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Sex-specific associations between body mass index, waist circumference and the risk of Barrett's oesophagus: a pooled analysis from the international BEACON consortium

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Abstract

Objective—Barrett's oesophagus is a precursor lesion of oesophageal adenocarcinoma, a cancer that, in the USA, has increased in incidence over 600% during the past 40 years. Barrett's oesophagus and oesophageal adenocarcinoma are much more common among men than among women; this finding is unexplained and most earlier studies lacked sufficient numbers of women to evaluate sex-specific risk factors. We leveraged the power of an international consortium to assess sex-specific relationships between body mass index (BMI), abdominal circumference and Barrett's oesophagus.

Design—Four case–control studies provided a total of 1102 cases (316 women, 786 men) and 1400 population controls (436 women, 964 men) for analysis. Study-specific estimates, generated using individual participant data, were combined using random effects meta-analysis.

Results—Waist circumference was significantly associated with Barrett's oesophagus, even after adjustment for BMI; persons in the highest versus the lowest quartiles of waist circumference had approximately 125% and 275% increases in the odds of Barrett's oesophagus among men and women, respectively (OR 2.24, 95% CI 1.08 to 4.65, I^2=57; OR 3.75, 95% CI 1.47 to 9.56, I^2=0). In contrast, there was no evidence of a significant association between BMI and the risk of Barrett's oesophagus, with or without adjustment for waist circumference.

Conclusions—Waist circumference, independent of BMI, was found to be a risk factor for Barrett's oesophagus among both men and women. Future studies examining the biological

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mechanisms of this association will extend our knowledge regarding the pathogenesis of Barrett's oesophagus.

BACKGROUND

Barrett's oesophagus is a precursor to oesophageal adenocarcinoma, a cancer that has undergone a rapid increase in incidence (over 600%) during the past four decades.[1–4] Approximately 10% of adult Americans over the age of 50 years with gastroesophageal reflux disease (GERD) are predicted to harbour Barrett's oesophagus,[5] and the US prevalence may be as high as 3 million individuals.[6] The importance of Barrett's oesophagus relates to its potential for neoplastic progression into oesophageal adenocarcinoma;[7–9] its presence is associated with a 10–40-fold increased risk of oesophageal adenocarcinoma (approximately one in 200 person-years) compared with the general population.[7][10–13]

Barrett's oesophagus is approximately twice as prevalent among men as women, and five times as prevalent among Caucasian as African-American individuals.[14] As the most well-known risk factor for Barrett's oesophagus, GERD symptoms, is not markedly differentially distributed by race or sex,[15] increasing attention has been paid to obesity as a risk factor for Barrett's oesophagus, particularly because of the parallel increases in obesity and the incidence of oesophageal adenocarcinoma and Barrett's oesophagus. General obesity, often measured using the proxy body mass index (BMI), and abdominal obesity have been fairly consistently associated with the risk of oesophageal adenocarcinoma.[16–21] However, associations between BMI and Barrett's oesophagus have been inconsistent.[17][22][23] On the other hand, abdominal obesity, measured as waist circumference or visceral adipose tissue, appears to be more consistently associated with Barrett's oesophagus.[14][18–21] Abdominal obesity is more common among men than women;[24] however, individual studies of Barrett's oesophagus have lacked the ability to evaluate sex-specific associations of obesity, the effect of abdominal obesity independent of BMI, and/or the interaction between obesity and GERD—all in relation to this premalignant metaplasia.[17][22][25][26]

The investigation of sex-specific differences in risk factors of Barrett's oesophagus may help explain the marked differences in demographic distributions of these disorders and provide potential targets for intervention and/or further investigation. Previous studies were unable to evaluate risk factors stratified by sex due to insufficient numbers of women in study populations. We took advantage of a large international consortium of Barrett's oesophagus case–control studies—the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON, http://beacon.tlvnet.net/). We investigated the sex differences in the relationships between obesity, abdominal obesity and Barrett's oesophagus and assessed whether these relationships were modified by GERD and cigarette smoking.

MATERIALS AND METHODS

BEACON consortium

BEACON was formed in 2005 by an international group of investigators in collaboration with the US National Cancer Institute. The consortium consists of completed or ongoing case–control and cohort studies of oesophageal adenocarcinoma and/or Barrett's oesophagus, and its primary aim is to provide an open scientific forum for epidemiological research into the aetiology and prevention of these diseases by facilitating the sharing of data across population-based studies. Therefore, rather than relying on a meta-analytical approach of published risk estimates, which often have different variable definitions and statistical models, BEACON enables pooled analyses of individual participant data from

population-based studies using a standard model, after harmonisation of variable definitions and common confounders.

Study population

The present analysis used data from four case–control studies within BEACON: the FINBAR (Factors Influencing the Barrett's/ Adenocarcinoma Relationship) study, based in Ireland;[16] the Epidemiology and Incidence of Barrett's Oesophagus, based in the Kaiser Permanente Northern California population, USA;[25] the Study of Reflux Disease based in western Washington state, USA;[26] and the Study of Digestive Health, based in Brisbane, Australia.[17] Cases were compared with population-based controls that represented the source population from which the Barrett's oesophagus cases arose. The original studies and the current data pooling were approved by the institutional review board or research ethics committee of each sponsoring institution.

Study variables

Exposure variables used for this analysis were: BMI (weight (kg) divided by square of height (m)) and waist circumference (cm). The waist–hip ratio was also available from three studies, but given its high correlation with waist circumference (r=0.73 in the combined population control dataset), our analyses focus on BMI and waist circumference. All anthropometric measures were taken in-person using study-specific protocols. In the Brisbane study, waist circumference data were available only for a subset of the case (61%) and population-based control groups (38%).

For analyses, BMI was categorised into an ordinal variable with four groups based on WHO criteria:[27] healthy (BMI 18.5–24.9), overweight (BMI 25–29.9), obese class I (BMI 30–34.9), and obese class II+ (BMI 35+). We evaluated the association between abdominal adiposity and Barrett's oesophagus by assessment of the exposure waist circumference. We further conducted analyses including both BMI and waist circumference in the model: this effectively compares differences in waist circumference among persons within the same BMI, and differences in BMI among persons within the same waist circumference. We created quartile categories for waist circumference based on a sex-specific population-based control group. We also assessed BMI and waist circumference continuously to assess the dose–effect relationship. The proportions of individuals with abdominal obesity among cases and controls were also compared using cut-off points defined by the National Heart, Lung, and Blood Institute, American Heart Association and International Diabetes Federation[28] (>102 cm for men, >88 cm for women).

Covariates were measured using questionnaires; variables assessed for inclusion in regression models were: calories per day; alcohol (drinks per day); vegetables and fruit servings per day; vitamin supplement use; self-reported GERD symptoms (frequency of heartburn and regurgitation); *Helicobacter pylori* seropositivity; and the use of non-steroidal anti-inflammatory drugs. A covariate was retained in the fully adjusted models if it altered the summary estimate by more than 10% or it was considered a known potential confounder (age, sex, smoking and education).

Statistical methods

The analyses used a two-step approach. First, we used multivariable logistic regression models to obtain study-specific OR and 95% CI of the association between each exposure and Barrett's oesophagus within each study. Second, to pool the study-specific OR, we used both fixed effects and random effects meta-analytical models to generate summary OR. Because these two models provided essentially identical results, we only show the results for the random effects models, which generally provide more conservative summary OR.[29] We

used the I^2 statistic[21] to examine heterogeneity. The I^2 statistic estimates the percentage of total variation across studies due to heterogeneity. An I^2 statistic of 0% indicates no heterogeneity that cannot be attributed to chance, whereas larger values indicate increasing heterogeneity beyond chance: I^2 of 25%, 50% and 75% are generally considered low, moderate and high levels of heterogeneity, respectively.[30]

We conducted analyses stratified by sex, as well as men and women combined. Referent categories in categorical analyses were 18.5–24.9 for BMI and the first quartile for waist circumference. We evaluated continuous variables to test for linear trend by using OR per unit BMI and per 5 cm waist circumference. Models that compared cases with population-based controls were further adjusted for self-reported GERD symptoms (ordinal variable: either heartburn or regurgitation never; less than once a week; weekly; more than weekly and less than daily; and more than daily) to evaluate potential confounding effects of GERD symptoms. All models were adjusted for age (<50, 50–59, 60+ years); sex (when men and women were combined); race (white vs non-white); cigarette smoking (pack-years); harmonised education (school only, tech/diploma, university).

To assess for effect-measure modification, the models were stratified by cigarette smoking (ever vs never) and GERD symptoms (weekly or more heartburn or regurgitation vs less than weekly). The likelihood ratio test was conducted to assess the significance of effect-measure modification by these variables using a pooled dataset of all four studies with adjustment for age, study, smoking, education, BMI and waist circumference (mutual adjustment). The full (saturated) model also included a cross-product term between the categorical anthropometric variable (BMI or waist circumference) and either the dichotomous cigarette smoking exposure (ever vs never) or the ordinal GERD symptom variable (never vs weekly or more).

Two-sided p values less than 0.05 were considered statistically significant. All analyses were conducted using STATA 10.1.

RESULTS

Participant characteristics

Detailed descriptions of recruitment procedures and study definitions for cases and controls have been described previously.[31] A total of 1130 subjects with Barrett's oesophagus (cases) and 1434 population controls from the four case–control studies were available for pooling. We excluded subjects for whom either height or weight were missing (10 cases; 17 population controls). We also excluded subjects with unlikely anthropometric data (ie, waist circumference <50 cm and BMI >20: two cases; four population controls) and individuals with a BMI less than 18.5 (16 cases; 13 population controls). After exclusions, there remained 1102 Barrett's oesophagus cases and 1400 population-based controls for analysis (table 1).

Cases were more likely than controls to be current or former smokers and to have more frequent GERD symptoms, for both men and women (table 2). A higher mean waist circumference, but not mean BMI, was also more common among cases than controls, for both men and women.

Pooled analyses

Body mass index—When compared with population-based controls, male subjects with a BMI of 30–34.9 were slightly more likely to have Barrett's oesophagus than subjects with a BMI of 18.5–24.9, although no consistent pattern was observed in the association between increasing BMI and Barrett's oesophagus (see supplementary table S1, available online

only). For instance, the OR for each BMI category for men were: $OR_{>25-29.9}$ 1.05 (95% CI 0.82 to 1.34, I^2=0%); $OR_{>30-34.9}$ 1.37 (95% CI 1.01 to 1.86, I^2=8%); OR_{35} 1.10 (95% CI 0.74 to 1.66, I^2=0%) (model 1). No significant associations were found between BMI and Barrett's oesophagus among women and these analyses had evidence of at least moderate heterogeneity (per unit increase in BMI, OR 1.02, 95% CI 0.98 to 1.07, I^2=52%). When the model was adjusted for self-reported GERD symptoms, the effect estimates were very slightly attenuated for men, women and combined analyses (model 2, table 3). When the model was adjusted for waist circumference (table 3), the associations attenuated, and most of the OR became close to 1.

Waist circumference—Table 4 presents the results of the association between waist circumference and Barrett's oesophagus adjusting for BMI, which effectively estimates the effect of waist circumference on the risk of Barrett's oesophagus among persons with the same BMI. The risk of Barrett's oesophagus increased with larger waist circumferences. For instance, being in the highest quartile of waist circumference was associated with approximately a 125% and 275% increase in the risk of Barrett's oesophagus among men and women, respectively (OR 2.24, 95% CI 1.08 to 4.65, I^2=57; OR 3.75, 95% CI 1.47 to 9.56, I^2=0, respectively). When the waist circumference variable was analysed continuously, there was a trend towards statistical significance for both men and women (p=0.07). When the model was further adjusted for GERD symptoms (table 4, model 2), the associations remained significant among men while among women the 95% CI were wide and included 1. When men and women were combined, using sex-specific quartile cut points, there were strong dose–effect associations in models with or without adjustment for GERD (p=0.03 and p=0.01, respectively).

When the models were not adjusted for BMI (see supplementary table S1, available online only), similar associations were observed, although the associations were slightly weaker than the model adjusted for BMI (table 4). For instance, being in the highest quartile of waist circumference was associated with an approximately 60% and 180% increase in the risk of Barrett's oesophagus among men and women (OR 1.62, 95% CI 1.09 to 2.41, I^2=34; OR 2.80, 95% CI 1.39 to 5.64, I^2=25, respectively). There was a significant dose–effect association among men (p=0.05) and a trend towards a significant association for women (p=0.08).

Waist to hip ratio—We also conducted an analysis examining the association between waist to hip ratio and Barrett's oesophagus (see supplementary table S4, available online only). Due to skewed distribution in the waist to hip ratio in one study in which no woman was in the lowest quartile, we used the second quartile as referent. Overall, the waist to hip ratio was associated with the risk of Barrett's oesophagus, particularly among men. Being in the first quartile of the waist to hip ratio was associated with half the risk of Barrett's oesophagus (OR 0.44, 95% CI 0.29 to 0.67, I^2=0), although for the third and fourth quartiles the associations were non-significant (OR 0.96, 95% CI 0.66 to 1.40; OR 1.07, 95% CI 0.60 to 1.91, respectively). For women there were no associations between the waist to hip ratio and Barrett's oesophagus (data not shown).

Supplementary analyses

Effect-modification (stratified analyses) by smoking and GERD symptoms—
The associations between BMI or waist circumference and Barrett's oesophagus were similar among male smokers versus non-smokers and among persons with versus without GERD symptoms (see supplementary table 3, available online only). These models were adjusted for age, race, education, pack-years of cigarette smoking, BMI and waist

circumference (mutual adjustment). Among women, we were unable to assess effectmeasure modification due to the smaller sample size.

Exploration of heterogeneity—The associations between waist circumference and Barrett's oesophagus results were fairly homogeneous (tables 2 and 3; see also Forrest plots, figures 1A,B). For BMI analyses (unadjusted for waist circumference), there was evidence of moderate to high heterogeneity among women (table 3). This heterogeneity was mainly driven by the low effect estimates from the FINBAR study. The FINBAR study also did not have any women who were in the highest BMI category. When the FINBAR study was excluded, I^2 were reduced to 0% and 11% for the second and third BMI categories, and the effect estimates were strengthened: $OR_{>25-29.9}$ 1.97 (95% CI 1.31 to 2.96, I^2=0%); $OR_{30-34.9}$ 1.73 (95% CI 1.05 to 2.87, I^2=11%), although the effect estimate was unchanged for the highest BMI category (see supplementary figure S1, available online only).

DISCUSSION

This is the first study to evaluate the sex-specific associations between BMI, waist circumference and the risk of Barrett's oesophagus within a large population-based sample. There are several findings. First, the study demonstrated that there is no association between BMI and the risk of Barrett's oesophagus. Second, abdominal obesity is significantly associated with the risk of Barrett's oesophagus in both men and women. Finally, the association between waist circumference and Barrett's oesophagus strengthened when the model was adjusted for BMI.

Our results demonstrate that abdominal obesity is a strong predictor of Barrett's oesophagus, independent of BMI. This suggests that previous studies that reported associations between BMI alone and Barrett's oesophagus were likely to have been confounded by unmeasured abdominal obesity. Previous studies have also been limited in their capacity to stratify data by sex. The BEACON consortium, which takes advantage of pooling studies of Barrett's oesophagus and oesophageal adenocarcinoma, both of which are relatively uncommon in women compared with men, enabled us to assemble a large sample size of Barrett's oesophagus subjects from four independent case–control studies. Our analyses suggest that increasing waist circumference is associated with the risk of Barrett's oesophagus among both men and women, therefore the strengths of sex-specific association alone do not explain the sex disparities in the incidence of Barrett's oesophagus. However, men, particularly of white race, tend to accumulate visceral (abdominal) fat more than women; a recent study using the National Health and Nutrition Examination Survey data showed that the prevalence of abdominal obesity was higher among men and white individuals than women and other racial/ethnic subgroups.[24] Therefore, we cannot exclude the possibility that the greater prevalence of abdominal obesity among men than women, may, at least partly explain the observed sex disparities in the incidence of Barrett's oesophagus.

It remains unclear how abdominal obesity increases the risk of Barrett's oesophagus. It has been hypothesised that abdominal obesity may induce GERD through mechanical mechanisms via increased abdominal pressure, which subsequently relaxes the lower oesophageal sphincter, exposing the lower oesophagus to gastric acid, resulting in an increase in the risk of GERD and thus Barrett's oesophagus.[32–34] Although the present analysis found some attenuation of the association between waist circumference and Barrett's oesophagus when using populationbased controls with adjustment for GERD symptoms, a positive association persisted when the model was adjusted for BMI and GERD symptoms. These results suggest that the mechanism is more complex and that there are other pathways besides GERD through which abdominal obesity affects the aetiology of Barrett's oesophagus. For instance, the risk of developing insulin resistance and metabolic

syndrome is higher in individuals with visceral (abdominal) obesity than in those with subcutaneous obesity.[35] Insulin resistance and metabolic syndrome are associated with several cancers;[36–42] such metabolic dysregulation may mediate the association between abdominal obesity and the carcinogenesis process of oesophageal adenocarcinoma. In addition, visceral fat is associated with particular metabolic compounds and a different balance of adipose-related hormones including insulin-like growth factor, tumour necrosis factor , interleukin 6, and adipokines (eg, leptin, adiponectin), many of which have also been found to be linked to the carcinogenesis processes of other cancers and with mechanisms of healing and injury to gastrointestinal mucosal surfaces.[3643–47] Future studies that investigate the effects of adipose-related hormones will extend our knowledge regarding the pathogenesis of Barrett's oesophagus.

There were several strengths of this study. First, this study pooled individual participant data through a large international consortium; this method provides more comparable statistical estimates than standard meta-analyses, which pool published OR that differ in their variable definitions and in their inclusion of potential confounding variables. Therefore, the results of this analysis are the strongest available data to date regarding obesity and abdominal obesity as risk factors for Barrett's oesophagus. Its large sample size also provided additional statistical power to investigate sex-specific associations between obesity and Barrett's oesophagus as well as an assessment of effect-measure modification. Second, the data were of high quality. Anthropometric measurements used trained personnel in all studies, rather than self-report, avoiding measurement and recall biases, and other variables were obtained through direct interviews or questionnaires.

There are a few limitations of this study. First, observational studies cannot definitively establish cause and effect,[48] and are subject to confounding by other unmeasured variables. Although analyses that evaluated all the measured potential confounders provided little evidence of confounding, we cannot exclude the possibility that some measured or unmeasured factors might have influenced the results. Third, there is a difference between self-reported GERD symptoms and the actual amount of acid reflux; thus analyses adjusting for GERD symptoms do not fully adjust for the presence of reflux. Fourth, there was evidence of moderate levels of heterogeneity for some analyses, specifically for the analysis of BMI among women. The heterogeneity decreased and effect estimates strengthened when the FINBAR study was excluded. It is unclear why the associations between BMI and Barrett's oesophagus were lower in this Irish study population. The cases included only persons with long-segment (>3 cm) Barrett's oesophagus and we observed unusual distributions of BMI and waist to hip ratio in this population; there were no female population controls who were in the BMI greater than 35 or the first quartile waist to hip ratio categories in this study. However, the proportion of normal weight individuals among FINBAR was equivalent to the average of all studies, and it does not explain why this study produced low estimates of the association between obesity and Barrett's oesophagus. The heterogeneity may also be partly explained by their matching method, which differed from all other studies: the FINBAR study matched the controls to their oesophageal adenocarcinoma cases rather than Barrett's oesophagus cases, although any of this effect should have been lessened by adjustment for the matching factors in this analysis.

In conclusion, abdominal obesity is a risk factor for Barrett's oesophagus among both men and women, independent of BMI; individuals with higher waist circumferences were at a 1.5–2.8-fold increased risk of having Barrett's oesophagus among general populations. Future studies examining the biological mechanisms of this association will extend our knowledge regarding the pathogenesis of Barrett's oesophagus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Significance of this study

What is already known on this subject?

► Incidence rates of Barrett's oesophagus and oesophageal adenocarcinoma have increased rapidly over the past few decades, while the reasons for such are poorly understood.

► Men, white individuals, and those with gastroesophageal reflux are at a higher risk of Barrett's oesophagus and oesophageal adenocarcinoma, but these factors alone do not explain the rise in incidence.

► Obesity has been thought to increase the risk of Barrett's oesophagus but little is known as to whether BMI or abdominal obesity is the effector of this relationship.

What are the new findings?

► Our finding suggests that increasing abdominal obesity, not BMI, increases the risk of Barrett's oesophagus.

► Similar associations were observed for both men and women.

► The association was not altered when adjusted for symptoms of GERD.

How might it impact on clinical practice in the foreseeable future?

► Future research examining biomarkers can lead to the identification of high-risk populations for closer monitoring of the progression to cancer.

► Among a high-risk population (male, white, GERD symptoms), interventions to reduce abdominal obesity may help prevent the occurrence of Barrett's oesophagus.
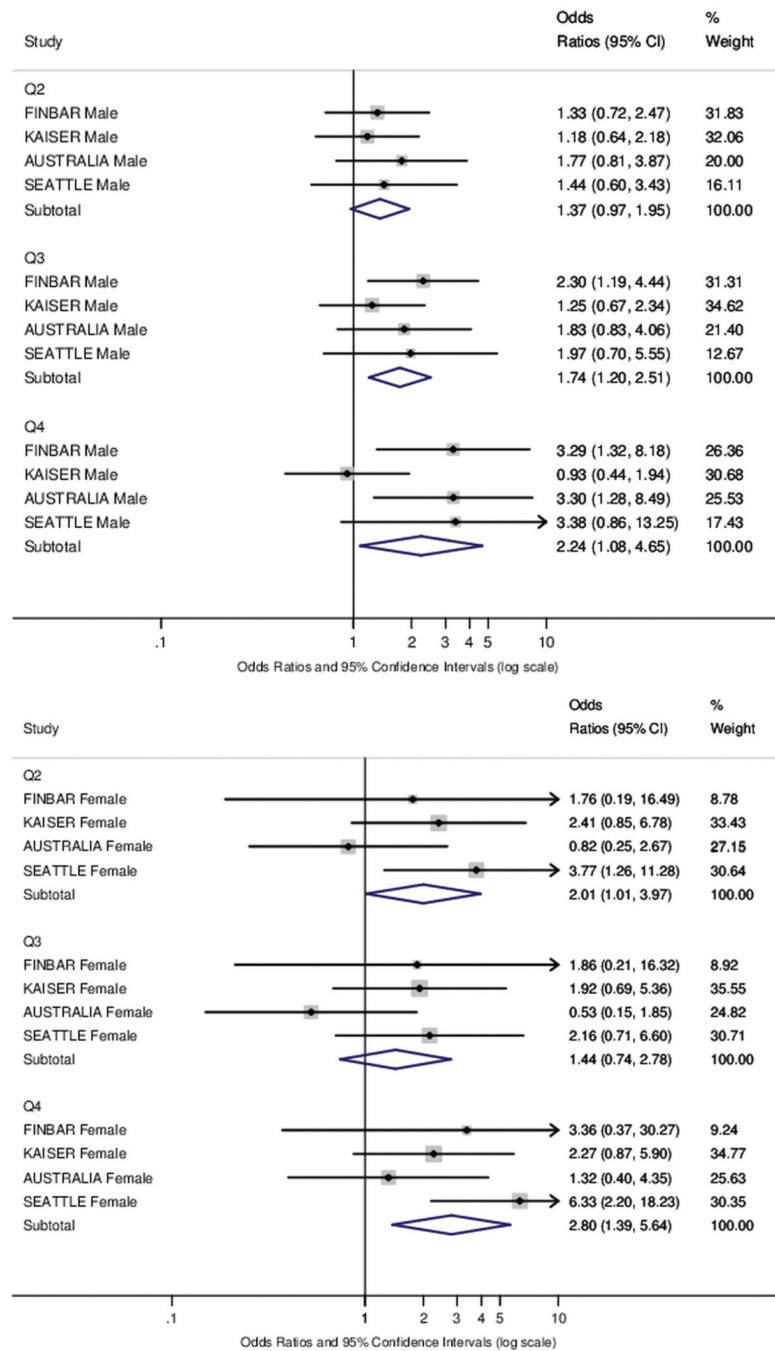
Figure 1.
Forrest plots of the relationship between quartiles of waist circumference and Barrett's oesophagus for men (a) and women (b). (a) Men, model was adjusted for age (categorical), race, education, smoking (pack-years) and body mass index (BMI) (continuous). (b) Women, model was adjusted for age (categorical), race, education, smoking (pack-years) and BMI (continuous).

Table 1

Characteristics of the individual studies included in this pooled analysis

Study	Location	Study period	Barrett's oesophagus cases (men/women)	Population-based controls (men/women)
The FINBAR study	Northern Ireland and Republic of Ireland	2002–2004	(183/37)	(218/40)
Kaiser Permanente	Northern California, USA	2002–2005	(230/84)	(209/102)
Washington state	Washington, USA	1997–2000	(117/73)	(130/74)
Study of Digestive Health	Brisbane, Queensland, Austraia	2003–2006	(256/122)	(407/220)

FINBAR, Factors Influencing the Barrett's/Adenocarcinoma Relationship.

Table 2

Characteristics of the combined study populations

	Men				Women			
	Cases		Population controls		Cases		Population controls	
	No/mean	%*/SD	No/mean	%*/SD	No/mean	%*/SD	No/mean	%*/SD
Total no of subjects	786		964		316		436	
Mean age (SD)	59.8	±12.0	59.2	±12.0	58.8	±12.0	58.9	±11.8
Race								
White	738	95%	858	89%	270	87%	398	91%
GERD symptoms (heartburn or regurgitation)								
Few times a week or more	382	49%	260	27%	182	58%	76	17%
Once a week	119	15%	111	12%	38	12%	42	10%
Smoking status								
Current	134	17%	133	14%	50	16%	47	11%
Former	403	51%	392	42%	124	39%	115	27%
Never	236	30%	406	44%	139	44%	268	62%
Mean BMI (kg/m²)	27.9	±4.7	27.9	±4.7	27.7	±5.9	27.7	±5.9
Mean waist circumference (cm)	102.8	±12.1	101.2	±12.1	93.2	±14.9	89.5	±14.3
Abdominal obesity†	398	51%	367	52%	146	46%	149	51%

*Total percentage may not add up to 100% due to missing values and some categories not presented.

†Defined by National Heart, Lung, and Blood Institute, American Heart Association and International Diabetes Federation greater than 102 cm for men, greater than 88 cm for women.

BMI, body mass index; GERD, gastroesophageal reflux disease.

Table 3

Association between BMI and Barrett's oesophagus stratified by sex (adjusted for waist circumference)

BMI categories	Model 1			Model 2		
	OR (95% CI)	I² (95% UI)	N	OR (95% CI)	I² (95% UI)	N
Men						
18.5–24.9	ref (1.0)			ref (1.0)		
25–29.9	0.94 (0.68 to1.28)	0 (0–74)	4	0.92 (0.66 to1.27)	0 (0–84)	4
30–34.9	0.95 (0.59 to1.52)	6 (0–86)	4	0.98 (0.60 to	4 (0–85)	4
35+	0.80 (0.36 to1.81)	25 (0–88)	4	0.90 (0.42 to1.90)	6 (0–86)	4
Per unit increase	0.95 (0.88 to1.03)	67 (4–89)	4	0.95 (0.88 to1.03)	57 (0–86)	4
p Value for trend	0.22			0.20		
Women						
18.5–24.9	ref (1.0)			ref (1.0)		
25–29.9	0.96 (0.35 to2.64)	72 (21–90)	4	0.89 (0.29 to2.72)	74 (28–91)	4
30–34.9	0.95 (0.35 to2.63)	44 (0–81)	4	0.84 (0.28 to2.54)	47 (0–83)	4
35+	0.96 (0.31 to2.98)	0 (0–87)	3	1.00 (0.30 to3.35)	4 (0–90)	3
Per unit increase	0.98 (0.91 to1.05)	17 (0–87)	4	1.00 (0.92 to1.09)	43 (0–81)	4
p Value for trend	0.56			0.98		
Combined						
18.5–24.9	ref (1.0)			ref (1.0)		
25–29.9	1.03 (0.74 to1.44)	36 (0–78)	4	1.01 (0.69 to1.48)	47 (0–83)	4
30–34.9	1.00 (0.66 to1.50)	11 (0–86)	4	0.99 (0.67 to1.48)	0 (0–84)	4
35+	0.90 (0.52 to1.58)	0 (0–52)	4	0.99 (0.55 to1.77)	0 (0–0)	4
Per unit increase	0.97 (0.93 to1.01)	38 (0–79)	4	0.97 (0.94 to1.01)	3 (0–85)	4
p Value for trend	0.17			0.15		

Model 1: adjusted for age (categorical), race, education, smoking (pack-years, continuous) and waist circumference (continuous).

Model 2: also adjusted for GERD symptoms (ordinal variable) defined as: either heartburn or regurgitation never, less than once a week, weekly, more than weekly but less than daily and daily or more.

BMI, body mass index; GERD, gastroesophageal reflux disease; UI, uncertainty intervals.

Table 4

Association between waist circumference and Barrett's oesophagus, stratified by sex (adjusted for BMI)

Waist circumference	Barrett's oesophagus versus population controls					
	Model 1			Model 2		
	OR (95% CI)	I² (95% UI)	N	OR (95% CI)	I² (95% UI)	N
Men						
Q1	ref (1.0)			ref (1.0)		
Q2	1.37 (0.97 to 1.95)	0 (0–32)	4	1.43 (0.99 to 2.06)	0 (0–0)	4
Q3	1.74 (1.20 to 2.51)	0 (0–75)	4	1.70 (1.16 to 2.50)	0 (0–58)	4
Q4	2.24 (1.08 to 4.65)	57 (0–86)	4	2.26 (1.12 to 4.55)	49 (0–83)	4
Per 5 cm increase	1.19 (0.98 to 1.44)	79 (44–92)	4	1.17 (0.98 to 1.39)	72 (21–90)	4
p Value for trend	0.07			0.08		
Women						
Q1	ref (1.0)			ref (1.0)		
Q2	2.39 (1.19 to 4.80)	16 (0–87)	4	2.04 (1.00 to 4.16)	13 (0–87)	4
Q3	1.68 (0.66 to 4.30)	38 (0–79)	4	1.34 (0.41 to 4.36)	57 (0–86)	4
Q4	3.75 (1.47 to 9.56)	0 (0–82)	4	2.77 (0.84 to 9.08)	31 (0–75)	4
Per 5 cm increase	1.13 (0.99 to 1.29)	0 (0–65)	4	1.10 (0.96 to 1.26)	0 (0–83)	4
p Value for trend	0.07			0.16		
Combined						
Q1	ref (1.0)			ref (1.0)		
Q2	1.02 (0.75 to 1.39)	0 (0–0)	4	1.00 (0.73 to 1.38)	0 (0–0)	4
Q3	1.63 (1.17 to 2.29)	4 (0–85)	4	1.52 (1.08 to 2.15)	0 (0–0)	4
Q4	1.87 (1.22 to 2.87)	0 (0–73)	4	1.75 (1.14 to 2.70)	0 (0–82)	4
Per 5 cm increase	1.16 (1.02 to 1.32)	36 (0–78)	4	1.14 (1.03 to 1.27)	51 (0–84)	4
p Value for trend	0.02			0.01		

Model 1: adjusted for age (categorical), race, education, smoking (pack-years, continuous) and BMI (continuous).

Model 2: also adjusted for GERD symptoms (ordinal variable) defined as: either heartburn or regurgitation never, less than once a week, weekly, more than weekly but less than daily and daily or more.

BMI, body mass index; GERD, gastroesophageal reflux disease; UI, uncertainty intervals.