33–1.94)
	18.5–29.9	3,574,679	2,051	1.00 (reference)	1,965,410	1,555	1.00 (reference)	1,609,269	496	1.00 (reference)
	≥30.0	41,099	22	1.02 (0.67–1.55)	19,148	13	0.92 (0.53–1.58)	21,951	9	1.24 (0.64–2.39)
≥30.0	<18.5	69	0	NA	35	0	NA	34	0	NA
	18.5–29.9	38,455	19	0.85 (0.48–1.51)	17,158	14	0.88 (0.45–1.73)	21,297	5	0.79 (0.27–2.31)
	≥30.0	62,783	32	1.00 (reference)	25,055	22	1.00 (reference)	37,728	10	1.00 (reference)
<23.0	<23.0	1,139,960	694	1.00 (reference)	573,991	521	1.00 (reference)	565,969	173	1.00 (reference)
	23.0–24.9	253,210	120	0.79 (0.65–0.96)	137,968	91	0.78 (0.63–0.98)	115,242	29	0.83 (0.56–1.23)
	≥25.0	29,555	16	0.89 (0.54–1.46)	15,070	10	0.77 (0.41–1.43)	14,484	6	1.26 (0.56–2.86)
23.0–24.9	<23.0	234,069	139	1.04 (0.85–1.26)	122,244	104	0.99 (0.79–1.24)	111,825	35	1.22 (0.81–1.85)
	23.0–24.9	597,156	326	1.00 (reference)	347,434	265	1.00 (reference)	249,722	61	1.00 (reference)
	≥25.0	233,347	127	1.01 (0.83–1.24)	134,290	99	0.99 (0.79–1.25)	99,056	28	1.11 (0.71–1.74)
≥25.0	<23.0	32,365	20	0.99 (0.63–1.55)	14,996	14	1.01 (0.59–1.72)	17,369	6	0.94 (0.42–2.13)
	23.0–24.9	237,164	133	0.91 (0.76–1.10)	132,804	88	0.79 (0.63–1.00)	104,360	45	1.28 (0.92–1.79)
	≥25.0	1,065,568	625	1.00 (reference)	602,036	469	1.00 (reference)	463,532	156	1.00 (reference)

BMI, body mass index; HR, hazard ratio; CI, confidence interval; NA, not available.
*Adjusted for age, sex, smoking status, alcohol consumption frequency (drinks per week), past history of diabetes mellitus, and hypertension status with consideration of 2-year latency period; †Adjusted for age, smoking status, alcohol consumption frequency (drinks per week), past history of diabetes mellitus, and hypertension status with consideration of 2-year latency period.

the risk for developing GC.

For non-cardia GC risk according to changes in BMI, even if individuals had a BMI expected to be at high risk for developing GC (BMI <23.0 kg/m^2 or ≥25.0 kg/m^2), changing BMI to 23.0–24.9 kg/m^2 later was shown to significantly reduce the risk for non-cardia GC. However, these results were observed only among males (HR, 0.78; 95% CI, 0.63 to 0.98 [for change in BMI from <23.0 to 23.0–24.9 kg/m^2]; HR, 0.79; 95% CI, 0.63 to 1.00 [for change in BMI from ≥25.0 to 23.0–24.9 kg/m^2]) (Table 4). Additionally, when evaluating the risk for non-cardia GC with each 1 kg/m^2 increase in BMI, the relationship between BMI increase and non-cardia GC risk, which had previously exhibited a negative association, shifted to a positive association in males, starting from the group with a past BMI ≥23 kg/m^2 (Fig. 2B). This result further supports the U-shaped association between changes in BMI and the risk for non-cardia GC.

4. Risk for GC according to WC

Among the study participants, 133,071 subjects including 1,981 GC cases confirmed at least 2 years from the follow-up start, had information on WC in 2008. The WC cutoff value for obesity in Asians is 90 cm for males and 85 cm for females, which corresponds to the fourth quintile in this study. The analysis showed that, among males, those in the third quintile of WC had the lowest risk of non-cardia GC, while those in the second quintile (with smaller WC) had the highest risk of non-cardia GC (HR, 1.46; 95% CI, 1.12 to 1.90) (Supplementary Table 3). Additionally, although not statistically significant, an increase in GC risk was observed in males with WC in the fourth and fifth quintiles. In females, a similar trend was noted, where both smaller and larger WC were associated with an increased non-cardia GC risk, though these results were not statistically significant. Another interesting finding was that while an increase in non-cardia GC risk was not observed in females with the highest BMI, those in the group with the largest WC showed a significantly increased risk for overall GC (HR, 1.37; 95% CI, 1.07 to 1.74).

DISCUSSION

In this study, obesity (BMI ≥25.0 kg/m^2) was associated with an increased overall risk for GC, while the overweight group (BMI, 23.0–24.9 kg/m^2) had the lowest risk for GC, especially for non-cardia GC. Moreover, it has been confirmed that even if BMI was at a high-risk level in the past, the risk for GC could be reduced if BMI was later adjusted to the optimal level for males (BMI, 23.0–24.9 kg/m^2). Additionally, the association between BMI level and the risk for non-cardia GC was consistent in individuals ≥50 years of age.

The main finding of the present study was that, even if an individual had a BMI associated with a relatively high risk for developing GC in the past, this risk could be reduced if the BMI is later altered to an optimal level, although this result was limited to males. Previous studies evaluating prognosis in relation to BMI among postoperative patients with GC have been extensive.[24-26] However, only a few studies have examined the effects of precancerous BMI especially changes in BMI on the development of GC.[11,12] According to a case-control study published in 2021, changing body weight from underweight to normal/overweight/obese, or from normal to overweight/obese only in *Helicobacter pylori* infected subjects, was significantly associated with a reduced risk for developing GC.[12] This result is consistent with the findings of our study, which revealed that changing BMI to an overweight level (23.0–24.9 kg/m^2) was associated with a reduced risk for developing GC. However, sex differences were not considered in the aforementioned study and *H. pylori* infection status was not considered in our study, making a direct comparison of the results between this and our study exceedingly difficult. Additionally, a recent study conducted in Korea found that males with an overweight BMI who lost weight had a reduced risk for developing GC compared with those who maintained the same weight.[11] Notably, these results were limited to males, and no significant association between changes in BMI and risk for GC was confirmed in females.

This study revealed a relatively reduced risk for developing non-cardia GC in overweight males. Because the relationship between BMI and the risk for non-cardia GC has not been definitively established, the mechanism explaining the link between being overweight and having the lowest GC risk particularly in males has not yet been clarified. However, several biological mechanisms can be proposed. GC is far more common among males than in females,[18] and some studies suggest that the preventive effect of female sex hormones on non-cardia GC may contribute to the difference in GC incidence rates between males and females.[19,20] Additionally, several studies have shown that female hormone levels increase with BMI in both males and females.[21,27] This supports the concept that the risk for GC may be lower in the overweight state due to the protective effect of higher estrogen levels compared with underweight or normal-weight.

However, the obese population had a high risk for GC despite having high female hormone levels in the present study. This may be due to several mechanisms, including

increased levels of insulin, insulin-like growth factor, and inflammatory cytokines caused by obesity, which act independently of the preventive effect of female hormones on the development of GC. Obesity is known to cause hyperinsulinemia and increase insulin-like growth factor and inflammatory cytokine levels[28,29] which lead to increased cell proliferation, survival, and apoptosis inhibition, which are the major mechanisms of carcinogenesis.[29]

Additionally, the finding that setting BMI to an overweight level can lower the risk for developing non-cardia GC was confirmed only in males. The difference in the correlation between estrogen levels and BMI between elderly males and females may explain sex differences in the association between BMI and non-cardia GC. Most participants in this study were elderly; therefore, most female participants were postmenopausal. Previous studies have shown that BMI is positively correlated with increases in parental estrogen and estrogen metabolites even in postmenopausal females.[30,31] However, postmenopausal females receiving hormone therapy have very high estrogen levels regardless of BMI; therefore, the association between BMI and natural estrogen concentration may be masked in females. Further studies are required to elucidate these sex-related differences. Additionally, since estrogen is supposed to prevent the intestinal type of GC,[32] which occurs more frequently in males than females,[33] the protective effect of sex hormones on GC development may have been more pronounced in males.

In this study, we identified a possible U-shaped association between WC and non-cardia GC risk, particularly in men, which was similar to the association observed between BMI and non-cardia GC risk. A noteworthy finding is that the overall GC risk significantly increased in the group of women with the largest WC contrasting with the lack of an increase in GC risk in the group of women with the highest BMI. This difference is likely due to difference in body fat distribution between men and women.[14] Generally, males tend to have obesity characterized by fat accumulation in the abdominal region, while females tend to have obesity with a higher proportion of body fat in the gluteal-femoral region. Therefore, BMI may not be as effective at reflecting abdominal obesity in women as it is in men. Since visceral fat is closely associated with gastrointestinal carcinogenesis,[13] and WC is a better indicator of visceral obesity than BMI, it is thought that additional analysis evaluating the association between WC and GC risk might reveal that excessive abdominal obesity increases GC risk in women as well.

The well-established association between elevated cardia GC risk and obesity was not confirmed in the present study. Several factors may explain the absence of an observed increased risk. First, the study may have lacked sufficient statistical power due to the limited number of cardia GC cases (n=196), which may not have been enough to detect a significant association. Second, the proportion of severely obese individuals in the study cohort was relatively small. Previous studies to assess the association between obesity and cardia GC risk mostly included a larger proportion of severely obese individuals (BMI ≥30 kg/m^2), ranging from as low as about 7% to more than 20%, and also had higher average BMI levels (>25 kg/m^2 on average).[34-40] In contrast, the proportion of severely obese participants (BMI ≥30 kg/m^2) was only 2.7%, with an average BMI of 24.0 kg/m^2 (standard deviation, 2.9 kg/m^2) in this study. Therefore, this study likely did not have a sufficiently large sample of severely obese individuals and cardia GC cases to adequately verify the association between obesity and cardia GC risk.

The present study had some limitations. First, important information regarding factors, including *H. pylori* (noninvasive or invasive test)[41] or histological classification, such as the Lauren classification, was not collected. These factors should be considered when evaluating the association between BMI and risk for GC. Second, only 45.5% of the participants had available information regarding anatomical location. Third, changes in BMI after the start of the follow-up were not considered. Although we assessed the association between changes in BMI and the development of GC, the median follow-up period was 12 years. Thus, changes in BMI after the second BMI measurement may have occurred but were not considered in the analyses.

Despite these limitations, this study had several strengths. GC is a heterogeneous disease with varying locations and histopathology.[42] However, previous studies have not considered anatomical location or histology in their analyses to assess the association between changes in BMI and the risk for GC.[10,11] In contrast, we attempted to analyze as homogeneous a GC population as possible by conducting analyses targeting all patients with GC, as well as those limited to non-cardia GC. Additionally, we focused on sex differences in the association between changes in BMI and the onset of GC. To this end, a sex-stratified analysis was performed, revealing that changing body weight to an optimal level was associated with reduced risk for GC only in males. Weight loss is common among patients with cancer,[43] and not accounting for the timing of BMI measurement and GC onset can lead to reverse causality in the evaluation of BMI and the development of GC. To mitigate this risk, we excluded GC cases confirmed within 2 years from the start of follow-up in all analyses.

This study demonstrated that maintaining a BMI in the range of 23.0–24.9 kg/m^2 is optimal for minimizing the risk

of non-cardia GC, particularly in males over the age of 50 years. Furthermore, adjusting BMI to this optimal level can reduce GC risk even in individuals with a BMI that is expected to be at a high risk for developing GC (<23.0 kg/m^2 or ≥25.0 kg/m^2) specifically in males. However, it remains unclear why the risk for developing GC is lowest in overweight individuals and whether this result is exclusive to males, highlighting the need for further research. Despite the inherent limitations of this study, our findings are anticipated to provide meaningful evidence suggesting that weight control which can be modified through individual efforts may positively impact the primary prevention of GC.

CONFLICTS OF INTEREST

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

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Study concept and design: N.K., J.J. Data acquisition: N.K., Y.C. Data analysis and interpretation: J.J. Drafting of the manuscript: J.J. Critical revision of the manuscript for important intellectual content: N.K., Y.C. Statistical analysis: J.J. Obtained funding: N.K. Administrative, technical, or material support; study supervision: N.K., Y.C. Approval of final manuscript: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl240555.

DATA AVAILABILITY STATEMENT

This study used the National Health Insurance Service–Health Screening Cohort (NHIS-HEALS) data (NHIS-2023-2-047) made by NHIS. The data for this study are publicly available through the National Health Insurance Service–Big Data Platform. As such, the corresponding author does not have the authority to share the data directly. Any researcher can access the database by submitting a study proposal and obtaining approval from the review committee.

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