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Gastroesophageal Reflux Does Not Alter Effects of Body Mass Index on Risk of Esophageal Adenocarcinoma

Short Title: BMI, reflux and esophageal adenocarcinoma

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Abbreviations: EAC = esophageal adenocarcinoma; JAC = gastroesophageal junctional adenocarcinoma; BMI = body mass index; OR = odds ratio; CI = confidence interval;

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Abstract

Background & Aims: A history of high body mass index (BMI) is strongly associated with risk of esophageal adenocarcinoma (EAC). We investigated whether gastroesophageal reflux is involved in this association.

Methods: We analyzed data from a population-based Swedish nationwide study of patients with a new diagnosis of EAC (n=189) or gastroesophageal junction adenocarcinoma (n= 262), and matched controls (n=816), from 1995 through 1997. Our analysis included data on BMI 20 y before study inclusion; maximum adult BMI; frequency, severity and duration of gastroesophageal reflux symptoms; tumor features; and covariates (sex, age, smoking, alcohol, fruit and vegetables intake, and socio-economic status). We conducted stratified analyses and synergy tests, adjusting for covariates.

Results: Odds ratios (ORs) for EAC among subjects with BMI ≥25 20 y before inclusion, compared with those with BMI <25, did not differ significantly, without or with adjustment for gastroesophageal reflux frequency (OR, 3.1; 95% confidence interval [CI], 2.2–4.4 and OR, 3.3; 95% CI, 2.2–4.8), severity (OR, 3.3; 95% CI, 2.2–4.8), or duration (OR, 3.2; 95% CI, 2.2–4.7). However, there were strong interactions and synergisms between BMI and gastroesophageal reflux categories. BMI appeared to have the largest effect on gastroesophageal reflux frequency (synergy index 8.9; 95% CI, 2.3–34.1 for maximum BMI and gastroesophageal reflux >3 times weekly).

Conclusions: Based on a population-based study, the association between BMI and EAC does not appear to be affected by symptomatic gastroesophageal reflux, although BMI and reflux act synergistically.

Keywords: Obesity; overweight; reflux symptoms; synergism.

Introduction

Among all obesity-related cancers, esophageal adenocarcinoma (EAC) has the strongest known association with body mass index (BMI),[1, 2] and the association is linear.[3-5] There are several potential mechanisms behind the overall increased risk of developing cancer among overweight persons,[6] but the particularly strong association with EAC indicates the presence of a more organ-specific mechanism being involved. The most obvious explanation would be that overweight, through an increased intra-abdominal pressure due to visceral adiposity, facilitates gastroesophageal reflux which in turn causes Barrett's esophagus and EAC.[7] This postulated carcinogenic pathway is supported by the dose-dependent association between BMI and gastroesophageal reflux,[8, 9] and by studies showing that abdominal and visceral adiposity, facilitating gastroesophageal reflux, are stronger risk factors for EAC than BMI alone.[10] Existing epidemiological studies have consistently found that, with mutual control, overweight and gastroesophageal reflux symptoms are independent risk factors for EAC.[2-5, 11, 12] The degree to which gastroesophageal reflux mediates the body mass-EAC association deserves more in-depth studies.[13] We have previously studied the role of both BMI and gastroesophageal reflux in the etiology of EAC and gastroesophageal junctional adenocarcinoma (JAC) in a nationwide Swedish case-control study,[3, 7] but we did not conduct any in-depth analyses of how various levels BMI and gastroesophageal reflux interact in the development of EAC. An Australian study addressed combined effects of BMI, gastroesophageal reflux and tobacco smoking on the risk of EAC and found that adjustment for gastroesophageal reflux only modestly attenuated the association between BMI and EAC.[11] To further explore whether the strong association between BMI and EAC, we hypothesized that the effect of BMI is modified by gastroesophageal reflux at certain levels of frequency, severity or duration.

Methods

Design

The organization and design of our Swedish population-based case-control study has been described in detail elsewhere.[7] In brief, the study base consisted of all Swedish-born residents aged between 40 and 80 years in 1995 through 1997. Cases were all those newly diagnosed with EAC or JAC during this period. All 195 hospital departments involved in the diagnosis or management of these patients in Sweden collaborated in the recruitment of patients. Controls were randomly selected from the Swedish Register of the Total Population and were frequency matched for age and sex of the EAC case patients. Exposure information was obtained through personal interviews with all study participants. The interviews were conducted by professional interviewers employed by Statistics Sweden. The interviewers were trained to treat the cases and control in equal manner. The tumor classification was rigorous and uniform, which allowed us to distinguish between adenocarcinomas of the esophagus and those of the gastroesophageal junction (tumors within 2 cm above and 3 cm below the junction). All histological specimens were later re-examined by one experienced pathologist to make the classification more uniform for study purposes.

Exposure variables and covariates

Body mass index

BMI was calculated as the weight in kilograms divided by the square of body height in meters (kg/m^2). Data on weight and height 20 years prior to interview as well as maximum adult weight was retrospectively collected during the interviews. Normal weight was defined as BMI <25, overweight as 25≤BMI<30, obesity as 30≤BMI<35, and severe obesity as BMI

≥35. In some analyses, categories for overweight, obesity and severe obesity were combined into one category ("overweight/obese" – BMI ≥25).

Gastroesophageal reflux symptoms

Gastroesophageal reflux symptoms were defined as the presence of heartburn or regurgitation at least weekly during at least 6 months, occurring at least 5 years prior to interview. This definition is well in line with the current definition of gastroesophageal reflux disease.[14] Information about frequency and duration of reflux was collected through interview questions with open answers and categorized prior to the initiation of the analyses. We devised a severity score based on 1) symptom characteristics (heartburn only = 1 point, regurgitation only = 1 point, both heartburn and regurgitation = 1.5 points), 2) nightly reflux symptoms (= 2 points), and 3) frequency of symptoms, (once per week = 0 points, 2–6 times per week = 1 point, 7–15 times per week = 2 points, and >15 times per week = 3 points).

Covariates

Six potential confounding variables were evaluated: sex and age, along with tobacco smoking, alcohol consumption, dietary intake of fruit and vegetables, and socio-economic status. These covariates were selected because they have been found to have confounding effects in previous analyses of our case-control study.[3, 7, 15-17]

Statistical analysis

Unconditional logistic regression (frequency matching) was used to calculate odds ratios (OR) with 95 % confidence intervals (95% CI) for various aspects of body mass and reflux symptoms in relation to EAC and JAC. We fitted separate models of BMI in relation to the cancer outcomes including and not including reflux symptoms as covariate. Furthermore, evaluation of effect measure modification was performed using stratification to investigate if the association between each single exposure and EAC or JAC varied over strata of a second variable. This was performed both for BMI as the exposure with reflux symptoms as the stratification variable and for reflux symptoms stratified by BMI. Synergy index (S) was used to test additive interaction of the combined effect of BMI and reflux symptoms.[18] Interaction is present if there is departure from the additivity scale S≠1. All models were adjusted for sex (men, women), age (in 5-year classes), tobacco smoking status (never, previous, or current user of any type of tobacco, as assessed 2 years prior to inclusion), alcohol consumption (0, 1-15, 16-70, or >70 grams per week), dietary intake of fruit and vegetables (low, intermediate or high), and educational level (0-6 years, 7-10 years, or >10 years of formal education). Four controls of 820 were excluded due to missing values on the BMI variables. All data management and analysis was carried out by using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Participants

Included were 189 patients with EAC, 262 patients with JAC, constituting 87% and 83%, respectively, of all eligible incident cases that occurred within the study base. The 816 control subjects constituted 75% of all subjects who had been originally selected. Some characteristics of the participants are presented in Table 1. Presence of overweight and reflux was highest in cases of EAC, followed by cases of JAC, and lowest in the control participants. Use of tobacco and alcohol was highest in JAC patients, slightly lower in cases of EAC, and lowest among controls. A highest attained educational level of >10 years was most common among control participants and least common among EAC cases (Table 1).

Mutually adjusted associations

The crude ORs were generally similar to the multivariably adjusted ORs. Therefore, only the adjusted ORs are presented. The associations between BMI 20 years before inclusion and risk of EAC were similarly strong without (OR 3.1, 95% CI 2.2-4.4) and with adjustment for gastroesophageal reflux frequency (OR 3.3, 95% CI 2.2-4.8), severity (OR 3.3, 95% CI 2.2-4.8) or duration (OR 3.2, 95% CI 2.2-4.7). The same pattern was found for maximum BMI and for risk of JAC, i.e. the risk estimates were not attenuated after adjustment for gastroesophageal reflux variables (Table 2). Similarly, when gastroesophageal reflux frequency, severity and duration were analyzed in relation to risk of EAC and JAC the adjustment for BMI variables did not attenuate the results (Table 2). When, for example, comparing gastroesophageal reflux severity score >4 with 0, the risk of EAC was of similar strength without and with adjustment for BMI 20 years before inclusion (OR 18.0, 95% CI

10.9-29.6 and OR 19.2, 95% CI 11.4-32.3, respectively). The analyses were repeated for more categories of BMI, and although hampered by low statistical precision, the patterns were similar to those reported above (data not shown).

Stratified analyses

Tables 3 and 4 present stratified analyses in various combinations of BMI and gastroesophageal reflux variables. The relative risk estimates for gastroesophageal reflux frequency, severity and duration were similar among participants with BMI ≥25 and <25 (20 years before interview) (Table 3), the only exception being a lower point estimate for gastroesophageal reflux with a duration over 20 years among individuals with BMI ≥25 (OR 9.3, 95% CI 3.8-23.0) than among those with BMI <25 (OR 24.4, 95% CI 10.8-55.3). When analyses were stratified according to the maximum BMI in adult life, point estimates for the highest category of each gastroesophageal reflux variable suggested higher relative risks of EAC and JAC among participants with maximum BMI ≥25, but the precision was poor and the differences were not statistically significant (Table 3). In Table 4, the BMI categories <25 and ≥25 were compared in various levels of gastroesophageal reflux frequency, severity and duration. The risk estimates of EAC increased with a higher frequency and severity of gastroesophageal reflux in participant with BMI ≥25 compared to normal BMI, but no such pattern was seen for gastroesophageal reflux duration. Poor precision also limited analyses of the association between BMI and risk of EAC and JAC, stratified by gastroesophageal reflux status (Table 4), but by and large the risk gradient tended to be steeper in the strata with the highest gastroesophageal reflux frequency, severity and duration.

Synergy analysis

There were mostly strong and statistically significant synergisms between BMI and gastroesophageal reflux, particularly gastroesophageal reflux frequency, in their association with EAC. Synergy indexes typically ranged between 2 and 4 (Table 5), but the strongest one (8.9, 95% CI 2.3-34.1) was between maximum adult BMI (<25 versus ≥25) and gastroesophageal reflux frequency dichotomized into ≤3 versus > 3 gastroesophageal reflux episodes per week. The synergisms tended to be somewhat weaker when JAC was the outcome, and none of these synergy indexes attained statistical significance.

Discussion

This study did not reveal any evidence in support of the hypothesis that gastroesophageal reflux is a mediator of the association between BMI and risk of EAC or JAC. We found suggestive evidence of additive interactions and synergisms between these two exposures in relation to risk of these tumors, and when EAC was the outcome, the evidence of synergisms was convincing.

Strengths of the study include the population-based design with rapid case ascertainment and high participation rates, thorough tumor characterization, personal interviews with all study participants, the detailed information about the study exposures and covariates, and the ability to adjust the results for confounding by other known risk factors. Among limitations is the risk of misclassification of the exposures, which might be different in cases and controls, i.e. recall bias. Separate analyses were, however, conducted also among 167 cases of squamous cell carcinoma of the esophagus, and no associations were found between BMI, gastroesophageal reflux or any combinations of these two study exposures and risk of this cancer (data not shown). This finding might argue against strong influence of recall bias, since such bias would be expected in these patients as well, but recall bias can nevertheless not be ruled out. Finally, the statistical power was limited, particularly in sub-group analyses, leaving a risk of chance findings.

The additive effect was seemingly more pronounced for maximum BMI than BMI 20 years before interview. This might be due to the higher level of BMI in the former variable, or that the gastroesophageal reflux co-exists more often in the latter variable. There was a lack of additive interaction (S=1.1) when gastroesophageal reflux duration and BMI 20 years before interview were analysed, i.e. when the exposures were obviously present at the same time.

The association between BMI and EAC is stronger than that of any other obesity-related cancer.[1, 2] Since BMI is a dose-dependent risk factor for gastroesophageal reflux,[8, 9] and gastroesophageal reflux is a strong and organ-specific risk factor for EAC,[7, 19] there are good reasons to believe that the association between BMI and EAC is mediated by gastroesophageal reflux. However, most previous epidemiological studies have reported a similar strength in the association between BMI and EAC in individuals with and without gastroesophageal reflux symptoms.[2-5, 11, 20] A population-based case-control study from Australia found similar patterns regarding gastroesophageal reflux combined with BMI, but that study did not include analyses of how higher levels of frequency, severity or duration of gastroesophageal reflux symptoms influenced the results.[11] The lack of evidence from previous research together with the present in-depth analysis of this issue argues against the hypothesis that the association between obesity and EAC is mediated only by gastroesophageal reflux. Perhaps asymptomatic gastroesophageal reflux could play a role, since 40% of the cases EAC do not report gastroesophageal reflux symptoms,[7] while most of them likely have Barrett´s esophagus.[21] There is, however, some empiric evidence in support of a high frequency of asymptomatic gastroesophageal reflux in obese individuals.[4, 22] Nevertheless, there is a need to also consider other organ-specific mechanisms that might explain the overweight-EAC association, e.g., a prolonged esophageal emptying,[4] a divergent microflora,[23] and an increased consumption of food in general in obese individuals might result in an increased esophageal exposure to carcinogenic dietary factors.

In conclusion, this carefully conducted population-based study found no support for the hypothesis that the association between BMI and EAC is importantly mediated by symptomatic gastroesophageal reflux. Other organ-specific mechanisms explaining why the association between BMI and EAC is stronger than that of any other cancer deserve attention.

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Table 1. Characteristics of control participants and cases of esophageal adenocarcinoma (EAC) and gastroesophageal junctional adenocarcinoma (JAC).

	Controls	EAC	JAC
Characteristic	**Number (%)**	**Number (%)**	**Number (%)**
Sex			
Men	676 (83)	165 (87)	223 (85)
Women	140 (17)	24 (13)	39 (15)
Age (years)			
<54	128 (16)	23 (12)	53 (20)
55-59	80 (10)	15 (8)	22 (8)
60-64	106 (13)	25 (13)	36 (14)
65-69	139 (17)	36 (19)	48 (18)
70-74	180 (22)	52 (28)	62 (24)
75-79	183 (22)	38 (20)	41 (16)
BMI 20 years before interview			
<25	573 (70)	78 (41)	147 (56)
≥25	243 (30)	111 (59)	115 (44)
BMI maximum as adult			
<25	300 (37)	32 (17)	70 (27)
≥25	516 (63)	157 (83)	192 (73)
Reflux frequency (times per week)			
<1	681 (83)	76 (40)	187 (71)
1-3	109 (13)	72 (38)	57 (22)
>3	26 (3)	41 (22)	18 (7)
Reflux severity (score)			
0	681 (83)	76 (40)	187 (71)
1-4	101 (12)	49 (26)	48 (18)
>4	34 (4)	64 (34)	27 (10)
Reflux duration (years)			
0	681 (83)	76 (40)	187 (71)
1-20	108 (13)	73 (39)	53 (20)
>20	27 (3)	40 (21)	22 (8)
Tobacco smoking status			
Never	323 (40)	57 (30)	43 (16)
Previous	313 (38)	89 (47)	124 (47)
Current	180 (22)	43 (23)	95 (36)
Alcohol use (grams of ethanol per week)			
0	131 (16)	41 (22)	34 (13)
1-15	219 (27)	54 (29)	73 (28)
16-70	289 (35)	51 (27)	79 (30)
>70	177 (22)	43 (23)	76 (29)
Intake of fruit and vegetables			
Low	215 (26)	69 (37)	97 (37)
Intermediate	325 (40)	69 (37)	98 (37)
High	276 (34)	51 (27)	67 (26)

Educational level (years)			
0-6	180 (22)	48 (25)	43 (16)
7-10	317 (39)	94 (50)	126 (48)
>10	319 (39)	47 (25)	93 (35)

Table 2. Risk of esophageal adenocarcinoma and junctional adenocarcinoma, expressed as odds ratio (OR) with 95% confidence intervals (CI) in various categories of body mass index (BMI) and gastroesophageal reflux symptoms with and without mutual adjustments.

	Esophageal adenocarcinoma	Junctional adenocarcinoma
Variable	**OR (95% CI)**	**OR (95% CI)**
BMI 20 years before interview		
≥25 vs. <25*	3.1 (2.2-4.4)	2.0 (1.5-2.7)
≥25 vs. <25, adjusted for reflux frequency +*	3.3 (2.2-4.8)	2.0 (1.5-2.7)
≥25 vs. <25, adjusted for reflux severity +*	3.3 (2.2-4.8)	2.0 (1.4-2.7)
≥25 vs. <25, adjusted for reflux duration +*	3.2 (2.2-4.7)	2.0 (1.5-2.7)
BMI maximum as adult		
≥25 vs. <25	2.6 (1.7-3.9)	1.6 (1.2-2.2)
≥25 vs. <25, adjusted for reflux frequency +*	2.6 (1.7-4.1)	1.6 (1.1-2.2)
≥25 vs. <25, adjusted for reflux severity +*	2.6 (1.7-4.1)	1.6 (1.1-2.2)
≥25 vs. <25, adjusted for reflux duration +*	2.7 (1.7-4.2)	1.6 (1.1-2.2)
Reflux frequency (per week)		
1-3 vs. <1	6.2 (4.2-9.2)	2.0 (1.3-2.9)
1-3 vs. <1, adjusted for BMI 20 years ago +*	6.0 (4.0-9.0)	1.9 (1.3-2.8)
1-3 vs. <1, adjusted for maximum BMI +*	6.2 (4.1-9.3)	1.9 (1.3-2.8)
>3 vs. <1	14.4 (8.2-25.5)	2.3 (1.2-4.5)
>3 vs. <1, adjusted for BMI 20 years ago +*	16.3 (9.0-29.5)	2.4 (1.2-4.6)
>3 vs. <1, adjusted for maximum BMI +*	14.7 (8.2-26.2)	2.4 (1.2-4.6)
Reflux severity (score)		
1-4 vs. 0	4.4 (2.9-6.8)	1.8 (1.2-2.7)
1-4 vs. 0, adjusted for BMI 20 years ago +*	4.3 (2.8-6.7)	1.8 (1.2-2.7)
1-4 vs. 0, adjusted for maximum BMI +*	4.4 (2.9-6.9)	1.8 (1.2-2.6)
>4 vs. 0	18.0 (10.9-29.6)	2.8 (1.6-4.9)
>4 vs. 0, adjusted for BMI 20 years ago +*	19.2 (11.4-32.3)	2.7 (1.5-4.8)
>4 vs. 0, adjusted for maximum BMI +*	18.1 (10.9-30.2)	2.7 (1.6-4.8)
Reflux duration (years)		
1-20 vs. 0	6.2 (4.2-9.3)	1.7 (1.2-2.6)
1-20 vs. 0, adjusted for BMI 20 years ago +*	6.1 (4.0-9.1)	1.7 (1.2-2.5)
1-20 vs. 0, adjusted for maximum BMI +*	6.1 (4.1-9.2)	1.7 (1.2-2.5)
>20 vs. 0	14.2 (8.0-25.1)	3.4 (1.8-6.4)
>20 vs. 0, adjusted for BMI 20 years ago +*	15.8 (8.7-28.7)	3.4 (1.8-6.5)
>20 vs. 0, adjusted for maximum BMI +*	15.3 (8.5-27.5)	3.4 (1.8-6.5)

* Adjusted for sex, age, tobacco smoking, alcohol use, intake of fruit and vegetables, and educational level.

Table 3. Association between gastroesophageal reflux symptoms and esophageal or junctional adenocarcinoma stratified by body mass index (BMI), expressed as odds ratio (OR) with 95% confidence intervals (CI).

	Esophageal adenocarcinoma		Junctional adenocarcinoma	
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
	BMI 20 years before interview			
	BMI<25	BMI≥25	BMI<25	BMI≥25
Reflux frequency (per week)				
<1	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-3	6.7 (3.6-12.3)	5.4 (3.0-9.5)	2.3 (1.4- 3.8)	1.7 (0.9-3.2)
>3	17.6 (7.9-38.8)	17.9 (6.2-51.7)	2.0 (0.8- 4.7)	3.3 (1.0-11.0)
Reflux severity (score)				
0	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-4	4.5 (2.3- 8.8)	4.1 (2.2-7.7)	2.1 (1.3- 3.6)	1.5 (0.8-3.0)
>4	22.3 (10.9-45.8)	18.1 (7.7-42.4)	2.4 (1.1- 5.2)	3.2 (1.3-8.0)
Reflux duration (years)				
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-20	5.8 (3.1-10.8)	6.3 (3.5-11.2)	1.7 (1.0- 2.9)	1.8 (0.9-3.4)
>20	24.4 (10.8-55.3)	9.3 (3.8-23.0)	5.2 (2.2-12.0)	2.4 (0.8-6.6)
	BMI maximum as adult			
	BMI<25	BMI≥25	BMI<25	BMI≥25
Reflux frequency (per week)				
<1	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-3	9.3 (3.6-24.2)	5.7 (3.6-9.0)	1.7 (0.8-3.9)	2.1 (1.3-3.2)
>3	5.8 (1.5-22.6)	19.0 (9.4-38.6)	1.3 (0.4-4.7)	3.0 (1.3-6.8)
Reflux severity (score)				
0	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-4	6.1 (2.2-17.2)	4.2 (2.6-6.8)	1.8 (0.8-3.9)	1.8 (1.1-2.9)
>4	12.7 (4.0-40.6)	20.9 (11.3-38.6)	1.3 (0.4-4.6)	3.5 (1.8-6.8)
Reflux duration (years)				
No	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
1-20	6.2 (2.3-16.7)	6.0 (3.9-9.5)	1.5 (0.7-3.4)	1.8 (1.1-2.8)
>20	15.0 (4.3-51.7)	17.0 (8.3-35.0)	1.9 (0.5-7.1)	4.7 (2.2-10.0)

Table 4. Association between body mass index (BMI) and esophageal or oesophago-gastric junctional adenocarcinoma stratified by gastroesophageal reflux symptoms, expressed as odds ratio (OR) with 95% confidence intervals (CI).

	Esophageal adenocarcinoma			Junctional adenocarcinoma		
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
	Reflux frequency (per week)					
	<1	1-3	>3	No symptoms	1-3	>3
BMI 20 years ago						
<25	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
≥25	3.2 (1.9-5.3)	4.0 (1.9-8.1)	6.5 (1.4-29.7)	2.0 (1.4-2.8)	2.3 (1.0-5.1)	11.8 (1.1-131.9)
BMI maximum						
<25	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	
≥25	2.1 (1.1-3.9)	2.0 (0.9-4.2)	16.6 (3.2-85.6)	1.4 (1.0-2.1)	2.2 (0.9-5.2)	n.a.
	Reflux severity (score)					
	0	1-4	>4	No symptoms	1-4	>4
BMI 20 years ago						
<25	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
≥25	3.2 (1.9-5.3)	5.1 (2.1-12.2)	3.3 (1.2-9.2)	2.0 (1.4-2.8)	1.8 (0.8-4.1)	4.9 (1.1-21.8)
BMI maximum						
<25	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
≥25	2.1 (1.1-3.9)	2.2 (0.9-5.3)	10.0 (2.7-37.1)	1.4 (1.0-2.1)	1.9 (0.8-4.5)	13.6 (2.0-91.3)
	Reflux duration (years)					
	0	≤20	>20	No symptoms	≤20	>20
BMI 20 years ago						
<25	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
≥25	3.2 (1.9-5.3)	4.7 (2.4-9.2)	1.1 (0.2-6.1)	2.0 (1.4-2.8)	3.0 (1.4-6.8)	2.4 (0.3-19.7)
BMI maximum						
<25	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	

≥25	2.1 (1.1-3.9)	3.3 (1.5-7.5)	8.9 (1.2-69.1)	1.4 (1.0-2.1)	2.0 (0.9-4.7)	n.a.

Table 5. Odds ratios and synergy index (S) of combined exposure for BMI (exposure A) and gastroesophageal reflux (exposure B) with 95% confidence intervals. S = (OR_{AB} – 1) / ($OR_{A\bar{B}}$ – 1 + $OR_{\bar{A}B}$ – 1), A and B denote the presence of and Ā and B̄ absence of two exposures. Where reference: BMI<25 and not gastroesophageal reflux symptoms, OR_{AB}: [BMI≥25 and gastroesophageal reflux symptoms vs. reference], $OR_{A\bar{B}}$: [BMI≥25 and not gastroesophageal reflux symptoms vs. reference], $OR_{\bar{A}B}$: [BMI<25 and gastroesophageal reflux symptoms vs. reference].

	Esophageal adenocarcinoma				Junctional adenocarcinoma			
	$OR_{A\bar{B}}$ (95% CI)	$OR_{\bar{A}B}$ (95% CI)	OR_{AB} (95% CI)	S (95% CI)	$OR_{A\bar{B}}$ (95% CI)	$OR_{\bar{A}B}$ (95% CI)	OR_{AB} (95% CI)	S (95% CI)
BMI 20 years before interview								
Reflux frequency (per week)								
1-3	3.3 (2.0-5.5)	6.3 (3.5-11.4)	19.7 (10.8-36.0)	2.4 (1.3-4.6)	2.0 (1.4-2.9)	2.1 (1.3-3.4)	3.5 (1.9-6.2)	1.2 (0.5-2.9)
>3	3.1 (1.9-5.1)	14.5 (6.8-31.0)	64.1 (21.6-190.4)	4.0 (1.2-13.4)	2.0 (1.4-2.9)	1.8 (0.8-4.3)	7.1 (2.3-22.6)	3.3 (0.7-16.4)
Reflux severity (score)								
1-4	3.3 (2.0-5.5)	4.2 (2.2-8.0)	15.0 (7.8-28.8)	2.6 (1.2-5.3)	2.0 (1.4-2.8)	2.0 (1.2-3.3)	3.0 (1.6-5.6)	1.0 (0.3-2.8)
>4	3.1 (1.9-5.2)	19.0 (9.7-37.3)	58.3 (25.0-136.1)	2.8 (1.1-7.2)	2.0 (1.4-2.9)	2.3 (1.1-4.9)	7.0 (2.9-17.0)	2.6 (0.7-9.3)
Reflux duration (years)								
≤20	3.3 (2.0-5.4)	5.3 (2.9-9.5)	22.7 (12.4-41.5)	3.3 (1.7-6.3)	2.0 (1.4-2.8)	1.6 (1.0-2.7)	3.7 (2.1-6.8)	1.7 (0.7-4.5)
>20	3.2 (1.9-5.4)	24.3 (11.1-53.2)	30.2 (11.9-76.6)	1.1 (0.4-3.4)	2.0 (1.4-2.8)	4.4 (1.9-9.8)	4.5 (1.7-12.3)	0.8 (0.2-3.5)
BMI maximum as adult								
Reflux frequency (per week)								
1-3	2.3 (1.3-4.3)	7.2 (3.1-16.5)	13.8 (7.2-26.7)	1.7 (0.8-3.6)	1.4 (1.0-2.1)	1.6 (0.7-3.3)	3.0 (1.8-5.0)	2.0 (0.5-7.8)
>3	2.1 (1.1-3.9)	5.0 (1.4-17.9)	46.2 (19.5-109.5)	8.9 (2.3-34.1)	1.4 (1.0-2.1)	1.3 (0.4-4.4)	4.5 (1.9-10.6)	4.7 (0.4-55.7)
Reflux severity (score)								
1-4	2.2 (1.2-4.1)	4.5 (1.8-11.6)	9.7 (4.9-19.3)	1.8 (0.8-4.4)	1.4 (1.0-2.1)	1.6 (0.7-3.4)	2.6 (1.5-4.4)	1.6 (0.4-6.6)
>4	2.2 (1.2-4.1)	10.1 (3.6-27.9)	50.2 (23.1-108.8)	4.8 (1.7-13.2)	1.5 (1.0-2.1)	1.2 (0.4-4.1)	5.4 (2.6-11.0)	6.4 (0.6-71.4)
Reflux duration (years)								
1-20	2.2 (1.2-4.1)	4.7 (1.9-11.6)	14.4 (7.5-27.7)	2.7 (1.2-6.1)	1.4 (1.0-2.1)	1.4 (0.7-3.0)	2.6 (1.6-4.3)	2.0 (0.4-8.8)

>20	2.2 (1.2-4.1)	11.6 (3.9-34.1)	42.8 (17.8-103.0)	3.5 (1.1-11.1)	1.5 (1.0-2.1)	1.7 (0.5-5.9)	6.6 (3.0-14.8)	4.7 (0.6-35.1)