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The risk of Barrett's esophagus associated with abdominal obesity in males and females

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Abstract

Esophageal adenocarcinoma arises from Barrett's esophagus (BE). Both occur predominantly in males. The role of abdominal obesity in this sex distribution is uncertain. This study aimed to determine whether there is an association between abdominal obesity and risk of BE and if present was it modified by sex. A structured interview and anthropometric measures were conducted within a population based case-control study. We recruited 237 BE cases (70% male) and 247 population controls, frequency matched by age and sex. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression analysis. In the overall group and males, all measures of abdominal obesity (waist circumference - WC, waist-hip ratio - WHR, sagittal abdominal diameter - SAD and waist-height ratio - WHtR) were strongly associated with risk of BE. (Overall - WC OR 2.2 95%CI 1.4-3.5, WHR 1.8 95%CI 1.2-2.9, SAD 2.3 95%CI 1.4-3.7, WHtR 1.9 95%CI 1.2-3.0, Males WC 2.5 95%CI 1.4-4.3, WHR 2.4 95%CI 1.3-4.2, SAD 2.5 95%CI 1.4-4.3, WHtR 1.9 95%CI 1.1-3.4). These associations were minimally attenuated by adjusting for ever-symptoms of gastroesophageal reflux (GER). These findings suggest in males, non-GER factors related to abdominal obesity may be important in the development of BE. In females, there was modest association between measures of abdominal obesity and risk of BE but

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these were all abolished after adjusting for ever-symptoms of GER. The power to detect differences between sexes in the risk of BE associated with abdominal obesity was limited by the number of females in the study.

Keywords

Barrett's esophagus; Case-Control; Risk-Factors; Obesity

INTRODUCTION

Over the last three decades the incidences of esophageal adenocarcinoma (EA) and Barrett's esophagus (BE) have increased sharply in developed countries.¹⁻⁷ EA arises from BE, a metaplastic change in the distal esophagus.⁸⁻¹⁰ There is general acceptance that gastroesophageal reflux (GER) is the principal risk factor for the development of BE and EA.¹¹⁻¹⁹ A feature of both diseases is their male predominance, with BE being twice as common and EA seven times as common in males than females.^{13, 20}

In parallel with the increasing incidence of EA and BE, the prevalence of obesity in developed countries has been increasing.²¹ Obesity is associated with an increased risk of a number of epithelial cancers including EA.^{18, 22, 23} However in EA, direct anthropometric measurements of obesity and abdominal obesity are difficult to interpret as 60% of patients with EA have weight loss at the time of presentation.²⁴ Because EA arises from underlying BE, a condition not associated with weight loss, the study of the relationship between obesity and abdominal obesity in BE is important in helping understand the role of these factors in EA.

Previous studies have suggested an association between abdominal obesity and risk of BE.^{11, 12, 25, 26} In these studies the effects of GER on this risk of BE have given variable results and there are minimal data regarding the potential effect of sex on modifying this risk. Study of these relationships is important and may have implications in terms of screening, prediction models and community based risk modification strategies for BE and EA. In this study we sought to determine whether there is an association between abdominal obesity and risk of BE and if present was this association modified by sex after controlling for the effects of other potential confounding factors.

METHODS

This study was nested within the Study of Digestive Health (SDH), a population-based study conducted between 2003-06 and previously described.²⁷ In the SDH study, cases were defined as people aged 18-79 years newly diagnosed with BE. BE was defined as the presence of intestinal metaplasia (columnar epithelium with goblet cells) in a biopsy taken from the esophagus by upper gastrointestinal endoscopy, regardless of the extent of involved mucosa.²⁸ In the SDH study, control participants from the same geographic region were randomly selected from the Australian Electoral Roll (enrolment is compulsory by law in Australia), matched by sex and broadly by age (in 5-year age groups) to the case series. Approval to undertake the current study was obtained from the Human Research Ethics

Committee of the Queensland Institute of Medical Research in 2007. We obtained written informed consent from case patients and control participants. Those who did not speak English, were too ill to participate or moved out of the geographical study area were excluded.

Study Participants

BE cases and population controls that took part in the SDH were sent a letter inviting them to take part in this anthropometric study. If after one week of the initial letter being sent there was no response, up to five phone calls were made over a two-week period in an attempt to make contact. If still no contact was made a second letter of invitation was sent. If no response was obtained from the second letter, a secondary contact was phoned and if still no response the SDH participant's general practitioner was contacted to obtain current contact details. All 359 BE cases from the SDH were approached to take part in the current study. 237 (66%) of these patients completed the study, 69 (19%) declined to participate and 53 (15%) were found to be ineligible. 419 age and sex matched population controls were approached to take part in the current study. 247 (59%) of these controls completed the study, 108 (26%) declined to participate and 64 (15%) were found to be ineligible.

Data collection

Data were collected from participants through structured, self-completed questionnaires, followed by a standardized interview and anthropometric measures conducted by a trained research nurse from 2007-2009. We collected information in the questionnaire and interview about symptoms of GER. Information was also collected with regard to current and past smoking, alcohol and recent use of other medications including aspirin and non-steroidal anti-inflammatory drugs (NSAID).

At interview, the following anthropometric measures were collected using standardized protocols (see Appendix 1 online for details of protocol): Height, weight, body mass index (BMI), waist circumference (WC), hip circumference, waist-hip ratio (WHR), sagittal abdominal diameter (SAD) and waist-height ratio (WHtR).²⁹

Statistical analyses

The primary aim of the analysis was to assess the associations between the anthropometric measures and risk of BE after accounting for the potentially confounding effects of age, sex, smoking and GER symptoms. Because the distribution of some measures deviated from the normal, we used medians and interquartile (IQ) range to describe measures of central tendency. Wilcoxon rank sum test was used to test for differences between cases and controls for those continuous measures that deviated from the normal distribution and t-test for those with a normal distribution in the control population. Chi-square tests were used to test for differences between cases and controls for categorical variables. To estimate the relative risk of BE associated with anthropometric measures, aspirin and NSAID use, alcohol intake and ever-symptoms of GER, we calculated the odds ratio (OR) and 95% confidence interval (95% CI) by unconditional multivariable logistic regression analysis. For anthropometric measures, our approach was to fit models that contained terms for each measure as a categorical variable according to WHO categories for BMI (<25 kg/m², 25 to

29.9 kg/m², 30.0 kg/m²)²⁹ and sex-specific tertile cutpoints in the control distribution for the other anthropometric measures, adjusting for exact age in years, sex and smoking status. The lowest tertile for each categorical variable was used as the reference category. We fitted further models, which adjusted for ever-symptoms of GER, alcohol intake and aspirin and NSAID use. We tested for biological interaction between ever-symptoms of GER and anthropometric measures that were positively associated with risk of BE in a simple logistic model, by testing for departures from additivity of effect by calculation of the synergy index (SI).³⁰ The reference category for each anthropometric measure for these calculations combined those in the first and second tertile for each measure. To test for trend, categorical variables were included in the model as continuous data (with category values taking the median of the category) and the Wald test was used as an approximation of the Mantel extension chi-square with 1 degree of freedom. We also undertook stratified analyses separately for males and females for all analyses. Statistical interaction (effect modification) was assessed using Type 3 analysis of effects of interaction terms combining each anthropometric measure with sex and each anthropometric measure with ever-symptoms of GER in the full-model.

Correlations between self reported variables in the Studies of Digestive Health (smoking status, heartburn and BMI) and self reported (smoking status and heartburn) and measured variables (BMI) in the current study were tested using simple kappa (smoking and heartburn) and weighted kappa (BMI) coefficients.

A t-test for continuous variables (age) and Chi-square tests for categorical variables (sex, GER symptoms, self-reported BMI, alcohol intake, smoking, aspirin use, ethnicity and education) were used to test for differences between SDH participants that did and those that didn't agree to participate in the current study,

Statistical significance was determined at $\alpha = .05$, and all tests for statistical significance were two-sided. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Finally, to explore the shape of the dose-response relationship between anthropometric measures and risk of BE, we fitted an age and sex adjusted logistic regression model with restricted cubic spline for each anthropometric measure by means of generalized additive logistic models (CRAN package mgcv in R software). Smoothing splines fixed at 3 degrees of freedom, resulting in placements of knots equally through the data, were used to test for significance of nonlinearity against the linear effect.

RESULTS

Study Population (Table 1 and 2)

Characteristics of the 237 cases (165 males, 72 females) and 247 control participants (164 males, 83 females) are presented in Table 1. The distributions for age and sex of cases and controls were similar because of the frequency matching. There was no difference in ethnicity between cases and controls (Caucasian 97% BE cases, 95% controls). BE cases reported higher prevalences of cigarette smoking (Current smoker 14% BE cases, 8%

controls OR 3.0 95%CI 1.6-5.7) and ever-symptoms of GER (ever-symptoms 95% BE cases, 75% controls OR 6.9 95%CI 3.5-13.5) than population controls. This strong association with ever-symptoms of GER was found in both males (OR 7.5 95%CI 3.2-17.3) and females (OR 6.0 95%CI 2.0-18.6). There were no differences in the prevalence of ever-symptoms of GER between male and female BE cases (males 96%, females 94% - $p = 0.65$) or male and female population controls (males 75%, females 73% - $p = 0.7$). BE cases reported lower prevalence of higher education (University education 14% BE cases, 25% controls OR 0.4 95%CI 0.3-0.7) Mean anthropometric measures for the overall case and control groups and sub-group analysis by sex are shown in Table 2. In the overall group, all anthropometric measures other than height and hip circumference were significantly greater in BE cases than population controls. In males, BE cases had significantly greater WC, WHR, SAD and WHtR but no significant difference in weight, height, hip circumference or BMI. In females, BE cases had significantly greater weight, WC, hip circumference, WHtR and BMI but no significant difference in height, WHR or SAD.

Minimally adjusted analysis (Table 3)

Associations after minimally adjusting for age, sex (in the overall group) and smoking status were calculated for all anthropometric measures.

BMI—There was a strong and statistically significant association between a high BMI (>30 kg/m²) and risk of BE (OR 2.4 95%CI 1.4-4.1) in the overall group. There was a similarly strong association between high BMI and risk of BE in both males (OR 2.2 95%CI 1.2-4.4) and females (OR 2.7 95%CI 1.1-6.8).

Measures of abdominal obesity—There was a strong and statistically significant association between all measures of abdominal obesity (waist circumference, WHR, SAD and WHtR) and risk of BE in the overall group. This risk was greatest for the highest tertile of SAD (OR 2.3 95%CI 1.4-3.7). In males there was a strong and statistically significant association between all measures of abdominal obesity and risk of BE. This risk was greatest for the highest tertile of SAD (OR 2.5 95%CI 1.4-4.3) and WC (OR 2.5 95%CI 1.4-4.3). In females there was a moderate association between WC, SAD and WHtR and risk of BE, although none of these reached statistical significance with wide confidence intervals secondary to reduced power from the smaller numbers of females in the study.

Adjusting measures of abdominal obesity for ever-symptoms of GER (Table 4)

—In the overall group and in males, there was minimal attenuation of the associations with measures of abdominal obesity and risk of BE after adjusting for ever-symptoms GER. In females however, all associations for measures of abdominal obesity were abolished after adjusting for ever-symptoms of GER.

Adjusting measures of abdominal obesity for other potential confounders—

We found there was no significant association between other potential confounders (alcohol intake and aspirin and NSAID use) and risk of BE on minimally adjusted analyses (See Supplementary Table 1 online). Adjusting for these factors in the multivariable logistic

regression model had no substantial effect on the association between measures of abdominal obesity and risk of BE (See Supplementary Table 2 online).

Testing for departures from additivity—We found evidence suggestive of biological interaction between measures of abdominal obesity and ever-symptoms of GER in the overall group and males (See Supplementary Table 3 online). This was greatest for WHR (Overall SI 2.0 95%CI 1.0-3.8, males SI 2.0 95%CI 1.0-3.9). There were insufficient female participants to analyze for biological interaction between these factors in females. There was no evidence of any biological interaction between measures of abdominal obesity and sex.

Supplemental analyses

For the majority of anthropometric measures there was no evidence of a nonlinear dose relationship between the anthropometric measures and risk of BE overall or in males or females. However there was a statistically significant nonlinear relationship for SAD and risk of BE in the overall group ($p=0.01$) and males ($p=0.01$) and for waist-height ratio in males ($p=0.03$). (See Supplementary Figure 1 and Supplementary Table 4 online).

There was no evidence for statistical interaction between measures of abdominal obesity and sex and ever-symptoms of GER in any of the overall group, males or females. (See Supplementary Table 5 online).

Given the length of time between entry into the SDH (when the cases of BE were incident cases) and entry into this study, we compared the self-reported smoking and heartburn history in both studies and self-reported BMI in the original study and measured BMI in this study. There was good correlation between abdominal obesity at the two time points for both BE cases and population controls (See Supplementary Table 6 online). Additional analyses of SDH data from those SDH participants that did and those that didn't agree to participate in this study, showed no significant difference in age, sex, GER symptoms, self-reported BMI, smoking, aspirin use, ethnicity and education. There were significantly more life-long non-drinkers in the SDH controls who participated in this study compared to those SDH controls who did not participate in this study ($p=0.009$). (See Supplementary Table 7 online).

DISCUSSION

We have found that all measures of abdominal obesity were strongly associated with an increased risk of BE in the overall group and males. When simultaneously modeled for GER symptoms, these strong associations were minimally attenuated. However in females, measures of abdominal obesity were only modestly associated with an increased risk of BE and these associations were abolished when simultaneously modeled for ever-symptoms of GER. These findings suggest that in males, non-GER factors related to abdominal obesity may be important in the development of BE.

Two previous population based case-control studies from the United States have examined the association between abdominal obesity and risk of BE.^{11, 12, 26, 31} Both of these studies, one from California and the other from Washington, showed strong associations between

abdominal obesity and risk of BE in the overall group, similar to our study. In the California study, larger waist circumference was associated with the risk of BE in the overall group (OR 2.24 95%CI 1.21-4.15) with partial attenuation of the association after adjustment for GER symptoms (OR 1.78 95%CI 0.86-3.66). In the Washington study, high WHR was associated with the risk of BE (OR 2.8 95%CI 1.5-5.1) in the overall group and this increased after adjustment for GER symptoms (OR 2.9 95%CI 1.3-6.3). The Washington study reported sub-group analysis by sex and found associations between high WHR and risk of BE in both sexes, but greater in males (OR 3.2 95%CI 1.4-7.5) and not reaching statistical significance in females (OR 2.3 95%CI 0.9-5.9).

There are a number of strengths of our study. Firstly, the interviews and anthropometric measures were extensive and undertaken by research nurses trained in the study methods. This minimized the chance of measurement errors and overcame problems associated with self-reported anthropometric measures. Additionally the cases were all recruited from a defined geographical area with the control group from the same area and were matched for age and sex and had similar ethnicity to the cases. Lastly, the case status of the BE patients was determined according to strict endoscopic and histological criteria.

There are a number of potential limitations of the study. Firstly, the sample size led to limitations in numbers of female BE cases and population controls in the study. This reduced the power of the study to detect differences between males and females in the risk of BE associated with abdominal obesity. Conducting a study large enough to address this issue would likely require multiple centers. This may introduce potential heterogeneity in case definitions and control recruitment, particularly if the study was multinational. Secondly, while the patients had an incident diagnosis of BE when first recruited, anthropometric measures were not performed up to seven years after initial diagnosis. After diagnosis of BE, factors such as cigarette smoking and anthropometric measures may have changed as a result of prescribed lifestyle changes however these changes would be more likely to bias the findings towards the null. We addressed this by comparing self reports of smoking history, heartburn and BMI at the time of first recruitment, (i.e. when the patients were incident cases) to the findings from the current study, and there was good correlation between these factors for both cases and controls at the two time points. Lastly, there may have been possible selection bias as not all of those approached from the SDH agreed to participate in this study. A comparison between those from the SDH that did and did not participate in this study showed no significant difference between the two groups, making selection bias unlikely to explain our findings.

In diseases such as BE and EA with marked sex differences in incidence, it is likely that there are factors that mediate the disease in both sexes and other factors that potentiate or protect one sex over the other. In this study, we have confirmed that the principal risk for BE is GER.^{11, 12, 19} We have also shown that GER occurs equally in males and females not only among population controls but also in BE cases. This makes it unlikely that GER alone explains the sex difference in BE and that other factors may biologically interact with GER in the development of BE. In males the strong associations between measures of abdominal obesity remained after adjusting for GER. We also found evidence suggestive of biological interaction between abdominal obesity and GER in males on testing for departures from

additivity. These findings suggest that non-GER factors related to abdominal obesity may be important in the development of BE in males. In females, the modest associations with abdominal obesity were abolished when adjusting for GER, suggesting that the main pathway for the association between abdominal obesity and risk of BE in females is likely to be mediated via the GER pathway. However the numbers of females in the study limit the power to determine more precisely these associations.

What are the potential mechanisms underlying the independent association between abdominal obesity and risk of BE in males? This may be related to the differential pattern of obesity between the sexes, with males having higher volumes of metabolically active intra-abdominal adipose tissue resulting in hormonal and adipokine changes.³² Studies *in-vitro* of a number of adipokines have shown them to have effects on cellular proliferation, apoptosis, angiogenesis and inflammation.³³⁻³⁶ The adipokines, leptin and adiponectin have been shown to be associated with the risk of BE suggesting that this mechanism may have a role in BE and EA.^{27, 31, 37} Additionally, higher volumes of non-abdominal subcutaneous adipose tissue has been found to be independently associated with reduced metabolic effects of obesity after accounting for intra-abdominal adipose tissue.³⁸ It is postulated that non-abdominal subcutaneous adipose tissue acts as a “metabolic sink” for non-esterified fatty acids thereby offering protection against their deleterious metabolic effects.³⁹ It is possible that the higher volumes of non-abdominal subcutaneous adipose tissue in females are acting in this way and offering greater protection from the cellular proliferative and anti-apoptotic effects of the adipokines secreted by intra-abdominal adipocytes.

A Unites States study of predominantly males with BE assessed intra-abdominal adipose tissue using CT scans.²⁵ The study showed an increased risk of BE associated with obesity that was likely to be predominately mediated by intra-abdominal adipose tissue. Larger studies using imaging techniques to accurately assess body fat distribution in both males and females with BE are required to further understand the relationship between anthropometric measures, body fat distribution and risk of BE in males and females. The currently available imaging techniques of CT scan and MRI have limitations including radiation exposure and expense. The development of a safe, inexpensive and reliable technique to determine regional body fat stores that can be used in large population based studies is vital to further studies.

In summary, we have found that abdominal adiposity appears to be an independent risk factor for BE in males but not females. This finding may in part explain the male predominance of BE, the precursor of EA. The mechanism of this association remains unknown but hormonal and systemic inflammatory changes associated with abdominal obesity in males, are factors warranting further study. Additionally, larger studies using imaging techniques to assess body fat distribution are required to examine further the relationship between obesity, intra-abdominal fat, sex and BE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BE	Barrett's esophagus
BMI	Body mass index
CI	Confidence interval
CT	Computed topography
EA	Esophageal adenocarcinoma
GER	Gastroesophageal reflux
IR	Inter-quartile range
MRI	Magnetic resonance imaging
N	Number
NSAID	Non-steroidal anti inflammatory drugs
OR	Odds ratio
SAD	Sagittal abdominal diameter
SDH	Study of Digestive Health
SI	Synergy Index
WC	Waist circumference
WHR	Waist-hip ratio
WHtR	Waist-height ratio

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Brief description

The incidences of esophageal adenocarcinoma and Barrett's esophagus is increasing. Both occur predominantly in males. The reason for this sex difference is uncertain. We conducted a population based case-control study and found in males, but not females, a strong association between abdominal obesity and Barrett's esophagus. These findings may have implications on understanding the relationship between obesity, sex and cancer risk and impact on screening and risk modification strategies for Barrett's esophagus and esophageal adenocarcinoma.

Table 1

Characteristics of BE cases and controls.

	BE Cases (n=237)		Controls (n=247)		p value *
	n	%	n	%	
Sex					
Female	72	30%	83	34%	0.45
Male	165	70%	164	66%	
Age (yrs)					
<39	10	4%	9	4%	0.85
40-49	23	10%	29	12%	
50-59	52	22%	63	25%	
60-69	86	36%	85	34%	
>70	66	28%	61	25%	
BMI					
< 25 kg/m ²	41	17%	68	28%	0.004
25-29.99 kg/m ²	114	48%	122	49%	
30 kg/m ²	82	35%	57	23%	
Heartburn / acid reflux /					
Never	11	5%	62	25%	<0.0001
Ever	224	95%	183	75%	
Smoking					
Never	79	33%	142	58%	<0.0001
Ex-smoker	124	53%	84	34%	
Current smoker	34	14%	21	8%	
Alcohol – standard drinks					
Non drinker	33	14%	28	11%	0.19
One-two daily	159	67%	184	75%	
More than two daily	45	19%	35	14%	
Aspirin and NSAID use /					

	BE Cases (n=237)		Controls (n=247)		p value*
	n	%	n	%	
Never	74	31%	73	30%	0.58
Less than weekly	87	37%	102	41%	
Weekly or more often	76	32%	72	29%	
Education					
High school	101	43%	86	35%	0.005
Tech/Trade College	103	43%	98	40%	
University	33	14%	63	25%	

I Columns do not sum to total due to missing values.

* Chi-square test

Table 2

Anthropometric measures (median – inter-quartile range) of BE cases and controls – All participants (male and females) and sub-group analysis according to sex. (BE Cases – All = 237, male = 165, females = 72; Controls – All=247, male=164, females = 83)

Measure and Group	BE Cases	Controls	p-value
Weight (kg)			
All	83.4 (18.4)	79.6 (19.1)	0.02
Male	86.5 (18.9)	83.4 (16.8)	0.22
Female	76.2 (18.0)	69.2 (16.5)	0.04
Height (m)			
All	1.71 (0.14)	1.71 (0.13)	0.93
Male	1.74 (0.10)	1.74 (0.10)	0.89
Female	1.62 (0.08)	1.63 (0.09)	0.44
BMI (kg/m²)			
All	28.5 (5.4)	27.4 (5.3)	0.005
Male	28.4 (4.8)	27.5 (4.9)	0.10
Female	28.6 (7.1)	27.0 (5.1)	0.02
Waist circumference (cm)			
All	101.8 (16.6)	97.4 (16.7)	0.002
Male	104.9 (13.3)	101.0 (14.7)	0.02
Female	91.1 (21.2)	88.6 (17.4)	0.04
Hip circumference (cm)			
All	106.4 (13.0)	105.0 (10.4)	0.05
Male	105.7 (11.0)	104.8 (10.1)	0.26
Female	109.9 (16.2)	105.6 (13.3)	0.04
WHR			
All	0.94 (0.12)	0.92 (0.12)	0.002
Male	0.98 (0.08)	0.96 (0.08)	0.002
Female	0.86 (0.11)	0.83 (0.10)	0.16
Sagittal abdominal diameter (cm)			
All	23.9 (4.2)	22.7 (4.4)	0.0003
Male	24.5 (3.9)	23.3 (4.1)	0.002
Female	22.4 (4.8)	21.8 (4.0)	0.07
Waist-height ratio			
All	0.60 (0.10)	0.57 (0.10)	0.0004
Male	0.60 (0.08)	0.58 (0.08)	0.007
Female	0.57 (0.12)	0.54 (0.09)	0.04

Table 3

Odds ratios (OR) and 95% confidence intervals (CI) for risk of BE associated with anthropometric measures in all participants (male and females) and stratified analysis according to sex.

Measure	All ^{1,2} Odds ratio (95% CI)	Males ^{2,3} Odds ratio (95% CI)	Females ^{2,3} Odds ratio (95% CI)
BMI			
< 25	Ref	Ref	Ref
25-29.99	1.7 (1.0-2.8)	1.8 (1.0-3.3)	1.6 (0.7-3.6)
≥ 30	2.4 (1.4-4.1)	2.2 (1.2-4.4)	2.7 (1.1-6.8)
p trend	0.002	0.03	0.03
WC			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.2 (0.8-2.0)	1.4 (0.8-2.5)	0.9 (0.4-2.2)
Tertile 3	2.2 (1.4-3.5)	2.5 (1.4-4.3)	1.6 (0.7-3.7)
p trend	0.001	0.001	0.21
WHR			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.0 (0.6-1.6)	1.3 (0.7-2.5)	0.5 (0.2-1.2)
Tertile 3	1.8 (1.2-2.9)	2.4 (1.3-4.2)	1.2 (0.5-2.7)
p trend	0.006	0.002	0.58
Sagittal abdominal diameter			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.7 (1.1-2.8)	1.6 (0.9-3.0)	1.8 (0.8-4.5)
Tertile 3	2.3 (1.4-3.7)	2.5 (1.4-4.3)	2.0 (0.8-4.7)
p trend	0.001	0.002	0.16
Waist-height ratio			
Tertile 1	Ref	Ref	Ref
Tertile 2	1.2 (0.8-2.0)	1.4 (0.8-2.5)	1.0 (0.4-2.5)
Tertile 3	1.9 (1.2-3.0)	1.9 (1.1-3.4)	1.8 (0.8-4.2)
p trend	0.007	0.02	0.13

¹ Odds ratio adjusted for age, sex, smoking status

² Tertiles categorized according to sex-adjusted cut points

³ Odds ratio adjusted for age, smoking status

Cutpoints for tertiles: *WC* Male: T1 0-95.67; T2 95.67-104.30; T3 > 104.30; Female: T1 0-82.33; T2 82.33-93.30; T3 > 93.30; *WHR* Male: T1 0-0.933; T2 0.933-0.983; T3 > 0.983; Female: T1 0-0.803; T2 0.803-0.8578; T3 > 0.8578; *Sagittal abdominal diameter* Male: T1 0-22.05; T2 22.05-24.50; T3 > 24.50; Female: T1 0-20.30; T2 20.30-22.95; T3 > 22.95; *Waist-height ratio* Male: T1 0-0.555; Q2 0.555-0.603; Q3 > 0.603; Female: T1 0-0.514; Q2 0.514-0.578; Q3 > 0.578;

Table 4

Odds ratios (OR) and 95% confidence intervals (CI) of risk of BE associated with waist circumference, WHR, sagittal abdominal diameter and Waist-height ratio adjusted for ever-symptoms of GER.

Measure and Group	Minimally adjusted ¹ Odds ratio (95% CI)	Adjusted for ever-symptoms GER ³ Odds ratio (95% CI)
Waist circumference²		
All	2.2 (1.4-3.5)	1.8 (1.1-3.0)
Male	2.5 (1.4-4.3)	2.4 (1.3-4.2)
Female	1.6 (0.7-3.7)	1.1 (0.4-2.6)
WHR²		
All	1.8 (1.2-2.9)	1.6 (1.0-2.6)
Male	2.4 (1.3-4.2)	2.2 (1.2-4.0)
Female	1.2 (0.5-2.7)	0.9 (0.4-2.2)
Sagittal abdominal diameter²		
All	2.3 (1.4-3.7)	1.9 (1.1-3.1)
Male	2.5 (1.4-4.3)	2.3 (1.3-4.1)
Female	2.0 (0.8-4.7)	1.3 (0.5-3.4)
Waist-height ratio²		
All	1.9 (1.2-3.0)	1.6 (1.0-2.6)
Male	1.9 (1.1-3.4)	1.8 (1.0-3.3)
Female	1.8 (0.8-4.2)	1.2 (0.5-3.0)

¹ Minimally adjusted OR adjusted for age, sex, smoking status in all category and age and smoking status for male and female category.

² OR of Tertile 3 compared to reference category of Tertile 1 for measure categorized according to sex-adjusted cut points

³ Minimally adjusted OR adjusted for ever-symptoms of GER.