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

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**Gluteofemoral obesity and risk of Barrett's esophagus: a pooled analysis from the international BEACON consortium**

**Short title:** Gluteofemoral obesity and risk of Barrett's esophagus

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***Abbreviations used in this paper:*** BEACON, Barrett's Esophagus and Esophageal Adenocarcinoma Consortium; BMI, body mass index; CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

**BACKGROUND & AIMS:** Increasing visceral obesity has been convincingly shown to be related to risk of esophageal adenocarcinoma and its precursor, Barrett's esophagus. However, the independent role of gluteofemoral obesity on the risk of Barrett's esophagus has not been studied.

**METHODS:** Data were from seven case-control studies participating in the international Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). We compared data from cases of Barrett's esophagus (n=1,454) separately with two control groups: 1,850 population-based controls and 1,949 gastroesophageal reflux disease (GERD) controls. Study-specific odds ratios (OR) and 95% confidence intervals (95% CI), estimated using individual participant data and multivariable logistic regression, were combined using random effects meta-analysis.

**RESULTS:** We found a statistically significant inverse relationship between hip circumference and Barrett's esophagus (OR=0.89; 95% CI: 0.81-0.99) 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 comparisons with GERD controls and in stratified analyses based on history of GERD symptoms. The inversed association with hip circumference was only seen among males (OR=0.85; 95% CI: 0.74-0.98 for males; OR=1.00; 95% CI: 0.80-1.25 for females; $P_{interaction}$ = .002). Among men with any category of waist circumference, larger hip circumference was associated with reduced risk of Barrett's esophagus. Conversely, increasing waist circumference was associated with increased risk of Barrett's esophagus in the mutually adjusted model.

**CONCLUSIONS:** These findings confirm that while visceral adiposity increases risk of Barrett's esophagus, gluteofemoral adiposity decreases risk, particularly among men.

*Keywords:* Obesity; Esophageal Cancer; Epidemiology; Risk Factors.

Abdominal obesity is associated with an increased risk of esophageal adenocarcinoma and its precursor lesion Barrett's esophagus.[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] Abdominal obesity 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 has found they may be important in Barrett's esophagus.[5]

Abdominal obesity is also strongly associated with an increased risk of diabetes mellitus and cardiovascular disease.[6] These risks are modified by subcutaneous fat stores in the hip and thigh region with gluteofemoral obesity having a protective effect.[7, 8] One postulated mechanism for this protective effect is that gluteofemoral obesity acts as a metabolic "sink" reducing the levels of circulating free fatty acids, insulin and adipocytokines that lead to metabolic and cardiovascular disease.[9]

There are few studies examining the effects of gluteofemoral obesity on the risks of esophageal adenocarcinoma and Barrett's esophagus. A large cohort study involving 391,456 participants (of whom 124 developed esophageal adenocarcinoma during follow-up) found that after mutual adjustment, the risk of esophageal adenocarcinoma was strongly positively associated with abdominal obesity but inversely associated with gluteofemoral obesity, providing evidence of a protective effect of gluteofemoral obesity.[10] In a case-control study of Barrett's esophagus conducted among male colorectal cancer screenees, 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 men.[11]

Investigating the effects of fat distribution patterns on the risk of Barrett's esophagus is important in furthering our understanding of the role of obesity in Barrett's esophagus. If

there is evidence that gluteofemoral obesity has a protective effect on the risks associated with abdominal obesity, this strongly supports the hypothesis that potentially modifiable non-GERD metabolic factors related to abdominal obesity are important in the pathogenesis of the disease. In addition there are sex difference in fat distribution that may be an important factor in the strong sex differences seen in esophageal adenocarcinoma and Barrett's esophagus, both of which are more common in men than women.[12, 13]

The Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON, http://beacon.tlvnet.net/) is a large international consortium that has pooled and harmonized detailed participant data including anthropometric measurements from seven Barrett's esophagus case-control studies. Using this unique resource, the aim of this study was to determine the risks of Barrett's esophagus associated with gluteofemoral and abdominal obesity and assess 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 Barrett's esophagus.

## Methods

### *Study population*

We analyzed individual participant data from independent case-control studies participating in BEACON. BEACON was formed in 2005 in collaboration with the US National Cancer Institute and now includes seven case-control studies on 1759 Barrett's esophagus cases, 2461 population-based controls and 2516 GERD controls: the Study of Digestive Health (Brisbane, Australia)[14]; the Factors Influencing the Barrett's/Adenocarcinoma Relationship (FINBAR) study (Ireland)[15]; the Epidemiology and Incidence of Barrett's Esophagus study (Kaiser Permanente, Northern California; KPNC)[16]; the Study of Reflux Disease (western Washington State)[17]; the Epidemiologic Case-Control Study of Barrett's Esophagus (Chapel Hill, North Carolina; UNC-Chapel Hill); the Houston Barrett's Esophagus study[18]; and The Newly Diagnosed Barrett's Esophagus Study (Ann Arbor, Michigan)[11]. Details of the case-control studies and data pooling methods for BEACON have been described in detail elsewhere.[19, 20] 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. The studies included a mix of cases with prevalent and newly diagnosed Barrett's esophagus.[19] The cases are compared with population-based controls, that represent the source population from which the cases arose, and GERD controls, the population undergoing endoscopy from which BE cases are diagnosed. 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 hip circumferences (425 population-based controls, 408 GERD controls and 206 Barrett's esophagus cases). We additionally restricted our analyses to white non-Hispanic study

participants (1850 population-based controls, 1949 GERD controls, 1454 Barrett's esophagus cases) due to low numbers of cases from non-white ethnic groups. Six studies provided a population-based control group and five 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.[16] 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, history of GERD symptoms and cigarette smoking. 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) and the effect of each exposure after mutual adjustment with the risk of Barrett's esophagus. 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.[21] 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 because of instability. We used the inconsistency index, $I^2$, to assess heterogeneity between studies.[22] 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 Barrett's esophagus 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), and smoking status (never, ever). Finally, we further mutually adjusted for hip and waist circumference to examine their independent effects on risk of Barrett's esophagus. Models that compared cases with population-based controls were also subsequently adjusted for self-reported GERD symptoms (never vs ever) to evaluate potential confounding effects of GERD symptoms. 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, using the same methodology as for the overall analyses, we conducted stratified analyses by sex and GERD symptoms to assess potential effect modification. We included interaction terms (hip circumference X sex and hip circumference X GERD) in the full models to assess the statistical significance of the difference in association across strata.

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

## Results

The numbers of cases and controls, and summary data for anthropometric measurements by study, are shown in Table 1. Cases were older, on average, than GERD controls but not population-based controls (Table 2). As expected, cases were more likely than controls to have smoked and report having had GERD symptoms (Table 2).

Table 3 shows the estimates of association between waist and hip circumferences and Barrett's esophagus compared with both population-based controls and GERD controls. After adjusting for age, sex, education, and smoking status, waist circumference was positively associated with risk of Barrett's esophagus (population-based controls: summary OR per 5cm increase = 1.05; 95% CI: 0.99-1.12; GERD controls: summary OR per 5cm increase = 1.06; 95% CI: 1.03-1.09). After further adjustment for hip circumference, the magnitude of the association between waist circumference and Barrett's esophagus was strengthened (population-based controls: summary OR per 5cm increase = 1.14; 95% CI: 1.04-1.24; GERD controls: summary OR per 5cm increase = 1.10; 95% CI: 1.02-1.18).

In contrast, there was no association between hip circumference and risk of Barrett's esophagus 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 risk of Barrett's esophagus (population-based controls: summary OR per 5cm increase = 0.89; 95% CI: 0.81-0.99; GERD controls: summary OR per 5cm increase = 0.95; 95% CI: 0.85-1.07) (Figure 1). The associations with waist and hip circumference were essentially unchanged after additional adjustment for GERD symptoms in the models comparing cases with population-based controls (summary OR per 5cm increase in waist = 1.11; 95% CI: 1.01-1.23; summary OR per 5cm increase in hip = 0.88; 95% CI: 0.80-0.97) (Supplementary Table 1).

When stratified by sex (Table 4), waist circumference was associated with increased risk of Barrett's esophagus in both men and women. We found no evidence for statistical interaction between waist circumference and sex in relation to risk of Barrett's esophagus (population-based controls: $P_{interaction}$ = .11). However, hip circumference was inversely associated with Barrett's esophagus in men (population-based controls: summary OR per 5cm increase = 0.85; 95% CI: 0.74-0.98) but was not associated with Barrett's esophagus in women (population-based controls: summary OR per 5cm increase = 1.00; 95% CI: 0.80-1.25; $P_{interaction}$ = .002). Similar evidence of effect modification by sex were seen when GERD controls were the comparison group; although the interaction term was not statistically significant (GERD controls: $P_{interaction}$ = .40). We additionally performed analyses separately in individuals with and without GERD symptoms and found no evidence for effect modification by GERD symptoms (Table 5).

Supplementary Table 2 displays the estimated effects of combinations of categories of waist circumference and hip circumference. Among men with any category of waist circumference, larger hip circumference is associated with decreasing risk of Barrett's esophagus. Men at the highest risk of Barrett's esophagus simultaneously have waist circumference in the highest tertile and hip circumference in the lowest tertile. Men at the lowest risk of Barrett's esophagus have waist circumference in the lowest tertile and hip circumference in the highest tertile. The pattern was different for women with hip circumference not reducing the risk of Barrett's esophagus; however, these analyses were limited by smaller numbers of women in all categories.

There was evidence of low to moderate heterogeneity for the association between hip circumference (continuous) and Barrett's esophagus. 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 46% to 12%. Importantly the effect estimate was only minimally attenuated and hip circumference remained inversely associated with Barrett's esophagus (summary OR per 5cm increase in hip = 0.92; 95% CI: 0.85-1.00).

## Discussion

We conducted pooled analyses of seven case-control studies, examining the independent effects of abdominal obesity and gluteofemoral obesity on the risk of Barrett's esophagus. As has been shown previously, we confirmed that abdominal obesity is associated with Barrett's esophagus. But in addition, we found that gluteofemoral obesity was inversely associated with Barrett's esophagus. This association was strongest when we compared cases with population-based controls, and persisted even after adjusting for GERD symptoms. Finally, we found evidence of modification of the effect of gluteofemoral obesity by sex; the effect was only present among men, and not among women.

In a prior cohort study, Steffen et al. found that gluteofemoral obesity was inversely associated with risk of esophageal adenocarcinoma, 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 Barrett's esophagus or erosive esophagitis, adjusting for abdominal obesity, but the study was too small to accurately estimate the effect on Barrett's esophagus alone, and did not include any women.[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, 23] 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 Barrett's esophagus strongly suggests that abdominal obesity is a risk factor not only due to a mechanical effect promoting GERD, but also a metabolic effect. Multiple studies have demonstrated an association between levels of multiple different circulating adipokines and Barrett's esophagus or esophageal adenocarcinoma.[5, 24-27] 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 Barrett's esophagus and esophageal adenocarcinoma.

Importantly, we found evidence for modification of the effect of gluteofemoral obesity by sex. There was no evidence of a protective effect among women. For unclear reasons, men are at much greater risk than women for Barrett's esophagus,[28] and especially for esophageal adenocarcinoma.[29, 30] Women and men differ in their distribution of adipose tissue, with men having 52% greater intra-abdominal fat mass and 30% less subcutaneous fat, including gluteofemoral fat, than women.[31] In addition, estrogen regulates the secretion of adipokines from adipose tissue.[32] 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 Barrett's esophagus.

Our study had some limitations. First, we were only able to study the outcome of Barrett's esophagus, and not esophageal adenocarcinoma. In addition, the studies included a mix of patients with newly diagnosed and prevalent diagnoses of Barrett's esophagus, which could have biased the results unpredictably. Finally, there was moderate heterogeneity in some effect estimates. However, there are also a number of strengths to the study. Notably, we were able to combine data from seven independent studies from different geographic regions. The component studies used a uniform diagnosis of Barrett's esophagus, 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 a protective effect of gluteofemoral obesity on the risk of Barrett's esophagus in the setting of abdominal obesity among men. The association is

independent of GERD, and not present in women. These findings support a metabolic explanation for the effect of obesity on Barrett's esophagus and for the risk of male sex on Barrett's esophagus. Further studies are required to determine whether the distribution of obesity and metabolic effects promote the progression from Barrett's esophagus to esophageal adenocarcinoma, and whether modifying these factors can prevent the cancer.

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**Figure 1** Forest plot of the association between increasing tertiles of hip circumference and risk of Barrett's esophagus compared with (A) population-based controls and (B) GERD controls. Models included terms for age (<50, 50-<60, 60-<70, 70+), education (except UNC), smoking (ever, never), and were simultaneously adjusted for waist circumference and hip circumference.

**Guarantor of the article:** Aaron P. Thrift, PhD

**Specific author contributions:** BJK contributed to the design of the study, interpretation of data and drafting of the manuscript. APT contributed to the design of the study, data analysis, interpretation of data, and drafting of the manuscript. JHR contributed to interpretation of data and drafting of the manuscript. MLB contributed to drafting of the manuscript. JHR, TLV, LAA, LJM, NJS, DAC, HES, and DCW designed, obtained funding and collected data from individual case-control studies, contributed to the concept of the consortium, interpretation of data and refinement of the manuscript. All authors approved the final draft submitted.

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