Research Article

Cancer Epidemiology, Biomarkers & Prevention

Body Mass Index and Risk of Intestinal Metaplasia: A Cohort Study

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Abstract

Background: We examined the association between body mass index (BMI) and development of endoscopic intestinal metaplasia.

Methods: This retrospective cohort study included 142,832 Korean adults free of endoscopic intestinal metaplasia and atrophic gastritis who underwent upper endoscopy at baseline and subsequent visits and were followed for up to 5 years. A parametric proportional hazards model was used to estimate the adjusted HR with 95% confidence interval (CI) for incident intestinal metaplasia.

Results: In more than 444,719.1 person-years of follow-up, 2,281 participants developed endoscopic intestinal metaplasia (incidence rate, 5.1 per 1,000 person-years). Increased BMI categories were associated with increased risk of new-onset intestinal metaplasia in a dose-response manner. After adjustment for age, sex, center, year of screening exam, smoking status, alcohol intake, exercise, total calorie intake, history of diabetes and hypertension, and history of *Helicobacter pylori* infection, the multivariable adjusted HRs (95% CIs) for incident intestinal metaplasia comparing BMIs of <18.5, 23–24.9, 25.0–29.9, and >30 kg/m^2 with a BMI of 18.5–22.9 kg/m^2 were 0.84 (0.64–1.09), 1.03 (0.93–1.16), 1.07 (0.96–1.20), and 1.48 (1.20–1.83), respectively. These associations did not differ by clinically relevant subgroups. Risk of endoscopic atrophic gastritis also increased as the baseline BMI category increased.

Conclusions: In a large cohort of Korean men and women, obesity was independently associated with increased incidence of endoscopic atrophic gastritis and intestinal metaplasia.

Impact: Excessive adiposity appears to play a role in development of stomach precursor lesions of stomach cancer, requiring further studies to determine whether strategies to reduce obesity will also help reduce precancerous lesions and, in turn, gastric cancer.

Introduction

Despite a recent decline, gastric cancer is still the fifth most common cancer and the third leading cause of cancer-related deaths worldwide (1, 2). In the Republic of Korea, stomach cancer was the second most common cancer in 2014 (3). The development of gastric adenocarcinoma, particularly the intestinal type, is thought to progress sequentially through nonatrophic chronic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia to cancer (4, 5). Atrophic gastritis and intestinal metaplasia are considered the main precursor lesions of gastric cancer because the risk of gastric cancer is closely related to the extent and degree of intestinal metaplasia and atrophic gastritis (6, 7). Intestinal metaplasia is defined as replacement of gastric columnar epithelial cells by cells of intestinal morphology with the presence of goblet cells, Paneth cells, and absorptive cells (6, 8). The dysplasia occurs in metaplastic foci, and the rate of progression is affected by several factors, including virulence of the *Helicobacter pylori* strain and environmental and host genetic factors, but the etiology of stomach cancer and its precursors is not fully understood (9, 10).

Obesity is a major risk factor for various digestive organ cancers including esophageal, colorectal, and pancreatic cancers (11–13). Observational studies of gastric cancer have examined its relationship with obesity, but the findings remain controversial. Recent meta-analyses have reported a positive association between body mass index (BMI) and gastric cancer, especially cardia gastric cancer (11, 14–19). Notably, a recent study using Mendelian randomization found that higher genetically predicted BMI is associated with increased gastric cancer risk, supporting a causal role of high BMI in the development of gastric cancer (20). The effect of obesity on precursor lesions such as atrophic gastritis or intestinal metaplasia has also been examined in several observational studies, but results are inconclusive. Some studies reported a positive association between BMI and atrophic gastritis or intestinal metaplasia, whereas others reported no association (21–27). However, previous studies used cross-sectional design, limiting their ability to establish the temporal relationship between obesity and

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atrophic gastritis or intestinal metaplasia. In addition, the risk of atrophic gastritis or intestinal metaplasia in obese patients can be mediated by insulin resistance and other obesity-associated metabolic abnormalities, but no studies have evaluated whether the association of obesity with atrophic gastritis and intestinal metaplasia is mediated by such metabolic parameters. Therefore, we examined the association between BMI categories and risk of developing intestinal metaplasia in a large cohort of participants who underwent endoscopy as a part of a health screening program.

Materials and Methods

Study population

This cohort study was a part of the Kangbuk Samsung Health Study, which is a cohort study of Korean adults who underwent a comprehensive annual or biennial health examination at the clinics of Kangbuk Samsung Hospital Total Healthcare Screening Center in Seoul and Suwon, South Korea (28). Over 80% of participants were employees of various companies and local governmental organizations or their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health-screening exams of all employees, offered free of charge. The remaining participants voluntarily purchased screening examinations at the health-screening center. Upper endoscopy is a screening test for stomach cancer and is widely performed annually or biennially as part of a routine comprehensive health examination in Korea (29).

The present analysis included 208,702 participants who underwent baseline and at least one follow-up endoscopy between 2011 and 2016 (Fig. 1). We excluded participants who had any of the following conditions at baseline: intestinal metaplasia or atrophic gastritis based on endoscopy (n = 58,390); missing data on BMI, glucose, total cholesterol, or homeostatic model assessment of insulin resistance (HOMA-IR; n = 1,278); history of malignancy (n = 4,866); history of stomach surgery (n = 10); or use of gastrointestinal medication (n = 6,030). Because some individuals met more than one exclusion criterion, the total number of subjects included in the final analysis was 142,832.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC 2017-09-048), which waived the requirement for informed written consent due to the use of deidentified data obtained as part of routine health screening exams.

Data collection

Baseline and follow-up examinations were conducted at the clinics of Kangbuk Samsung Hospital Health Screening Center. Data on demographic characteristics, smoking status, alcohol consumption, physical activity, educational level, medical history, and medication use were collected by standardized, self-administered questionnaires, as described previously (28, 30). Medical conditions diagnosed by a physician, including *H. pylori* infection, were assessed via the same questionnaire. Smoking status was categorized into never, former, or current smoker, and alcohol consumption into none, moderate (<20 g/day), or high intake (≥20 g/day). We measured physical activity level using the validated Korean version of the International Physical Activity Questionnaire (IPAQ) Short Form (31, 32). Physical activity levels were categorized as described previously (33). Health-enhancing physically active (HEPA) was defined as physical activity that meets either of two criteria: (i) vigorous intensity activity on 3 or more days per week for a total ≥1,500 MET minute/week; or (ii) 7 days of any combination of walking, moderate intensity, or vigorous intensity activities achieving at least 3,000 MET minute/week (34). Typical diet was assessed using a 106-item self-administered food frequency questionnaire (FFQ) designed and validated for use in Korea (35).

Height, weight, and sitting blood pressure (BP) were measured by trained nurses. BMI was calculated as weight in kilograms divided by height in meters squared and was categorized according to Asian-specific criteria (36): underweight, BMI <18.5 kg/m^2;

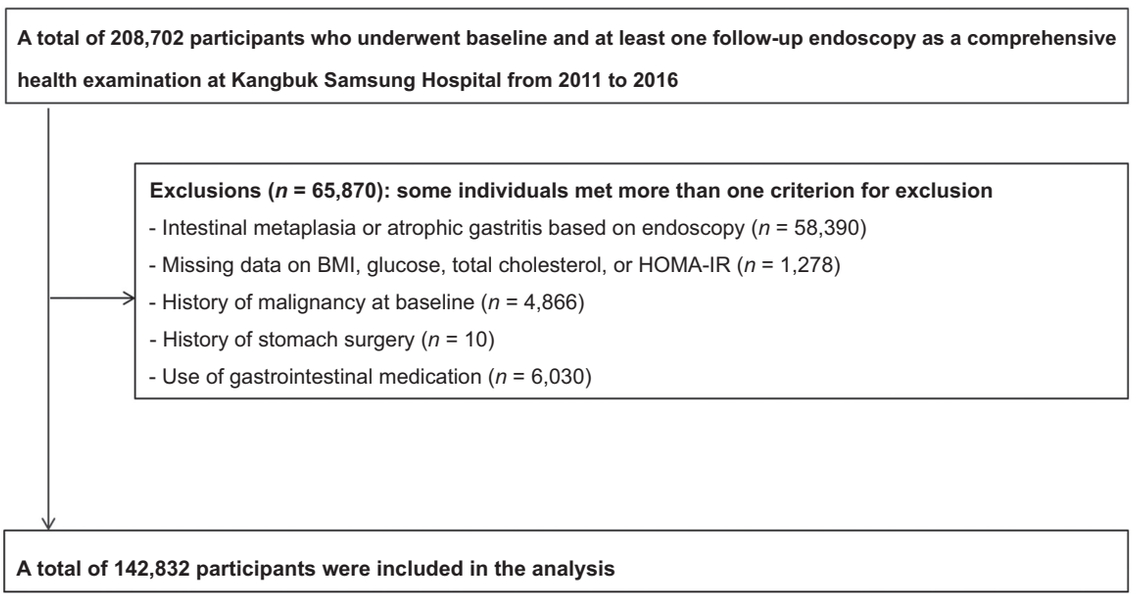

Figure 1.
Flow diagram for the selection of the study subjects, summarizing the inclusion and exclusion of study subjects.

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normal weight, BMI of 18.5 to 22.9 kg/m^2; overweight, BMI of 23 to 24.9 kg/m^2; obese I, BMI of 25 to 29.9 kg/m^2; and obese II, BMI $\geq$30 kg/m^2. Hypertension was defined as systolic BP $\geq$140 mm Hg, a diastolic BP $\geq$90 mm Hg, a self-reported history of hypertension, or current use of antihypertensive medications.

Serum levels of fasting glucose, uric acid, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and high-sensitivity C-reactive protein (hsCRP) were measured as described previously (28, 30). Insulin resistance was assessed with the HOMA-IR equation: fasting blood insulin (uU/mL) $\times$ fasting blood glucose (mmol/L) / 22.5. Diabetes was defined as a fasting serum glucose $\geq$126 mg/dL or current use of antidiabetic medications.

Endoscopic examinations were conducted by 13 experienced endoscopists using a conventional white light endoscope (GIF H260, Olympus Medical Systems). During endoscopy, any lesions suggestive of gastric pathology were imaged and described by location, size, and shape. Endoscopists reported presence of endoscopically suspected atrophy or intestinal metaplasia of background gastric mucosa. Endoscopic atrophic gastritis was defined as thinning, whitish mucosal change or visible submucosal vascular patterns, and endoscopic intestinal metaplasia as white plaque-like elevations in antrum and corpus (37). *H. pylori* infection status was evaluated histologically only when deemed necessary, such as in peptic ulcer disease, at the discretion of the endoscopist based on the Korean guidelines (38).

Statistical analysis

The characteristics of the study participants were explored according to BMI category (<18.5, 18.5–22.9, 23.0–24.9, 25.0-29.9, or $\geq$30 kg/m^2). The primary endpoint was development of endoscopic intestinal metaplasia. Because atrophic gastritis is a major precancerous lesion of gastric cancer, endoscopic atrophic gastritis was also analyzed as a secondary endpoint. Each participant was followed from his or her baseline exam until either development of endpoint or to his or her last health exam conducted prior to December 31, 2016, whichever came first. The incidence rate was calculated as the number of incident cases divided by number of person-years of follow-up. Because endoscopic intestinal metaplasia was known to have developed between the two visits, but the precise time at which it developed was unknown, a parametric proportional hazards model was used to account for this type of interval censoring (*stpm* command in Stata; ref. 39). In these models, the baseline hazard function was parameterized with restricted cubic splines in log time with four degrees of freedom.

The HR and 95% confidence interval (CI) were calculated for incident intestinal metaplasia and incident atrophic gastritis according to BMI category. Data were initially adjusted for age and sex and then were further adjusted for center (Seoul or Suwon), year of screening exam, smoking status (never, past, current, or unknown), alcohol intake (0, <20, $\geq$20 g/day, or unknown), physical activity level (inactive, minimally active, HEPA, or unknown), education level (high school graduate or less, community college or university graduate, graduate school or higher, or unknown), total calorie intake (in quintile or missing), history of *H. pylori* infection, history of diabetes, and history of hypertension (model 1). Model 2 was further adjusted for total cholesterol, triglycerides, glucose, and HOMA-IR. The proportional hazards assumption was assessed by examining the graphs of estimated log (−log) survival. To determine linear trends of incidence, the number of categories was used as a continuous variable and tested on each model. To further explore the shape of the dose-response relationship of BMI levels with the development of intestinal metaplasia, restricted cubic splines with knots were used at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of BMI distribution.

Additional subgroup analyses stratified by age (<40 vs. $\geq$40 years), sex (female vs. male), smoking status (current smoker vs. noncurrent smoker), alcohol intake (<20 vs. $\geq$20 g of alcohol per day), physical activity (no HEPA vs. HEPA), HOMA-IR (<2.5 vs. $\geq$2.5), hsCRP (<1.0 mg/L vs. $\geq$1.0 mg/L), and exam payee (company-paid vs. individual-paid) were performed. Interactions between BMI categories and subgroup characteristics were tested using likelihood ratio tests comparing models with versus without multiplicative interaction terms.

Statistical analyses were carried out using STATA version 15.0 (StataCorp LP). All P values less than 0.05 were considered statistically significant.

Results

The mean (SD) age of study participants was 37.3 (6.3) years and the proportion of males was 56.3% (Table 1). Participants with higher BMI were more likely to be older, male, current smokers, alcohol drinkers, and to have company-paid examination, a history of hypertension, diabetes, or *H. pylori* infection. BP, glucose, uric acid, total cholesterol, LDL-C, triglycerides, liver enzymes, hsCRP, HOMA-IR, and total energy intake were positively associated with BMI, whereas HDL-C was inversely associated with BMI (Table 1).

During 444,719.1 person-years of follow-up, 2,281 participants developed incident intestinal metaplasia. The median follow-up period for participants was 3.2 years (interquartile range, 2.0–4.1). Risk of endoscopic intestinal metaplasia increased as baseline BMI category increased ($P_{trend} < 0.001$). The age- and sex-adjusted HR and 95% CI for endoscopic intestinal metaplasia comparing BMIs <18.5, 23–24.9, 25–29.9, and >30 with a BMI of 18.5–22.9 kg/m^2 were 0.84 (0.65–1.09), 1.04 (0.93–1.16), 1.09 (0.98–1.22), and 1.48 (1.20–1.82), respectively ($P_{trend} = 0.001$). This association remained significant after adjusting for center, year of screening exam, smoking status, alcohol intake, physical activity, education level, total calorie intake, history of *H. pylori* infection, history of diabetes, and history of hypertension. To explore whether the increased risk of incident intestinal metaplasia observed in higher BMI categories was mediated by metabolic components associated with obesity, we performed additional analyses adjusted for metabolic parameters. Adjusting for fasting total cholesterol, triglycerides, glucose, and HOMA-IR slightly reduced the associations, but they remained statistically significant (Table 2, model 2). In spline regression analyses, there was a dose-response relationship between BMI levels and the development of intestinal metaplasia (Fig. 2).

The associations between BMI categories and development of intestinal metaplasia was stronger in younger (<40) compared with older participants ($\geq$40 years) and in those with low alcohol intake of <20 g of alcohol per day than those with higher alcohol intake of $\geq$20 g of alcohol per day (Table 3). Otherwise, there were no significant interactions by sex (women vs. men), smoking status (current smoker vs. noncurrent smoker), physical activity

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Table 1. Baseline characteristics of study participants by BMI category

		BMI Category (kg/m^2)					
Characteristic	**Overall**	**<18.5**	**18.5–22.9**	**23.0–24.9**	**25.0–29.9**	**≥30**	**P_{trend}**
Number	142,832	8,234	65,214	31,289	33,732	4,363	
Age (years)[a]	37.3 (6.3)	35.2 (5.3)	36.9 (6.1)	38.0 (6.6)	38.1 (6.4)	37.0 (5.9)	<0.001
Sex (%)	56.3	11.8	38.4	73.9	82.7	78.9	<0.001
Current smoker (%)	23.2	7.6	15.6	28.1	34.4	37.1	<0.001
Alcohol intake (%)[b]	22.0	7.1	14.7	26.4	33.6	34.6	<0.001
HEPA (%)	15.2	9.2	14.4	16.6	16.8	15.1	<0.001
Higher education (%)[c]	86.0	86.8	85.8	86.5	86.1	82.5	0.096
Hypertension (%)	8.3	1.3	3.7	8.9	15.4	29.5	<0.001
History of *H. pylori* (%)	5.8	4.9	5.5	6.1	6.2	5.8	<0.001
Diabetes (%)	2.5	0.5	1.0	2.7	4.7	10.5	<0.001
Company exam	95.9	95.9	95.7	95.9	96.2	96.5	<0.001
Systolic BP (mm Hg)[a]	108.6 (12.8)	98.9 (9.9)	104.1 (11.5)	111.1 (11.5)	115.6 (11.6)	121.7 (12.1)	<0.001
Diastolic BP (mm Hg)[a]	69.6 (9.7)	64.2 (7.8)	66.7 (8.7)	71.0 (9.2)	74.1 (9.5)	77.5 (9.9)	<0.001
Glucose (mg/dL)[a]	94.2 (12.8)	89.0 (8.4)	91.8 (10.0)	95.4 (12.7)	98.0 (15.1)	102.7 (21.9)	<0.001
Uric acid (mg/dL)[a]	5.3 (1.5)	4.2 (0.9)	4.8 (1.3)	5.6 (1.3)	6.1 (1.4)	6.5 (1.5)	<0.001
Total cholesterol (mg/dL)[a]	192.9 (33.5)	178.3 (28.3)	186.0 (30.9)	197.2 (33.6)	203.8 (34.5)	207.9 (36.0)	<0.001
LDL-C (mg/dL)[a]	118.6 (31.3)	98.1 (23.7)	110.3 (28.3)	124.8 (30.6)	131.7 (31.0)	135.5 (32.4)	<0.001
HDL-C (mg/dL)[a]	58.5 (14.9)	70.7 (14.2)	63.5 (14.4)	55.3 (13.0)	50.5 (11.7)	46.6 (10.4)	<0.001
Triglycerides (mg/dL)[d]	88 (63–132)	62 (50–78)	73 (56–100)	100 (73–143)	128 (91–181)	153 (111–214)	<0.001
ALT (U/L)[d]	18 (13–27)	12 (10–16)	14 (11–20)	20 (15–29)	27 (19–40)	39 (26–64)	<0.001
AST (U/L)[d]	19 (16–24)	17 (15–20)	18 (15–21)	20 (17–25)	23 (18–29)	28 (21–39)	<0.001
GGT (U/L)[d]	20 (13–34)	13 (10–17)	15 (11–22)	23 (16–37)	33 (22–54)	46 (29–72)	<0.001
hsCRP (mg/L)[d,e]	0.4 (0.2–0.8)	0.2 (0.2–0.4)	0.3 (0.2–0.6)	0.5 (0.3–0.9)	0.7 (0.4–1.3)	1.4 (0.8–2.6)	<0.001
HOMA-IR[d]	1.14 (0.76–1.70)	0.76 (0.51–1.10)	0.94 (0.64–1.34)	1.21 (0.84–1.71)	1.63 (1.14–2.30)	2.71 (1.90–3.92)	<0.001
Total energy intake (kcal/d) [d,f]	1578.4 (1228.5–1976.4)	1436.1 (1091.7–1781.0)	1514.3 (1170.9–1898.3)	1618.3 (1275.4–2020.1)	1679.4 (1330.3–2098.9)	1743.1 (1366.4–2232.4)	<0.001

[a]mean (standard deviation).
[b]≥20 g of ethanol per day.
[c]≥College graduate.
[d]Median (interquartile range).
[e]Among 123,194 participants without missing value on hsCRP.
[f]Among 112,418 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake).

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Table 2. Development of intestinal metaplasia by BMI category

BMI Category (kg/m^2)	Person-years	Incident cases	Incidence rate (cases per 1,000 person-years)	Age-sex adjusted HR (95% CI)	Multivariable-adjusted HR[a] (95% CI)	
					Model 1	Model 2
<18.5	25,058.9	61	2.4	0.84 (0.65–1.09)	0.84 (0.64–1.09)	0.85 (0.65–1.11)
18.5–22.9	201,620.6	846	4.2	1.00 (reference)	1.00 (reference)	1.00 (reference)
23.0–24.9	98,611.8	587	6.0	1.04 (0.93–1.16)	1.03 (0.93–1.16)	1.01 (0.90–1.13)
25.0–29.9	105,975.2	687	6.5	1.09 (0.98–1.22)	1.07 (0.96–1.20)	1.03 (0.91–1.15)
≥30.0	13,452.7	100	7.4	1.48 (1.20–1.82)	1.48 (1.20–1.83)	1.36 (1.08–1.71)
P_{trend}				0.001	0.003	0.099

[a]Estimated from parametric proportional hazards models. Multivariable model 1 was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, educational level, total calorie intake, history of *H. pylori*, history of diabetes, and history of hypertension. Model 2: model 1 plus adjustment for total cholesterol, triglycerides, glucose, and HOMA-IR (homeostasis model assessment of insulin resistance).

(no HEPA vs. HEPA), hsCRP level (<1.0 mg/L vs. ≥1.0 mg/L), HOMA-IR (<2.5 vs. ≥ 2.5), or exam payee (company-paid vs. individual-paid).

We also performed analyses to assess the association between BMI category and risk of atrophic gastritis as a secondary endpoint (Fig. 3; Supplementary Table S1). During 400,463.3 person-years of follow-up, 38,014 participants developed incident atrophic gastritis (incidence rate, 94.9 per 1,000 person-years). Risk of atrophic gastritis increased as baseline BMI category increased (P_{trend} < 0.001). The multivariable-adjusted HR (95% CI) for endoscopic atrophic gastritis comparing BMIs <18.5, 23–24.9, 25–29.9, and >30 with BMI of 18.5–22.9 kg/m^2 were 0.96 (0.91–1.01), 1.09 (1.06–1.12), 1.15 (1.12–1.18), and 1.13 (1.07–1.20), respectively (model 1, $P_{trend} = 0.001$). Adjustment for fasting total cholesterol, triglycerides, glucose, and HOMA-IR slightly attenuated the associations, but they remained statistically significant (model 2).

Discussion

In this large cohort study of young and middle-aged Korean adults who were followed with upper endoscopy, obesity was associated with higher risk of incident atrophic gastritis and intestinal metaplasia, with risk increasing as BMI category increased. This association persisted even after adjusting for possible confounders and obesity-associated metabolic factors, indicating that the excess adiposity on its own affects the risk of atrophic gastritis and intestinal metaplasia, a precursor lesion of stomach cancer.

Although obesity is suspected as a risk factor for gastric cancer, the effects of intragastric subsite and its carcinogenic mechanisms remain controversial (11, 14–18, 20). A meta-analysis by Yang and colleagues showed that excess body weight was associated with increased risk of overall gastric cancer, but this association was evident in only cardia gastric cancer (14). In another meta-analysis, obesity was associated with increased risk of overall gastric cancer, whereas overweight and obesity were positively associated with risk of cardia gastric cancer (19). Indeed, epidemiologic studies consistently report that increased BMI increases risk of cardia cancer development (40, 41). On the other hand, the relationship between obesity and noncardia gastric cancer remains controversial. A recent cohort study of 1,087,358 Israeli Jewish males and 707,212 Israeli Jewish females with a median follow-up of 23 years demonstrated that obesity in adolescence was positively associated with increased risk of noncardia gastric cancer, suggesting that prolonged exposure to obesity plays a role in the pathogenesis of gastric cancer (42). Although atrophic gastritis and intestinal metaplasia are obvious precancerous lesions for gastric cancer, few studies to address the association between obesity and precancerous lesions provide conflicting

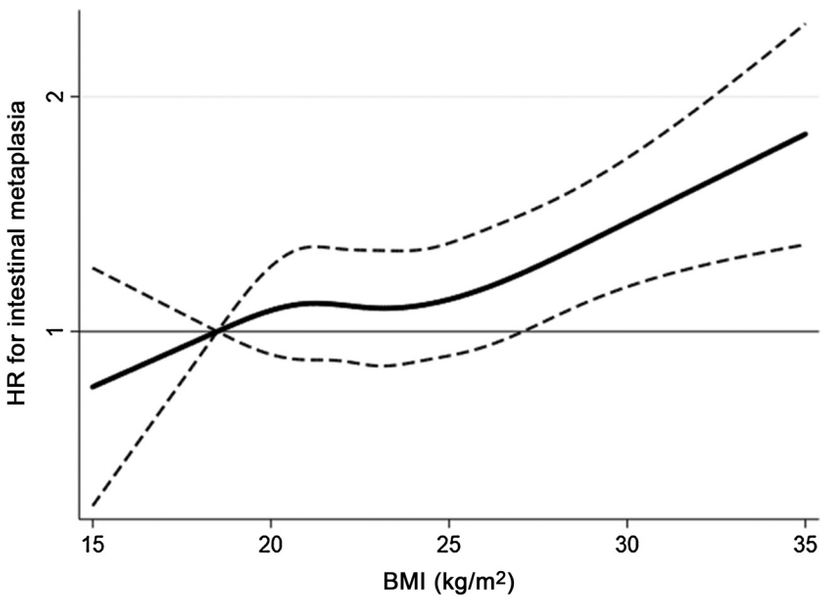

Figure 2.
Multivariable-adjusted HRs for intestinal metaplasia. Curves represent adjusted HRs for intestinal metaplasia based on restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of BMI distribution. Models were adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, educational level, total calorie intake, history of *H. pylori*, history of diabetes, and history of hypertension.

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Table 3. HRs[a] (95% CI) of incident intestinal metaplasia by BMI category in clinically relevant subgroups

	BMI Category (kg/m^2)						
Subgroup	**<18.5**	**18.5–22.9**	**23.0–24.9**	**25.0–29.9**	**≥30**	P_{trend}	$P_{interaction}$
Age							0.005
<40 years (n = 98,532)	0.93 (0.87–1.00)	Reference	1.14 (1.09–1.19)	1.22 (1.17–1.27)	1.16 (1.07–1.26)	<0.001	
≥40 years (n = 44,300)	0.90 (0.82–0.98)	Reference	1.10 (1.06–1.14)	1.12 (1.08–1.16)	1.01 (0.93–1.10)	<0.001	
Sex							0.176
Female (n = 62,365)	0.94 (0.88–1.00)	Reference	1.10 (1.05–1.15)	1.18 (1.12–1.24)	1.18 (1.04–1.34)	<0.001	
Male (n = 80,467)	1.07 (0.95–1.21)	Reference	1.08 (1.05–1.12)	1.14 (1.10–1.17)	1.12 (1.04–1.20)	<0.001	
Current smoking							0.232
No (n = 98,609)	0.96 (0.90–1.02)	Reference	1.09 (1.05–1.13)	1.15 (1.11–1.19)	1.13 (1.05–1.23)	<0.001	
Yes (n = 29,738)	1.03 (0.87–1.22)	Reference	1.06 (1.00–1.12)	1.08 (1.03–1.14)	1.08 (0.98–1.20)	0.044	
Alcohol intake							0.028
<20 g/day (n = 104,989)	0.95 (0.90–1.01)	Reference	1.11 (1.08–1.15)	1.17 (1.13–1.21)	1.17 (1.08–1.26)	<0.001	
≥20 g/day (n = 29,613)	0.98 (0.82–1.17)	Reference	1.03 (0.98–1.09)	1.07 (1.02–1.13)	1.03 (0.93–1.15)	0.062	
HEPA							0.539
No (n = 118,790)	0.95 (0.90–1.01)	Reference	1.10 (1.06–1.13)	1.15 (1.11–1.18)	1.13 (1.06–1.21)	<0.001	
Yes (n = 21,275)	1.02 (0.87–1.20)	Reference	1.05 (0.99–1.12)	1.16 (1.09–1.23)	1.12 (0.97–1.30)	<0.001	
HOMA-IR							0.725
<2.5 (n = 129,671)	0.96 (0.91–1.01)	Reference	1.09 (1.06–1.12)	1.14 (1.10–1.17)	1.14 (1.05–1.25)	<0.001	
≥2.5 (n = 13,161)	0.74 (0.33–1.67)	Reference	1.05 (0.92–1.20)	1.12 (1.00–1.25)	1.04 (0.92–1.19)	0.157	
hsCRP							0.532
<1.0 mg/L (n = 96,007)	0.95 (0.90–1.01)	Reference	1.10 (1.06–1.13)	1.15 (1.11–1.19)	1.08 (0.97–1.20)	<0.001	
≥1.0 mg/L (n = 27,187)	1.01 (0.83–1.24)	Reference	1.09 (1.02–1.16)	1.19 (1.12–1.26)	1.17 (1.07–1.28)	<0.001	
Company-paid exam							0.897
No (n = 5,841)	1.33 (0.48–3.72)	Reference	1.12 (0.71–1.75)	1.16 (0.74–1.82)	1.19 (0.37–3.85)	0.075	
Yes (n = 136,990)	0.82 (0.62–1.08)	Reference	1.03 (0.92–1.15)	1.07 (0.95–1.19)	1.49 (1.20–1.85)	0.061	

[a]Estimated from parametric Cox models. Multivariable model was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, educational level, total calorie intake, history of *H. pylori*, history of diabetes, and history of hypertension.

results (22–27). In a cross-sectional study of 10,197 subjects participating in a Japanese mass gastric cancer screening, BMI was inversely associated with atrophic gastritis based on pepsinogen (PG) I to II ratio (22). Another cross-sectional study of 617 Japanese individuals showed lower BMI in the atrophic gastritis–positive group ascertained by the PG I and PG I/II ratio than in the atrophic gastritis–negative group (23). A cross-sectional study of 217 patients demonstrated an inverse association between BMI and biopsy-proven intestinal metaplasia (24). On the other hand, a cross-sectional study of 2,997 Korean patients who underwent gastroscopy reported that multivariable adjusted ORs (95% CI) for the presence of intestinal metaplasia comparing overweight, obesity, and severe obesity to normal weight were 2.25 (1.5–3.37), 2.32 (1.58–3.42),and 4.86 (2.04–11.5), respectively, among men, whereas corresponding ORs (95% CI) were 2.66 (1.29–5.47), 4.46 (2.28–8.75), and 9.57 (95% CI, 3.26–28.12), among women (25). In the same study, there was no significant association between BMI and atrophic gastritis (25). In another large-scale retrospective study of 60,261 Korean adults, obesity was significantly associated with endoscopically diagnosed precancerous lesions including atrophic gastritis and intestinal metaplasia, with a multivariable adjusted OR (95% CI) of 1.10

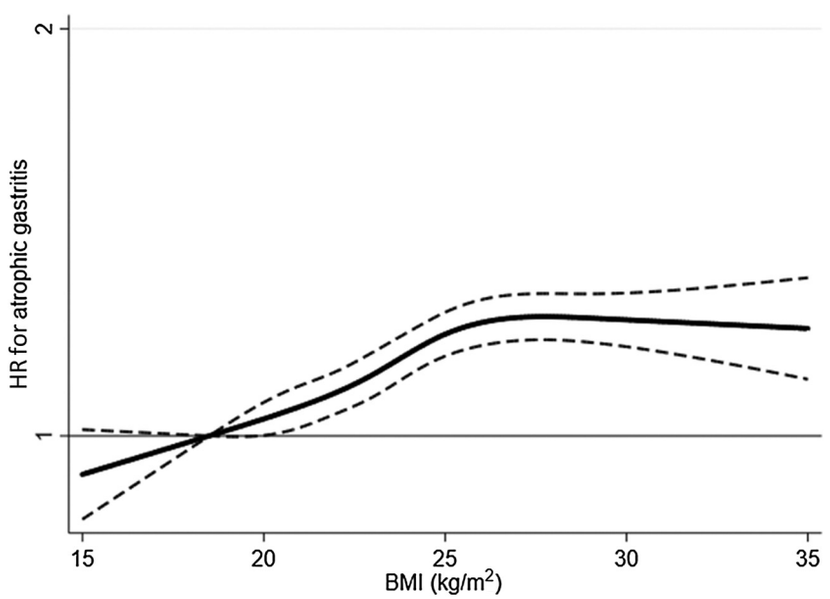

Figure 3.
Multivariable-adjusted HRs for atrophic gastritis. Curves represent adjusted HRs for atrophic gastritis based on restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of BMI distribution. Models were adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, educational level, total calorie intake, history of *H. pylori*, history of diabetes, and history of hypertension.

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(1.01–1.18; ref. 26). However, these previous studies are all cross-sectional studies limited by the temporal ambiguity between obesity and atrophic gastritis and intestinal metaplasia. This is important given that atrophic gastritis and intestinal metaplasia can affect nutritional absorption, possibly lowering the BMI. In the present large-scale cohort study of 142,832 Korean men and women in a regular health screening setting, obesity was independently associated with an increased risk of new-onset atrophic gastritis and intestinal metaplasia in a dose-response manner. Differential detection by BMI category might be another consideration in interpretation of our findings: for example, obese individuals may be less likely to undergo tests, or conversely more likely to be tested and found to have atrophic gastritis or intestinal metaplasia. In our study, the median frequency (interquartile) of follow-up endoscopy was similar across BMI categories: 3 (2–3) in BMI category <18.5 and 3 (2–4) in all other BMI categories; thus, differential detection in relation to BMI categories is unlikely.

The strengths of our study are not only the large sample size, but also the prospective cohort study design, which eliminates reverse causation and recall bias. Importantly, baseline and occurrence of atrophic gastritis and intestinal metaplasia were confirmed on the basis of baseline and subsequent follow-up gastroduodenal endoscopy during annual or biennial health check-up examinations. Our study population is a relatively young (mean age 38.8 years) and healthy group that attended health screening exams; thus, our findings are less likely to be affected by biases related to comorbidities compared with prior studies in higher risk populations.

The exact mechanisms underlying an association between obesity and intestinal metaplasia are not fully understood. One possible explanation is mediation by obesity-related metabolic disturbances (43). However, in our study, even after adjustment for metabolic parameters including total cholesterol, triglycerides, glucose, and HOMA-IR, the association between increased BMI and new-onset intestinal metaplasia remained significant, indicating that obesity-associated metabolic abnormalities could not fully explain the relationship. Indeed, adipose tissue is a highly active endocrine organ and an important source of adipokines, the biologically active substances with local and/or systemic action. Dysfunctional adipose tissue in obesity can lead to disturbed profiles of adipokines with elevated levels of proinflammatory cytokines (44, 45). Leptin was initially thought to be expressed exclusively in and secreted by adipocytes, but leptin and leptin receptors are also expressed in human gastric mucosa (46). A recent study with mice revealed that obesity can induce intestinal metaplasia and atrophic gastritis through activation of the leptin signaling pathway (47). However, there is debate on how leptin is secreted when *H. pylori* gastritis progresses. Jun and colleagues reported that leptin production was increased by *H. pylori*, whereas Roper and colleagues reported that leptin decreased because of gastric mucosal change, including changes in intestinal metaplasia and atrophic gastritis (48, 49). The chronically elevated levels of TNFα, IL6, and IL1 seen in obesity may be involved in the pathogenesis of intestinal metaplasia with increased mitogenic and antiapoptotic effects (45). In addition to mechanisms involving inflammatory substances and adipokines, the immune system–mediated mechanism has also been suggested. One study using *Helicobacter*-infected mice reported that obesity significantly increased the severity of inflammation, epithelial defects, and metaplasia and dysplasia in the stomach, suggesting that obesity can accelerate *Helicobacter*-mediated gastric carcinogenesis (50). That study found that obesity can affect gastric mucosal change, not only by the activation of STAT3 pathways, but also by enhancing immature myeloid cell recruitment and T_H17-associated responses (50). Future studies are required to elucidate the mechanism of obesity involvement in gastric cancer development.

In this study, a positive association between BMI and incident intestinal metaplasia was more evident in the individuals younger than 40 years old compared with the older age group. This suggests that BMI may be a more important contributor to development of intestinal metaplasia in young Koreans. It is presumed that the effect of BMI on incident intestinal metaplasia is lessened in individuals over the age of 40 years because not only do the prevalence of stomach cancer and its precancerous lesions increase with age, but also the possibly because accumulative exposure to environmental risk factors increases with age. A stronger association between BMI and incident intestinal metaplasia was also observed in those with low alcohol intake (<20 g of alcohol per day) compared with those with higher alcohol intake (≥20 g of alcohol per day). Heavy alcohol consumption (between 4 and 6 drinks/day) itself has been associated with increased risk of gastric cancer, but there is still controversy surrounding this (51, 52). Alcohol drinkers may be more likely to partake in other unhealthy behaviors, which were not measured in our study: thus, the relative contribution of BMI to incident intestinal metaplasia might be weak in those with higher alcohol intake. Because of the use of multiple comparisons, chance might be another possible explanation for the observed difference across subgroups.

We note that there are also some limitations of this study. First, the diagnosis of atrophic gastritis and intestinal metaplasia was made only by endoscopic findings without histologic confirmation. In our study, the information on concordance between endoscopy and histology was not available; although a few studies have reported acceptable agreement between endoscopic and histologic diagnoses of atrophic gastritis and intestinal metaplasia, and also that endoscopically diagnosed atrophic gastritis and/or intestinal metaplasia were significantly associated with gastric cancer (53–56). In addition, a reliability test among doctors who performed gastroduodenal endoscopy was not performed. Different gastroenterologists were involved in endoscopy over time; however, they were unaware of the study aims. If the degree of misclassification does not differ by exposure status, this type of error was likely nondifferential, resulting in the underestimation of the association between BMI and incident atrophic gastritis/intestinal metaplasia seen in this study. Second, information on the extent and intragastric distribution of intestinal metaplasia, or histologic subtype of intestinal metaplasia including complete or incomplete intestinal metaplasia were not available, although relative risks of gastric cancer were reported to be from 4- to 11-fold higher in the presence of incomplete type in comparison with complete type or in comparison with the absence of incomplete type, supporting the utility of subtyping intestinal metaplasia as a predictor of gastric cancer risk (57). Further studies to address gastric mucosal change by obesity are needed on the basis of intragastric locations and detailed histologic features including the subtypes of intestinal metaplasia. Third, we used BMI as a measure of obesity, but BMI can be of limited use for distinguishing fat tissue from lean tissue. Fourth, even though *H. pylori* is an important risk factor for atrophic

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gastritis, intestinal metaplasia, and gastric cancer, we were able to use self-reported history of *H. pylori* infection without detailed history of *H. pylori* eradication or other measures such as serum *H. pylori*--specific IgG or histologic confirmation. Because *H. pylori* infection status was evaluated histologically only when it was indicated, such as in the case of peptic ulcer disease, at the discretion of the endoscopist based on Korean guidelines (38), only a small proportion of participants had information on endoscopy-assessed H. pylori status; thus, we could not incorporate this information into the analysis. However, we were able to use endoscopic information on the presence of atrophic gastritis and intestinal metaplasia at baseline and follow-up in all participants. We found a consistent association of BMI category with both atrophic gastritis and intestinal metaplasia. Fifth, salt intake and chronic bile reflux are considered potential confounders (51, 58, 59), but that information was not available in this study and might have resulted in some degree of residual confounding. Finally, the subjects included in this study consisted of young and middle-aged Koreans in an endemic area of *H. pylori*; thus, generalizability of our findings may be limited in other age groups, populations with a higher prevalence of comorbidities, or other race/ethnicity groups.

In this large-scale cohort study of young and middle-aged Korean men and women, obesity was positively associated with an increased risk of new-onset atrophic gastritis and intestinal metaplasia, and this association was independent of obesity-related metabolic abnormalities. Our study suggests that excessive adiposity *per se* plays a role in the pathogenesis of atrophic gastritis and intestinal metaplasia, a precursor lesion of gastric cancer. Future studies are needed to determine whether strategies to reduce obesity will also help reduce the precancerous lesions and, in turn, gastric cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: Y. Chang, S. Ryu
Development of methodology: Y. Chang, S. Ryu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Chang, H.-J. Yang, J.Y. Jung, S. Kim, C.I. Sohn, S. Ryu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.-J. Yang, S. Ryu
Writing, review, and/or revision of the manuscript: K. Kim, Y. Chang, H.-J. Yang, S. Ryu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Chang, J. Ahn, J.Y. Jung, S. Kim, S. Ryu
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