Meta-Analysis: Obesity and the Risk for Gastroesophageal Reflux Disease and Its Complications

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Background: **The association of body mass index and gastroesophageal reflux disease (GERD), including its complications (esophagitis, Barrett esophagus, and esophageal adenocarcinoma), is unclear.**

Purpose: **To conduct a systematic review and meta-analysis to estimate the magnitude and determinants of an association between obesity and GERD symptoms, erosive esophagitis, Barrett esophagus, and adenocarcinoma of the esophagus and of the gastric cardia.**

Data Sources: **MEDLINE search between 1966 and October 2004 for published full studies.**

Study Selection: **Studies that provided risk estimates and met criteria on defining exposure and reporting outcomes and sample size.**

Data Extraction: **Two investigators independently performed standardized search and data abstraction. Unadjusted and adjusted odds ratios for individual outcomes were obtained or calculated for each study and were pooled by using a random-effects model.**

Data Synthesis: **Nine studies examined the association of body mass index (BMI) with GERD symptoms. Six of these studies found statistically significant associations. Six of 7 studies found significant associations of BMI with erosive esophagitis, 6 of 7 found significant associations with esophageal adenocarcinoma, and 4 of 6 found significant associations with gastric cardia adenocarcinoma. In data from 8 studies, there was a trend toward a dose–response relationship with an increase in the pooled adjusted odds ratios for GERD symptoms of 1.43 (95% CI, 1.158 to 1.774) for BMI of 25 kg/m^2 to 30 kg/m^2 and 1.94 (CI, 1.468 to 2.566) for BMI greater than 30 kg/m^2. Similarly, the pooled adjusted odds ratios for esophageal adenocarcinoma for BMI of 25 kg/m^2 to 30 kg/m^2 and BMI greater than 30 kg/m^2 were 1.52 (CI, 1.147 to 2.009) and 2.78 (CI, 1.850 to 4.164), respectively.**

Limitations: **Heterogeneity in the findings was present, although it was mostly in the magnitude of statistically significant positive associations. No studies in this review examined the association between Barrett esophagus and obesity.**

Conclusion: **Obesity is associated with a statistically significant increase in the risk for GERD symptoms, erosive esophagitis, and esophageal adenocarcinoma. The risk for these disorders seems to progressively increase with increasing weight.**

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Frequent symptoms of gastroesophageal reflux disease (GERD) affect between 10% and 20% of adults in the United States. The prevalence of GERD-related complications, including erosive esophagitis, Barrett esophagus, and esophageal adenocarcinoma, has been steadily increasing in the United States and western Europe. For instance, hospitalizations with GERD among veterans increased 10-fold from the 1970s to the 1990s (1). Similarly, the incidence of esophageal adenocarcinoma increased 4-fold over the past 20 years (2–5). The reasons for the increase in GERD and its complications are not known. Changes in diet, prescription medication use, smoking, and alcohol intake and the declining prevalence of *Helicobacter pylori* infection have been proposed (6–11). Studies have also hypothesized that the increasing trend of obesity in western populations has paralleled the increase in esophageal adenocarcinoma and may be an important factor in this change (12–14).

The notion of obesity as a cause of GERD is biologically plausible. Obesity has been associated with increased intra-abdominal pressures (15), impaired gastric emptying (16), decreased lower esophageal sphincter pressure, and increased frequency of transient sphincter relaxation (17, 18), thus leading to increased esophageal acid exposure. However, the epidemiologic evidence linking obesity to GERD and its complications has not been critically reviewed. We aimed to evaluate, quantify, and summarize the association of obesity to GERD and its complications.

METHODS

Literature Search

Two investigators independently searched the published English-language literature (through October 2004) by using MEDLINE. Search terms included *obesity* or *body mass* or *anthroprometry* searched with *reflux* or *heartburn*, (*o*)*esophagitis*, *Barrett's* or *Barretts*, and (*o*)*esophageal cancer* or (*o*)*esophageal adenocarcinoma*. We performed a recursive hand search of cited bibliographies to increase completeness.

Study Selection Criteria

The following inclusion criteria had to be fulfilled: 1) cross-sectional, case–control, or cohort study that permitted assessment of a causal association between overweight

See also:

Web-Only
Appendix Figures
Conversion of figures and tables into slides

Table 1. **Characteristics of 9 Studies of Body Mass Index and Symptoms of Gastroesophageal Reflux Disease***

Author, Publication Year (Reference)	Years of Study	Country	Participation Rate, %	Study Sample	Method of Data Collection	Case Definition
Andersen and Jensen, 1991 (22)	NA	Denmark	87	Random sample of general population	Mailed, validated questionnaire	Participants with GERD symptoms
Locke et al., 1999 (23)	1988–1991	US	72	Random sample of residents 25–74 y of age in Olmsted County, Minnesota	Mailed, validated questionnaire	Participants with GERD symptoms
Oliveria et al., 1999 (24)	NA	US	86 (of eligible persons)	Random sample of persons ≥ 18 y of age from entire U.S. population	Telephone interview using validated questionnaire	Participants with heartburn more than once per week
Stanghellini, 1999 (25)	NA	Multinational	27	Random sample of persons ≥ 18 y of age from 7 urban areas in Canada, Italy, Japan, the Netherlands, Scandanavian countries, Switzerland, and the US	BMI from interview (in-person interview using structured questionnaire)	Participants with GERD symptoms
Lagergren et al., 2000 (26)	1995–1997	Sweden	73	Random sample of the general population (age- and sex-matched to patients with esophageal adenocarcinoma)	BMI from interview (in-person interview using structured questionnaire)	Participants with GERD symptoms at least once per week for ≥ 1 y
Wu et al., 2003 (27)	1992–1997	US	55	Random population-based sample of persons (age-, sex-, and race-matched to patients with esophageal cancer)	BMI from interview (in-person interview using structured questionnaire)	Participants with GERD symptoms at least once per week
Murray et al., 2003 (28)	1996–1998	UK	38	Randomly selected sample of patients 20–59 y of age registered with general practices in southwest England. Included in the current analysis are all 1634 *Helicobacter pylori*–positive persons and 3268 *H. pylori*–negative persons	BMI was directly measured (self-administered, structured questionnaire)	Participants with GERD symptoms were stratified by frequency, severity, and type of symptoms
Nilsson et al., 2003 (29)	1995–1997	Norway	73	65 363 persons representing 71% of the adult population of NordTrondelag county in Norway	BMI was directly measured (self-administered, structured questionnaire)	Participants with "severe" reflux symptoms
Diaz-Rubio et al., 2004 (30)	2002	Spain	71	Random sample of Spanish population 40–79 y of age	Telephone interview using structured questionnaire	Participants with any GERD symptoms in the past year

* All studies were cross-sectional. Non–case-patients were defined by excluding case-patients. BMI = body mass index; GERD = gastroesophageal reflux disease; NA = not available; NS = not statistically significant; NSAID = nonsteroidal anti-inflammatory drug; UK = United Kingdom; US = United States.

or obesity and esophageal disease; 2) clear definition of obesity as defined by a body mass index (BMI) in kg/m^2 or height-to-weight ratio; and 3) well-defined outcome of interest that included GERD symptoms defined by using validated symptom score, esophageal erosions defined by endoscopy, and Barrett esophagus or esophageal adenocarcinoma validated by pathology review. We excluded case reports and case series, studies with fewer than 50 case-patients, and studies that did not report risk estimates or raw data to allow independent calculation of these estimates. If a study met the selection criteria except for failure to report risk estimates, we contacted the study authors in an attempt to obtain these data.

Statistical Analysis

We abstracted or calculated odds ratios for cross-sectional and case–control studies and risk ratios for cohort studies as the risk estimates for associations between obesity and each outcome of interest. We pooled the results in 2 different ways. All studies either presented or had sufficient information to allow the calculation of unadjusted odds ratios estimates (and 95% CIs). We subsequently pooled these unadjusted estimates. Because of the in-

Table 1—**Continued**

Case-Patients, *n*	Controls, *n*	Demographic Characteristics of Case-Patients			BMI	Adjusted Odds Ratio (95% CI)	*P* Value	Adjustments
		Men, %	Age, *y*	White, %				
114	1207	52	Mode 50–59	NA	Direct measurement			None
					<25 kg/m^2	1.0	NS	
					25–29 kg/m^2	1.0 (0.7–1.5)		
					>30 kg/m^2	1.4 (0.8–2.4)		
872	652	48	Mean 51, SD 14	96	Self-reported			Age, sex, tobacco, alcohol, coffee use, NSAID use, family history of GERD, and psychosomatic symptom score
					<24 kg/m^2	1.0		
					24–27 kg/m^2	1.4 (0.9–2.3)		
					27–30 kg/m^2	2.0 (1.2–3.3)	<0.05	
					>30 kg/m^2	2.8 (1.7–4.5)		
916	1084	41	Mean 49	87	Self-reported continuous variable	1.02 (1.01–1.04)	<0.01	Age, sex, race, and education
530	5251	50	Mean 45	NA	Self-reported			None
					<25 kg/m^2	1.0		
					25–30 kg/m^2	1.8 (1.5–2.3)	<0.01	
					>30 kg/m^2	2.9 (2.2–3.8)		
135	685	87	Mean 66	NA	Self-reported maximum adult BMI			Age, sex, tobacco, alcohol, socioeconomic status, physical activity, and dietary factors
					<25 kg/m^2	1.0		
					25–30 kg/m^2	1.0 (0.6–1.4)	NS	
					>30 kg/m^2	1.1 (0.6–2.0)	NS	
258	1098	74	Mean 60, SD 11	62	Self-reported			Age, sex, race, education, and birthplace (US vs. non-US)
					<23 kg/m^2	1.0		
					23–25 kg/m^2	1.1 (0.7–1.6)	0.08	
					25–28 kg/m^2	1.3 (0.9–2.0)		
					>28 kg/m^2	1.4 (0.9–2.0)		
643	4045	46	Mean 46	NA	Direct measurement	Heartburn / Acid regurgitation		Age, sex, tobacco, alcohol, coffee use, *H. pylori* status, socioeconomic status, and NSAID use
					<25 kg/m^2	1.0 / 1.0		
					25–30 kg/m^2	1.8 (1.3–2.5) / 1.5 (1.1–2.0)	<0.01	
					>30 kg/m^2	2.9 (2.1–4.1) / 2.2 (1.4–3.5)		
3113	39 872	49	Mean 52	NA	Direct measurement	Men / Women		Age, tobacco, asthma medications, and hormone use in women; alcohol use, antihypertensive medications, diabetes mellitus, and dietary factors
					<25 kg/m^2	1.0 / 1.0		
					25–30 kg/m^2	2.2 (2.0–2.6) / 2.0 (1.7–2.4)		
					30–35 kg/m^2	3.1 (2.6–3.6) / 3.9 (3.3–4.7)	<0.01	
					>35 kg/m^2	3.3 (2.4–4.7) / 6.3 (4.9–8.0)		
791	1709	47	Mode 40–49	NA	Self-reported			Age, sex, alcohol, tobacco, coffee, NSAID use, family history of GERD, spousal history of GERD, education, geographic region, and employment status
					<25 kg/m^2	1.0		
					25–30 kg/m^2	1.5 (1.2–1.9)	<0.01	
					>30 kg/m^2	1.7 (1.3–2.3)		

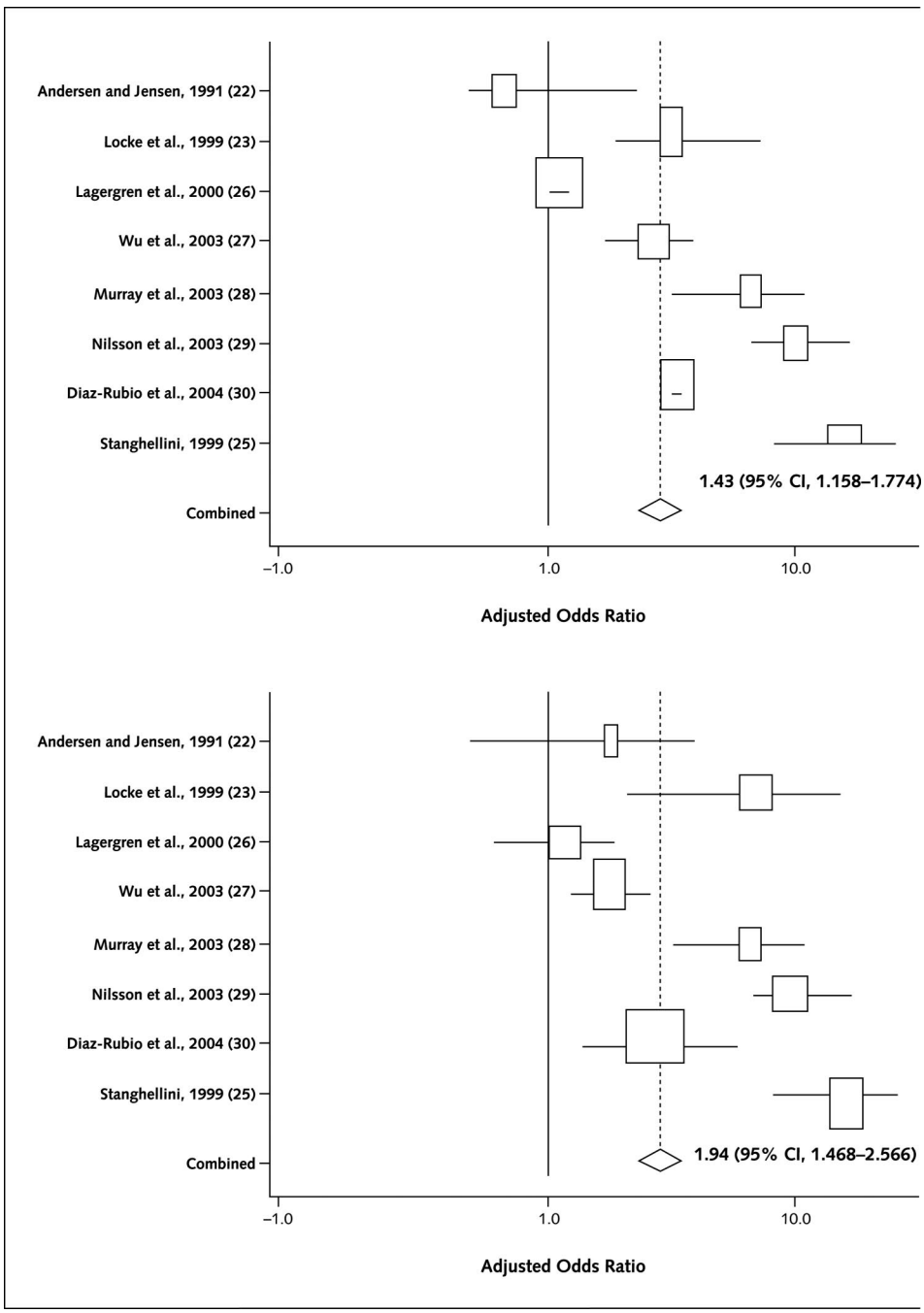
consistency in reporting adjusted risk estimates, we estimated the degree of confounding produced by uncontrolled variables in studies that did not report adjusted risk estimates by using a factorization of the relative risk by external adjustment (19). Subsequently, we pooled the adjusted estimates. In addition, we displayed the adjusted odds ratios in a tabular form, indicating the variables that were adjusted for. We conducted pooling by using a random-effects model. We examined the weighted pooled risk estimates for 2 recognized categories: overweight and obesity (20, 21). We assessed heterogeneity with a chi-square test and by visual inspection of Forest plots. We performed statistical analyses with Comprehensive Meta-Analysis (Biostat, Englewood, New Jersey) and Stata 8.0 (Stata Corp., College Station, Texas). We examined funnel plots to evaluate for publication bias.

Results

GERD Symptoms

We identified 370 potentially relevant titles. Of these, 9 studies satisfied our inclusion and exclusion criteria (22–30). All studies were cross-sectional examinations of GERD symp-

Figure 1. **Adjusted odds ratios for the association of overweight (body mass index 25 kg/m^2 to 30 kg/m^2) and gastroesophageal reflux disease symptoms (*top*) and for the association between obesity (body mass index > 30 kg/m^2) and gastroesophageal reflux disease symptoms (*bottom*).**



toms in randomly selected samples of the general population (**Table 1**). Only 3 studies (Nilsson and colleagues [29], Murray and colleagues [28], and Lagergren and colleagues [26]) were conducted for the primary purpose of evaluating the relationship between obesity and GERD.

Of the 9 studies, 6 studies showed a statistically significant association between obesity and GERD (23–25, 28–30), and 3 studies showed no association (22, 26, 27). Eight of the studies presented data to allow for calculation of unadjusted and adjusted odds ratios and 95% CIs for GERD, overweight (BMI, 25 kg/m^2 to 30 kg/m^2), and obesity (BMI > 30 kg/m^2). In these 8 studies, the pooled weighted unadjusted odds ratios for GERD symptoms among overweight and obese persons were 1.5- and 2.0-fold, respectively, greater than normal-weight persons (**Figure 1**; **Appendix Figure 1**, available at www.annals.org).

Table 1 presents the adjusted odds ratios. Seven studies adjusted for age and sex. Two studies adjusted for race (24, 27), 3 studies adjusted for nonsteroidal anti-inflammatory drug intake (23, 28, 30), 5 studies adjusted for cigarette smoking (23, 26, 28–30), 1 study adjusted for *H. pylori* status and socioeconomic status (28), and 1 study adjusted for physical activity (26). None of these adjustments changed the statistical significance or direction of the observed associations. Similarly, adjustments for alcohol (23, 26, 28–30), coffee consumption (23, 28–30), or other dietary factors (such as dietary fiber [29] or total energy intake [26]) resulted in no appreciable changes in the odds ratios. Nilsson and colleagues (29) found that adjustment for postmenopausal hormone therapy in women strengthened the association.

Two studies (Andersen and Jensen [22] and Stanghellini [25]) did not adjust for confounding factors. On the basis of findings from the studies that provided both adjusted and unadjusted odds ratios, we estimated the effect of confounding variables to reduce the unadjusted ratio by a factor of 0.13, which we applied to the 2 studies. The pooled adjusted odds ratios were 1.43 (95% CI, 1.158 to 1.774; $P = 0.001$) for BMI of 25 kg/m^2 to 30 kg/m^2 and 1.94 (CI, 1.468 to 2.566; $P < 0.001$) for BMI greater than 30 kg/m^2 (**Figure 1**). The heterogeneity among the results of these studies was statistically significant (chi-square, 82.1; $P < 0.001$).

Erosive Esophagitis

Our search identified 111 potentially relevant titles. Of these, 7 studies (4 case–control studies [31–34], 2 cross-sectional studies [35, 36], and 1 cohort study [37]) fulfilled the inclusion and exclusion criteria (**Table 2**). Three studies (Wilson and colleagues [33], Stene-Larson and colleagues [32], and Nilsson and colleagues [31]) were conducted for the primary purpose of evaluating the relationship between obesity and esophagitis.

We calculated a pooled odds ratio for the 4 case–control and 2 cross-sectional studies, excluding the 1 cohort study by Ruhl and Everhart (37). The pooled unadjusted odds ratio of esophagitis related to BMI of 25 kg/m^2 or higher was 1.7-fold greater than that of esophagitis related to BMI less than 25 kg/m^2 (**Appendix Figure 2**, available at www.annals.org). When we excluded the 2 studies from Asia (35, 36) from our analysis, the association between obesity and esophagitis did not appreciably change (pooled unadjusted odds ratio, 1.8 [CI, 1.5 to 2.2]) and there was no statistical heterogeneity (chi-square, 0.15; $P > 0.2$).

Table 2 shows adjusted odds ratios. Four studies adjusted for potential confounding factors (31, 33, 34, 37). Wilson and colleagues (33) found that the association lost statistical significance after adjustment for hiatal hernia. We estimated from these 4 studies that adjustment for confounding variables decreased the odds ratios by 0.16. We applied this factor to the studies by Stene-Larsen and colleagues (32) and Furukawa and colleagues (36). The pooled adjusted odds ratio for 6 studies was 1.76 (CI, 1.156 to 2.677; $P = 0.004$) (**Figure 2**). A heterogeneity test among the studies was also significant (chi-square, 18.9; $P = 0.002$).

Barrett Esophagus

No studies reporting the association of Barrett esophagus and obesity met the selection criteria of our review.

Figure 2. **Adjusted odds ratios from cross-sectional and case–control studies examining the association between overweight or obesity (body mass index ≥25 kg/m^2) and erosive esophagitis.**

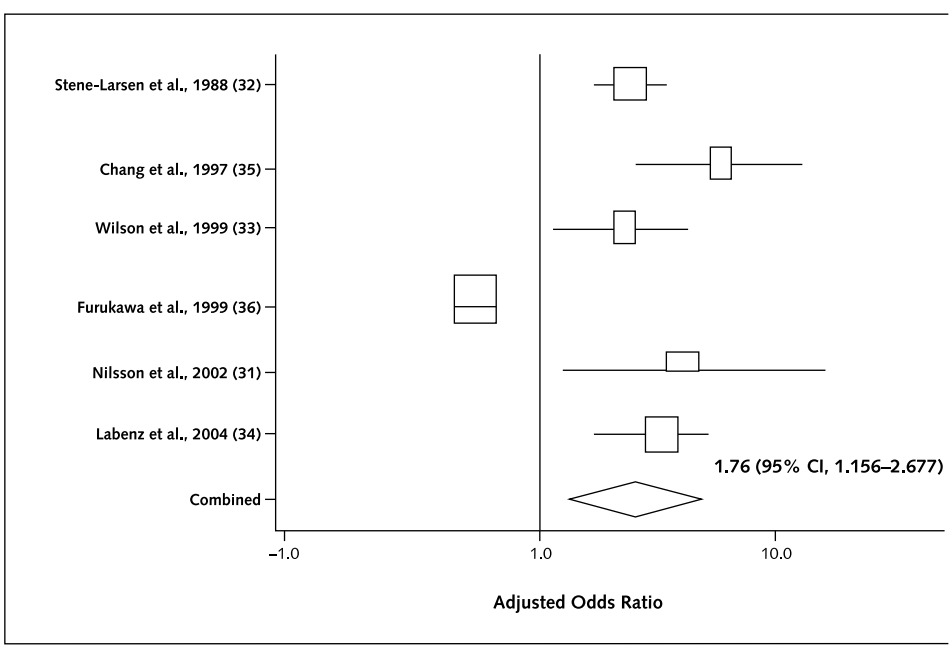


Table 2. **Characteristics of 5 Studies of Obesity and Erosive Esophagitis***

Author, Publication Year (Reference)	Years of Study	Country	Study Design	Case Selection	Case-Patients, *n*	Controls, *n*
Stene-Larsen et al., 1988 (32)	1985–1986	Sweden	Cross-sectional	All persons referred for EGD and found to have endoscopically diagnosed esophagitis at a single hospital	195	1029†
Chang et al., 1997 (35)	1995–1996	Taiwan	Cross-sectional	All persons presenting for routine physical examination (EGD included) and found to have esophagitis at a single institution were eligible	102	1942
Wilson et al., 1999 (33)	1974–1995	US	Cross-sectional	Persons with esophagitis based on endoscopic findings at a single hospital	189	1024
Furukawa et al., 1999 (36)	1996–1998	Japan	Cross-sectional	Persons > 30 y of age with esophagitis on endoscopy performed as part of routine physical examination at a single institution; persons were excluded if they were taking any medication for gastrointestinal disease	977	5023
Labenz et al., 2004 (34)	NA	Germany, Austria, and Switzerland	Cross-sectional	All patients > 18 y of age seen at 1 of the study centers with predominant heartburn symptoms and esophagitis on endoscopy	2455	2834
Nilsson et al., 2002 (31)	1996–1997	Sweden	Case–control†	Patients > 16 y of age with endoscopic esophagitis at 17 hospitals throughout Sweden	224	224
Ruhl and Everhart, 1999 (37)	1971–1993	US	Cohort	Using the NHANES I study cohort of 12 349 population-based case-patients; case-patients for the study included those hospitalized with reflux-related diagnoses (esophagitis and hiatal hernia)	526	11 823

* In cross-sectional studies, non–case-patients comprised patients without erosive esophagitis. BMI = body mass index; EGD = esophagogastroduodenoscopy; NA = not available; NS = not statistically significant; NHANES = National Health and Nutrition Examination Survey; NSAID = nonsteroidal anti-inflammatory drug; PUD = peptic ulcer disease; US = United States.
† Controls were a random sample of age-, sex-, and location-matched population-based controls.

Esophageal Adenocarcinoma and Adenocarcinoma of the Gastric Cardia

Our search strategy identified 93 titles. Of these, 9 case–control studies met the inclusion and exclusion criteria. Eight studies examined population-based samples, and 1 study examined hospital-based samples (38). Four studies (Chow and colleagues [39], Ji and colleagues [40], Zhang and colleagues [41], and Lagergren and colleagues [42]) were conducted for the primary purpose of evaluating the relationship between obesity and esophageal adenocarcinoma.

The studies of Chow and colleagues (39), Lagergren and colleagues (42), Vaughan and colleagues (43), and Wu and colleagues (44) examined esophageal adenocarcinoma as a separate category from gastric cardia adenocarcinoma. Cheng and colleagues (45) excluded cancer of the cardia but may have included cancer of the gastroesophageal junction. Brown and colleagues (46) and Zhang and colleagues (41) combined data for adenocarcinomas of the esophagus with the gastric cardia. The 2 studies from China included only cases of gastric cardia adenocarcinoma (38, 40).

Because substantial weight loss at the time of cancer diagnosis was a concern, all studies, except 1 study (38), obtained historical weight information. Among the 3 studies that collected several historical heights and weights (39, 42, 44), the magnitude or direction of the association between BMI at different time points and risk for adenocarcinoma did not statistically significantly differ.

Esophageal Adenocarcinoma

Seven studies examined the association between obesity and esophageal adenocarcinoma (**Table 3**). Weighted pooling of unadjusted odds ratios (**Appendix Figure 3**, available at www.annals.org) indicates that the risk for esophageal adenocarcinoma is 2.1 times higher in persons with BMI of 25 kg/m^2 or greater than in normal-weight persons. We did not include Zhang and colleagues' study (41) in the pooled odds ratio because the study combined cases of both esophageal and gastric cardia cancer.

All studies adjusted for age and sex, and these were not

Table 2—**Continued**

Demographic Characteristics of Case-Patients			BMI	Adjusted Odds Ratio (95% CI)		*P* Value	Adjustments
Men, %	Age, *y*	White, %					
62	Mean 61, SD 18	NA	Measured				None
			<25 kg/m^2	1.0			
			25–26 kg/m^2	0.9 (0.5–1.6)		<0.01	
			26–28 kg/m^2	1.6 (1.0–2.6)			
			>28 kg/m^2	2.5 (1.7–3.5)			
62	Mean 48, SD 12	NA	Measured				None
			<25 kg/m^2	1.0			
			25–30 kg/m^2	2.1 (1.4–3.3)		<0.01	
			>30 kg/m^2	4.5 (2.4–8.6)			
54	Mean 47	78	Measured				Age, sex, race, and hiatal hernia
			<20 kg/m^2	1.0			
			20–25 kg/m^2	1.0 (0.6–1.5)		NS	
			25–30 kg/m^2	1.5 (0.9–2.3)			
			>30 kg/m^2	1.6 (0.9–2.7)			
55	Mode 60–69	NA	Measured				None
			<25 kg/m^2	1.0			
			>25 kg/m^2	0.9 (0.7–1.0)		NS	
59	Mean 54, SD 14	99	Measured				Age, sex, race, education, smoking, alcohol, NSAID use, *Helicobacter pylori* status, duration of heartburn, concomitant medications, and concomitant diseases
			<25 kg/m^2	1.0			
			25–30 kg/m^2	1.7 (1.2–2.3)		<0.01	
			30–40 kg/m^2	2.0 (1.3–2.9)			
60	Mean 54	NA	From questionnaire	Men	Women		Smoking, previous cholecystectomy, and prescription drug use
			<25 kg/m^2	1.0	1.0	NS (men); <0.01 (women)	
			25–30 kg/m^2	1.2 (0.7–2.2)	0.8 (0.3–2.3)		
			>30 kg/m^2	2.9 (1.1–7.6)	14.6 (2.6–81)		
38	Mode 65–74	86	Measured	Hazard Ratios			Age, sex, activity, race, education, marital status, PUD, arthritis, aspirin use, altered bowel habits, previous cholecystectomy, and nervous breakdown
			<22 kg/m^2	1.0			
			22–25 kg/m^2	1.1 (0.9–1.6)		<0.01	
			25–28 kg/m^2	1.5 (1.1–1.9)			
			>28 kg/m^2	1.9 (1.5–2.5)			

found to have any appreciable effect on the association. Further adjustments for race (41, 43, 44), smoking (39–46), alcohol consumption (40–43, 45, 46), caloric intake (40–42, 45, 46), history of reflux symptoms (42, 45), or education level (40–44) did not alter the statistical significance or direction of unadjusted associations. The pooled adjusted odds ratio from 6 studies for BMI of 25 kg/m^2 or greater was 2.02 (CI, 1.534 to 2.669; $P < 0.001$). There was a trend toward a dose–response relationship with an increase in pooled adjusted odds ratio for BMI of 25 kg/m^2 to 30 kg/m^2 and BMI greater than 30 kg/m^2 of 1.52 (CI, 1.147 to 2.009; $P = 0.004$) (**Figure 3**, *top*) and 2.78 (CI, 1.850 to 4.164; $P < 0.001$) (**Figure 3**, *bottom*).

Adenocarcinoma of the Gastric Cardia

Six studies examined the association of obesity and adenocarcinoma of the gastric cardia (**Table 3**). Four studies showed a statistically significant association (**Table 3**). Vaughan and colleagues (43) showed an association that did not reach statistical significance. One study from China by Zhang and colleagues (38) showed a statistically significant inverse association. We pooled unadjusted estimates from 5 studies (**Figure 3** and **Appendix Figure 3**, available at www.annals.org) with a modest, weighted pooled odds ratio of 1.5. In general, adjustment resulted in an increase in the odds ratios by a factor of 0.3. We applied this factor to derive adjusted odds ratios in studies that provided only unadjusted estimates. The pooled adjusted odds ratio from all 6 studies was 1.68 (CI, 1.197 to 2.351; $P = 0.003$). These results had statistically significant heterogeneity (chi-square, 45.3; $P < 0.001$). However, the 1 study with an inverse association examined BMI 1 year before the cancer diagnosis, whereas other studies used more distant BMI. Excluding that study reduced the heterogeneity (chi-square, 7.6; $P = 0.1$). Finally, funnel plots were not suggestive of publication bias (not shown).

Table 3. **Characteristics of 9 Studies of Body Mass Index and Esophageal Adenocarcinoma or Adenocarcinoma of the Gastric Cardia***

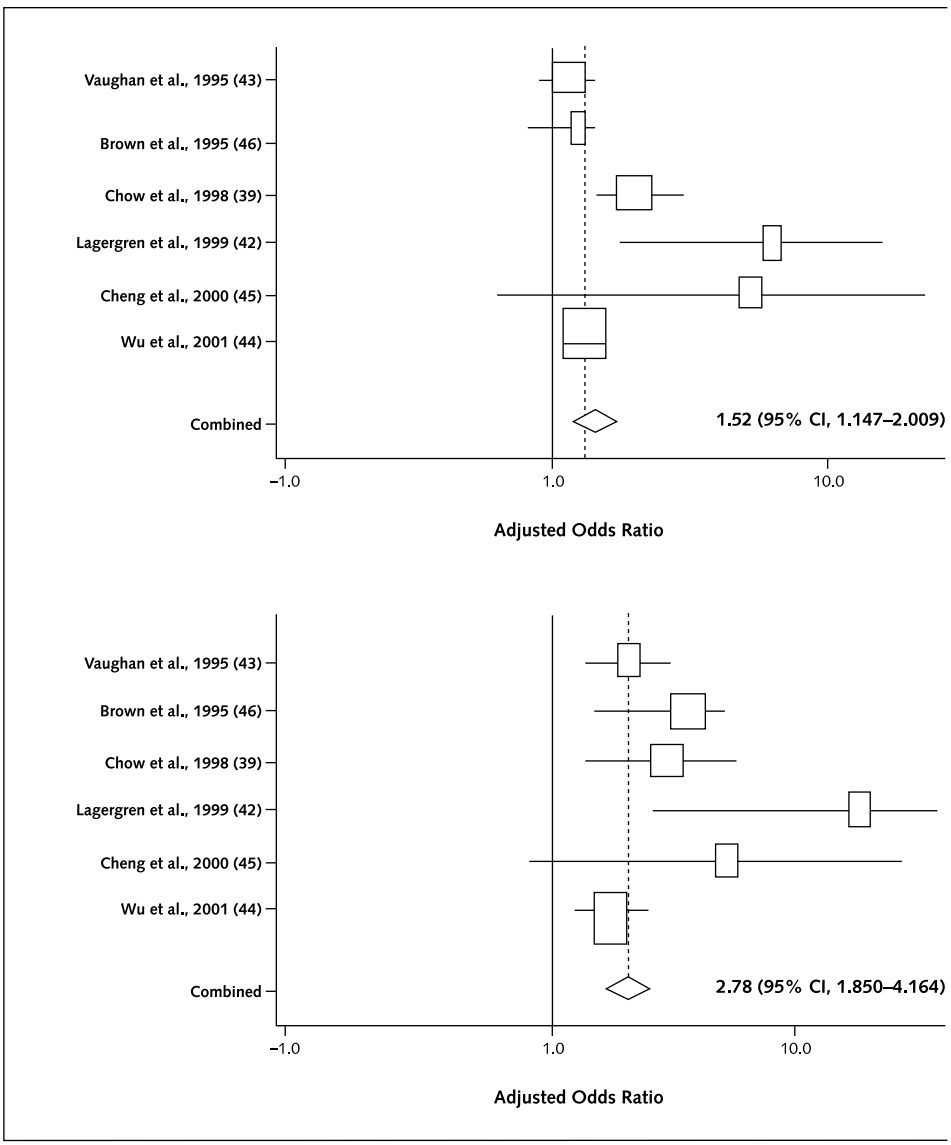
Author, Year (Reference)	Years of Study	Country	Response Rate, %	Case Selection	Case-Patients, *n*	Control Group	Controls, *n*	Method of Data Collection
Vaughan et al., 1995 (43)	1983–1990	US	83 (case); 77 (control)	Consecutive patients with prospectively diagnosed adenocarcinoma of esophagus or gastric cardia identified from population-based cancer registry (SEER)	133	1) Random sample of age- and sex-matched population-based controls; 2) patients with esophageal squamous-cell cancer	724	In-person interview using structured questionnaire
Brown et al., 1995 (46)	1986–1989	US	74 (case); 72 (control)	Consecutive patients with prospectively diagnosed adenocarcinoma of esophagus or gastric cardia identified from state population-based cancer registries in Georgia; Detroit, Michigan; and New Jersey	194	Random sample of age- and sex-matched population-based controls	750	In-person interview using structured questionnaire
Zhang et al., 1996 (41)	1992–1994	US	81	596 consecutive patients referred for EGD at 1 institution were eligible for inclusion into the study; case-patients included those with a diagnosis of adenocarcinoma of the esophagus or gastric cardia at time of EGD	95	1) Patients who underwent EGD with no diagnosis of cancer; 2) patients with noncardia gastric cancer	132	Self-administered, standardized questionnaire
Ji et al., 1997 (40)	1988–1989	China	65 (case); 86 (control)	Prospectively diagnosed cases of adenocarcinoma of gastric cardia from cancer registry	185	1) Random sample of age- and sex-matched population-based controls; 2) patients with noncardia gastric cancer	1451	In-person interview using structured questionnaire
Chow et al., 1998 (39)	1993–1995	US	81 (case); 74 (control)	Prospectively diagnosed cases of adenocarcinoma of esophagus or gastric cardia, identified from state population-based cancer registries in Connecticut, New Jersey, and Washington	292	1) Random sample of age- and sex-matched population-based controls; 2) patients with esophageal squamous-cell cancer; 3) patients with noncardia gastric cancer	694	Phone interview using structured questionnaire
Lagergren et al., 1999 (42)	1995–1997	Sweden	87 (case); 73 (control)	Prospectively diagnosed cases of adenocarcinoma of esophagus or gastric cardia identified from population-based cancer registries	189	1) Random sample of age- and sex-matched population-based controls; 2) patients with esophageal squamous-cell cancer	820	Phone interview using structured questionnaire
Cheng et al., 2000 (45)	1993–1996	UK	62 (case); 65 (control)	Prospectively diagnosed cases of adenocarcinoma of esophagus identified from population-based cancer registries	74	Random sample of age-, sex-, and location-matched population-based controls identified from primary care registers	74	Phone interview using structured questionnaire
Wu et al., 2001 (44)	1992–1997	US	55 (case)	Prospectively diagnosed cases of adenocarcinoma of esophagus or gastric cardia identified from population-based cancer registries	222	1) Random sample of age-, sex-, and race-matched population-based controls selected by using a systemic algorithm based on case-patient address; 2) controls with noncardia gastric cancer	1356	In-person interview with patient or next of kin using structured questionnaire
Zhang et al., 2003 (38)	1995–2002	China	100 (case)	Patients with adenocarcinoma of the gastric cardia retrospectively identified from hospital records	300	Random sample of controls presenting for routine physical examination	258	Chart review

* BMI = body mass index; EGD = esophagogastroduodenoscopy; NA = not available; PUD = peptic ulcer disease; SEER = Surveillance, Epidemiology, and End Results; UK = United Kingdom; US = United States.
† Percentile of the control population, wherein 50% corresponds to BMI of 26.2 kg/m^2 for men and 25.4 kg/m^2 for women.

Table 3—**Continued**

Demographic Characteristics of Case-Patients			BMI	Adjusted Odds Ratio for Esophageal Adenocarcinoma (95% CI)	Adjusted Odds Ratio for Adenocarcinoma of Gastric Cardia (95% CI)	Adjustments
Men, %	Age, *y*	White, %				
90	Mean 61	96	BMI 1 y before diagnosis†			Age, sex, education, race, smoking, and alcohol
			1–10%	1.6 (0.7–3.6)	0.8 (0.4–1.8)	
			11–49%	1.0	1.0	
			50–89%	1.2 (0.7–2.1)	1.3 (0.8–2.1)	
			90–100%	2.5 (1.2–5.0)	1.6 (0.8–3.0)	
100	Mean 63	100	"Usual adult" BMI		NA	Age, alcohol, smoking, annual income, location, and diet
			<23.1 kg/m^2	1.0		
			23.1–25.0 kg/m^2	1.1 (0.6–2.1)		
			25.1–27.0 kg/m^2	1.2 (0.6–2.3)		
			>27.0 kg/m^2	3.1 (1.8–5.3)		
83	<50 (12%)	95	Current BMI as continuous variable	0.9 (0.8–1.0)	NA	Age, sex, race, education, smoking, alcohol, dietary calories, iron deficiency, PUD, hypertension, and history of Barrett esophagus
78	Mean 61	NA	"Usual" adult BMI		Men / Women	Age, sex, education, income, smoking, alcohol, caloric intake, and chronic gastric diseases
			<19 kg/m^2	NA	1.0 / 1.0	
			19–21 kg/m^2		1.4 (0.7–2.6) / 0.9 (0.3–3.0)	
			21–22 kg/m^2		1.5 (0.8–2.8) / 2.0 (0.7–5.6)	
			22–25 kg/m^2		2.7 (1.5–4.8) / 1.3 (0.4–4.1)	
			>25 kg/m^2		5.4 (2.4–12.4) / 1.8 (0.5–6.4)	
84	Mode 70–79	NA	"Usual" BMI			Age, sex, smoking, and geographic location
			Men / Women			
			<23 kg/m^2 / <22 kg/m^2	1.0	1.0	
			23–25 kg/m^2 / 22–24 kg/m^2	1.3 (0.8–2.2)	0.9 (0.6–1.5)	
			25–27 kg/m^2 / 24–27 kg/m^2	2.0 (1.3–3.3)	1.4 (0.9–2.1)	
			>27 kg/m^2 / >27 kg/m^2	2.9 (1.8–4.7)	1.6 (1.1–2.6)	
87	Mean 69	NA	BMI 20 y before diagnosis			Age, sex, smoking, alcohol, education, reflux symptoms, diet, and activity
			<22 kg/m^2	1.03.2	1.0	
			22–25 kg/m^2	(1.6–6.7)	1.3 (0.8–1.9)	
			25–30 kg/m^2	6.9 (3.3–14.4)	2.2 (1.4–3.4)	
			>30 kg/m^2	16.2 (6.3–41.4)	4.3 (2.1–8.7)	
0	Mean 66	NA	BMI at age 20 y			Age, smoking, alcohol, social class, number of children, breastfeeding status, and diet
			<19.5 kg/m^2	1.0	NA	
			19.5–21.0 kg/m^2	0.9 (0.2–4.3)		
			21.0–22.7 kg/m^2	4.9 (0.9–28.0)		
			>22.7 kg/m^2	6.0 (1.3–28.5)		
91	Mean 61, SD 9	78	BMI at age 20 y			Age, sex, race, smoking, education, and birthplace
			Men / Women			
			<22 kg/m^2 / <21 kg/m^2	1.0	1.0	
			22–25 kg/m^2 / 21–23 kg/m^2	1.2 (0.8–1.9)	1.1 (0.8–1.7)	
			25–27 kg/m^2 / 23–25 kg/m^2	1.3 (0.9–2.1)	1.4 (0.9–2.0)	
			>27 kg/m^2 / >25 kg/m^2	1.8 (1.1–2.7)	1.7 (1.2–2.6)	
83	Mean 62	NA	Current BMI as continuous variable	NA	0.85 (0.81–0.91)	Age and sex

Figure 3. **Adjusted odds ratios from case–control studies examining the association between overweight (body mass index ≥25 kg/m²) and adenocarcinoma of the esophagus (*top*) and the association between obesity (body mass index >30 kg/m²) and esophageal adenocarcinoma (*bottom*).**



DISCUSSION

We performed a systematic review of the literature examining the association between BMI and acid-related disorders of the esophagus. The risk for GERD symptoms, erosive esophagitis, or esophageal adenocarcinoma increased with overweight or obesity compared with normal BMI. The association of overweight and obesity with adenocarcinoma of the gastric cardia, a condition less frequently associated with GERD, was weaker and less consistent.

We did not provide a quality score for the individual studies included in our review. However, our inclusion and exclusion criteria ensured a minimum standard of quality. Thus, all studies used acceptable definitions of exposure (BMI) and outcomes of interest (symptoms, endoscopic findings, and pathologic confirmation). Most studies that examined symptoms and cancer were population-based studies with acceptable enrollment rates. However, only 10 of 25 studies stated that the primary purpose of the study was to examine the relationship between obesity and GERD. Another limitation that particularly applies to case–control studies evaluating adenocarcinoma is recall bias, where case-patients may overestimate their historical weight compared with noncancer controls. However, the consistency across studies provides some reassurance against recall bias. To minimize the possibility of recall bias, 3 studies examined patients with squamous-cell carcinoma of the esophagus (39, 42, 43) and 4 studies examined patients with distal gastric adenocarcinoma (38–40, 44) as a second cancer comparison group. These studies found that BMI had either no association or a statis-

tically significant negative association with the cancer controls. Furthermore, in all erosive esophagitis studies, BMI was measured directly.

The heterogeneity test indicated statistically significant degrees of heterogeneity among studies. However, the association between BMI and GERD complications was markedly consistent, and differences in the risk estimates were largely in the magnitude rather than the direction of the association. No studies had a negative association, and the 4 studies with no significant association indicated a trend toward statistical significance. Therefore, the use of pooled odds ratios was appropriate. In the case of esophagitis, the heterogeneity was largely attributed to geographic differences among the study samples. Removing studies that were conducted in Asia eliminated heterogeneity among studies of esophagitis.

Overweight and obesity satisfy several criteria for a causal association with GERD and its complications, including esophagitis and esophageal adenocarcinoma. Our review indicates a consistent modest statistical association, a correct temporal relationship, and possibly a weak dose–response relationship. However, estimates of BMI in most studies were obtained for several years predating the outcomes. The cross-sectional and case–control design of most studies makes it difficult to be emphatic about temporal association, especially for chronic slowly progressive conditions, such as GERD symptoms and erosive esophagitis.

Obese patients may experience extrinsic gastric compression by surrounding adipose tissue, leading to an increase in intragastric pressures and subsequent relaxation of the lower esophageal sphincter (47–49). The findings of manometric studies, however, have been inconsistent, indicating both decreased (50) and normal (17, 51–53) lower esophageal sphincter pressures in obese persons.

Studies have also suggested that rather than obesity, the amount and type of dietary intake, notably fat, are responsible for GERD. Seven studies in our review examined total caloric intake and dietary intake of fiber, fruits and vegetables, or other macronutrients or micronutrients. In all, the effect of BMI on GERD-related disorders was independent of dietary intake, which is further supported by a recent smaller study (54). Moreover, all studies found no consistent association between dietary fat and GERD or esophageal adenocarcinoma.

Obese patients may have an increased risk for hiatal hernia, which has a role in initiating and promoting GERD (55). In our review, 3 studies specifically examined hiatal hernia in relation to obesity and GERD or esophagitis (27, 32, 33). Wilson and colleagues (33) found obesity to be statistically significantly associated with esophagitis. However, after the authors controlled for the presence of hiatal hernia, this association lost statistical significance, implying that hiatal hernia was the mechanism by which obesity leads to esophagitis. Wu and colleagues (44), on the other hand, found no statistically significant association between BMI and hiatal hernia. In a study that examined the association of BMI and grade of esophagitis in persons with esophagitis, El-Serag and Johanson (56) also found that obesity remained an independent risk factor for severe versus mild esophagitis while controlling for the presence of hiatal hernia. The cross-sectional nature of these studies makes it impossible to distinguish temporal associations between obesity and hiatal hernia. In sum, data about hiatal hernia as a cause of increased esophageal reflux in obesity are conflicting.

Humoral factors have also been considered as a mechanism relating obesity to reflux and esophageal adenocarcinoma. Two studies identified in our review conducted by the same group of investigators from Sweden observed that the association of obesity and GERD might be mediated by estrogen (29, 31). The first study reported a statistically significant association between obesity and esophagitis in women, which was potentiated by the use of estrogen in postmenopausal women (31). The second study examined a large population-based cohort and found that obese women had an increased risk for GERD symptoms compared with obese men; the risk was highest in premenopausal women and postmenopausal women receiving estrogen therapy (29). Furukawa and colleagues (36) reported that overweight women older than 70 years of age were the only group to have a statistically significantly increased risk for esophagitis. The authors did not report on estrogen use in these patients. However, several other studies have found that the obesity-related increased risk for esophageal disease was neither confounded nor modified by sex (27, 56).

Some evidence suggests that a change in weight can also affect the risk for GERD and its complications. For example, Nilsson and colleagues (29) found that a weight gain greater than 3.5 kg/m^2 was associated with a 2.7-fold (CI, 2.3- to 3.2-fold) increased risk for developing new reflux symptoms. On the other hand, although weight loss is often recommended as a therapeutic measure in reflux disease (57), the studies yielded conflicting results on its efficacy (58, 59). Small nonrandomized studies suggest that weight loss after bariatric surgery for morbid obesity is associated with an improvement in GERD symptoms (60, 61). Finally, no data suggest that weight loss can affect risk for esophageal adenocarcinoma.

The mechanism of obesity-related esophageal adenocarcinoma is unclear. Of interest, no studies satisfying our inclusion and exclusion criteria assessed the association between obesity and Barrett esophagus. Excluded because of the absence of a control group, Caygill and colleagues' study (62) reported a BMI greater than 30 kg/m^2 in 24% of patients in their case series of 102 patients with Barrett esophagus, as compared with an obesity prevalence of 13% in the general population of England. Excluded because of few cases, a case–control study by Chak and colleagues (63) and a cross-sectional study by Gerson and colleagues (64) both reported no apparent increase in risk for obesity in 35 and 27 patients with Barrett esophagus, respectively,

although Chak and colleagues reported that the duration of obesity was statistically significantly longer in patients with Barrett esophagus.

Our review suggests that overweight and obesity are risk factors for acid-related esophageal disease. Future studies should examine the mechanism by which obesity causes these complications, as well as the potential effects of weight loss. In the meantime, however, it is prudent to counsel all overweight patients who present with GERD-related diseases that weight loss may help improve symptoms.

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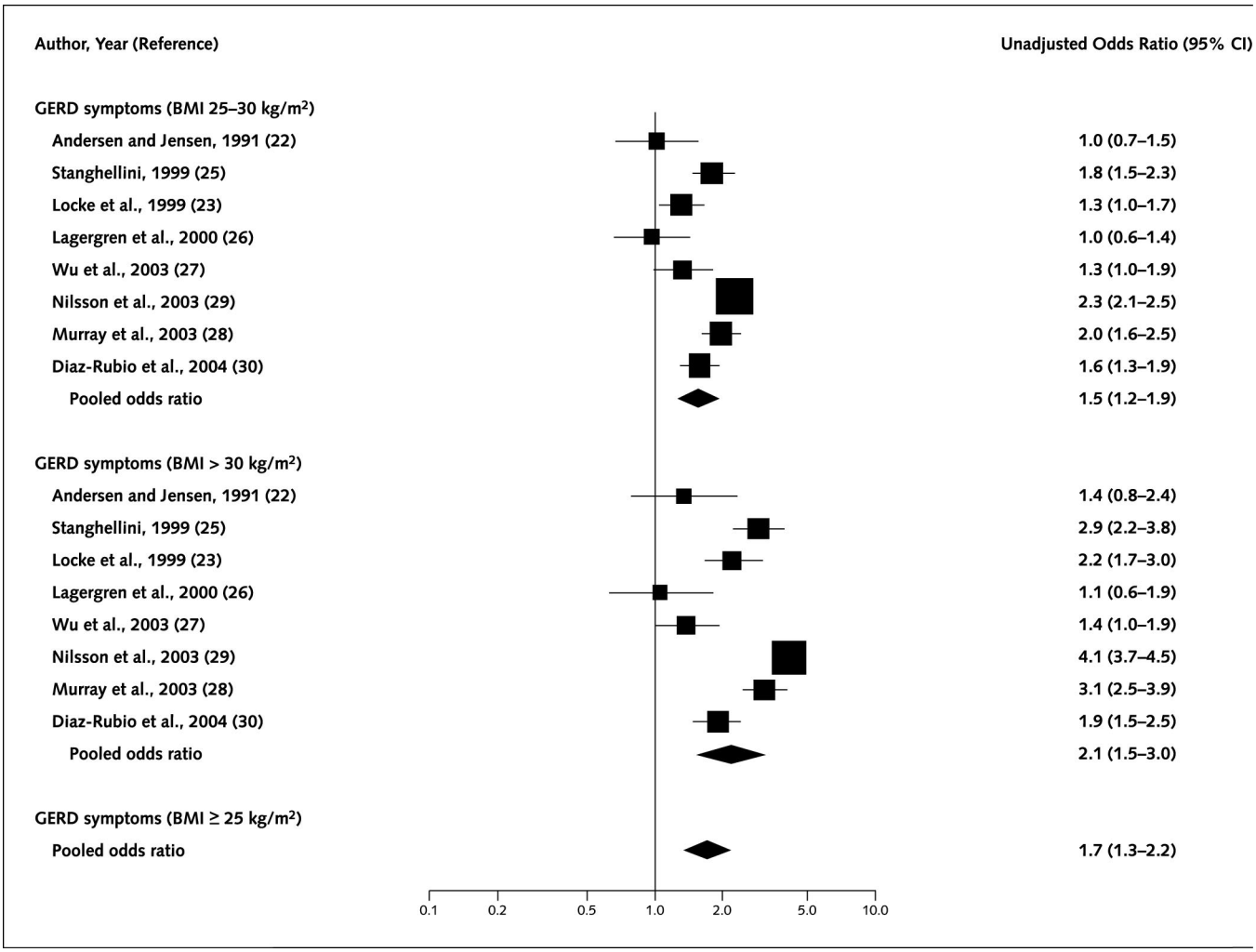
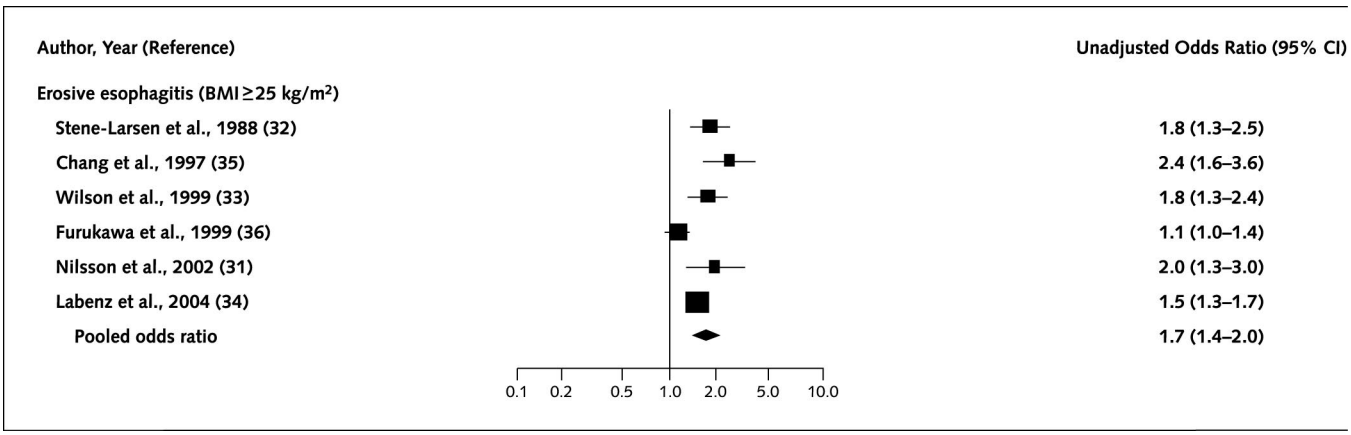
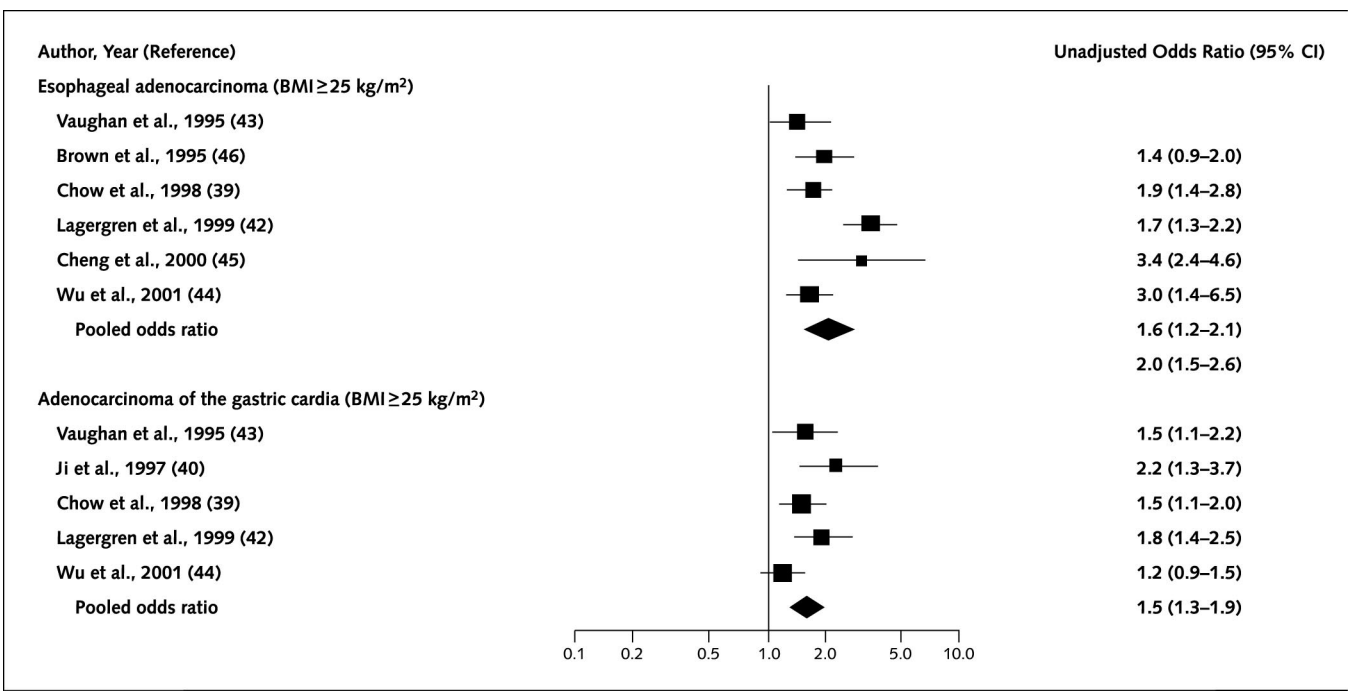
Appendix Figure 1. **Unadjusted odds ratios (95% CIs) for the risk for gastroesophageal reflux disease (*GERD*) symptoms among overweight (*top*) and obese (*bottom*) versus normal-weight individuals.**



Normal weight is defined as a body mass index (BMI) less than 25 kg/m^2 for all studies, except for the study by Locke and colleagues (BMI $<$ 24 kg/m^2) (23). Overweight is defined as a BMI of 25 kg/m^2 to 30 kg/m^2 for all studies, except for Locke and colleagues' study (BMI, 24 to 30 kg/m^2) (23) and Wu and colleagues' study (BMI, 25 kg/m^2 to 28 kg/m^2) (27). Obese is defined as a BMI greater than 30 kg/m^2 for all studies, except Wu and colleagues' study (BMI $>$ 28 kg/m^2) (27). Pooled weighted odds ratios are also given for overweight and obesity (that is, BMI $\geq$ 25 kg/m^2 compared with BMI $<$ 25 kg/m^2).

Appendix Figure 2. **Unadjusted odds ratios (95% CIs) from cross-sectional and case–control studies examining the risk for erosive esophagitis among overweight (body mass index [*BMI*] ≥ 25 kg/m^2) versus normal-weight (BMI < 25 kg/m^2) individuals.**



Appendix Figure 3. **Unadjusted odds ratios (95% CIs) from case–control studies examining the association between overweight or obesity (body mass index [*BMI*] ≥25 kg/m^2) and adenocarcinoma of the esophagus or gastric cardia.**