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Waist-to-Hip Ratio, but Not Body Mass Index, is Associated with an Increased Risk of Barrett's Esophagus in White Men

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Abstract

Background & Aims—Abdominal obesity increases the risk of gastroesophageal reflux disease (GERD) and might also contribute to development of Barrett's esophagus (BE), although results are inconsistent. We examined the effects of waist-to-hip ratio (WHR) and body mass index

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(BMI) on the risk of BE and investigated whether race, GERD symptoms, or hiatus hernia were involved.

Methods—We conducted a case-control study using data from eligible patients who underwent elective esophagogastroduodenoscopy (EGD); 237 had BE and the other 1021 served as endoscopy controls. We also analyzed data and tissue samples from enrolled patients who were eligible for screening colonoscopies at a primary care clinic (colonoscopy controls, n=479). All patients underwent EGD, completed a survey, and had anthropometric measurements taken. WHR was categorized as high if was ≥ 0.9 for men and ≥ 0.85 for women. Data were analyzed with logistic regression.

Results—There was no association between BMI and BE. However, more patients with BE had a high WHR (92.4%) than endoscopy controls (79.5%) or colonoscopy controls (84.6%) ($P<.001$ and $P=.008$, respectively). In adjusted analysis, patients with BE were 2-fold more likely to have a high WHR than endoscopy controls (odds ratio [OR], 1.93; 95% confidence interval [CI], 1.1–3.5), this association was stronger for patients with long-segment BE (OR, 2.81; 95% CI, 1.0–7.9). A high WHR was significantly associated with BE only in Whites (OR=2.5; 95% CI, 1.2–5.4)—not in Blacks or Hispanics. GERD symptoms, hiatus hernia, or gastroesophageal valve flap grade could not account for the association.

Conclusions—High WHR, but not BMI, is associated with a significant increase in the risk of BE, especially long-segment BE and in Whites. The association is not due to GERD symptoms or hiatus hernia.

Keywords

visceral obesity; epidemiological study; Veterans Affairs; risk factors

INTRODUCTION

Barrett's esophagus (BE) is the precancerous lesion for esophageal adenocarcinoma, and both conditions have been increasing in the Western world.^{1, 2} The prevalence of BE in persons with chronic gastroesophageal reflux disease (GERD) is between 6 and 12%^{3, 4} and up to 1% of the general adult population.^{5, 6} Patients with BE are 11 to 30 times more likely to develop esophageal adenocarcinoma.⁷ The increase in esophageal adenocarcinoma has paralleled that of the obesity epidemic in several world regions including the United States.

Obesity as measured by body mass index (BMI) is a risk factor for GERD symptoms, esophageal erosions and esophageal adenocarcinoma.⁸ However, the evidence for an association between BMI and BE is inconsistent. A meta-analysis published in 2009 reported a weak association of BMI and BE with pooled risk estimates from 11 studies ranging between 1.33 to 1.70 depending on the categorization of BMI.⁹ Seven of the 11 studies reported a non-significant association between BMI and BE. A second meta-analysis published in 2008 reported no significant association of BMI and BE when pooling the results of 10 studies that used mostly GERD controls for comparison (only 3 studies were in both papers).¹⁰

In addition to BMI, several recent studies examined abdominal obesity, as measured by waist circumference and waist to hip ratio (WHR), and reported varying degrees of association of these measures with the risk of BE. Corley et al. reported a 2-fold increased likelihood of BE for waist circumference >80 cm compared with population controls [Odds ratio (OR)=2.24; 95% confidence interval (CI): 1.21–4.15] but not compared with endoscopy controls, and no significant association between BMI and BE.¹¹ Edelstein et al. reported an association of high WHR (defined as ≥ 0.9 for males and ≥ 0.85 for females) and

BE (OR=2.4; 95%CI: 1.4–3.9).¹² On the other hand, Jacobson et al. reported no association between WHR or waist circumference and BE in a nested case-control study of women in the Nurses' Health Study cohort, but a moderate effect of BMI >30 vs. normal BMI (OR=1.52, 95%CI: 1.02–2.28).¹³ Few previous studies reported a stronger association between obesity measured with BMI or WHR and long segment BE more than short segment.^{12, 14, 15} Other studies have not shown a relationship between obesity and BE length.^{5, 13, 16–18} Lastly, most previous studies were performed in mostly White patient populations, and given known racial differences in fat distribution, this effect may be different in other races.

Therefore, we examined the effect that BMI and WHR have on the risk of BE. Also, we determined if the association was different for long versus short segment BE. Lastly, we examined how factors such as race and ethnicity, presence and duration of GERD symptoms, proton pump inhibitor (PPI) and/or histamine-2 receptor antagonist (H2RA) medications, hiatal hernia, and gastroesophageal valve flap dysfunction may modulate this effect.

METHODS

Study Population and Design

We performed a case-control study at the Michael E. DeBakey VA Medical Center (MEDVAMC) in Houston, TX. To obtain the cases and controls, we first conducted two cross-sectional studies in subjects seeking health care at the MEDVAMC. In one cross-sectional study we recruited all eligible patients who were scheduled for an elective esophagogastroduodenoscopy (EGD) at MEDVAMC from September 1, 2008 to July 31, 2011, and for the second cross-sectional study we recruited patients eligible for screening colonoscopy from seven selected primary care clinics at the same hospital between September 1, 2008 and December 31, 2010. All subjects who were diagnosed with BE were considered cases. We used two control groups; one consisting of subjects without BE who presented to MEDVAMC Primary Care Clinic and were eligible for a screening colonoscopy (referred to as 'colonoscopy controls'), and the other consisting of the endoscopy patients without BE (referred to as 'endoscopy controls').

Based on administrative data of the 90,973 unique users of services at MEDVAMC aged 40–80 during the time period of our study (09/2008–07/2011), 29.1% were Black, 58.7% were White, and 4.8% were other race (7.4% had unknown race) and 91.6% were male.

Recruitment and eligibility criteria

For the colonoscopy group we invited patients at their primary care visit who were eligible for screening colonoscopy to participate in this study and undergo a study EGD on the same day as their colonoscopy. Study eligibility was based on: 1) age between 50–80 years (unless had a reason for screening colonoscopy before 50, but >40); 2) no previous gastroesophageal surgery; 3) no previous or current cancer of the stomach or esophagus; 4) no active lung, liver, colon, breast, or stomach cancer; 5) not currently taking anticoagulants; 6) no significant liver disease indicated by platelet count below 70,000, ascites, or known gastroesophageal varices; and 7) no history of major stroke or mental condition that would limit their ability to answer questions. For the endoscopy group, the same eligibility criteria were used with the exception of the age limit, which was lowered to age 40.

For both groups of eligible patients, we sent invitation letters before the appointment for endoscopy or clinic visit, respectively, and on the day of the endoscopy or visit approached patients who did not decline participation to obtain informed consent for enrollment. The eligibility criteria were further checked on the day of the EGD.

This research was approved by the Institutional Review Boards for the MEDVAMC and Baylor College of Medicine.

Data Collection

Surveys—Prior to the study EGD, all participants completed a computer assisted survey with the guidance of a research assistant. The survey ascertained lifetime history and current use of alcohol and smoking; medical history, frequency and severity of GERD symptoms; use of medication such as H2RAs and PPIs; as well as physical activity.

Study EGD—All study participants underwent an EGD with systematic recording of suspected BE,¹⁹ hiatus hernia (absent, <3 cm, and 3 cm and greater) and Hill's classification of gastroesophageal flap valve in the retroflexed endoscopic view (scores range from 1 to 4).²⁰ At least one targeted biopsy from suspected BE areas was taken using Jumbo biopsy forceps. BE length was determined by the Prague CM classification.¹⁹ We performed gastric mapping by taking 7 mucosal biopsy samples from the antrum (from the greater and lesser curvatures), the corpus (from the distal greater, distal lesser, proximal greater, and proximal lesser curvatures) and the cardia.²¹ Live-case orientation sessions were conducted with the endoscopists to demonstrate landmarks, biopsy sites, and recorded findings regarding suspected BE. *Case definition*: A subject was considered to have definitive BE if intestinalized columnar epithelia (confirmed by alcian-PAS stain) under histopathological examination was present in at least one biopsy sample obtained from tubular esophagus. Two expert pathologists reviewed all slides for suspected BE to determine the presence of definitive BE (GV, MR). Subjects with endoscopic BE only were defined by the presence of suspected BE in the absence of specialized intestinal epithelium, and were excluded from this analysis. Subjects were defined as positive for *H. pylori* if organisms were seen on histopathology of any of the study gastric biopsies, or if review of the medical record showed a previous positive biopsy, presence of serum antibodies, or treatment received if biopsy results were not available.

Anthropometric measurements—We measured participant body weight in bare feet using a digital upright scale (Health o meter® Professional) designated for our study. Height in inches was also obtained using a study designated stadiometer, and was entered directly into the scale for calculation of BMI using the Quetlet index formula weight in pounds $\times$ 703/squared height in inches. A flexible tape measure was used to obtain waist circumference rounded down to nearest half inch at umbilicus level at the narrowest part of the waist. Hip circumference was measured over the participant's right side at greatest buttock protrusion. WHR was calculated as the ratio of waist circumference divided by hip circumference. All research staff was trained to systematically perform and record anthropometric measurements.

Data Analysis

The main exposure variables were BMI and WHR. BMI was categorized as normal (<24.9), overweight, (25–29.9), and obese ($\geq$ 30) according to the World Health Organization. The high WHR cutoff was considered $\geq$ 0.9 for males and $\geq$ 0.85 for females as in previous studies.^{12, 22} We also examined if a different cutoff was important in this study by analyzing finely categorized groups of WHR for any observed substantial increases in risk. We calculated estimates of the association between BE and anthropometric measures both unadjusted as well as adjusted for age, sex, race, recruitment source (in model using combined control group only), cigarette smoking, alcohol use, *H. pylori* status, and physical activity (see Appendix for definitions). We also estimated these associations for long segment BE ($\geq$ 3 cm) and short segment BE (<3 cm) separately. We subsequently evaluated the possible mediating effect of race and ethnicity, the presence and duration of GERD

symptoms, PPI/H2RA medications, hiatal hernia, BMI, and gastroesophageal flap grade assessed by Hill classification on the association between WHR and BE.

We evaluated the statistical interaction of WHR with race by creating a traditional interaction variable with race and WHR as well as a variable that compared Whites with high WHR, Blacks with high WHR, and Whites with low WHR to Blacks with low WHR as the reference group. In addition, we estimated the effect of BMI and WHR on BE for each race category by performing race-stratified analyses as well as in White men only. Finally, we conducted a sensitivity analysis that excluded the patients with previously diagnosed BE as well as one excluding patients <50 years old due to the different lower age limits in the endoscopy and screening colonoscopy groups.

For the unadjusted comparisons, Chi-square tests were used for categorical variables and student's t-test for continuous variables. Logistic regression models were used for multivariable adjustment with the variables mentioned above. Parameter estimates and standard errors from the model were used to calculate ORs and their accompanying 95% CIs.

RESULTS

Enrollment

Among 1424 primary care patients who met the study criteria and were invited to undergo a screening colonoscopy and participate in our study, 580 were subsequently enrolled in the study (Figure 1). Among 1966 preliminarily eligible patients who came for a scheduled EGD and were contacted by our study staff, 1735 were verified to fulfill the study inclusion and exclusion criteria, and 1346 were enrolled in the study (Figure 1). For this analysis, we further excluded 7 patients who withdrew consent, 11 patients diagnosed with gastric or esophageal cancer during the study EGD, 49 patients without a complete study EGD, and 122 patients with endoscopic, but not definitive BE. Patients with suspected BE were not significantly different with respect to BMI, race/ethnicity, and gender compared with patients with confirmed BE. However, they were younger and less likely to have GERD or high WHR than patients with confirmed BE. Approximately 90% of patients with suspected BE had short length BE <3 cm compared with 60% of the patients with confirmed BE on biopsy ($p<0.001$). These exclusions resulted in 1737 patients in our analysis overall; 237 cases with definitive BE (52 had previous BE; 54% with BE ≥ 3 cm), 479 colonoscopy controls from primary care, and 1021 endoscopy controls.

Descriptive Characteristics of Study Cohort

The mean age of the study cohort was 61.5 years (standard deviation (sd)=7.6) and 92.5% were male. The majority were White (57.4%), 32.6% were Black and 7.4% were Hispanic. The mean BMI of the cohort was 30 (sd=6.05). The demographic, anthropometric, and specific clinical characteristics of the BE cases, each separate control group, and all controls combined are listed in Table 1. BE cases were significantly more likely to be male than the endoscopy controls. BE cases were significantly more likely to be White compared with both control groups (80.6% vs. endoscopy: 57.2% and colonoscopy: 46.5%). Of the 235 BE cases with Prague CM classification, 91 (38.7%) had long-segment BE and 144 (61.3%) had short-segment BE.

Association of BE with BMI

Colonoscopy controls had the highest mean BMI (30.8) followed by BE cases (30.3) and endoscopy controls (29.7); however these differences were small and not statistically significant (Table 1). There were also no significant differences in the distribution of BMI

categories between BE cases and colonoscopy controls; however, the endoscopy control group was less likely to be obese than both the cases and colonoscopy controls (42.0% vs. 47.7% vs. 49%).

Because the estimate of the effect of BMI and WHR on BE obtained from the multivariable analyses using all BE cases and the combined controls groups were similar to those obtained when the analysis was limited to BE cases versus endoscopy controls (data not shown), we chose to report the effect estimates for the combined control group as well as the colonoscopy control group only.

There was no significant difference in the unadjusted analysis for BMI categories between cases and the combined control group; odds ratios were 1.35 (95%CI: 0.9–2.0) and 1.26 (95%CI: 0.8–1.9) for obese and overweight, respectively, versus normal BMI. When the colonoscopy controls only were used, no association was observed between being obese (or overweight) and BE (obese OR=1.01, 95%CI: 0.3–1.6; overweight OR=1.08, 95%CI: 0.7–1.7). Similarly, in the adjusted multivariate models using the overall cohort, BMI as a categorical variable was not significantly associated with BE overall, nor with long or short segment BE (Table 2). Likewise, when only colonoscopy controls were used there was neither a significant association observed between BMI and BE overall nor for long or short segment BE. Finally, when excluding the 52 cases with previously diagnosed BE, BMI was still not associated with BE.

Association of BE with WHR

The endoscopy controls had slightly smaller waist circumference compared with BE cases (107.4 vs. 111.4; $p=0.01$), but there were no differences compared with the colonoscopy controls (Table 1). The mean WHR was significantly larger for BE cases compared with both control groups. To examine the best WHR cutoff, we calculated the empirical logit values of BE over a moderately fine categorization of the continuous WHR variable. After examining the effects on BE of various cutoffs using this fine categorization we observed a substantial increase in risk for the effect of WHR on BE using 0.9 for males and 0.85 for females. Therefore, we validated that this previously used cutoff for WHR was the most informative and important in this study as well. There were no observed “dose related” associations between WHR and BE.

BE cases were also significantly more likely to have a high WHR (92.4%) than colonoscopy controls (84.6%) or endoscopy controls (79.5%) (Table 1). High WHR was associated with increased risk of BE in the unadjusted analysis (OR=2.58; 95%CI: 1.5–4.4), $p<0.001$ in the overall cohort. The association between WHR and BE persisted after adjustment for age, sex, race, *H. pylori* infection, alcohol drinking, smoking, and physical activity. Cases with BE had approximately a two-fold increased likelihood to have a high WHR compared to the combined control group (OR=1.93; 95% CI: 1.1–3.5). When we excluded patients <50 years old from all comparisons these results were unchanged. When the 52 patients with previous BE were excluded, WHR remained an elevated predictor of the risk of BE although the OR was slightly attenuated (OR=1.67 (95%CI: 0.91–3.1).

The effect of WHR on BE was more pronounced when examining long segment BE as the outcome (OR=2.81; 95% CI: 1.0–8.0) compared with short BE segments (Table 2). When using only the colonoscopy controls, the adjusted OR was 1.85 (95%CI: 0.9–3.8) for any BE, and the OR was 2.23 (95% CI: 0.7–6.9) for long-segment BE.

The Influence of Race on the Association of WHR on BE

Race appeared to be a confounder as for the association between WHR and BE. White race was significantly associated with high WHR as well as with BE risk. Adjusting for race

attenuated the estimated effect of WHR on BE from 2.55 (95% CI: 1.43–4.54) to the reported adjusted estimate of 1.93 (95% CI: 1.1–3.5) in the overall cohort, and also attenuated the OR of 2.70 (1.37–5.34) to 1.85 (95%CI: 0.9–3.8) when colonoscopy controls only were used.

In a race-stratified analysis of WHR and BE, the strong effect of high WHR on BE was only observed among Whites but not among other races. The estimated effect of high WHR on BE in Whites was 2.5 (95% CI: 1.2–5.4) in 191 cases and 806 controls and even higher when limited to White men (OR=2.70; 95%CI: 1.19–6.14). While among 25 cases and 540 controls who were Black, the OR was 1.06 (95% CI: 0.2–5.9); and in the 18 cases and 111 controls who were Hispanic it was 1.14 (95% CI: 0.4–3.6). Blacks were significantly more likely to be infected with *H. pylori* than Whites (45.3% vs. 19.3; $p<0.001$) (data not shown) but removing *H. pylori* from a model limited to Blacks did not change the observed lack of association between BE and WHR.

We further examined a four level variable that combines race with WHR, and found that Whites with a *high* WHR were 6 times more likely to have BE compared with Blacks with a *low* WHR; (OR=6.01; 95% CI: 2.2–16.8) (Table 3). Blacks with a *high* WHR had a non significant association with BE compared to Blacks with a *low* WHR (OR=1.23; 95% CI: 0.4–3.8). In addition, Whites with a *low* WHR had an elevated risk for BE compared to Blacks with *low* WHR, but this was only significant when comparing to colonoscopy controls (OR=4.35; 95% CI: 1.0–18.8). The traditional interaction term was not significant.

Analysis of Possible Mediating Factors (GERD Symptoms, H2RA/PPI use, BMI and Hiatal Hernia)

BE cases and endoscopy controls had similar distributions for the duration of GERD symptoms, and, as expected the colonoscopy controls were significantly less likely to have ever have GERD symptoms (Table 1). The estimates for the association between BE and high WHR became slightly elevated when we added the presence and duration of GERD symptoms (1.93 to 1.97) or history of PPI/H2RA use (1.93 to 1.96) to the model in the overall cohort (Table 3). The estimates of risk increased even more (1.85 to 2.28) with the addition of history of PPI/H2RA use to the model when colonoscopy controls were used. BMI attenuated the effect of WHR to OR=1.73 (95%CI: 0.93–3.2) in the overall group but not when using PCP controls [OR=1.88 (0.88–4.0)]. BMI was still not significantly associated with BE when including WHR in the model for both groups.

BE patients were significantly more likely to have a hiatal hernia greater than 3 cm and a higher Hill Classification for gastroesophageal flap grade (3 and 4) than either control group (Table 1). However, the WHR-BE association estimates were only slightly attenuated from 1.93 to 1.83 when gastroesophageal flap valve grade or hiatus hernia (1.93 to 1.90) were added to the model.

DISCUSSION

Abdominal obesity as measured by high WHR (0.9 for males and 0.85 for females) is associated with a greater than 85% increase in BE risk. This effect is pronounced for the risk of long-segment but not short-segment BE. The high WHR- BE association seems to be limited to only Whites. This association persists while adjusting for the confounding effects of age, gender, cigarette smoking, alcohol drinking, physical activity, and *H. pylori* infection. The estimated effect was not explained by GERD symptoms or hiatus hernia formation.

There are several possible mechanisms for abdominal obesity's effect on the risk of BE. Increased intra-gastric pressure caused by abdominal obesity has been associated with an increase in GERD symptoms, esophageal acid exposure and transient relaxation of the lower esophageal sphincter.²³ Our analyses as well as a previous study by Edelstein et al.¹² examining GERD symptoms could not explain any of the WHR effect on BE.

Formation and enlargement of hiatus hernia may partly explain the association between large waist to hip ratio and the increased risk of BE. Previous studies with GERD or healthy volunteer study populations have shown a strong association between waist circumference and increased separation of the gastroesophageal pressure components (indicative of enlargement of hiatus hernia).²⁴ Similarly, the prevalence of hiatus hernia, especially large ones, are significantly higher in patients with erosive esophagitis (especially severe grade) and BE compared to GERD patients without BE.^{25–28} Previous studies have also shown a proportionate increase in esophageal acid exposure with higher degree of gastroesophageal flap valve dysfunction as measured by the Hill classification.^{20, 29, 30} We observed that BE was associated with higher prevalence of hiatus hernia (3 cm or greater) and with higher degrees of dysfunction of the gastroesophageal flap valve as indicated by higher scores on the Hill classification. However, adjusting for the presence of hiatus hernia or high Hill classification attenuated the observed association by only 1.5% and 5%, respectively which does not explain the observed high WHR-BE association. On the other hand, the current exposure to high WHR and the potential mediating factors (hiatal hernia and GERD) may not reflect the relevant exposure period whereby these factors may affect BE. Therefore, we cannot completely rule out GERD or hiatus hernias as important factors in the mechanism whereby high WHR could affect BE.

Visceral abdominal fat, in addition to its mechanical effect, produces several proinflammatory cytokines (e.g., tumor necrosis factor- α and leptin). These cytokines can lower serum adiponectin, which has an anti-apoptotic and antiproliferative effect which could, in aggregate, increase inflammation and hence the transformation to BE or cancer in patients with GERD.^{31, 32} These mechanisms need to be further examined.

We reported large racial differences in the effect of WHR on BE. The prevalence of BE is lower in Blacks than Whites in this as well as previous studies.^{33–36} Race may be both an effect modifier and a proxy confounder for unmeasured genetic and environmental factors confounding the association between high WHR and BE. The racial differences in BE are unlikely explained by differences in GERD symptoms because several studies found that the distribution of the severity and reflux related complications (except for BE) are similar among racial groups.^{36, 37} Adjustment for race (using the colonoscopy controls) attenuated the estimated effect of high WHR on BE from 2.70 to 1.85. This may be explained by the different racial distribution of the two groups (42.5% Black participants in the colonoscopy control group versus 10.5% Blacks in the BE case group) and that blacks were less likely to have high WHR (80% vs. 91% in Whites). Further, when we conducted the analyses stratified by race we observed that high WHR was only associated with BE among Whites, but not in Blacks or Hispanics. Other than reduced power due to relatively small sample sizes in the Black race strata (25 cases and 540 controls who were Black) while the reason for the lack of an association between high WHR and BE in Blacks could be related to confounding by *H. pylori* infection, which was significantly higher in Blacks than Whites we could not confirm this explanation in our analysis.

There are major advantages and some limitation for our study. We examined a large racially diverse study population with a racial distribution that was very similar to that of patients from the MEDVAMC, which suggests minimal selection bias. We also used a unique group of controls recruited from primary care clinics who were eligible for screening colonoscopy.

The choice of this control group reduced the likelihood of selection bias since they would likely represent the base population from where the BE cases arise better than endoscopy controls in terms of the occurrence of obesity. However, because we studied predominantly male veterans, our results may not be generalizable to women and nonveterans. The prospective enrolment of study participants allowed us to assess anthropometric measurements before the BE diagnosis in most cases, which reduced the likelihood of recall bias. Furthermore, we used a standardized endoscopic and histologic definition to diagnose BE and excluded cases with visible BE only and no histologic confirmation to avoid misclassification of our outcome. Finally, we used a comprehensive survey to capture detailed data on several potential confounders. However, we cannot completely rule out residual confounding from unmeasured or poorly measured variables.

In conclusion, we found a significant association between high WHR (but not BMI) and increased risk of BE. This association is mainly seen for long-segment BE, and in White individuals. GERD symptoms and PPI/H2RA use did not explain the association. Further research needs to be conducted that examines the effect of pro and anti-inflammatory cytokines, as well as more elaborate means to measure body fat distribution, to further understand the effect of abdominal obesity on the risk of BE.

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Abbreviations

BE	Barrett's esophagus
GERD	gastroesophageal reflux disease
BMI	body mass index
WHR	waist-to-hip ratio
OR	odds ratio
CI	confidence interval
PPI	proton pump inhibitor
H2RA	histamine-2 receptor antagonist
MEDVAMC	Michael E. DeBakey VA Medical Center
EGD	esophagogastroduodenoscopy
sd	standard deviation

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Appendix

Appendix: Definition of study variables:

Variable	Source	Definition
Outcome variable		
Barrett's esophagus	Study endoscopy	Defined as in the presence of specialized small intestinal epithelium in the histopathological examination of biopsy samples obtained from suspected BE areas. Long segment ≥ 3 cm & short segment < 3cm.
Exposure variables		
BMI	Anthropometric measurements	Normal weight: < 24.9, overweight: 25–29.9, and obese: ≥ 30
High risk WHR	Anthropometric measurements	Average waist measurement / average hip measurement High risk: ≥ 0.9 for males and ≥ 0.85 for females

Variable	Source	Definition
Confounders		
Age, gender	Study questionnaire	Age categorized as 40–49, 50–59, 60–69, 70–79
Race/ethnicity	Study questionnaire	White, Black, others
Recruitment source	In overall model only	Primary care or EGD
<i>H. pylori</i>	Study endoscopy and medical record	Defined as organisms seen on hisopathology of any gastric biopsy, or if there was any indication in the medical record (previously positive biopsy or serum or treatment received) of a history of <i>H. pylori</i> infection
Smoking status	Study questionnaire	Categorized using cigarettes only as: non-smoker, 1–29.9 pack-years, and ≥30 pack-years
Alcohol status	Study questionnaire	Categorized as: lifelong non-drinker, ex-drinker (none in 12 months prior), and current drinker
Physical activity	Study questionnaire (IPAC)	Categorized as: low, moderate, and high during the 7 days prior to endoscopy
GERD person-years	Study questionnaire	Sum of all years with reported symptoms of heartburn or acid reflux at least weekly
PPI/H2RA use	Study questionnaire	Any self-reported use of PPIs or H2RA medications
Esophageal flap valve grade	Study endoscopy	Hill classification 1 and 2 vs. 3 and 4
Hiatal hernia	Study endoscopy	Presence of hiatal hernia <3 cm or ≥3 cm

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; EGD, esophagogastroduodenoscopy; IPAC, International Physical Activity Questionnaire; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor; H2RA, histamine-2-receptor antagonist

Figure 1.
Enrollment Flow Diagram

Table 1
Demographic, Anthropometric and Clinical Characteristics of BE Cases and the Two Control Groups for the 1,737 Study Participants

Characteristic	BE Cases (n=237)		All Controls (n=1500)		All BE Cases vs. All Controls, P -value ¹		Endoscopy Controls (n=1021)		BE Cases vs. Endoscopy Controls, P -value ^{1,2}		Colonoscopy Controls (n=479)		BE Cases vs. Colonoscopy Controls, P -value ¹	
	n (%)	n (%)	n (%)	n (%)	P -value ¹		n (%)	n (%)			n (%)	n (%)		
Age														
40–50	11 (4.6)	143 (9.5)	0.001	132 (12.9)	0.001		11 (2.3)	0.034						
50–60	60 (25.3)	478 (31.9)		319 (31.3)			159 (33.2)							
60–70	141 (59.5)	684 (45.6)		437 (42.8)			247 (51.6)							
70–80	25 (10.6)	195 (13.0)		133 (13.0)			62 (12.9)							
Mean years (SD)	62.1 (6.8)	61.4 (7.7)	0.270	61.0 (8.1)	0.11		62.0 (6.9)	0.918						
Sex														
Male	232 (97.9)	1375 (91.7)	0.001	912 (89.3)	<0.001		463 (96.7)	0.358						
Female	5 (2.1)	125 (8.3)		109 (10.7)			16 (3.3)							
Race/ethnicity														
White	191 (80.6)	806 (53.7)	<0.001	584 (57.2)	<0.001		222 (46.3)	<0.001						
Hispanic	18 (7.6)	111 (7.4)		68 (6.7)			43 (9.0)							
Black or African	25 (10.5)	540 (36.0)		336 (32.9)			204 (42.6)							
Other/unknown	3 (1.3)	43 (2.9)		33 (3.2)			10 (2.1)							
BMI														
<25	36 (15.2)	284 (18.9)	0.347	209 (20.5)	0.559		75 (15.6)	0.911						
25–29.9	88 (37.1)	553 (36.9)		383 (37.5)			170 (35.4)							
30+	113 (47.7)	663 (44.2)		429 (42.0)			234 (49.0)							
Mean BMI (SD)	30.3 (5.4)	30.1 (6.1)	0.602	29.7 (6.1)	0.837		30.8 (6.2)	0.295						
Waist circumference (cm)														
63–99.5	41 (17.3)	374 (24.9)	0.025	274 (26.8)	0.042		100 (20.9)	0.663						
99.55–108.0	57 (24.1)	363 (24.2)		259 (25.4)			104 (21.7)							
108.1–117.5	70 (29.5)	254 (23.6)		220 (21.5)			134 (28.0)							
117.6–167.1	67 (28.3)	355 (23.7)		225 (22.0)			130 (27.1)							
Missing information	2 (0.8)	54 (3.6)		43 (4.2)			11 (2.3)							
Mean cm (SD)	111.4 (13.1)	108.3 (14.4)	0.002	107.4 (14.2)	0.010		110.3 (14.4)	0.342						

Characteristic	BE Cases (n=237)		All Controls (n=1500)		All BE Cases vs. All Controls, P -value ¹		Endoscopy Controls (n=1021)		BE Cases vs. Endoscopy Controls, P -value ^{1,2}		Colonoscopy Controls (n=479)		BE Cases vs. Colonoscopy Controls, P -value ¹	
	n (%)	n (%)	n (%)	n (%)			n (%)	n (%)			n (%)	n (%)		
Median cm	110.2	107.7	107.7	106.5			106.5	109.8			109.8			
Waist-to-hip ratio														
Low risk	16 (6.8)	229 (15.3)	229 (15.3)	166 (16.3)	<0.001		166 (16.3)	63 (13.2)	<0.001		63 (13.2)	0.008		
High risk	219 (92.4)	1217 (81.1)	1217 (81.1)	812 (79.5)			812 (79.5)	405 (84.6)			405 (84.6)			
Missing information	2 (0.8)	54 (3.6)	54 (3.6)	43 (4.2)			43 (4.2)	11 (2.3)			11 (2.3)			
Mean ratio (SD)	0.98 (0.06)	0.95 (0.07)	0.95 (0.07)	0.95 (0.07)	<0.001		0.95 (0.07)	0.96 (0.06)	<0.001		0.96 (0.06)	<0.001		
Presence and Duration of GERD symptoms														
None	104 (43.9)	795 (53.0)	795 (53.0)	464 (45.4)	0.002		464 (45.4)	331 (69.1)	0.095		331 (69.1)	<0.001		
1-5 years	16 (6.8)	128 (8.5)	128 (8.5)	97 (9.5)			97 (9.5)	31 (6.5)			31 (6.5)			
>5 years	97 (40.9)	447 (29.8)	447 (29.8)	369 (36.1)			369 (36.1)	78 (16.3)			78 (16.3)			
Missing information	20 (8.4)	130 (8.7)	130 (8.7)	91 (8.9)			91 (8.9)	39 (8.1)			39 (8.1)			
Mean years (SD)	10.0 (13.2)	7.4 (12.0)	7.4 (12.0)	9.2 (12.9)	0.008		9.2 (12.9)	3.7 (8.7)	<0.001		3.7 (8.7)	<0.001		
Hiatal hernia														
Absent	35 (14.8)	580 (38.7)	580 (38.7)	362 (35.5)	<0.001		362 (35.5)	218 (45.5)	<0.001		218 (45.5)	<0.001		
Present <3	91 (38.4)	592 (39.5)	592 (39.5)	420 (41.1)			420 (41.1)	172 (35.9)			172 (35.9)			
Present >3	110 (46.4)	318 (21.2)	318 (21.2)	231 (22.6)			231 (22.6)	87 (18.2)			87 (18.2)			
Missing information	1 (0.4)	10 (0.7)	10 (0.7)	8 (0.8)			8 (0.8)	2 (0.4)			2 (0.4)			
Gastroesophageal flap valve grade														
1 and 2	66 (27.8)	750 (50.0)	750 (50.0)	500 (49.0)	<0.001		500 (49.0)	250 (52.2)	<0.001		250 (52.2)	<0.001		
3 and 4	167 (70.5)	722 (48.1)	722 (48.1)	501 (49.0)			501 (49.0)	221 (46.1)			221 (46.1)			
Missing	4 (1.7)	28 (1.9)	28 (1.9)	20 (2.0)			20 (2.0)	8 (1.7)			8 (1.7)			

¹ P -value is calculated without including patients with missing values

² P -value comparing BE cases from endoscopy (N=193) to endoscopy controls

Table 2

Multivariate Odds Ratios for Association of Anthropometric Measurements with any BE and for Short and Long Segment BE in Overall Study Population and vs. Colonoscopy Controls

Characteristic	All BE Cases vs. All Controls					
	Any BE vs. No BE		Short Segment BE vs. No BE		Long Segment BE vs. No BE	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
BMI*						
<25 (ref)	1.0		1.0		1.0	
25–29.9	1.50 (0.95–2.36)	0.082	1.60 (0.89–2.86)	0.115	1.50 (0.76–2.93)	0.239
30+	1.13 (0.71–1.81)	0.602	1.32 (0.73–2.40)	0.355	0.95 (0.47–1.93)	0.889
WHR*						
Low risk (ref)	1.0		1.0		1.0	
High risk	1.93 (1.07–3.49)	0.028	1.57 (0.79–3.13)	0.196	2.81 (1.00–7.99)	0.050
All BE Cases vs. Colonoscopy Controls						
BMI*						
<25 (ref)	1.0		1.0		1.0	
25–29.9	1.06 (0.61–1.86)	0.835	1.31 (0.66–2.60)	0.438	0.84 (0.39–1.79)	0.651
30+	0.86 (0.48–1.55)	0.624	1.13 (0.55–2.30)	0.741	0.63 (0.28–1.40)	0.251
WHR*						
Low risk (ref)	1.0		1.0		1.0	
High risk	1.85 (0.90–3.82)	0.096	1.65 (0.72–3.78)	0.240	2.23 (0.72–6.87)	0.162

* Adjusted for age, sex, race, *H. pylori* infection, alcohol drinking, smoking, physical activity, and recruitment source (for overall models)

Table 3

The association of WHR stratified by race and additional adjustment for GERD symptoms with/without PPI/H2RA, hiatal hernia, and gastroesophageal flap valve grade

Characteristic	Overall		BE cases vs. Colonoscopy Controls	
	OR (95%CI)	P-value	OR (95%CI)	P-value
WHR and Race *				
Blacks with low risk WHR (ref)	1.0 (Ref)		1.0 (Ref)	
Whites with high risk WHR	6.01 (2.15–16.78)	0.001	8.08 (2.39–27.35)	0.001
Blacks with high risk WHR	1.23 (0.40–3.82)	0.720	1.39 (0.37–5.19)	0.620
White with low risk WHR	2.81 (0.84–9.47)	0.095	4.35 (1.01–18.76)	0.049
WHR * with GERD presence and duration				
Low risk (ref)	1.0 (Ref)		1.0 (Ref)	
High risk	1.97 (1.07–3.62)	0.029	2.00 (0.91–4.40)	0.083
WHR * with PPI/H2RA				
Low risk (ref)	1.0 (Ref)		1.0 (Ref)	
High risk	1.96 (1.08–3.53)	0.026	2.28 (1.02–5.10)	0.045
WHR * with both GERD and PPI/H2RA				
Low risk (ref)	1.0 (Ref)		1.0 (Ref)	
High risk	1.92 (1.07–3.47)	0.030	2.10 (0.95–4.64)	0.067
WHR * with hiatal hernia				
Low risk (ref)	1.0 (Ref)		1.0 (Ref)	
High risk	1.90 (1.04–3.44)	0.035	1.84 (0.87–3.89)	0.110
WHR * with gastroesophageal flap valve grade				
Low risk (ref)	1.0 (Ref)		1.0 (Ref)	
High risk	1.83 (1.01–3.33)	0.048	1.77 (0.84–3.71)	0.131

* Adjusted for age, sex, race, *H.pylori* infection, alcohol drinking, smoking, physical activity, and recruitment source (for overall models)