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Inverse Association Between Gluteofemoral Obesity and Risk of Barrett's Esophagus in a Pooled Analysis

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Abstract

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Background & Aims—Gluteofemoral obesity (determined by measurement of subcutaneous fat in hip and thigh regions) could reduce risks of cardiovascular and diabetic disorders associated with abdominal obesity. We evaluated whether gluteofemoral obesity also reduces risk of Barrett's esophagus (BE), a premalignant lesion associated with abdominal obesity.

Methods—We collected data from non-Hispanic white participants in 8 studies in the Barrett's and Esophageal Adenocarcinoma Consortium. We compared measures of hip circumference (as a proxy for gluteofemoral obesity) from cases of BE (n=1559) separately with 2 control groups: 2557 population-based controls and 2064 individuals with gastroesophageal reflux disease (GERD controls). Study-specific odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using individual participant data and multivariable logistic regression and combined using random effects meta-analysis.

Results—We found an inverse relationship between hip circumference and BE (OR per 5 cm increase, 0.88; 95% CI, 0.81–0.96), compared with population-based controls in a multivariable model that included waist circumference. This association was not observed in models that did not include waist circumference. Similar results were observed in analyses stratified by frequency of GERD symptoms. The inverse association with hip circumference was only statistically significant among men (vs population-based controls: OR, 0.85; 95% CI, 0.76–0.96 for men; OR, 0.93; 95% CI, 0.74–1.16 for women). For men, within each category of waist circumference, a larger hip circumference was associated with decreased risk of BE. Increasing waist circumference was associated with increased risk of BE in the mutually adjusted population-based and GERD control models.

Conclusions—Although abdominal obesity is associated with increased risk of BE, there is an inverse association between gluteofemoral obesity and BE—particularly among men.

Keywords

BEACON; Obesity; Esophageal Cancer; Epidemiology; Risk Factors

Abdominal obesity is associated with an increased risk of esophageal adenocarcinoma (EA) and its precursor lesion Barrett's esophagus (BE).[1,2] These associations remain after controlling for the confounding effects of gastroesophageal reflux disease (GERD) symptoms, suggesting that non-GERD factors are important.[3] In abdominal obesity, increased intra-abdominal adipose tissue stores may cause a number of systemic effects including insulin resistance, alteration in adipokines and cytokines, and systemic chronic inflammation.[4] These systemic effects have been associated with non-esophageal cancers and a recent meta-analysis found they may be important in BE.[5]

Abdominal obesity is also strongly associated with an increased risk of diabetes mellitus and cardiovascular disease.[6] In contrast, gluteofemoral obesity, manifested by increased subcutaneous fat in the hip and thigh region, has a protective association with these disorders.[7,8] One postulated mechanism for this protective effect is that gluteofemoral adipose tissue acts as a metabolic “sink” reducing the levels of circulating free fatty acids, insulin and adipocytokines that lead to metabolic and cardiovascular disease.[9]

Few studies have examined the effects of gluteofemoral obesity on the risks of EA and BE. A large cohort study of 391,456 participants (of whom 124 developed EA during follow-up) found that, after mutual adjustment, the risk of EA was strongly positively associated with abdominal obesity but inversely associated with gluteofemoral obesity.[10] In a case-control study of BE, conducted among males referred for colorectal cancer screening, there was a suggestion of a similar inverse association with gluteofemoral obesity, although the precision of the estimates were limited by study size and sex-specific effects were unable to be analyzed as all participants were males.[11]

Investigating the effects of fat distribution patterns on the risk of BE is important in furthering our understanding of the role of obesity in BE. If gluteofemoral obesity were found to reduce the risks associated with abdominal obesity, this would support the hypothesis that potentially modifiable metabolic factors related to abdominal obesity (but unrelated to GERD) are important in the pathogenesis of the disease. In addition, sex differences in fat distribution may help explain the large male-predominance seen at each stage of the natural history of EA including BE.[12-15]

The international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON, http://beacon.tlvnet.net/) is a large international consortium that has pooled and harmonized detailed individual participant data including anthropometric measurements from case-control studies of BE. Using this unique resource, this analysis determined the risks of BE associated with gluteofemoral and abdominal obesity and assessed the effects of each exposure after mutual adjustment. Further, we sought to determine if there were sex differences in these associations and whether the associations with gluteofemoral and abdominal obesity were confounded or modified by other known risk factors for BE.

Materials and Methods

Study population

BEACON was formed in 2005 in collaboration with the US National Cancer Institute. For the purpose of this analysis, we initially pooled individual participant data from 1909 BE cases, 3618 population-based controls and 2666 GERD controls from eight independent case-control studies participating in BEACON (see Supplementary Material)[11,16-21]. Details of the five original case-control studies in BEACON and the data pooling methods for BEACON have been described in detail elsewhere.[22,23] The remaining three case-control studies were recently added to the BEACON dataset, are included in this study, and have been described previously.[11,20,21] In all studies, cases included persons with endoscopic evidence of columnar mucosa in the tubular esophagus, accompanied by the presence of specialized intestinal metaplasia in an esophageal biopsy, and cases included persons with prevalent and newly diagnosed BE.[11,20-22] The cases are compared with population-based controls, that represent the underlying source population from which cases arose, and GERD controls, the population undergoing endoscopy from which BE cases are diagnosed. Population-based controls were frequency matched to BE cases on sex and age in most,[16,18,19,21] but not all studies.[11,20] GERD controls were matched to the BE group on age and sex in only two studies.[18,21] The FINBAR study matched controls to their EA cases rather than BE cases.[17] The original studies and the current data pooling were approved by

the institutional review board or research ethics committee of each sponsoring institution. Written informed consents were obtained from all study subjects.

For the current analysis, we excluded persons with missing data for waist and/or hip circumferences (431 population-based controls, 421 GERD controls and 236 BE cases). We additionally restricted our analyses to non-Hispanic white study participants (2557 population-based controls, 2064 GERD controls, 1559 BE cases) due to low numbers of cases from non-white ethnic groups. Seven studies provided a population-based control group and six studies provided a GERD control group (Table 1).

Study variables

At interview, the following anthropometric measures were collected in-person using study-specific protocols: height, weight, waist circumference, and hip circumference. In the Kaiser Permanente study, measurements of mid-thigh circumference were taken instead of hip circumference and used as a proxy for gluteofemoral obesity.[18] As detailed below, for the analysis, we used study-specific tertiles to overcome the issue of differences in distributions between the included studies. Excluding Kaiser Permanente from the analysis did not change the results. We calculated body mass index (BMI) as weight in kilograms divided by height in meters squared (kg/m^2). In addition to the anthropometric data, individual-level harmonized clinical, demographic, and questionnaire data for each study participant were merged into a single de-identified dataset and included information on study, case-control status, age at diagnosis for cases and age at study enrolment for controls, sex, ethnicity, highest level of education, frequency of GERD symptoms and history of cigarette smoking. Frequency of GERD symptoms was the highest reported frequency of either heartburn or acid regurgitation symptoms. We defined “frequent symptoms” as those occurring at least weekly. The data were checked for consistency and completeness and any apparent inconsistencies were followed-up with individual study investigators.

Statistical analysis

The primary aim of the analysis was to examine the associations of hip circumference and waist circumference (in tertiles and as a continuous measure) with the risk of BE, and then the effect of each measure after mutual adjustment with the risk of BE. Because distributions of anthropometric measures varied across studies and sexes, we derived study-and sex-specific tertiles for hip and waist circumferences. We used a two-step analytic approach.[24] In the first stage, study-specific odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression models. In the second stage, the study-specific ORs were combined using random-effects meta-analytic models to generate summary ORs. We excluded studies from the second-step if the logistic regression model failed to converge. We used the inconsistency index, I^2, to assess heterogeneity between studies.[25] Larger I^2 values reflect increasing heterogeneity, beyond what is attributable to chance. I^2 values of 25%, 50% and 75% were used as evidence of low, moderate, or high levels of heterogeneity, respectively.

Exposure variables were assessed in relation to risk of BE using population-based controls and GERD controls as comparison groups. Our approach was, first, to examine the

unadjusted associations of hip circumference and waist circumference with risk of BE. We then adjusted for age (<50, 50-<60, 60-<70, ≥70 years), sex, education (school only, technical college/diploma, university/college; unavailable and so unadjusted for in the University of North Carolina at Chapel Hill study), and smoking status (never, ever). Finally, we further mutually adjusted for hip and waist circumference to examine their independent effects on risk of BE. Models that compared cases with population-based controls were also subsequently adjusted for self-reported GERD symptoms (less than weekly vs. at least weekly) to evaluate potential confounding effects of GERD symptoms. The study-specific ORs for the Cleveland Barrett's Esophagus Study were unadjusted for education, smoking status and GERD symptoms due to unavailable data for these variables among population-based controls. The lowest tertile for each categorical variable was used as the reference category. We evaluated continuous variables to test for linear trend by using OR per 5 cm increase in hip and waist circumference.

Finally, we assessed whether the association between hip circumference (and waist circumference) and risk of BE was modified by sex (male, female) by performing likelihood ratio tests of nested models with and without the hip circumference-sex interaction term. Likewise, but for comparisons with population-based controls only, we also assessed for effect modification by frequency of GERD symptoms (less than weekly, at least weekly).

All tests for statistical significance were two-sided at α=0.05 and analyses were conducted using Stata 13.1 (StataCorp LP, College Station, TX).

Results

The numbers of cases and controls, summary data for anthropometric measurements by study, and characteristics of the pooled dataset are shown in Tables 1 and 2. Cases and population-based controls were similar in terms of age and sex due to matching in most studies. There was considerable variation in average BMI, and waist and hip circumferences across the studies and case-control groups.

Table 3 shows the estimates of association between waist and hip circumferences and BE compared with both population-based controls and GERD controls. After adjusting for age, sex, education, and smoking status, waist circumference was positively associated with BE for comparisons with population-based controls (summary OR per 5cm increase = 1.08; 95% CI: 1.01-1.15). After further adjustment for hip circumference, the magnitude of the association between waist circumference and BE was strengthened (vs. population-based controls: OR = 1.18; 95% CI: 1.06-1.31; Tertile 3 vs. Tertile 1, OR = 2.18; 95% CI: 1.35-3.51, P_{trend}<.001). While the association with waist circumference adjusted for hip circumference was somewhat attenuated when we compared cases with GERD controls, waist circumference remained statistically significantly associated with increased BE risk (OR = 1.09; 95% CI: 1.02-1.16).

In contrast, when compared with population-based controls, there was no association between hip circumference and BE in the unadjusted model or in the model adjusted for only age, sex, education, and smoking status (Table 3). However, after further adjustment for

waist circumference, we found an inverse association between hip circumference and BE for comparisons with population-based controls (OR = 0.88; 95% CI: 0.81-0.96). Compared to persons in the lowest tertile of hip circumference, persons in the highest tertile of hip circumference had 25% lower risk of BE (95% CI: 0.58-0.98, P_{trend} = .04) in the mutually adjusted model (Supplementary Figure 1). We found no consistent association between hip circumference and BE when cases were compared with GERD controls (OR = 0.97; 95% CI: 0.87-1.08). For comparisons with population-based controls, the positive association with waist circumference (OR = 1.10; 95% CI: 1.01-1.21) and inverse association with hip circumference (OR = 0.89; 95% CI: 0.81-0.97) remained after additional adjustment for frequency of GERD symptoms (Supplementary Table 1).

When stratified by sex (Table 4), the strength of the association of waist circumference with BE was similar in males and females in the mutually adjusted population-based control model; although risk estimates for females did not reach statistical significant perhaps due to small numbers. We found no evidence for statistical interaction between waist circumference and sex in relation to risk of BE ($P_{interaction}$ = .10). However, hip circumference was inversely associated with BE in males in the mutually adjusted population-based control model (OR = 0.85; 95% CI: 0.76-0.96) but was not associated with BE in females (OR = 0.93; 95% CI: 0.74-1.16; $P_{interaction}$ = .004). We additionally performed stratified analyses by GERD symptom history using the population-based control group as the comparator (Table 5). Waist circumference appeared to be more strongly associated with BE in those with infrequent GERD symptoms. The inverse association between hip circumference and BE was similar in magnitude in both those with infrequent and frequent GERD symptoms and frequency of GERD symptoms does not appear to modify the inverse association with hip circumference ($P_{interaction}$ = .62).

Among males within each category of waist circumference, larger hip circumference was associated with a decreased risk of BE (Supplementary Table 2). Males at the highest risk of BE simultaneously had waist circumference in the highest tertile and hip circumference in the lowest tertile. Males at the lowest risk of BE had waist circumference in the lowest tertile and hip circumference in the highest tertile. The pattern was different for females with hip circumference not reducing the risk of BE within each waist category; however, these analyses were limited by smaller numbers of females in all categories.

We found evidence for moderate to high between-study heterogeneity for associations between waist circumference and BE (Table 3). However, removal of the Cleveland Barrett's Esophagus Study reduced the between-study heterogeneity to below 10%. The association with waist circumference was somewhat attenuated as a result ($OR_{Tertile\ 2}$ = 1.37; 95% CI: 1.08-1.74; I^2 = 9%; $OR_{Tertile\ 3}$ = 1.68; 95% CI: 1.28-2.22; I^2 = 4%). Likewise, there was evidence of low to moderate between-study heterogeneity for the association between hip circumference (continuous) and risk of BE (Table 3). This heterogeneity was mainly driven by a stronger inverse association from The Newly Diagnosed Barrett's Esophagus Study. When this study was excluded, I^2 reduced from 42% to 20%. Importantly the effect estimate was only minimally attenuated and hip circumference remained inversely associated with BE (OR = 0.90; 95% CI: 0.83-0.98) when compared with population-based controls.

Discussion

We conducted pooled analyses of eight case-control studies, examining the independent effects of abdominal obesity and gluteofemoral obesity on the risk of BE. As has been shown previously, we confirmed that abdominal obesity is associated with increased risk of BE. But in addition, we found that gluteofemoral obesity was inversely associated with BE. This association was strongest when we compared cases with population-based controls, and persisted even after adjusting for frequency of GERD symptoms. Finally, we found evidence of modification of the effect of gluteofemoral obesity by sex; the inverse association with hip circumference was statistically significant for analyses among males, but not in analyses among females.

In a prior cohort study, Steffen et al. found that gluteofemoral obesity was inversely associated with risk of EA, adjusting for abdominal obesity.[10] However, that study was not able to adjust for potential confounding by GERD. In a prior case-control study, Rubenstein et al. found that gluteofemoral obesity was inversely associated with a combined outcome of BE or erosive esophagitis, adjusting for abdominal obesity, but the study was too small to accurately estimate the effect on BE alone, and did not include any females.[11] Gluteofemoral obesity has previously been shown to be protective against diabetes mellitus and cardiovascular disease.[7,8]

Adipose tissue in the gluteofemoral compartment behaves differently metabolically than adipose tissue in the abdominal compartment.[7,9,26] It has been hypothesized that gluteofemoral adipose tissue may serve as a “metabolic sink” where excess calories can be safely stored without detrimental metabolic effects. Our finding of an inverse association of gluteofemoral obesity with the risk of BE suggests that abdominal obesity may not only exert its effects on risk via mechanical effects in promoting GERD but also via non-GERD metabolic effects. Multiple studies have demonstrated an association between levels of different circulating adipokines and BE or EA.[5,21,27-29] It seems unlikely that a single factor is responsible for all of the risk attributable to obesity; rather it would seem that abdominal obesity (if not counteracted by gluteofemoral obesity) results in a milieu of circulating metabolic factors that promote BE and EA. Risk prediction models for BE that include a term for waist-to-hip ratio have been shown to have reasonable discriminatory ability;[30,31] whether gluteofemoral (hip circumference) and abdominal (waist circumference) obesity separately discriminate better between persons with and without BE than waist-to-hip ratio is unknown and requires further study.

Importantly, we found evidence for modification of the effect of gluteofemoral obesity by sex. There does not appear to be a protective effect among females. For unclear reasons, males are at much greater risk than females for BE,[12] and especially for EA.[32,33] Females and males differ in their distribution of adipose tissue, with males having over 50% greater intra-abdominal fat mass and a third less subcutaneous fat, including gluteofemoral fat, than females.[34] In addition, estrogen regulates the secretion of adipokines from adipose tissue.[35] Taken together, these findings suggest that the differential compartments for deposition of adipose tissue and metabolic effects may explain much of the risk of male sex for BE.

Our study had some limitations. First, we were only able to study the outcome of BE and not EA. In EA nearly two-thirds of patients have substantial weight loss at diagnosis, making the study of obesity related factors difficult in case-control studies.[36] In addition, the studies included a mix of patients with newly diagnosed and prevalent diagnoses of BE, which could have biased the results unpredictably. While we attempted to control for confounding, information on some known risk factors for BE (e.g. *Helicobacter pylori* status, diet, medication use) was not uniformly available across the studies, and it is possible that unmeasured (and/or unknown) variables might have influenced our results. Whether obesity (gluteofemoral and/or abdominal) affects risk of BE independently of GERD is further complicated in observational studies as it is impossible to exclude residual confounding by GERD because symptom history is imperfectly correlated with the occurrence of GERD, and reporting can be compromised by treatment history. Studies combining genetic and observational data are attempting to address this issue.[37] We examined associations separately in males and females; however, even with the large resources of BEACON, the number of females in our study was still small and the risk estimates for females were imprecise as a result. Finally, there was moderate heterogeneity in some effect estimates. This between-study heterogeneity was largely driven by a single study. However, removal of the study only minimally attenuated the inverse association with hip circumference and risk of BE. While hip circumference was inversely associated with BE among persons with frequent GERD symptoms for comparisons with population-based controls, there was no association when we compared cases with GERD controls. There was however moderate to high between-study heterogeneity for these risk estimates, some of which may be due to differences between the individual study inclusion criteria for GERD controls.

There are also a number of strengths to the study. Notably, we were able to combine data from eight independent studies from different geographic regions. The component studies used a similar diagnosis of BE, and all measured anthropometrics rather than using self-report. We were able to compare the effects to both population controls and GERD controls, adjust for a number of important potential confounders, and examine for effect modification by sex.

In summary, we found that while abdominal obesity is associated with increased risk of BE, gluteofemoral obesity is inversely associated with the risk of BE. The inverse association with gluteofemoral obesity is independent of GERD, and may not be present in females. These findings support a metabolic explanation for the effect of obesity on BE and for the risk of male sex on BE. Further studies are required to determine whether the distribution of obesity and metabolic effects promote the progression from BE to EA, and whether modifying these factors can prevent the cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

BEACON	Barrett's and Esophageal Adenocarcinoma Consortium
BMI	body mass index
CI	confidence interval
GERD	gastroesophageal reflux disease
OR	odds ratio

Study population

We used data from eight independent case-control studies participating in BEACON: the Study of Digestive Health (based in Brisbane, Australia)[16]; the Factors Influencing the Barrett's/Adenocarcinoma Relationship (FINBAR) study (based in Ireland)[17]; the Epidemiology and Incidence of Barrett's Esophagus study (based in the Kaiser Permanente Northern California population)[18]; the Study of Reflux Disease (based in western Washington State)[19]; the Epidemiologic Case-Control Study of Barrett's Esophagus (based at The University of North Carolina at Chapel Hill, NC); the Houston Barrett's Esophagus study (based at the Michael E. DeBakey VA Medical Center at Houston, TX)[20]; The Newly Diagnosed Barrett's Esophagus Study (based at the University of Michigan and Ann Arbor Veterans Affairs Medical Center at Ann Arbor, MI)[11], and the Cleveland Barrett's Esophagus Study (based at two hospitals in the Case Comprehensive Cancer Center at Cleveland, OH: University Hospitals Case Medical Center and Cleveland Clinic Foundation)[21].

Table 1

Distribution of Body Mass Index, Waist Circumference and Hip Circumference by Study

	Population-based controls				GERD controls				BE cases			
		BMI (kg/m^2)	Waist (cms)	Hip (cms)		BMI (kg/m^2)	Waist (cms)	Hip (cms)		BMI (kg/m^2)	Waist (cms)	Hip (cms)
Study	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**n**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Houston	273	31.1 (6.2)	112.6 (14.0)	115.7 (12.8)	823	30.1 (5.9)	108.7 (13.7)	113.0 (11.9)	287	30.3 (5.5)	110.9 (13.4)	112.9 (11.2)
Cleveland	707	27.8 (5.8)	94.5 (16.1)	105.1 (14.3)	115	29.5 (5.8)	105.1 (17.0)	107.2 (15.1)	105	30.8 (5.7)	108.6 (13.4)	109.9 (13.9)
FINBAR	256	27.7 (4.0)	97.6 (11.2)	102.1 (9.3)	229	29.2 (4.0)	98.0 (9.9)	102.9 (8.4)	224	27.8 (4.4)	99.2 (11.7)	103.1 (10.0)
KPNC	263	29.5 (5.7)	99.5 (15.7)		251	29.2 (4.9)	98.2 (14.4)	*a*	260	29.5 (5.6)	101.3 (14.7)	
NDB	639	29.8 (5.5)	107.4 (13.6)	107.2 (10.7)	0	-	-	-	133	30.5 (5.0)	110.0 (12.7)	107.3 (9.2)
SDH	233	26.8 (4.5)	97.6 (13.3)	106.4 (8.6)	0	-	-	-	231	27.7 (4.6)	101.6 (12.9)	107.9 (9.5)
Washington	186	27.7 (5.0)	94.9 (14.2)	107.0 (9.6)	371	28.4 (5.5)	96.5 (13.7)	108.5 (10.9)	171	29.3 (5.1)	100.0 (13.1)	109.5 (10.7)
UNC	0	-	-	-	275	28.0 (6.2)	91.4 (16.5)	103.6 (15.0)	148	28.4 (5.8)	97.2 (16.9)	103.9 (14.5)

NOTE.

*1*KPNC includes thigh measures and not hip circumference: Population controls, 49.9 cms (6.3); GERD controls, 49.1 cms (5.7); BE cases, 49.9 cms (6.9). Participating studies: Houston, the Houston Barrett's Esophagus study; Cleveland, the Cleveland Barrett's Esophagus Study(Case Comprehensive Cancer Center: University Hospitals Case Medical Center and Cleveland Clinic Foundation); FINBAR, the Factors Influencing the Barrett's/Adenocarcinoma Relationship study (Ireland); KPNC, the Epidemiology and Incidence of Barrett's Esophagus study (Kaiser Permanente, Northern California); NDB, The Newly Diagnosed Barrett's Esophagus Study (University of Michigan and Ann Arbor Veterans Affairs Medical Center, Michigan); SDH, the Study of Digestive Health (Brisbane, Australia); Washington, the Study of Reflux Disease (western Washington State); and UNC, the Epidemiologic Case-Control Study of Barrett's Esophagus (Chapel Hill, North Carolina).

BE, Barrett's esophagus; BMI, body mass index, GERD, gastroesophageal reflux disease; SD, standard deviation.

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Table 2
Characteristics of the Combined Study Population within the BEACON Consortium

	BE cases (n = 1559)	Population-based controls (n = 2557)	GERD controls (n = 2064)
Age, y, mean (SD)	60.0 (11.1)	58.2 (9.9)	57.3 (12.1)
Male sex, n (%)	1253 (80.4)	1839 (71.9)	1489 (72.1)
Education, n (%)			
School only	425 (28.9)	385 (21.1)	620 (37.0)
Tech/Diploma	615 (41.7)	764 (41.8)	502 (29.9)
University	433 (29.4)	677 (37.1)	555 (33.1)
Missing	49	731	113
Smoking status, n (%)			
Never	489 (32.2)	760 (41.6)	779 (39.5)
Ever	1030 (67.8)	1066 (58.4)	1192 (60.5)
Missing	40	731	93
Frequency of GERD symptoms, n (%)			
Less than weekly	453 (31.0)	1355 (77.3)	686 (37.0)
At least weekly	1009 (69.0)	399 (22.7)	1170 (63.0)
Missing	97	803	208

NOTE. All population-based controls from Cleveland (n=707) were missing data for education, smoking status and frequency of GERD symptoms.

BE, Barrett's esophagus; GERD, gastroesophageal reflux disease; SD, standard deviation; y, years.

Table 3

Odds Ratios and 95% Confidence Intervals for the Associations Between Waist and Hip Circumferences and Risk of Barrett's Esophagus

	No. of studies	OR (95% CI)[a]	I^2	OR[b] (95% CI)	I^2	OR[c] (95% CI)	I^2
Barrett's esophagus vs population-based controls							
Waist circumference							
Tertile 1	7	Referent		Referent		Referent	
Tertile 2	7	1.34 (1.06-1.69)	37%	1.37 (1.04-1.80)	51%	1.53 (1.13-2.07)	45%
Tertile 3	7	1.88 (1.19-2.98)	85%	1.83 (1.12-2.97)	85%	2.18 (1.35-3.51)	68%
Per 5 cm increase	7	1.09 (1.02-1.18)	88%	1.08 (1.01-1.15)	82%	1.18 (1.06-1.31)	75%
Hip circumference							
Tertile 1	7	Referent		Referent		Referent	
Tertile 2	7	1.05 (0.88-1.25)	0%	1.08 (0.90-1.29)	0%	0.83 (0.67-1.03)	0%
Tertile 3	7	1.28 (0.85-1.93)	82%	1.32 (0.86-2.01)	81%	0.75 (0.58-0.98)	4%
Per 5 cm increase	7	1.04 (0.97-1.12)	75%	1.05 (0.97-1.13)	76%	0.88 (0.81-0.96)	42%
Barrett's esophagus vs GERD controls							
Waist circumference							
Tertile 1	6	Referent		Referent		Referent	
Tertile 2	6	1.17 (0.97-1.41)	0%	1.15 (0.95-1.40)	0%	1.24 (0.99-1.55)	0%
Tertile 3	6	1.53 (1.28-1.83)	0%	1.46 (1.22-1.76)	0%	1.57 (1.21-2.04)	0%
Per 5 cm increase	6	1.08 (1.05-1.11)	0%	1.06 (1.03-1.09)	0%	1.09 (1.02-1.16)	38%
Hip circumference							
Tertile 1	6	Referent		Referent		Referent	
Tertile 2	6	0.99 (0.83-1.19)	0%	0.94 (0.78-1.14)	0%	0.79 (0.64-0.99)	0%
Tertile 3	6	1.27 (1.00-1.61)	40%	1.31 (0.98-1.76)	56%	0.93 (0.60-1.43)	57%
Per 5 cm increase	6	1.02 (0.99-1.06)	0%	1.05 (1.00-1.09)	25%	0.97 (0.87-1.08)	62%

[a] Unadjusted models.

[b] Models included terms for age (<50, 50-<60, 60-<70, 70+), sex (except NDB), education (except UNC and Cleveland), smoking (ever, never; except Cleveland) and either waist circumference or hip circumference.

[c] Models adjusted for same factors as (b) but also waist circumference and hip circumference.

CI, confidence interval; OR, odds ratio; GERD, gastroesophageal reflux disease.

Table 4

Fully Adjusted Odds Ratios and 95% Confidence Intervals for the Associations Between Waist and Hip Circumferences and Risk of Barrett's Esophagus, Stratified by Sex

	Males			Females		
	No. of studies	**OR (95% CI)**	**I^2**	**No. of studies**	**OR (95% CI)**	**I^2**
Barrett's esophagus vs population-based controls						
Waist circumference	No. of studies	OR (95% CI)	I^2	No. of studies	OR (95% CI)	I^2
Tertile 1	7	Referent		5	Referent	
Tertile 2	7	1.41 (1.09-1.84)	14%	5	1.10 (0.44-2.78)	63%
Tertile 3	7	2.07 (1.32-3.25)	55%	4	1.89 (0.70-5.09)	44%
Per 5 cm increase	7	1.18 (1.05-1.32)	72%	5	1.20 (0.97-1.48)	70%
Hip circumference						
Tertile 1	7	Referent		5	Referent	
Tertile 2	7	0.86 (0.66-1.11)	12%	5	0.65 (0.25-1.71)	58%
Tertile 3	7	0.68 (0.48-0.98)	33%	5	0.97 (0.29-3.25)	68%
Per 5 cm increase	7	0.85 (0.76-0.96)	54%	5	0.93 (0.74-1.16)	58%
Barrett's esophagus vs GERD controls						
Waist circumference	No. of studies	OR (95% CI)	I^2	No. of studies	OR (95% CI)	I^2
Tertile 1	6	Referent		4	Referent	
Tertile 2	6	1.20 (0.93-1.55)	0%	4	1.17 (0.64-2.17)	23%
Tertile 3	6	1.57 (1.17-2.12)	0%	4	1.22 (0.67-2.22)	0%
Per 5 cm increase	6	1.10 (1.03-1.17)	13%	5	1.02 (0.90-1.15)	26%
Hip circumference						
Tertile 1	6	Referent		4	Referent	
Tertile 2	6	0.82 (0.63-1.05)	0%	4	0.82 (0.45-1.48)	24%
Tertile 3	6	0.94 (0.62-1.43)	40%	4	1.00 (0.54-1.84)	0%
Per 5 cm increase	6	0.96 (0.86-1.07)	34%	5	1.04 (0.85-1.28)	58%

NOTE. Models included terms for age (<50, 50-<60, 60-<70, 70+), education (except UNC and Cleveland), smoking (ever, never; except Cleveland), waist circumference and hip circumference.

NDB and Houston were excluded from Female-only analyses.

CI, confidence interval; OR, odds ratio; GERD, gastroesophageal reflux disease.

Table 5

Fully Adjusted Odds Ratios and 95% Confidence Intervals for the Associations Between Waist and Hip Circumferences and Risk of Barrett's Esophagus, Stratified by GERD symptoms

		Barrett's esophagus vs population-based controls					
		Less than weekly GERD symptoms			At least weekly GERD symptoms		
		No. of studies	OR (95% CI)	I^2	No. of studies	OR (95% CI)	I^2
Waist circumference							
	Tertile 1	6	Referent		6	Referent	
	Tertile 2	6	1.65 (1.12-2.44)	0%	6	1.22 (0.67-2.22)	52%
	Tertile 3	6	2.15 (1.33-3.48)	0%	6	1.19 (0.58-2.44)	55%
Per 5 cm increase		6	1.16 (1.06-1.28)	6%	6	1.06 (0.92-1.22)	56%
Hip circumference							
	Tertile 1	6	Referent		6	Referent	
	Tertile 2	6	0.73 (0.50-1.07)	0%	6	0.86 (0.58-1.29)	0%
	Tertile 3	6	0.66 (0.42-1.05)	0%	6	0.71 (0.44-1.13)	0%
Per 5 cm increase		6	0.83 (0.73-0.95)	6%	6	0.90 (0.78-1.04)	22%

NOTE. Models included terms for age (<50, 50-<60, 60-<70, 70+), sex (except NDB), education (except UNC and Cleveland), smoking (ever, never; except Cleveland), waist circumference and hip circumference.

CI, confidence interval; OR, odds ratio; GERD, gastroesophageal reflux disease.